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REIJA KLEMETTI

The Use of Assisted Fertilization in Finland: Health Effects and Equity

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Tutkimuksen taustaa: Koeputkihedelmöitys (IVF, joka sisältää mikroinjektion ja pakastetun alkion siirron) ja munasarjojen lääkkeellinen induktio (OI, johon voi sisältyä keinosiemennys) ovat yleisiä hedelmöityshoitoja Suomessa. Niiden käytöstä ja terveysvaikutuksista hoitoja saaneille naisille ja hoitojen jälkeen syntyneille lapsille ei kuitenkaan vielä tiedetä riittävästi. Oikeudenmukaisuus on suomalaisessa terveydenhuollossa määritelty siten, että samanlaisessa tarpeessa olevilla on samanlainen mahdollisuus päästä hoitoon ja saada hoitoa. Terveydenhuoltoon käytettävien resurssien tulisi jakautua oikeudenmukaisesti sukupuolen, iän, asuinalueen ja sosioekonomisen aseman suhteen. IVF on kallis hoito, jossa naisen iän lisääntymisen myötä onnistuminen laskee. Samoin äidin ja lapsen terveysongelmien riski kasvaa.

Tutkimuksen tarkoitus: Tämän tutkimuksen tarkoituksena on useita terveydenhuollon rekistereitä käyttäen selvittää IVF:n ja OI:n käyttöä, sairaalahoitoon johtaneita komplikaatioita ja keskenmenoja hoitoja saaneilla naisilla, hoitojen jälkeen syntyneiden lasten terveyttä ja kuvata IVF-hoitoihin käytettyjen resurssien jakautumista hoitoja saaneiden naisten iän ja sosioekonomisen aseman sekä hoitosektorin (yksityinen tai julkinen) mukaan sekä pohtia IVF:n käytön ja resurssien jaon oikeudenmukaisuutta.

Tutkimusaineisto ja menetelmät: Tässä rekisteripohjaisessa tutkimuksessa IVF-hoitoja (N = 9175) ja OI-hoitoja (N = 10 254) vuosina 1996–1998 saaneet naiset identifioitiin Kelan lääke- ja toimenpidekorvausrekistereistä ja heitä seurattiin vuoteen 2000 yhdistämällä aineisto hoitoilmoitus- ja kuolinsyyrekistereihin. IVF-naisille valittiin iän ja asuinpaikan suhteen kaltaistetut vertailunaiset (N = 9175). IVF:n (N = 4559) ja OI:n (N = 4467) jälkeen syntyneet lapset identifioitiin syntymärekisteristä, josta heille poimittiin vertailulapset (kaikki muut lapset, N=190 398, tutkittaessa vastasyntyneisyysajan terveyttä, sairaalahoitoja ja kuolleisuutta, ja satunnaisotos näistä lapsista, n = 26 877 tutkittaessa synnynnäisiä epämuodostumia ja pitkäaikaissairaiden lasten hoitotukia ja korvattuja lääkkeitä). Lapsia seurattiin vuoden 2003 loppuun yhdistämällä aineisto hoitoilmoitus-, epämuodostuma- ja kuolinsyyrekisteriin sekä Kelan rekistereihin. Naisten taustatiedot saatiin Kelasta ja Väestörekisteristä ja hoitojen korvaus- ja kustannustiedot Kelasta ja hoitoja antavilta klinikoilta.

Tulokset: Keskimääräisen 1,5 vuoden seurannan aikana vanhimmat, 40 vuotta täyttäneet naiset, saivat hieman enemmän IVF-hoitosyklejä kuin nuorimmat, alle 30-vuotiaat naiset (2,2 vrt. 3,0). Yksityissektorilla oli julkista sektoria enem-

män korkeammassa sosioekonomisessa asemassa olevia IVF-hoitoja saaneita naisia. Nämä naiset saivat muita enemmän IVF-syklejä. IVF-hoitojen onnistuminen – elävänä syntyneiden lasten lukumäärä IVF-syklejä kohti – laski naisen iän myötä: 22 % alle 30-vuotiailla ja 6 % yli 40-vuotiailla.

IVF:n jälkeen 23 ja OI:n jälkeen yksi tuhannesta naisesta joutui tutkimusajankohtana (keskimäärin 2,7 hoitoa) sairaalaan munasarjojen hyperstimulaatiosyndrooman (OHSS) takia. Sekä IVF:n että OI:n jälkeen sairaalahoitoon johtaneita keskenmenoja oli 42 tuhatta hoidettua naista kohti. Noin 15 % IVF-naisista ja 8 % OI-naisista joutui komplikaatioiden tai keskenmenon takia ainakin kerran sairaalahoitoon seurannan aikana.

IVF-lasten vastasyntyneisyysajan terveys oli huonompi ja sairaalahoito yleisempää kuin muilla lapsilla. IVF-lapsilla oli kohonnut riski CP-vammaisuuteen (OR-luku 2.9 ja 95 % luottamusväli 1.6–5.3), psykologisiin ja kehityksellisiin häiriöihin (1.7, 1.1–2.5) sekä synnynnäisiin merkittäviin epämuodostumiin (1.3, 1.1–1.6). Tulokset selittyivät osin monisikiöisten raskauksien suurella määrällä. IVF-yksösillä oli muita yksösiä huonompi vastasyntyneisyysajan terveys, enemmän sairaalahoitoja ja pojilla kohonnut synnynnäisten epämuodostumien riski. IVF-kaksosten ja -kolmosten terveys oli samanlainen kuin muilla kaksosilla ja kolmosilla.

Keskimääräiset kokonaiskustannukset elävänä syntynyttä IVF-lasta kohti lisääntyivät naisen iän myötä 12 851 eurosta (alle 30-vuotiaat) 40 662 euroon (40 vuotta täyttäneet). Väestökohtaisesti laskettuna (kutakin ikäluokkaa ja sosioekonomista asemaa kohti) yhteiskunnan resursseja käytettiin eniten 30–39-vuotiaiden naisten ja korkeimmassa sosioekonomisessa asemassa olevien naisten hoitamiseen. Alueelliset erot olivat pieniä.

Johtopäätökset: Vaikka suurin osa IVF-lapsista oli terveitä, heillä oli enemmän terveyteen liittyviä ongelmia kuin muilla lapsilla. Yksittäiseen IVF-sykliin liittyvien komplikaatioiden riski oli pieni, mutta useampien hoitosyklien antaminen johti vakaviin komplikaatioihin useilla naisilla; IVF:n jälkeen selvästi useammin kuin OI:n jälkeen. Lisätutkimuksia tarvitaan selvittämään IVF- ja OI-naisten ja heidän lastensa pidemmän ajan terveyttä. Tutkimuksessa ei ollut tietoa hoidon tarpeesta eli hedelmättömyyden yleisyydestä eikä toiveesta saada lapsi, joten ei voi varmasti sanoa, suositaanko hedelmöityshoidoissa tietyn ikäisiä naisia. Korkeammat kustannukset, suuremmat terveysriskit ja hoitojen huonompi onnistuminen vanhemmilla naisilla puoltavat keskittymistä nuorempien, hedelmällisessä iässä olevien naisten hoitamiseen. Erot sosioekonomisen aseman suhteen IVF:n käytössä ja resurssien jaossa voivat kertoa epäoikeudenmukaisuudesta.

Avainsanat: koeputkihedelmöitys, ovulaation induktio, rekisteritutkimus, terveysvaikutukset, komplikaatiot, OHSS, lasten terveys, synnynnäiset epämuodostumat, kustannukset, oikeudenmukaisuus

SAMMANFATTNING

Klemetti Reija. The Use of Assisted Fertilization in Finland: Health Effects and Equity [Användningen av assisterad befruktning i Finland: Hälsoeffekter och rättvisa.]STAKES, Research Reports, 158. Helsingfors, Finland, 2006. ISBN 951-

Bakgrund till undersökningen: In vitro fertilisering (IVF, som omfattar en mikroinjektion och överföring av ett fryst embryo) och medicinsk ovulationsinduktion (OI, som kan omfatta artificiell insemination) är vanliga fertilitetsbehandlingar i Finland. Om deras användning och hälsopåverkan på kvinnorna som fått behandling och på barnen som föds efter behandlingen vet man dock tillsvidare inte tillräckligt. Rättvisa har inom den finländska hälso- och sjukvården definierats så, att de som har samma behov har samma tillgång till vård och samma möjlighet att få vård. De resurser som används för hälso- och sjukvård borde fördelas rättvist i förhållande till kön, ålder, bostadsort och socioekonomisk ställning. IVF är en dyr behandling, och med ökad ålder hos kvinnan minskar behandlingens utfall. Samtidigt ökar risken för hälsoproblem hos modern och barnet.

Syftet med undersökningen: Syftet med denna undersökning är att med hjälp av flera av hälso- och sjukvårdens register utreda användningen av IVF och OI, komplikationer och missfall som lett till sjukhusvård hos kvinnor som erhållit behandlingar och hälsan hos barn som fötts efter behandlingarna samt att beskriva fördelningen av de resurser som använts för IVF-behandlingar i förhållande till de behandlade kvinnornas ålder och socioekonomiska ställning samt vårdsektor (privat eller offentlig). Syftet är även att bedöma användningen av IVF och rättvisan i fördelningen av resurserna.

Undersökningsmaterial och metoder: I denna registerbaserade undersökning identifierades kvinnor som fått IVF-behandling (N = 9175) och OI-behandling (N = 10 254) under åren 1996–1998 i Folkpensionsanstaltens (FPA) register över ersättningar för läkemedel och åtgärder, och kvinnorna följdes upp till år 2000 genom att materialet sammanställdes med vårdanmälnings- och dödsorsaksregistren. För IVF-kvinnorna valdes en kontrollgrupp av kvinnor (N = 9175) som matchades utifrån ålder och bostadsort. Barnen som fötts efter IVF (N = 4559) och OI (N = 4467) identifierades i födelseregistret, från vilket en jämförelsegrupp av barn valdes (alla övriga barn, N=190 398, vid undersökning av hälsan under perinataltiden, sjukhusvård och dödlighet, och ett slumpmässigt urval av barn, n = 26 877 vid undersökning av medfödda missbildningar och vårdstöd för långtidssjuka barn och ersättningar för läkemedel). Barnen följdes upp till slutet av år 2003 genom att materialet sammanställdes med vårdanmälnings-, missbildnings- och dödsorsaksregistren samt FPA:s register. Bakgrundsinformation om kvinnorna erhölls från FPA och Befolkningsregistret och uppgifterna om ersättningar och kostnader för behandlingarna från FPA och de kliniker som gav behandling.

Resultat: Under den i medeltal 1,5 år långa uppföljningstiden fick de äldsta kvinnorna, som fyllt 40 år, något fler IVF-behandlingscykler än de yngsta, under 30 år gamla kvinnorna (2,2 mot 3,0). Inom den privata sektorn fanns fler kvinnor med högre socioekonomisk ställning som fått IVF-behandling än inom den offentliga sektorn. Dessa kvinnor erhöll fler IVF-cykler än andra. Antalet lyckade IVF-behandlingar – antalet levande födda barn per IVF-cykel – minskade med kvinnans ålder: 22 % vid under 30 års ålder och 6 % vid över 40 års ålder.

Efter IVF togs 23 och efter OI en av tusen kvinnor under undersökningsperioden (i medeltal 2,7 behandlingar) in på sjukhus på grund av ovarialt överstimuleringssyndrom (OHSS). Efter både IVF och OI var frekvensen av missfall som ledde till sjukhusvård 42 per tusen behandlade kvinnor. Cirka 15 % av IVF-kvinnorna och 8 % av OI-kvinnorna togs minst en gång in på sjukhus på grund av komplikationer eller missfall under uppföljningen.

IVF-barnens hälsa under perinataltiden var sämre och sjukhusvård vanligare än för andra barn. IVF-barnen hade förhöjd risk för CP-skador (oddskvot 2,9 och 95 % konfidensintervall 1,6–5,3), psykologiska störningar och utvecklingsstörningar (1,7, 1,1–2,5) samt medfödda betydande missbildningar (1,3, 1,1–1,6). Resultaten förklaras delvis av det stora antalet flerbörder. IVF-enlingar hade sämre hälsa under perinataltiden än andra enlingar, mera sjukhusvård och pojkarna förhöjd risk för medfödda missbildningar. IVF-tvillingars och trillingars hälsa motsvarade andra tvillingars och trillingars.

De genomsnittliga totalkostnaderna per levande fött IVF-barn ökade med kvinnans ålder från 12 851 euro (under 30 år) till 40 662 euro (för 40 år fyllda). Beräknat i förhållande till befolkningen (för varje åldersgrupp och socioekonomisk grupp) användes mest av offentliga resurser för behandling av kvinnor i åldern 30–39 år och kvinnor i den högsta socioekonomiska ställningen. De regionala skillnaderna var små.

Slutsatser: Även om den största delen av IVF-barnen var friska, hade de fler hälsorelaterade problem än andra barn. Risken för komplikationer vid en enstaka IVF-cykel var liten, men flera behandlingscykler ledde till allvarliga komplikationer hos flera kvinnor; betydligt oftare efter IVF än efter OI. Ytterligare undersökningar krävs för att utreda hälsan för IVF- och OI-kvinnor och deras barn på längre sikt. I undersökningen fanns inte uppgifter om behovet av behandling, det vill säga hur allmän ofruktsamhet är, och inte heller om önskan att skaffa barn, varför man inte med säkerhet kan säga huruvida kvinnor av någon viss ålder favoriseras vid fertilitetsbehandlingar. De högre kostnaderna, de större hälsoriskerna och det sämre utfallet vid behandling av äldre kvinnor talar för koncentration på behandling av yngre kvinnor i fruktsam ålder. Skillnaderna i fråga om den socioekonomiska ställningen vid behandling med IVF och fördelningen av resurser kan vittna om orättvisa.

Nyckelord: Provrörsbefruktning, in vitro fertilisering, ovulationsinduktion, registerundersökning, hälsopåverkan, komplikationer, OHSS, barnens hälsa, medfödda missbildningar, kostnader, rättvisa

ABSTRACT

Klemetti Reija. **The Use of Assisted Fertilization in Finland: Health Effects and Equity,** STAKES, Research Reports, 158. Helsinki, Finland, 2006. ISBN 951-33-1912-1

Background: Though Assisted Fertilization (AF), consisting of in vitro fertilization (IVF, including intracytoplasmic sperm injection and frozen embryo transfer) and ovulation induction (OI with or without inseminations), is widely used as a treatment for infertility, not enough is known about its utilization and health effects. Equity in health care should mean equal access to care according to need and an equitable distribution of health care resources by gender, age, living area, and socioeconomic position. IVF is a costly treatment in which effectiveness and appropriateness decrease by women's age while need and complications increase.

Objective: The purpose of this study is to investigate via nationwide registers the use of AF, i.e. IVF and OI, the occurrence of serious complications and miscarriages of treated women, and the health of their children, as well as to describe equity in the allocation of resources to IVF by women's age and socioeconomic position and by the treatment sector (public vs. private). Finally, the aim is to discuss whether the usual criteria of equity apply to IVF.

Materials and methods: In this register-based study, women who received IVF (N=9175) and OI (N=10 254) between 1996 and 1998 were identified from the reimbursement records of the Social Insurance Institution (SII) that cover all Finns and were followed until 2000 by means of register linkages (The Hospital Discharge Register and The Cause-of-Death Register). Population controls, matched by age and municipality, were selected for IVF women (N = 9175). IVF women's children (N = 4559) and OI women's children (N = 4467) were identified from the Medical Birth Register (MBR) and followed until 2003 by using the Hospital Discharge Register, the Register of Congenital Malformations, the Cause-of-Death statistics, and reimbursements records of the SII. Two control groups were selected from the MBR: all other children from the same period (N = 190 398, for studying perinatal health, hospitalizations and mortality) and also a random sample of them (n = 26 877, for studying congenital anomalies (CAs) and health-related benefits). Information on treatment costs were received from IVF clinics and the SII.

Results: During a mean follow-up period of 1.5 years, older women received 1.4 times more IVF treatment cycles than younger women (2.2 vs. 3.0). In the private sector, women in the highest socioeconomic position were over-represented and had more cycles than other women. The success rate—live-births per cycle—decreased by women's age: from 22% among women aged below 30, to 6% among women aged 40 or older.

After IVF, 23 per 1000 and after OI, 1 per 1000 women had a serious case of OHSS (ovarian hyperstimulation syndrome) during the study period (mean of 2.7 treatments). The rates of registered miscarriages after both IVF and OI were 42 per 1000 treated women. Overall, 15% of IVF and 8 % of OI women had at least one hospital episode during the study period.

Perinatal outcomes of IVF children were worse and hospital episodes were more common than among control children; odds ratios (OR) for cerebral palsy (2.9, 95% CI 1.6–5.3) and psychological and developmental disorders (1.7, 1.1–2.5) were increased as well as OR for congenital anomalies (1.3, 1.1–1.6). These results were partly explainable by the great number of twins among IVF children. Among IVF singletons, poorer results were found for perinatal outcomes and hospitalizations, while for singleton IVF boys an increased risk of major CAs were also found. The health of IVF multiples was comparable to the health of control multiples.

The mean cost of a live birth after IVF increased by women's age from EUR 12 851 among women aged under 30 to EUR 40 662 among women aged 40 or older. Calculated per population, society contributed most to the women aged 30–39 years and women from the highest socioeconomic position. Regional differences were not remarkable.

Conclusion: Although the health of most IVF children was good, they had more health problems than other children. The risk of complications for women after each IVF treatment cycle was low, but repeated attempts resulted in serious complications for many women, and these occurred much more often than after OI alone. Further studies are needed to examine the long-term health of IVF and OI women and their children. No information on the need for IVF and OI treatments, i.e. infertility rates and the wish for a child, was available in the study. It is therefore uncertain whether women from a certain age-group are favoured in treatments in Finland. Due to the higher costs, increased health risks and decreased IVF success for older women, concentrating on the treatment of younger women is a fairer solution than provision solely based on need. Socioeconomic differences in the use of IVF services and the allocation of resources may indicate inequality.

Key words: IVF, ovulation induction, health effects, register-based study, complications, OHSS, child health, perinatal health, congenital anomaly, equity, costs

CONTENTS

List of original publications

The present thesis is based on the following articles, which are referred to in the text by their Roman numerals:

I Klemetti Reija, Gissler Mika, Hemminki Elina.
Equity in the use of IVF in Finland in the late 1990s.
Scandinavian Journal of Public Health 2004;32:203–209.

II Klemetti Reija, Sevón Tiina, Gissler Mika, Hemminki Elina.
Complications of IVF and ovulation induction.
Human Reproduction 2005;20:3293–3300.

III Klemetti Reija, Sevón Tiina, Gissler Mika, Hemminki Elina.
Health of Children Born as a Result of In Vitro Fertilization.
Pediatrics 2006;118:1819–1827.

IV Klemetti Reija, Gissler Mika, Sevón Tiina, Koivurova Sari, Ritvanen Annukka, Hemminki Elina.
Children born after assisted fertilization have an increased rate of major congenital malformation.
Fertility & Sterility 2005;84:1300–1307.

V Klemetti Reija, Gissler Mika, Sevón Tiina, Hemminki Elina.
Equity in the allocation of resources in IVF (Submitted).

Abbreviations

AF = Assisted fertilization
ART = Assisted reproductive technologies
CA = Congenital anomaly
CI = Confidence interval
CP = Cerebral palsy
CPR = Central Population Register
FET = Frozen embryo transfer
HDR = Hospital Discharge Register
ICD = International Classification of Diseases
ICSI = Intra cytoplasmic sperm injection
IUI = Intra uterine insemination
IVF = In vitro fertilization
MBR = Medical Birth Register
OI = Ovulation induction with or without insemination
OHSS = Ovarian hyperstimulation syndrome
OR = Odds ratio
RCM = Register of Congenital Malformations
SII = Social Insurance Institution

1 Introduction

Involuntary childlessness was earlier considered a social problem and accompanied by social solutions such as foster children, adoption, changing partners, or accepting a life without children. When knowledge of human reproduction developed and medical reasons for childlessness were found, childlessness became a medical problem defined as infertility or impaired fertility. Efforts then began to solve this issue by medical means.

Ovulation has been induced with hormonal drugs since the 1950s. Insemination is documented to have been made even earlier, during the 18th century (Hovatta, 1989). The greatest innovation in medicine in resolving the problem of childlessness was, however, the development of in vitro fertilization (IVF); the first baby was born in 1978 in the United Kingdom (Steptoe and Edwards, 1978) and the first in Finland in 1984 (Malin Silverio and Hemminki, 1996). During the past 30 years, IVF has become a common infertility treatment. In 2002, between approximately 2.4% (in Norway) and 4.2% (in Denmark) of all infants in the Nordic countries were born following IVF, with the figure being some 2.9% in Finland (Nyboe Andersen et al., 2006). In the United States the proportion is about 1 % (CDC report, 2003) and in the United Kingdom 1.4% (Nyboe Andersen et al., 2006). In addition, in Denmark 2.3% of all infants were born as a result of intra uterine insemination in 2002 (Nyboe Andersen and Erb, 2006). The number of children born with the help of ovulation induction and/or insemination (called in this study OI) in Finland is unknown.

Although OI has been used for many decades and IVF has rapidly become a normal clinical practice, the related health effects have not been properly studied. For example, in Finland only a few studies have been published on the health of IVF infants (Gissler et al., 1995a, Isaksson, 2002, Klemetti et al., 2002, Koivurova, 2005), with one study on the health of children born after intrauterine insemination (Nuojua-Huttunen, 1999), and no studies on the complications of women following IVF and OI (Jokimaa, 2006).

In spite of a large number of international studies on the health of IVF newborns (Helmerhorst et al., 2004), little is known about the long-term health effects on children (Hampton, 2004) or the short and long-term health of OI children. Even though various adverse effects of IVF and OI on treated women have been identified, many of the published studies and reports are insufficient. They are

based on voluntary reporting or on a small number of cases or treatment cycles. Others concentrate on only one complication, or lack information on the severity of the complications.

IVF is a costly treatment and much is debated about recipients' eligibility (age, sexual orientation, and marital status), how it should be funded (private or public resources) and how to allocate the scarce health care resources in a fair way. It is generally believed that IVF is unevenly distributed by socioeconomic position and urban–rural areas. However, there is not great deal of reliable data on the use or users of IVF or OI.

In the present study, first the use of IVF and OI in Finland is examined by considering the factors of age, socioeconomic position, and area of residence of those women who have used infertility treatments. Second, the safety of IVF and OI is studied by considering the complications and miscarriages of IVF and OI women as well as the health of IVF children. Hospitalization during pregnancy and childbirth as well as frequency of Caesarean sections could be studied, but data on other pregnancy outcomes were not available in this study. An identical study on the health of OI children has been done, but these results will be published separately and are not presented in this study. The results of congenital anomalies of OI children have already been published, while OI children are in this study also used as a control group—along with children born to infertile women treated with other infertility treatments than IVF—for IVF children; another control group was formed with naturally conceived children. Third, the success of IVF measured by live-births per number of cycles and per number of women is studied. Fourth, the costs of IVF treatment are estimated and the allocation of expenditures used in IVF is examined: how much is paid by Finnish society and how much by women themselves. Finally it is discussed how fairly the IVF resources are used in Finland.

2 Infertility and its treatment

2.1 Infertility

The prevalence of infertility is not easy to calculate due to the variable terminology used in reproductive medicine (Nguyen and Wilcox, 2005) and also the different definitions used in studies (Schimdt and Münster, 1995). It has been suggested that we avoid using the terms 'infertility, subfertility, and fecundity' and instead use the term 'reduced fertility' in different grades: from 0 (normal fertility) to grade 4 (sterility) (Habbema et al., 2004). Alternatively, it has been argued that the term 'subfertility' should be used and defined as any form of reduced fertility with prolonged time to successful conception (Gnoth et al., 2005). Because in this study it is not important to define different grades of reduced fertility, the term 'infertility' is used as a common term for involuntary childlessness. A common definition for infertility is an inability to achieve a pregnancy after regular unprotected intercourse within 12 months (Nguyen and Wilcox, 2005). The time limit in the definition was previously longer. In a guidebook for doctors (Therapia Fennica, 1975) the time limit was three years in 1975 and one year in the next edition in 1986 (Therapia Fennica, 1986). The World Health Organization still uses a definition of two years (WHO, 1997). It has been estimated that about 84–90% of couples conceive within one year (te Velde et al., 2000, Cahill and Wardle, 2002, Taylor, 2003, Habbema et al., 2004, Gnoth et al., 2005) and a half of the rest during the next year (te Velde et al., 2000). Thus, the definition has a great practical impact. About 5% of couples succeed in conceiving spontaneously "only sporadically" (Gnoth et al., 2005) or are "sterile couples" (Habbema et al., 2004). Furthermore, infertility is not only an inability to become pregnant but also a devastating personal experience (Greil, 1997). It can cause anxiety, stress and depression and affect the whole life spectrum: domestic and social lives as well as work.

According to population-based studies, infertility is common. In Finland, for example, 13–17% of women reported difficulties in trying to conceive within 12 months (Rantala and Koskimies, 1986, Notkola, 1995, Malin et al., 2001, Klemetti et al., 2004). Similar proportions have been reported from other industrialized countries (Gunnell and Ewings, 1994, Schmidt and Münster, 1995, Stephen and Chandra, 2000).

The most common causes of infertility are sperm dysfunction, ovulation disorder and fallopian tube damage (Cahill and Wardle, 2002). The suggested or discovered factors that underlie these causes are age, reproductive tract infections, obesity, anorexia, health-related behaviours like cigarette smoking, and too much exercise, as well as occupational exposures (Baird and Strassmann, 2000). About 15% of couples have more than one cause and 10–20% of couples suffer unexplained infertility, i.e. definite causes can not be found (Isaksson, 2002). Infertility can be primary: the failure ever to have achieved a pregnancy or secondary: inability to achieve pregnancy after having had a pregnancy (Nguyen and Wilcox, 2005).

Reproductive behaviour in our society has changed: Childbearing is delayed and births are planned (ESHRE, 2005). The mean age of motherhood has increased; for example in Finland the mean age of maternity was 27.0 years in 1977 and 30.0 in 2003 (Statistics of Finland and Stakes) and in France 26.5 in 1977 and 29.5 in 2000 (ESHRE, 2005). More importantly, postponing the first birth has become common. In Finland the mean age of the first birth increased from 25.4 in 1982 to 27.7 in 1996, but after that the age of first birth has only slightly increased; 28.0 in 2005 (Statistics of Finland and STAKES). Postponing childbearing increases the need for infertility treatments, because fecundity decreases with age.

Female fertility decreases with age due to several factors: the number of oocytes decreases, oocyte quality decreases, intercourse frequency declines (ESHRE, 2005) and unfavourable biological changes occur in the uterus (Baird and Strassmann, 2000). The monthly chance of achieving a pregnancy diminishes gradually after the age of 30 and more rapidly after age 36, being almost zero at the age of 41 (Broekmans and Klinkert, 2004). However, the age of losing fertility can vary according to the individual. How fertility changes by age among men is not well known, but time to pregnancy has been found to increase when the male partner is over 50 years old (ESHRE, 2005).

Strict planning of the timing of childbirth and taking the one-year definition of infertility as a strict rule can lead to impatience with waiting for a natural conception and result in premature use of infertility services (te Velde and Cohlen, 1999). It has been pointed out that appropriate timing for starting treatment is important to avoid over- and under-treatment (Brosens et al., 2004) and it is suggested that the general public has, in many countries, too optimistic a picture of childbearing in later life and of the success of infertility treatments (te Velde and Cohlen, 1999, Heffner, 2004, Cahill and Wardle, 2006). In 2004, the majority of female university students in Sweden would like to have children, but half of Swedish students planned to have children after the age of 35 years and did not know about decreased female fertility in the late 30s (Lampic et al., 2006). In Finland, 90% of university students desired children, but only 8% had a child, although the students were at the optimal childbearing age (Virtala et al., 2006). Leridon

(2004) pointed out that infertility treatments cannot compensate for all births not realised due to postponed childbearing.

2.2 Treatments

Medical treatments for infertility involve a treatment of physiological barriers (e.g. weight reduction or gaining weight), diseases causing infertility (e.g. acute infections) or damaging health habits (e.g. smoking, narcotic use), different surgical techniques (like opening blocked fallopian tubes), hormonal treatment (ovulation induction or ovarian stimulation) and assisted fertilization. In assisted fertilization (AF) the aim is to bring the egg and sperm close to each other to increase the chances of fertilization and achieve a pregnancy (Rowell and Braude, 2003). AF includes intrauterine insemination (IUI) and in vitro fertilization (IVF) with all its subtypes, such as intracytoplasmic sperm injection (ICSI) and frozen embryo transfer (FET), in which both eggs and sperm are handled outside the woman's body (Fig. 1). In IUI, prepared sperm are deposited in the uterus (Rowell and Braude, 2003). The term assisted reproductive technology (ART) has widely been used as a synonym for AF. However, in a recent publication ART has been suggested as including only procedures including in vitro handling of human oocytes and sperm or embryos but not insemination (Zegers-Hochshildt et al., 2006). This study uses the term AF, which here includes IVF with all its modifications including ICSI and FET, and hormonal treatment with or without insemination.

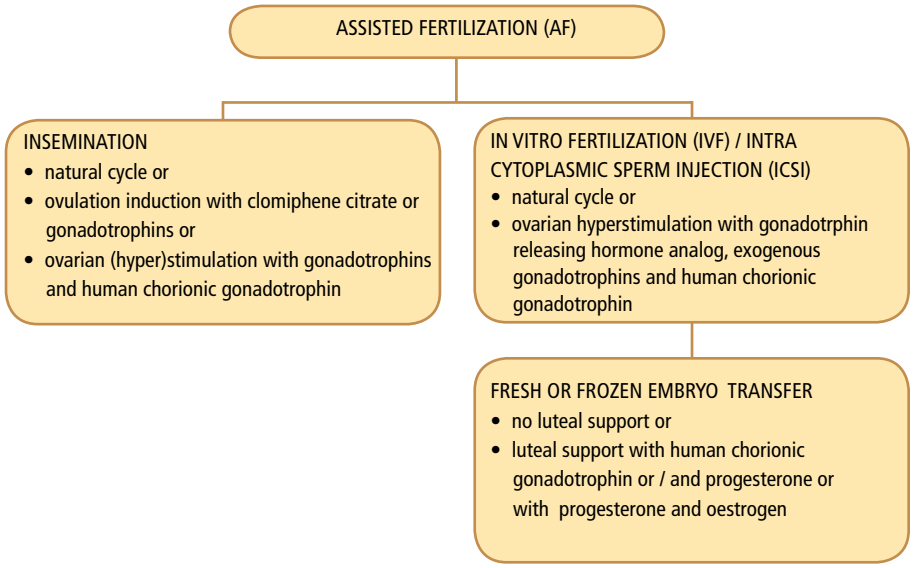

FIGURE 1. Different types of assisted fertilization (AF) and typical hormonal treatment used in AF.

In addition to medical treatments, psychological support is considered important for every couple as a part of infertility treatment (Bagshawe and Taylor, 2003). Counseling is suggested as helping couples in open communication, in clarifying their situation, needs and hopes, in adjusting to their circumstances, being supportive or therapeutic and in helping to understand what kind of effects treatment can have on couple's lives. It has been argued that the situation and experiences of infertile or involuntary childless people are culturally defined and that treatments and prevention of infertility should be seen in a cultural context (Bos et al., 2005).

IVF cannot cure or treat infertility, but it can help couples to conceive a child. This study concentrates on medical treatments, and in particular, hormonal treatment (with or without insemination) and IVF. The terms treatment and treatment cycle are used in spite the fact that AF is not curative.

2.2.1 Ovulation induction (OI)

Ovulation induction and ovarian (hyper)stimulation are two methods of hormonal treatment used in ovarian stimulation (Fauser et al., 2005). In ovulation induction, anovulatory women receive drugs (such as clomiphene citrate or gonadotrophins) to induce mono-ovulatory menstrual cycles. Ovarian (hyper)stimulation is used for women with normal menstrual cycles to induce development of multiple follicles. Both ovulation induction and ovarian (hyper)stimulation can be combined with intrauterine insemination (IUI) (Fig. 1). Particularly in ovarian (hyper)stimulation, the number of oocytes cannot be fully controlled. Multiple pregnancy rates after gonadotrophin ovulation induction have been reported to vary between 5 to 20% and after (hyper)stimulation from 10% to 40% per cycle. Hyperstimulation before IVF has a different aim than stimulation before the IUI. In IVF it is used to obtain a sufficient number of oocytes necessary to the procedure, and typically more drugs and higher dosages are used than in stimulation before the IUI. In this study, the term ovulation induction (OI) is used to describe both ovulation induction and low stimulation (lower dosages of drugs than in hyperstimulation) with or without insemination.

2.2.2 In vitro fertilization (IVF)

In vitro fertilization is the most famous type of AF. The first successful IVF treatment leading to the birth of Louise Brown in 1978 was done as part of a natural cycle without ovarian stimulation (Steptoe and Edwards, 1978). In the thirty years since, IVF has been modified and a current typical strategy includes six phases (Grainger and Tjaden, 2000, Unkila-Kallio, 2001, Fig. 1). However, there is varia-

tion in the drugs used and in their combinations. Firstly the natural function of ovaries is downregulated with various combinations of oral contraceptive pills, gonadotrophin releasing hormone analog, and progestins. Then ovaries are stimulated with exogenous gonadotrophins (follicle stimulating hormone and luteinizing hormone). After that oocytes are collected and fertilized. In this phase different micromanipulation techniques can be used: ICSI, assisted zona hatching or preimplantation genetic diagnosis. In ICSI one sperm is injected into one oocyte. Two to five days after retrieval, the embryo(s) is transferred to the uterus. The uterus is prepared for transfer (luteal support) with human chorionic gonadotrophin or progesterone, or both or with progesterone and oestrogen (Fig. 1).

If the embryo transfer is not possible or more embryos are fertilized than are needed, the embryos can be frozen and used later by thawing, called FET. If the hyperstimulation does not succeed, the procedure does not proceed to oocyte collection or thawed embryos can not be transferred, the treatment cycle is defined as a cancelled cycle (Zegers-Hochshildt et al., 2006). Both donated sperm and eggs can be used in IVF. If the woman has no uterus the embryo can be transferred to another woman's womb, called surrogacy.

3 IVF Success

IVF success can be calculated in many different ways, for example (clinical) pregnancy, delivery, live-birth or take-home baby rates per initiated cycles, per embryo retrievals or per embryo transfers. For most purposes, (one) live-birth or take-home baby rate per initiated cycle or cumulatively, is the best measure of success. The most important factors predicting good success in IVF have been women's young age (declining pregnancy and live-birth rates with increasing age), reasons of infertility (the highest live-birth rates being in male factor infertility and the lowest in respect of uterus-related reasons), the number of embryos transferred, good embryo quality, and previous live birth after IVF (Graigner and Tjaden, 2000).

Among younger women the live-birth rate increased by the number of embryos transferred up to three embryos and for older women up to four embryos, with the live-birth rate declining thereafter (Schieve et al., 1999). However, as the problems of multiplicity gained recognition, it was first recommended that two embryos were transferred and nowadays one embryo transfer is recommended (Tiitinen and Gissler, 2004, Kissin et al., 2005, Koivurova, 2005). According to Finnish experiences, the decreased number of transferred embryos has not led to a marked change in success rates (Tiitinen et al., 2003, Tiitinen and Gissler, 2004). In Finland success rate (live births per number of cycles) improved from 17% in 1994 to 19% in 2002, while the proportion of single embryo transfers has increased from 17% to 39%.

The success rates varied between the clinics and countries; in Europe deliveries per IVF cycle varied from 9.2% in Bulgaria to 25.2% in Norway, being mainly about 20% (Nyboe Andersen et al., 2006). Live-births per cycle and by female age were not reported. Of the register data on success rates found, the success rates and also the multiple birth-rates reported are highest in the United States (Table 1).

Calculations of success, both in terms of clinical pregnancy and live-births per cycle and per women's age showed that success decreased with increasing age (Table 1). It seems that success rates were somewhat improved between 1986 and 2004, but a comparison between earlier studies and currently available register data as well as between different countries have to be interpreted with reservations, due to the different definitions, data collection systems, and sample sizes.

TABLE 1. Success rates of IVF during different time-periods; pregnancy or live-births per initiated cycle, %

Document or Author	Country	Year(s)	Treatment	Multiplicity, %	Pregnancy	Live birth
Piette et al.1990	France	1986	IVF	NA		
<=24					15	
25–29					20	
30–34					19	
35–39					17	
>=40					13	
Devroye et al.1996	Belgium	1991–1993	ICSI	NA		
<40					23	
>=40					7	
Dew et al.1998	Australia	1987–1994	IVF			
<36				16	14	12
36-39				13	13	9
>=40				0	5	3
Meldrum et al.1998 [a]	USA	1994	IVF			
<40				NA	35	28
40–42				NA	21	14
>42				NA	10	5
Lass et al.1998	UK	1988–1995	IVF			
<40				NA	28	
>=40				5	11	
Klipstein et al. 2005	USA	1999–2002	IVF			
>=40				15		10
Waters et al. 2006	Australia and	2003	IVF			
Total	New Zealand			18		19
< 35				NA		25
35–39				NA		15
40+				NA		7
National summary of CDC [b]	USA	2003	IVF			
< 35				38		37
35–37				32		30
38–40				26		20
41–42				17		11
Swedish Statistics [a]	Sweden	2003	IVF+ICSI			
Total				12		23
< 35				NA		29
35–39				NA		20
40+				NA		10
Danish Statistics [a]	Denmark	2004	IVF+ICSI			
< 40				22		22–25
> 40				11		8-11
Statistics of HFEA [c]	UK	2003–2004	IVF			
< 35				28		28
35–37				23		24
38–39				19		18
40–42				12		11
>42				NS		3

[a] Deliveries per cycle started (%)
[b] CDC = Centers for Disease Control and Prevention, 99% is IVF and rest other types of assisted fertilization
[c] HFEA = Human Fertilisation & Embryology Authority, IVF includes fresh embryo transfers
NA = not avalable, NS = non-significant

Reported pregnancy and delivery rates have varied not only by woman's age but also by number of cycles; pregnancy rates have decreased after three or four cycles and delivery rates after four cycles (Meldrum et al., 1998, Lass et al., 1998). Cumulative live births rates per initiated cycles have varied from 3% to 71% by female age and number of cycles (Tan et al., 1994). Olivius et al. (2002) found that an overall cumulative live birth rate after three cycles varied from 56% to 66%. Wang (2006) has pointed out that calculating cumulative pregnancy rates can lead to an overestimation of treatment success. He suggests that the calculation should be limited only to the second or third cycle within one to two years to ensure that most women are included in the calculations.

4 Safety of infertility treatments

4.1 Women's health after IVF and OI

The safety issues related to infertility treatments for women include complications of the treatments and—following successful treatment—complications during pregnancy and delivery. The most common and serious consequence of infertility treatments is multiple pregnancy, which in the case of IVF often occurs with older age. IVF-pregnancies have been reported to be more complicated than natural pregnancies, with for example vaginal bleeding, pregnancy induced hypertension and Caesarean sections being more common (reviewed by Koivurova, 2005). This study concentrates on treatment complications, which have been studied less than pregnancy complications. They can occur during the ovulation induction (or stimulation), the oocyte collection procedure, and also post-operatively. The achieved pregnancy can be ectopic (embryo outside the uterus) or heterotopic (embryo both in and outside the uterus) and it can end up in a miscarriage. The frequency of miscarriages and ectopic pregnancies leading to hospital care is likewise covered in this study.

Ovarian hyperstimulation syndrome (OHSS) is considered the most serious complication of ovulation induction. It can vary from a mild illness to a critical, life-threatening disease requiring hospitalization (Table 2). Due to the various OHSS related symptoms and signs which can vary case by case, OHSS is typically not easy to diagnose. OHSS can occur within a few days of receiving of human chorion gonadotrophin ("early OHSS") or later ("late OHSS"). The multiple pregnancy has been associated with a higher risk of late OHSS (Mathur et al., 2000). The incidence of severe OHSS has been reported to vary from 0.7% to 1.7% per initiated cycle (Bergh and Lundkvist, 1992, Serour et al., 1998, Westergaard et al., 2000, Nyboe Andersen et al., 2006). OHSS has been estimated to lead to hospitalisation in 2.4% of IVF pregnancies (Källén et al., 2005a). Case reports (Cluroe and Synek, 1995, Koo et al., 2002), some studies (Bergh and Lundkvist 1992, Serour et al., 1998, Abramov et al., 1999a, Källén et al. 2005a) and reviews (Beerendonk et al., 1998, Whelan and Vlahos, 2000, Delvigne and Rozenberg, 2003, De Sutter, 2004, Jokimaa 2006) describe some serious aspects of OHSS, such as thromboembolic events, pulmonary manifestations, and death. However, the magnitude of the risk of OHSS is unclear. The frequency of OHSS after OI is unknown (Unkila-Kallio,

TABLE 2. Symptoms and signs related to different degrees of ovarian hyperstimulation syndrome (OHSS)

OHSS
Mild
Abdominal distension and discomfort
Nausea, vomiting and/or diarrhea
Enlarged ovaries
Moderate
Symptoms and signs of mild OHSS
Ascites
Severe
Symptoms and signs of moderate OHSS
Temperature of over 38 degrees
Ascites and / or hydrothorax or breathing difficulties
Weight increase
Hypovolemia
Hemoconcentration
Oligouria
Electrolyte imbalances
Critical
Symptoms and signs of severe OHSS
Impaired renal perfusion
Thromboembolism
Impending multiorgan failure

(Beerendonk et al.1998, Jokimaa 2006)

2001). In one small clinical study, the OHSS hospitalization rate per initiated cycle was 0.07% (Quasim et al., 1997).

The frequencies of IVF complications other than OHSS have been only sporadically reported. For oocyte collection, bleeding has been reported in 0.03 % to 0.5% and infections in 0.02% to 0.3% of embryo transfers (Bergh and Lundkvist, 1992, Nyboe Andersen et al., 2006). From 2% to 5% of IVF pregnancies have been reported to be ectopic and 0.1% to 1.0% heterotopic (Roest et al., 1995, Serour et al., 1998, Waters et al., 2006); both are higher than in naturally conceived pregnancies (Hemminki and Heinonen, 1987, Mäkinen, 1996, Roest et al., 1995). Estimates of IVF pregnancies ending in miscarriage have varied from 15% to 23% (Roest et al., 1995, Serour et al., 1998, Westergaard et al., 2000, Kupka et al., 2003, Schieve et al., 2003, Waters et al., 2006).

4.2 Health of IVF and OI children

Health of newborn

The most common health problems of IVF children are related to multiplicity (Schieve et al., 1999, Tiitinen et al., 2003, Kissin et al., 2005). Although IVF has been associated with an increased number of monozygotic twins (Ericson and Källén, 2001), the main reason for multiplicity is multiple embryo transfer and therefore IVF twins are much more often dizygotic compared to naturally conceived twins (99% vs. 70%, Schachter et al., 2001). Depending on the IVF practice, multiple birth rates have varied from 27% to 40%, being much higher in the United States than in Europe (Fauser et al., 2005): Single embryo transfer has become more common in Europe in recent years. With the preference for single embryo transfers, the multiple birth rate has decreased in Finland from 27% in 1992 to 13% in 2003 (calculated from IVF statistics, http://www.stakes.info/2/1/2,1,4.asp.). During the 1990s, an improved trend in the perinatal health of multiple IVF children was found in Finland, mainly due to a decrease in higher order multiple births (Klemetti et al., 2002).

IVF twins have had poorer perinatal health than IVF singletons but in previous publications no differences were found between the perinatal health of IVF and naturally conceived twins (reviewed by Ludwig et al., 2006). Contrary to these previous publications, recent studies show an increased risk of preterm birth and/or low birth weight for IVF twins (Verstraelen et al., 2005, Wang et al., 2005).

Poorer perinatal health in IVF children is however not only a consequence of multiplicity and a high frequency of twins: the perinatal health of IVF singletons has been found to be worse than that of naturally conceived singletons (Schieve et al., 2002, Helmerhorst et al., 2004, Jackson et al., 2004). Low birth weight and preterm birth were more common among IVF and ICSI singletons compared to naturally conceived singletons of previously infertile women (De Geyter et al., 2006).

Prematurity and low birth weight have been more common also among OI children than among naturally conceived children (Addor et al., 1998, Källén et al., 2002, Gaudoin et al., 2003, Wang et al., 2002, Verstraelen et al., 2006). Two small studies could not find any statistically significant differences between children conceived with intra uterine insemination (IUI) and spontaneously (Nuojua-Huttunen, 1999, De Geyter et al., 2006). In addition to low birth weight and prematurity, OI children have had a higher incidence of very low birth weight, treatment in the neonatal intensive care unit and of most neonatal morbidity parameters (Ombelet et al., 2006).

Some studies have shown an increase in congenital anomalies (CAs) among IVF or ICSI children (Bergh et al., 1999, Dohnt et al., 1999, Wennerholm et al.,

2000, Ericson and Källén, 2001, Anthony et al., 2002, Hansen et al., 2002, Koivurova, 2005, Katalinic et al., 2004), but other studies have not (Loft et al., 1999, Ritzk et al., 1991, Sutcliffe et al., 2001, Westergaard et al., 2000). The higher incidence of CAs among IVF children has involved musculoskeletal, cardiovascular, chromosomal and urogenital defects (Hansen et al., 2002, Koivurova, 2005).

Recently, sufficiently large studies on the CAs of IVF children have been published: two meta-analyses of earlier studies (Rimm et al., 2004, Hansen et al., 2005) and register-based studies from Sweden (Källén et al., 2005b) and Denmark (Zhu et al., 2006). According to the meta-analysis by Rimm et al. (2004), a 1.3-fold risk of major CAs was found among IVF and ICSI children and a 2.1-fold risk was found by Hansen et al. (2005). In the latter review the risk of CAs was increased also separately for singletons (OR 1.35, 1.20–1.51). Risk of specific malformations was not reported.

According to the Swedish study (Källén et al., 2005b) IVF children in total and singletons alone had a 1.3-fold risk of congenital anomalies. The risk was not increased among multiples. The risks for many specific malformations were increased, for example for neural tube defects, different gastrointestinal atresias, major cardiovascular defects, and hypospadias. No differences in the malformation rate by IVF method used were found with the exception of hypospadias after ICSI. In contrast, a meta-analysis comparing IVF children with ICSI children found no significantly increased risk after ICSI (Lie et al., 2005). A recent smaller study from the United States found the same 1.3-fold risk with a borderline significance among all IVF children and, contrary to earlier studies, an increased risk also for congenital anomalies among twins and triplets (Olson et al., 2005).

Olson et al. (2005) studied the risk of congenital anomalies among IUI children and could not find an increased risk. The number of IUI infants was however less than 100. Only one sufficiently large study on anomalies of children born as a result of ovarian stimulation could be found (Källén et al., 2002). There was an increased rate of congenital anomalies, but this could be mainly explained by maternal characteristics.

A Danish study found an increased risk among singletons born as a result of infertility treatments (IVF, ICSI, insemination and hormonal treatment) and interestingly also among naturally conceived children born to previously infertile couples (without treatments) (Zhu et al., 2006). Of the specific CAs, the risk of musculoskeletal and genital anomalies was increased for IVF children, but not the risk of genital anomalies among children born naturally to previously infertile couples. Risk among twins was not increased. The authors suggested that hormonal treatment might cause genital anomalies but otherwise the potential reason for anomalies could be infertility itself or its determinants.

Health in early childhood

According to previous small cohort studies, the morbidity, growth, and development of IVF children have been similar to that of control children (reviewed by Koivurova, 2005). A recent Finnish study found higher childhood morbidity and increased hospitalization (Koivurova et al., unpublished data). Large register-based studies having large sample sizes have been published from the Nordic countries (Ericson and Källén, 2001, Ericson et al., 2002, Strömberg et al., 2002, Pinborg et al., 2004a, Pinborg et al., 2004b, Lidegaard et al., 2005, Källén et al., 2005b, Källén et al., 2005c, Hvintjørn et al., 2006). These studies report an increased use of hospital services, long hospitalizations and an increased risk of infections, epilepsy and tumours (Ericson et al., 2002), asthma (Ericson et al., 2002, Källén et al., 2005c), cerebral palsy (Ericson et al., 2002, Strömberg et al., 2002, Lidegaard et al., 2005, Hvintjørn et al., 2006), sleep disturbances (Lidegaard et al., 2005), convulsions and behavioural problems and accidents (Källén et al., 2005c) among IVF children.

A review including both small cohort studies and some of these large register-based studies concluded that most studies did not find any differences in childhood morbidity, chronic illnesses, surgical interventions, physical development, mental health, and behavioural problems between IVF and naturally conceived singletons, but they found an increase in neurological problems among IVF singletons (Ludwig et al., 2006). Data on chronic illnesses, childhood morbidity, and surgical interventions were so contradictory that the authors could not draw a final conclusion. The data on IVF twins was limited and more data are needed to draw any conclusions on their childhood health. Long-term follow-up studies of OI children are lacking.

5 Use and service costs of infertility treatments

5.1 Human and reproductive rights

The Declaration of Human Rights of the United Nation from the 1948 (available at: www.un.org/Overview/rights.html) sets out the right to marry and establish a family without limitation due to race, nationality or religion. At the 1994 International Conference on Population and Development in Cairo, reproductive rights were defined as follows "…the basic right of all couples and individuals to decide freely and responsibly the number, spacing and timing of their children and to have the information and means to do so, and the right to attain the highest standard of sexual and reproductive health. They also include the right of all to make decisions concerning reproduction free of discrimination, coercion and violence." (available at: http://www.unfpa.org/icpd/summary.htm).

5.2 Right to infertility treatments

The question of whether a right exists for infertility treatments and if so who is eligible to treatments is problematic. Do the human and reproductive rights mean that everyone has the right to receive a child and a right to receive infertility treatments to fulfil these rights? McLean (1993) argued that the right to reproduce does not automatically mean the right to have a child. On the other hand, Blank (1997) pointed out that reproductive rights have different dimensions, for example the right to have a child or the right not to have a child. He continued that infertility treatments belong to the category of rights to have children i.e. positive rights. Positive rights include claims for society to offer services that are needed. If reproductive rights are understood as positive rights, an infertile couple can claim access to infertility services. According to McLean the last conclusion is right, but she argued that the declaration of human rights can be understood as a freedom to reproduce for those who have a capacity for that and not as a right for everyone. But she continued that because infertility technology is already available it is important to somehow control it. Furthermore, she pointed out that it would be necessary to asses how the technology is directed and developed taking into ac-

count related consequences. Daniels and Taylor (1993) argued that it is necessary to formulate selection policies for access to AF to be able to take into account the rights and needs of the child as well as to decide how much public funds are allocated to infertility services.

Daniels and Taylor (1993) pointed out that the criteria for eligibility for AF should be made through a public debate that asks whether access should be restricted, if so on what basis, and who should make the decisions. According to them, exclusion criteria could include for example previous children or females are beyond a certain age. They suggested that decisions should not be left to medical professionals alone but that some kind of expert committee should take into account public opinion.

5.3 Legislation on infertility treatments

Regulations of the eligibility for IVF of European countries, Canada and Israel were studied by a Steering Committee of Bioethics (CDBI), Council of Europe and published in 2005 (CDBI, 2005). They report that nowadays in most European countries, regulation governs who is eligible for IVF treatment, but that eligibility criteria vary between different countries. In 28 of the countries participating in the study, eligibility is regulated by the law. Two countries (Cyprus and Portugal) reported having no law and no regulations for assisted fertilization. The rest of the countries studied (7 including Finland) did not have a law at that time but drafting of legislation was in process or they have some kind of regulations for assisted fertilization. In the United States the criteria for eligibility have been found to vary also between clinics (Stern et al., 2001). AF was available only to heterosexual couples for example in Austria, Denmark, Norway, Germany and Italy, but allowed also for lesbian women in Sweden and for single or lesbian women in the United Kingdom, Israel and Canada.

In most countries, AF is given only for medical reasons but for example in the United Kingdom and Canada, AF could be received also for social reasons (i.e. without a diagnosed fertility problem, CDBI, 2005). Surrogacy was prohibited in most countries, but restrictively permitted for example in the United Kingdom, Canada, Israel, and Estonia. Sperm, oocyte and embryo donations were allowed in most countries but not in Italy, Lithuania and Turkey. In Croatia, Norway, Switzerland and Austria, sperm donation was permitted, but oocyte and embryo donations were not. Donations in studied countries were mostly anonymous, but not in the United Kingdom, Turkey, Sweden, Norway, Netherlands, Georgia and Germany.

Two Scandinavian countries have legally defined age-limits for AF: 45 years for women in Denmark and 42–45 for women and 50 for men in Iceland (Legislation

on biotechnology…, 2006). In Sweden women before their "normal age of menopause" and capable of "carrying out parental responsibilities throughout childhood" can receive AF. In the United Kingdom until the end of 2005 the infertile patient's suitability (family and social circumstances) to raise a child had to be examined by consulting the patient's general practitioner (Eaton, 2005). Nowadays, the examination of suitability is left to the fertility clinics.

In Finland, attempts to draw up a law on fertility treatments (insemination and IVF) have continued for twenty years. In October, 2006 a legislative proposal was accepted in the Finnish parliament. During the process, features that were problematic were the eligibility of single and lesbian women, children's right to know their biological origin, and surrogacy (Burrell, 2005). The law will be come into force in 2007. In the coming law, IVF and insemination will not be prohibited for single or lesbian women, children will have the right to know the identity of the donor at the age of 18, and surrogacy will not be allowed. Until now only heterosexual couples have been treated in the public sector, donations have been anonymous both in the public and private sector and about 20 pregnancies have been successful through surrogate mothers (CDBI, 2005). One quarter of parents of the first cases of using surrogacy in Finland has been foreign (Söderström-Anttila et al., 2002).

In the coming Finnish law on AF, no exact age-limit exists and the decision on the eligibility of women is left to medical doctors (Hallituksen esitys…, 2006). The doctor is not allowed to give AF if the achieved pregnancy were to be harmful to the health of the woman seeking AF or to the health of the newborn or if it is evident that the women cannot guarantee a balanced development for the child. Until now, the female age limit for public IVF services has varied between 38 and 42 years, but in the private sector no strict age limit has existed (Malin Silverio and Hemminki, 1996**,** CDBI 2005) and in practice there have been variations in the age of treated women between the clinics.

5.4 Funding of IVF services

It has been much debated whether health insurance should cover IVF. In some countries IVF is offered only in the private sector (for example in Canada and most states in the United States), where its use depends on a couple's ability to pay (Neumann, 1997, Stephen and Chandra, 2000). In the United States it has been found that insurance coverage of IVF increased utilization of IVF but on the other hand decreased the number of transferred embryos, i.e. making IVF more safe (Jain et al., 2002). In some countries IVF is offered both in the public and in the private sector (for example in Finland and Norway) and wealthy couples can shorten their waiting times by using services in both sectors (Svensson and

Stephenson, 1993). In the United Kingdom where 80% of IVF is given in the private sector, authorities have warned that IVF is becoming more commercial and people with insufficient income are in danger of remaining without treatments (Cole, 2006). In some countries IVF services are available mainly in the public sector (for example in France and Germany) (Jones and Cohen, 2004).

Criteria of coverage varied also between countries (Jones and Cohen, 2004, CDBI, 2005). For example in Austria, Switzerland, Turkey, and Poland, IVF is not covered by the social security system mainly because involuntary childlessness is not considered as a disease. Other limiting factors are age and number of cycles. Female age has been used as a criterion to cover IVF: from an age-limit of 35 years in the Ukraine to 45 years in Denmark and Israel (CDBI, 2005). The most common age-limit for coverage is 40 (in Austria, Cyprus, United Kingdom, Luxemburg and Germany). In Finland, the SII, in covering the infertility treatments, follows the limitations given by the Ministry of Social Affairs and Health (STM, 2005). In that document the suggested age-limit is 39 years, but if treatment is based on a specific disease and a medical certificate, treatment is covered regardless of the age of the woman. The advanced age of a male partner is a limitation for coverage in Austria and Germany (50 years) as well as in Norway ("reasonable difference in age" between partners). The coverage according to number of cycles varied: in Cyprus, coverage is for a single cycle, while Israel gives full coverage up until the birth of two children.

In Finland the private sector is an important provider of IVF: some 60% of all IVF cycles are offered by private clinics (IVF Statistics, http://www.stakes.info/2/1/2,1,4.asp.). In 1999, 12 of the 19 clinics were private, and in 2005 that figure was 12 of 18. In general, a woman can seek medical advice for infertility by visiting a general practitioner (GP) at a health care centre or a private gynaecologist at a private clinic. Simple diagnostic tests can be done in both places. After that the GP or gynaecologists can refer the woman to a public hospital for further diagnosis and infertility treatment or the woman can contact a private IVF specialist at a private clinic. About 70% of women who have sought help for infertility had visited private gynaecologists, 30% a gynaecologist at a hospital and 17% a GP in a health care centre (Malin et al., 2001).

In the public sector, women pay a small fee for their clinic visits, and the rest of visits costs are covered by taxes. Nevertheless, to receive IVF they often have to wait. In the private sector, IVF can be received quickly but patients pay more for their visits. However, up to about 60% of the private physician's charges and a part of the laboratory cost (75% of the standard fee) and interventions (60% of the standard fee) are reimbursed by the Social Insurance Institution (SII). Women both in the public and private sector pay for about half of the drug costs and the rest are reimbursed by the SII. If the individual's yearly upper limit of drug costs has been reached, all further costs are paid by the SII.

5.5 Use of IVF by age, socioeconomic position and area of residence

Not all infertile couples seek medical help for infertility in spite of growing number of fertility services and awareness of them. In population-based studies the proportion of infertile couples having sought medical advice (visit to general practitioner, private gynaecologist or hospital) varied from 22% to 95% (Gunnell and Ewings, 1994, Schmidt and Münster, 1995, Stephen and Chandra, 2000). Primarily infertile women sought help more often than secondarily infertile and younger generations more often than older generations. In population-based studies from Finland, 50–67% of infertile women had sought medical advice (examinations or treatments) for infertility (Malin et al., 2001, Klemetti et al., 2004).

There is little reliable data on the use or users of IVF. However, data on IVF treatments given—for example, number of cycles, transferred embryos, pregnancies, short term complications—are registered or collected voluntary in many countries. From these statistics and registers some aspects on the utilization of IVF can be estimated. The European Society for Human Reproduction and Embryology (ESHRE) has collected information on IVF in Europe since 1997 (Nyboe Andersen et al., 2006). Systems to collect the data are different across European countries and some data are lacking, especially from some Southern European countries. In the United States, the Department of Health and Human Services (Centres for Disease Control and Prevention, CDC) reports on the success rates and outcomes of assisted fertilization (http://www.cdc.gov/ART). Treatments given in Australia and New Zealand are registered and reported every year (Waters et al., 2006). In Finland statistical data on IVF treatments have been collected since 1992 as voluntary reporting (http://www.stakes.info/2/1/2,1,4.asp.).

The highest utilization of IVF services among the 25 European countries was reported in Finland and Denmark (Nyboe Andersen et al., 2006). In Finland the use of IVF increased during the 1990s, but has since levelled off (Gissler and Tiitinen, 2001). However, in 2004 the number of IVF cycles grew again (Table 3), with 7.0 cycles per 1000 women of reproductive age (15–49) resulting in increased number of IVF children (IVF Statistics, 2006, http://www.stakes.info/2/1/2,1,4.asp.). In a European context, the use of IVF in Finland is high, but for example in Australia the corresponding rate per 1000 women in 2003 was even higher, at 8.4 (Waters et al., 2006).

Age

According to the statistics of ESHRE (Nyboe Andersen et al., 2006) over 70% of women using IVF in Europe were aged 30 to 39. However, there was variation between the countries from 53% to 88%. About 13% (from 2 % to 25 %) were aged 40 or more. Almost the same proportions are reported from the United States (69% and 20%, http://www.cdc.gov/ART) and from Australia and New Zealand

TABLE 3. Number of IVF, ICSI and FET[a] cycles, pregnancies, life births and cycles per 1000 women aged 15–49 years in 1992–2004 in Finland.

	Year												
	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Cycles	2331	3189	4382	5043	6417	7336	7159	6968	6811	6766	7114	6990	8391
Pregnancies	502	670	840	1040	1496	1611	1663	1636	1536	1523	1662	1807	1848
Live births	392	489	612	763	1092	1205	1229	1191	1179	1147	1259	1353	1395
Cycles per 1000 women aged 15–49 years	1.8	2.5	3.4	4.0	5.1	5.8	5.7	5.6	5.5	5.6	5.9	5.8	7.0

[a] FET: the cycles with the embryo transfer.
Reference: IVF Statistics, 2006, http://www.stakes.info/2/1/2,1,4.asp.

(66% and 20%). In Finland the corresponding rates were 66% and 14% (Nyboe Andersen et al., 2006).

It is well known that complications during pregnancy and childbearing notably increase by female age (Nybo Anderssen et al., 2000, Salihu et al., 2003, Heffner, 2004. Furthermore, success in AF decreases by female age (Graigner and Tjaden, 2000, Table 1). However, the use of donated oocytes has made it possible to achieve occasional pregnancies and live births even among women aged over sixty. Treating older women—even post-menopausal women—raises many ethical questions, such as setting age-limits in the use of AF, the allocation of scarce health care resources, the shortage of donated eggs, and the risks for the child's and the woman's health (de Wert, 1998, Heffner, 2004). Raising children is hard work and it has been asked whether older women are fit enough for it (de Wert, 1998) or if there are too great risks for the child's later psychosocial development with old parents (or as orphan at an early age). On the other hand it has been discussed whether age-limits are violations of human rights (Blank, 1997), and it is assumed that older women have a good capability to raise their children, in that they may have a better education, better economical situation and better emotional preparedness compared to younger women (Eisenberg and Schenker, 1997).

Male partners' age is seldom reported (and limited), and the effect of paternal age on reproductive outcomes has almost been ignored. In Australia the oldest registered male partner in IVF was 87-years-old (Waters et al., 2006). The results of paternal age effects on the outcome of AF are conflicting (ESHRE, 2005). However, a recent study found increased failure to conceive following IVF among fathers over 40 years (De La Rochebrochard et al., 2006).

Socioeconomic position

The over-representation of women from the highest socioeconomic group among IVF users has been found in studies from Canada and Australia (Svensson and Stephenson, 1993), the United States (Wilcox and Mosher, 1993), and the United

Kingdom (Gunnell and Ewings, 1994). In the United States, women with higher levels of education and income were more likely to have received infertility services than women with a lower level of education and income (Stephen and Chandra 2000, CDC: National Survey of Family Growth 2005, Jain and Hornstein, 2005, Bitler and Schimdt, 2006). In France the use of IVF did not differ according to women's socioeconomic position (Tain, 2003).

In Finland, no differences in the education of women were found in those seeking help but those using infertility services more often had a longer education than non-users (Malin et al., 2001, Klemetti et al., 2004). IVF mothers have also been more educated or more often were of a higher socioeconomic position than other mothers (Gissler et al., 1995a, Malin Silverio and Hemminki, 1996, Bergh et al., 1999, Buitendijk, 2000, Klemetti et al., 2002).

Area of residence

It is generally believed that not only women from higher socioeconomic positions but also women in urban areas have easier access to infertility services and also use them more than women from rural areas. Rural women may live considerable distances from cities offering AF and long trips and a possible lack of social support (husbands, friends and relatives far away) needed during the treatment may affect the access and willingness to use AF services (Daniels and Taylor, 1993). So-called satellite clinics have been created at least in the United Kingdom, the United States and the Netherlands to make access easier outside the big cities (Kingsland et al., 1992, Kaplan et al., 1995, Roest et al., 1995).The experiences have been encouraging; success rates did not decline, but stress that was related to the treatment and the costs of treatments did so.

In Finland, IVF clinics have been unevenly distributed; all IVF clinics (19 clinics in 1999 and 18 in 2005) have been situated in eight towns (IVF Statistics, http://www.stakes.info/2/1/2,1,4.asp.). Three out of the 12 of the pre-1995 provinces have had no IVF clinic. Women in some areas have to make long trips (as much as 700 km) to obtain IVF treatments. OI services are available in all parts of Finland. With the exception of one previous study that found that IVF mothers came more often from southern Finland (Malin Silverio and Hemminki, 1996), no data on use by area existed before this study.

5.6 Costs of IVF treatments

The costs of IVF vary from country to country. Costs can be divided into direct and indirect costs. Direct costs include costs of medical consultations, personnel, equipment, drugs, complications, and monitoring, and indirect costs such

as women's travel, time off work, lost wages, long-term complications, multiple pregnancies, and obstetric and neonatal care (Fauser et al., 2002). Many studies on the cost and cost effectiveness of IVF have been published, as have a few studies on cost-effectiveness of IVF versus other AF, and so-called economic benefit studies (reviewed by Garceau et al., 2002). Most published studies have not included indirect costs. Economic-benefit studies have examined IVF couples' or potential child bearers' willingness to pay (WTP) for IVF or have had macroeconomic perspectives comparing costs of IVF to costs of other areas of health care. Problems in comparing these studies include for example different definitions for success in IVF and the high incidence of multiple births and its long-term costs.

Health care costs for IVF treatment by women's age have been previously described in a review by Broekmans and Klinkert (2004) that found that IVF costs EUR 13 000 (without sick-leave, cost of travelling, complications and pregnancy) for women up to the age of 40 and EUR 37 000 for women aged over 40. Based their own small data, the authors suggested that IVF is still cost-effective (cumulative pregnancy rate was 49% and the estimated IVF costs per one child were EUR 18 000) for a selected (tested to have a reasonable probability of ongoing pregnancy) group of women aged 41 to 42 years but not for women aged 43 or older.

Health care costs resulting from IVF have also been previously studied in Finland (Gissler et al., 1995a, Malin Silverio and Hemminki, 1996, Koivurova, 2005, unpublished data by Koivurova et al.). It was found that health care costs for an IVF newborn from pregnancy induction until the age of one week was 5.4-fold compared to that for other newborns (Gissler et al., 1995a), while costs for IVF singletons were higher compared to other singletons and multiple births increased the costs (Koivurova, 2005). Pre-school age health care costs are markedly higher among IVF children compared to other children (Koivurova et al., unpublished data).

The focus in these previous studies has not, however, been in the allocation of scarce health care resources. Empirical data that would quantify the question of equitable use of scarce resources have not been given, nor has the distribution of private and public expenditure been estimated.

6 Equity and infertility treatments

6.1 Equity as a principle in health care

Equity is a key objective of many health care systems and it is present in many policy documents (Mooney, 1994). The same is true also of Finland; many features in the Finnish health care system are intended to support social equity (Keskimäki, 1997). In health care, equity can be defined as equality of access, equality in health, or equality of use for equal need (Mooney, 1994). Equity has been chosen as the first regional target in the World Health Organization European Region and included also in many other targets of the WHO (Whitehead, 1990).

According to the WHO, equity in health care includes equal access to services for equal need, equal use for equal need and equal quality of care (Whitehead, 1990). Equal access does not come about if people are turned away from health care or are unable to use health services due to race, sex, age, religion, poor income or other factors not directly related to the need for care. According to Whitehead (1990) resources and facilities should not be unevenly distributed around the country, resources should not be used for specific services which benefit only a small population, services should not be organized in such a way that only a part of the population are capable of using them, while received care and its quality should be based on need and not on social factors. The different use of services by different social groups is not automatically unequal. But it is unequal if services are organized so that people in different social groups do not have the same possibility to use them.

Mooney (1994) has argued that the WHO's egalitarian view of equal use for equal need is problematic, because it requires people with the same need to use health care services without taking into account people's own preferences for their health and health care. People with the same need may not value their health equally and may not have the same willingness to use services. Mooney pointed out that equal access for equal need is not so problematic; it can be thought to include a desire for equal access. If equal access or use is required for equal need, it is also important to define the need. According to Mooney, a need can be defined as the extent of sickness (defined by a medical practitioner, health care system or some part of it) or the capacity to benefit. Definitions cause many problems, especially

the latter definition, as well as questions such as how different diseases or different grade of diseases will be taken into account, how to measure the benefit, and who will carry out such an assessment. However, the greater the capacity to benefit, the greater the need is, but Mooney reminds that not all diseases or conditions can be treated and that not all sufferers can be made healthier. Mooney commented that need and demand should be differentiated from each other; they are not the same. Need is defined by other people but demand is based on the person's own preferences. According to Mooney, use and consumption are not the same as demand or need. For example, due to factors such as prioritization, higher costs, or lack of services, people who would need services and who demand them have sometimes to wait. In other words, they cannot necessarily use or consume services in spite of a need or demand.

Equity in health care not only means that offering of services is based on need and that services are distributed equally. It has been argued that equity includes also the right to effective and safe treatments (Svensson and Stephensson, 1993). Because the health care system cannot afford to do everything, resources have to be allocated—according to priorities set by society—and in as equitably a way as possible (Svensson and Stephensson, 1993, Mooney, 1994). It has been argued that it would be useful if priorities are set—i.e. choices made—not only by health care professionals and decision makers but also by health care consumers and the public at large (STAKES report 161, 1994).

6.2 Equity in infertility treatments

What does equity mean in infertility treatments? Finding an adequate answer to this question is not easy (Daniels and Taylor, 1993, McLean, 1993, Svensson and Stephenson, 1993, Blank, 1997, Ashcroft, 2005). As in other health care, the first step is to define the need for infertility treatments in the population i.e. infertility prevalence and the wish for a child.

Secondly, it can be asked what priority should be given to infertility treatments compared to other treatments in health care. As in other countries (Daniels and Taylor, 1993, Nisker, 1996, Neumann, 1997), Finland has seen discussion on the following priority-related topics: Should infertility be considered a disease or not, should treatments be given only for medical reasons (infertility is diagnosed) or also for social reasons, and who should have the right to treatments or eligibility? Prioritization has not however been explicitly discussed. IVF is clearly prioritized only by women's age, as already explained in Chapter 5.

Thirdly, it can be discussed whether these treatments are efficacious and safe enough (Peters, 2004). The fourth significant question is how can scarce health care resources be distributed equitably (in terms of geographical variations as well

as variations by socioeconomic position, and age) and with maximum benefit to public health. The allocation of resources is linked to the funding of infertility treatments. If IVF services are available only in the private sector, access will depend on ability to pay.

7 Summary

Infertility is a common problem and IVF and OI are widely used infertility treatments, but not enough is known about their utilization and health effects. Data on the frequency of IVF complications for treated women are sparse and the number of studies reporting complications after OI is even rarer. In spite of the large number of studies on perinatal health of IVF children, some studies on the general health of IVF children are based on early experience of IVF. Some studies concentrate on specific diagnosis or hospital care utilization or singletons or twins only, or do not consider multiplicity. Results on the perinatal health of IVF twins are controversial. Studies on congenital anomalies of IVF children are also controversial and many of them have had methodological problems such as small sample sizes, lack of proper controls, and different definitions of congenital anomalies among IVF and naturally conceived children. Only a few studies have examined congenital anomalies among OI children.

Health care costs for a live-birth among IVF women by age have briefly been described previously but otherwise empirical data that would quantify the question of resource allocation have not been given, nor has the distribution of private and public expenditure been estimated. There are many general assumptions of inequalities in the use of infertility treatments (i.e. urban women and women from higher socioeconomic position use more IVF services than rural women or women from lower socioeconomic positions) but not enough data are available to verify these assumptions. Equity is considered an important principle in health care. To be able to discuss equity in assisted fertilization data on effectiveness or success, safety, costs and resource allocation as well as utilization of assisted fertilization are needed.

8 Aims of the study

8.1 General aims

The general aims of this study were to study the utilization of IVF and OI, the health effects of IVF and OI as well as the equity in the use and resource allocation of IVF by using nationwide Finnish health care registers.

8.2 Specific aims

The specific aims were to study

1. the use of IVF and OI in Finland in 1996–1998 by women's background characteristics.
2. the serious complications and miscarriages leading to women's hospitalization or operations after IVF or OI.
3. the health of IVF children until the age of four years.
4. the prevalence of major congenital anomalies among IVF children.
5. the treatment costs of IVF in Finland.
6. the equity in the resource allocation for IVF in Finland.

9 Methods

Six different nationwide registers were used in the present register-based longitudinal study: Reimbursement records of the Social Insurance Institution (SII), the Central Population Register, the Hospital Discharge Register (HDR), the Medical Birth Register (MBR), the Register of Congenital Malformations (RCM), and the Cause-of-Death Register.

The study plan was approved by the STAKES research ethics committee. For register linkages, the National Data Protection Authority was consulted and permissions from the register keepers were obtained.

9.1 Registers used in the study

9.1.1 Reimbursement records of the Social Insurance Institution

The reimbursements of medical expenses such, as drugs, doctor's fees, and treatment or examination fees, are available by the Finnish national sickness insurance provider, the Social Insurance Institution (SII, http://www.kela.fi/in/internet/English.nsf). Up to 60 % of the doctor's fees and part of the cost of examinations and treatments ordered by a physician in the private sector are covered according to a fixed scale of charges. The part exceeding the fixed charge is not reimbursed.

The reimbursements are filed in electronic registers with personal identification (ID) numbers. The register of reimbursed examinations and treatments also includes the code of the physician, the codes of the examinations or treatments, dates, costs, and the amounts of reimbursements. The register of reimbursed drugs includes the municipality of recipients, the name and class of the drug, the size and numbers of packages, the dose recommended, the dates prescribed and bought, and the code of the physician.

In Finland, patients with certain long-term illnesses are entitled to a higher reimbursement of their costs of medication and clinical nutrients. This so-called Special Refund Category consists of approximately 50 diseases. Among children, the most common special refunded diseases are asthma, epilepsy, diabetes, rheumatoid arthritis, and allergy to cow's milk and/or soya milk. For the present study, information of reimbursements of long-term medication was also available and

the reimbursed medications were taken into account (excluding reimbursements of the clinical nutrients). The data on Special Refunds included the start and end dates of an entitlement period, the types, and the reasons.

The SII also grants child disability allowance for families who have a disabled or a chronically sick child needing continuous help and surveillance at home. The parents applying for benefits are required to supply recent medical documents. The register of the child disability allowance contains information of the start and end dates, the nature of benefit (temporary and permanent), the level of benefit (normal, increased and special), and the diagnoses for the support.

9.1.2 The Central Population Register

The information of marital status and occupation of the women was received from the Central Population Register (http://www.vaestorekisterikeskus.fi). The socioeconomic position was defined by using their occupation and classified into five categories: upper white-collar workers, lower white-collar workers, blue-collar workers, other (entrepreneurs, students, pensioners, unemployed women, and women with an unclassified position), and unknown position (Central Statistical Office, 1989).

9.1.3 The Hospital Discharge Register and the Care Register for Social Welfare

The HDR (http://www.stakes.info/2/9/index.asp) and the Care Register for Social Welfare (http://www.stakes.info/2/10/index.asp) are maintained by STAKES. The HDR collects information of inpatient care as well as of visits to outpatient clinics involving surgical or other procedures. It gathers information of diagnoses (the tenth revision of the International Classification of Diseases, ICD-10 since 1996), operation codes, and dates of admission and discharge. The diagnoses include the main diagnosis (which can consist of separate diagnoses of the reasons and symptoms leading to hospitalization) and two secondary diagnoses (which can also consist of two separate diagnoses of the reasons and symptoms) for each hospital episode. From 1983 to 1995, operations were registered according to a national coding system and, since 1996, according to the Finnish version of the NOMESCO classification system for surgical operations (Toimenpideluokitus, STAKES, 1996). The Care Register for Social Welfare collects information of care episodes in social institutions. Institutional care does not include children taken into children's homes or custody but refers mainly to mentally handicapped children who have stayed in institutions for intellectually disabled persons.

9.1.4 The Medical Birth Register

The MBR (http://www.stakes.info/2/1/2,1,1.asp) includes the unique ID numbers of the mother and the child and contains information of maternal background and on the outcome of all infants born in Finland until the age of seven days. The duration and causes of infertility are not registered. The data are collected by the delivery hospitals and completed by linkage to the Central Population Register and the Cause-of-Death Register. The socioeconomic position of the mothers was defined by using their occupation when delivering, which is collected routinely from maternity hospitals and classified automatically by the MBR into five categories (Central Statistical Office, 1989, Statistics Finland).

9.1.5 The Register of Congenital Malformations

The RCM (http://www.stakes.info/2/1/2,1,5.asp) collects information of all infants with a congenital anomaly (CA) or birth defect through several data sources, including a notification completed by the delivery hospitals, neonatal, pediatric and pathology departments, and cytogenetic laboratories as well as by linkage to several other nationwide registers. In the RCM a CA has been defined as a major congenital structural anomaly, chromosomal defect or congenital hypothyroidism involved in a birth. The CAs reported to the RCM, which do not qualify the criteria of major CA, are not accepted to the register (rejected, not registered cases).The physician responsible for RCM routinely classifies CAs into major, other, and rejected. Other anomalies reported to the register can, for example, be minor anomalies related to major CAs. Rejected anomalies include some minor CAs as defined by the European Surveillance of Congenital Anomalies EUROCAT (http://www.eurocat.ulster.ac.uk) exclusion list (hereditary diseases, dysfunction of organs or tissues, developmental disabilities, congenital infections, isolated minor dysmorphic features, normal variations, and other less significant anomalies).

9.1.6 The Cause-of-Death Register

The Cause-of-Death Register is maintained by Statistics in Finland and it includes personal ID numbers, causes of death (diagnoses according to the ICD-10 since 1996), and dates of death. The data is obtained from the death certificates, which are supplemented with the data from the population information system of the Central Population Register. The data in the Cause-of-Death Register covers the persons who have died in Finland or abroad and who at the time of death were domiciled in Finland.

9.2 Identification of IVF and OI women and their children

The study includes two exposed cohorts: 20–59-year-old women having had IVF treatments (IVF, ICSI and FET, N = 9175) and women having had other infertility treatments including drugs (ovulation inductions or low stimulation with or without artificial insemination, OI, N = 10 254) between 1996 and 1998 in Finland, and their children (Fig. 2). The population controls, matched by age and municipality, were randomly selected for IVF women (N = 9175) from the SII population record (covering the total Finnish population).

The basis for the data collection was that all infertility treatment cycles (not natural cycles and a part of frozen embryo transfers) start with drugs, and some drugs and their combinations are specific to infertility treatments as such. The bought and reimbursement drugs can be found from the reimbursement files of the SII. An algorithm about which drug combination indicates each infertility treatment was created (detailed in Hemminki et al., 2003). The beginning of a treatment cycle was defined by the date of buying the first infertility drug. The cycles were classified as ovulation induction (with or without insemination), IVF without embryo transfer (cancelled cycles and cycles for ovum pick-up), IVF with embryo transfer, and frozen embryo transfer. IVF interventions done in the private sector (over 60%) which are covered and registered by the SII were added to the cycles. The functioning of the algorithm was checked manually 18 times (with the sample sizes between 200 and 2000 women), and the algorithm was improved with the received information. As a whole the algorithm worked well (Hemminki et al., 2003), and a total 24 318 IVF cycles could be identified, which was slightly higher than the number of cycles registered in IVF statistics (21 424). This can be partly explained by the cancelled cycles which were also included in this study and partly by incorrect classification. The number of identified OI cycles was 24 611, which could not be compared to any other number of cycles, since OI cycles are not collected in any statistics. The data on IVF and OI women were created from the women who had received IVF and OI treatment cycles.

To identify the children born after IVF or OI the data were linked to the nationwide MBR by using the personal identification numbers of the women and the dates of birth of the children as the linkage keys. For IVF births the time limit of 44 weeks after the beginning of treatment (the purchase of the first drug) to the date of birth was used as a standard and for OI births it was 48 weeks.

As controls for the children, two groups of children were selected from the MBR. The first control group consisted of all children other than IVF and OI children (N = 190 398) who had been conceived during the same time-period (1996–1998). The second control group (n = 26 877) was a random sample of the first control group and was selected to reduce the workload caused by large register linkages in the SII and the RCM; it was used to study the benefit payments from the SII, CAs from the RCM, and in the combined analysis.

9.3 Register linkages

The data on the identified women who had used IVF and OI were linked to the CPR to receive information of women's background characteristics. The data on the costs and reimbursements were received partly from the SII and partly from the clinics: Helsinki University Central Hospital and the biggest private IVF clinic recommended by other clinics (Paper V). The costs taken into account were direct costs, such as medications, visits, routine examinations, interventions, and costs of equipment and trained staff. Indirect costs, such as costs for travel and sick-leave, were not included. The expenditures were partly based on the average costs in clinics, partly on estimations, and partly on exact paid and reimbursed costs. Private expenditures include costs paid by the patient and public expenditures costs paid by the health care system. All costs and reimbursements have been inflated to correspond to 2005 prices (in euros) using a consumer price index compiled by Statistics Finland.

The data on care episodes at hospital were collected by register linkages to the HDR, and dates and causes of death (during the mean of 3.7-years of follow-up for IVF and control women and 3.8 years for OI women) from the Cause-of-Death Register by using personal ID numbers (Fig. 2).

The data on perinatal health of the IVF children and the ID numbers of the children were obtained from the MBR. To receive data on the health of early childhood the identified children were linked to five other nationwide registers by the ID numbers of the children: the Cause-of-Death Register, the HDR, the Care Register for Social Welfare, the RCM (without knowing the mode of conception of the children), and the health-related social benefits from the SII (Fig. 2).

9.4 Data analysis

Use and costs

To calculate the age-specific incidences of the use of IVF and OI, the number of women treated was divided by the number of all women in the same age group in the same area (SOTKA database 2001, STAKES). The age-adjustment was made by using direct age-standardisation. The mean price of different types of IVF cycles by the care sector were calculated as well as the private, public, and total expenditures by women's background characteristics and by live births. The mean population of females aged 20–49 years in Finland by socioeconomic position and area of residence according to census information for 1995 and 2000 available from Statistics Finland was used to count the expenditure by population groups.

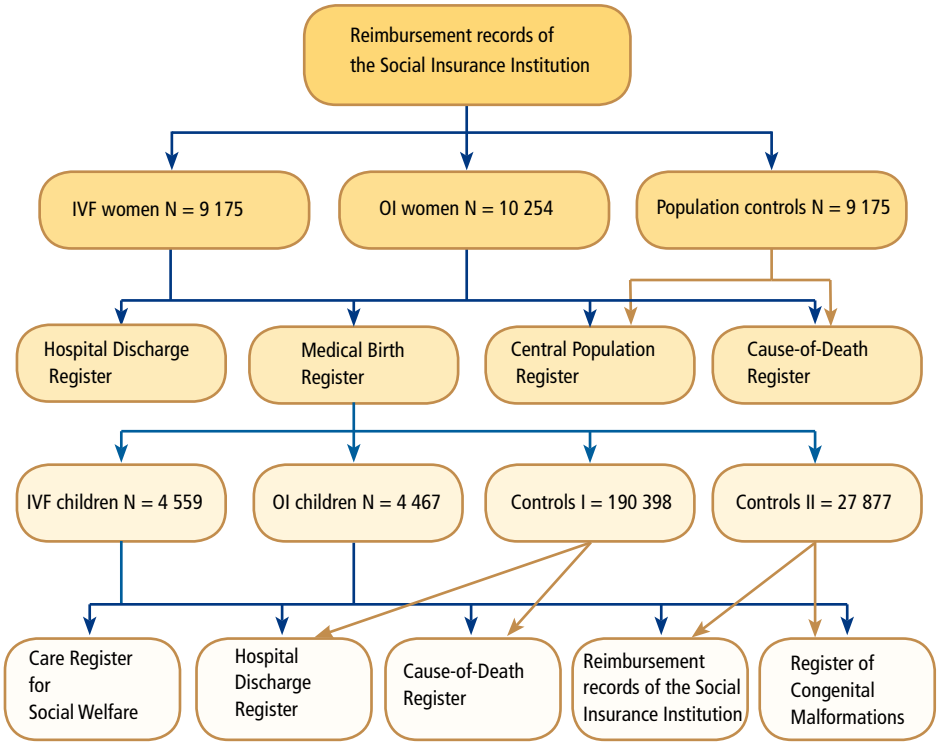

FIGURE 2. Registers, study population, and register-linkages used in the study.

The cycle was defined as having taken place in the private sector in cases where an intervention in the IVF cycle involved reimbursement by the SII. For the other IVF cycles the classification of cycles as private or public was made according to the main work place of the physicians given in a catalogue of physicians (STAKES, 1998). The catalogue is based on the register of health care personnel (TERHIKKI) which receives information of certificate doctors from the Finnish Medical Association. The classification for private and public cycles was crude, since the main work place could not always be defined. The OI cycles could not be classified as private or public.

Complications and miscarriages after IVF and OI and pregnancy and birth treatments

The proportion of the IVF and OI women with a complication (the first occurrence) after the first cycle and after all treatment cycles (in the study window) was calculated separately for each type of complication (risk for a complication after an average of 2.7 treatment cycles). The studied outcomes, follow-up times, and data sources are presented in the Appendix, and the ICD-10 codes of complications are detailed in the Appendix of Paper II. In addition, the diagnoses defined

in the HDR as OHSS (ICD-10 code) as well as symptoms or diseases potentially related to OHSS ("potential OHSS") were searched from the HDR. Some women had both the diagnosed OHSS (with the specific ICD-10 code) and the "potential OHSS".

The causes of death were classified into eight categories: reproductive mortality as defined by Fortney et al. (1986) with the addition of causes related to achieving the pregnancy, diseases of the circulatory system, cancers, suicides, homicides, accidents, other, and unknown causes.

The IVF mothers were compared to the mothers of the control children in their utilization of health care services during the pregnancy and child birth (hospitalization during the pregnancy, Caesarean section, and the hospitalization of seven or more days after the delivery). The same variables were studied also for OI women but were not reported in Paper IV for space reasons as suggested by the referees of the journal.

Health of IVF children

The IVF children were compared to the control children. The studied outcomes, follow-up times, and data sources are presented in the Appendix. The follow-up times varied, because the data were first collected until two years of age and then completed by the data on hospitalizations until the children were four years of age. Information of specific diseases was received by combining the different data sources and by calculating the number of children who had used the services—according to any of the data sources—due to an allergic or chronic disorder or common infection until two years of age. If the child was hospitalized more than once due to the same diagnosis, only the first hospitalization was included. The same variables were studied also for the OI children, but they were not reported in Paper IV for space reasons as suggested by the referees of the journal.

The occurrence of major CAs both among the IVF and OI children was reported (detailed in Paper III). Only major CAs, as defined in the RCM, were included in the analysis. In the analysis of the CAs by the organ system, a child appeared more than once if (s)he had more than one major CA affecting different organ systems. The IVF and OI women were linked to the Register of Induced Abortions to specify induced abortions performed due to a suspected or confirmed CA. The rates were compared to the national rates per 10 000 births.

Statistical analysis

The differences between the IVF and control groups as well as those between the OI and control groups were examined by using tests for relative proportions, t-tests, chi-square tests, and the one-sided analysis of variance. A P-value of less than 0.05 was considered significant.

The IVF mothers were compared to the mothers of the control children and the IVF and OI children were compared to the control children using odds ratios (OR) and 95 % confidence intervals (CI). When the health of the IVF children in the early childhood was studied, two logit models were made: an ordinary logit model where all the children were assumed to be independent and an additional analysis using the iterative generalized least squares method where siblings born in the same delivery were assumed to be dependent.

The singletons and multiples were analysed separately. When the ORs for congenital anomalies were studied, the children were stratified also by sex and multiplicity. For perinatal outcomes adjustment was made by the age of the mother, previous births, smoking, marital status, socioeconomic position, and the residence of region, for congenital anomalies by the age of the mother, parity, socioeconomic position, and the residence of region, and for other childhood outcomes by socioeconomic position using logistic regression.

10 Results and comments

10.1 Use of IVF and OI (Papers I and V)

The background characteristics of IVF, OI, and control women are presented in Table 4. The IVF women were more often married and from the higher socioeconomic position compared to the OI and control women.

TABLE 4. Background characteristics of IVF, OI, and control women[a] in 1996–1998.

	IVF (n=9 175)	OI (n=10 254)		Controls (n=9 175)	
Age group					
20–24	3.5	11.0		3.5	
25–29	20.8	31.4		20.8	
30–34	35.2	31.5		35.2	
35–39	27.7	17.8		27.7	
40–44	10.8	6.9		10.8	
45+	2.0	1.4		2.0	
Total	100.0	100.0	p<0.001[b]	100.0	p=1.000[d]
Marital status					
Non-married [c]	22.3	19.1		36.1	
Married	69.4	72.5		56.7	
Divorced	7.9	7.9		9.4	
Widow	0.4	0.5		0.4	
Unknown	0.0	0.0		1.4	
Total	100.0	100.0	p<0.001[b]	100.0	p<0.001[d]
Socioeconomic position					
Upper white-collar	25.3	20.6		16.3	
Lower white-collar	48.5	48.7		45.7	
Blue-collar	16.2	18.0		19.3	
Others	7.9	10.0		12.3	
Unknown	2.1	2.7		6.4	
Total	100.0	100.0	p<0.001[b]	100.0	p<0.001[d]

[a] Population controls for IVF women, matched by age and muncipality.

[b] P-values for chi square tests (IVF women and OI women).

[c] Includes cohabitation. Divorced and widowed women can also live in cohabitation.

[d] P-values for chi-square tests (IVF women and controls).

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TABLE 5. Number of IVF cycles per treated women by age, socioeconomic position and treatment sector in the study period (mean 1.5 years).

	Age					
	20–29	30–34	35–39	40+	Total	P-value[b]
Socioeconomic position						
Upper white-collar	2.28	2.83	2.91	3.14	2.82	< 0.001
Lower white-collar	2.16	2.69	2.77	2.98	2.62	< 0.001
Blue-collar	2.27	2.56	2.74	2.96	2.56	< 0.001
Others [a]	2.23	2.69	2.59	2.83	2.52	0.003
Sector						
Public	1.93	2.21	2.36	2.18	2.17	< 0.001
Private	2.21	2.65	2.66	2.92	2.61	0.573
Both	3.09	4.43	4.59	5.30	4.19	0.055
Total	2.21	2.71	2.79	3.01	2.65	0.066

[a] Entrepreneurs, students, pensioners, unemployed, and women with an unclassified or unknown position.

[b] P-values for one-sided analysis of variance.

The age-standardised IVF incidence per thousand 20–49-year-old women was 8.8 in the urban and 7.3 in the rural areas. The use of OI was highest in the semi-urban area (10.4) and lowest (8.5) in the capital area. The regional incidence of IVF varied from 6.5 (in eastern Finland) to 9.2 (in the capital area in southern Finland) and of OI from 5.2 (in eastern Finland) to 12.7 (in northern Finland). The northern region had no IVF clinic, and the use of OI was common.

Approximately 53% of IVF women received all IVF treatments from private doctors ('private users'), 35% from public doctors ('public users'), and 12% from both private and public doctors ('both-sector users'). The private users were older (mean age 34.3 years) than the public (32.3 years) and both-sector users (32.8 years, $p<0.001$). In the private sector, the women in the highest socioeconomic position were over-represented (29% private, 18% public, 16% controls). During the mean 1.5-years study period, the IVF women had received a total of 24 318 cycles; the minimum number was one and the maximum 14 cycles. The IVF women

TABLE 6. Rates (per 1000 female population) of women having received IVF by age and socioeconomic position in the study period.

	Age				
	20–29	30–34	35–39	40+	Total
Socioeconomic position					
Upper white-collar	14	30	24	4	13
Lower white-collar	13	25	17	2	9
Blue-collar	8	16	12	1	6
Others [a]	2	5	3	1	2
Total	7	18	14	2	7

[a] Entrepreneurs, students, pensioners, unemployed, and women with an unclassified or unknown position.

received slightly more treatment cycles in the private sector compared to the public sector (p-value for one-sided analysis of variance < 0.001); the frequency was not age-dependent, and the women in the highest socioeconomic position had slightly more cycles than the others (p-value < 0.001, Table 5). In the public sector the number of cycles did not differ by socioeconomic group, and the women aged from 30 to 39 years had more cycles than the others. In the population-based examination it was found that the women from the highest socioeconomic-group used IVF twice as much as the blue-collar women in every age-group.

The over-representation of women in the highest socioeconomic position among the IVF women is in accordance with previous studies (Svensson and Stephenson, 1993, Wilcox and Mosher, 1993, Gunnell and Ewings, 1994, Bachelot and Mouzon, 2002), but in the present study it was found only in the private sector. The higher number of cycles in the private sector cannot be explained solely by age, because the difference was also found in the age-specific analysis. It may indicate effectiveness and an ability to respond to demand, but also a sign of growing commercialism. In the United States, the growing numbers of fertility specialists and clinics have increased competition for clients, and some authors consider the marketing of infertility services aggressive (Mitchell 2002, Spar 2006). The older age of the treated IVF women in the private sector found in the present study can be explained by an informal age limit within the public sector. Some of the women treated were over 50 years of age, but their number was very insignificant.

It is possible that a widespread use of IVF eliminates socioeconomic differences in countries using public resources to provide IVF. In the present study, the public sector made the use of services more equitable for different socioeconomic groups, though it could not compensate for socioeconomic differences created in the private sector. On the other hand, if the private sector did not offer IVF services, the social class differences might be smaller but waiting lists might be longer, and the total number of treatments and women treated would be smaller. Since the regional differences were not great, it seems that long distances are no object; women are prepared to travel to obtain IVF treatments.

10.2 Success of IVF (Papers I and V)

The numbers and rates of women having received IVF was the highest among women aged 30–39 years (Tables 4 and 6), but the treatment was more intense for older women (number of cycles per woman, Table 5). The efficacy of IVF measured by the success rate per cycle and per woman decreased by age (Tables 7 and 8). The higher treatment intensity among the older women did not compensate for the lowered success rate, and approximately 47% of the women aged under 30 years and only 17% of those aged 40 years or older succeeded in achieving a live birth after the treatment period (mean 1.5 years).

TABLE 7. Live-births per number of IVF cycles[a] by age, socioeconomic position, and treatment sector.

	Age				
	20–29	30–34	35–39	40+	Total
Socioeconomic position					
Upper white-collar	0.25	0.18	0.13	0.06	0.15
Lower white-collar	0.23	0.17	0.14	0.05	0.16
Blue-collar	0.19	0.16	0.11	0.07	0.14
Others [b]	0.19	0.16	0.11	0.04	0.14
Sector					
Public	0.20	0.18	0.13	0.04	0.16
Private	0.26	0.20	0.15	0.06	0.17
Both	0.15	0.10	0.08	0.04	0.10
Total	0.22	0.17	0.13	0.06	0.15

[a] All live births and all cycles during the mean 1.5 years treatment period.

[b] Entrepreneurs, students, pensioners, unemployed, and women with an unclassified or unknown position.

The success of the IVF treatment was also dependant on the socioeconomic position: live-births per cycle were more common among the white-collar women than among the blue-collar ones aged less than 30 years (Table 7). Furthermore, the white-collar women in total achieved a live-birth more often than the blue-collar women (Table 8). The success per cycle did not vary much by the treatment sector, being the poorest among the both-sector users (Table 7), but the women treated in the private sector received more often a live-birth than those treated in public sector or in both (Table 8).

TABLE 8. Live-births per IVF women[a] by age, socioeconomic position, and treatment sector.

	Age				
	20–29	30–34	35–39	40+	Total
Socioeconomic position					
Upper white-collar	0.55	0.49	0.38	0.20	0.42
Lower white-collar	0.49	0.46	0.37	0.15	0.40
Blue-collar	0.42	0.40	0.30	0.21	0.36
Others [b]	0.42	0.41	0.29	0.12	0.35
Sector					
Public	0.39	0.40	0.31	0.08	0.35
Private	0.56	0.50	0.39	0.19	0.42
Both	0.44	0.44	0.36	0.23	0.40
Total	0.47	0.45	0.36	0.17	0.40

[a] One live birth per woman during the mean 1.5 years treatment period.

[b] Entrepreneurs, students, pensioners, unemployed, and women with an unclassified or unknown position.

The success rates in this study were age-dependent as also found earlier, but slightly lower than especially in recent publications (Table 1). This can be due to the improved success rates in the course of time or to the different ways to calculate the number of cycles; cancelled cycles were included in this study. The better success of the women from the higher socioeconomic position compared to the other women in the present study can be a consequence of seeking for medical advice after a shorter period of infertility, of more intense treatments or of more serious infertility among women from the lower socioeconomic position. On the other hand, the greater number of cycles received by women in the highest socioeconomic position can be a consequence of seeking for IVF services at an older age as well of a capability to pay for or to request more treatments. The both-sector users were not too old or 'sick' to receive treatment in the public sector and they had evidently enough money to purchase care in the private sector. Since they needed many treatment cycles, it can be assumed that their treatments were less successful. Some of these women may have little or no chance of becoming pregnant, but they did not want to stop trying. However, 40 % of them received a child as a result of the treatments; finally they succeeded as well as the women in this study on average. The number of cycles among the both-sector users was not dependent on the socioeconomic position, which suggests that the care itself was experienced as important and useful.

10.3 Complications after IVF and OI, and pregnancy and childbirth treatments (Papers II and III)

Only a few IVF women were hospitalized due to the OHSS after the first treatment cycle but more after repeated attempts and particularly when the 'potential OHSS' was taken into account (Table 9). After OI the hospitalization due to the OHSS was rare. The risk of having OHSS was highest after the first and the fifth or more IVF treatment cycles (Paper II) and it was more common among twin than among singleton pregnancies ending in birth (3.2% vs. 1.4%, p-value < 0.001 for a test of relative proportions). After IVF treatment, OHSS (ICD-10) was much more common among younger than older women: 3.2% of the women under the age of 35 years were hospitalized due to the OHSS compared to 1% of the older women.

Bleeding and infections necessitating hospital care were rare and even rarer after OI than after IVF (Table 9). Miscarriage was the most common reason for hospital care. The percentage of women that had miscarriage was similar after the first OI and IVF treatment cycle, but after all treatment cycles, miscarriage was 1.6 times more common among the IVF women than among the OI women. The number of miscarriages per 100 births was 23.0 after IVF and 15.0 after OI. Ectopic pregnancies were also more common among the IVF women compared to

TABLE 9. Health problems leading to hospitalization after the first and all IVF or OI treatment cycles in the study period, per 1000 women.

	IVF (N = 9175)		OI (N= 10 254)	
	First	All	First	All
Outcomes				
OHSS, ICD-10 [a]	14.1	22.9	0.3	0.8
Potential OHSS [b]	5.6	13.3	5.6	9.1
OHSS, ICD-10 or potential	19.0	34.7	5.7	9.8
Bleeding	1.0	2.4	0.3	0.3
Infection	5.1	10.9	1.5	3.1
Other [c]	1.1	1.9	0.1	0.5
Ectopic pregnancy	9.3	20.9	8.2	10.7
Miscarriage	41.9	93.1	42.1	61.8

[a] OHSS = Ovarian hyperstimulation syndrome (N98.1, ICD code).

[b] Symptoms potentially related to OHSS (see Paper II).

[c] Other complication than OHSS related to IVF or OI (see Paper II) and thromboembolic events.

the OI women. The ratio per 100 births after IVF was 5.0 and that after OI 0.03. Six IVF women (four registered as pregnant) and four OI women had a thromboembolic event (two registered as pregnant).

After all treatment cycles, 15% IVF and 8% OI women were hospitalized for complications. During the whole follow-up (mean 3.7 years for IVF women and 3.8 years for OI women from the exposure) one death in both the IVF and OI group was related to reproduction (Paper II).

The IVF mothers were older, more often married, and from a higher socioeconomic position than the other mothers (Paper III). They were seldom smokers, the child was more often their first, and they received more hospital care during the pregnancy and Caesarean sections compared to the other mothers. Adjustment to mothers' background characteristics did not change the results. The inspection of singletons and multiples separately showed that this difference was partly, but not totally, explained by IVF children being more often twins.

As reported earlier (Schenker, 1999), women under 35 years of age were at a greater risk of OHSS. The risk was also greater among the women with only one cycle and those with many cycles. In this study it is not known how many cycles the women had received before the year 1996. After many repeated cycles a woman may be in a greater risk due to the repeated doses of drugs (especially gonadotrophin). This should be considered when many attempts are needed. Furthermore, the risk was also higher among twin pregnancies than among singleton pregnancies ending in birth, which has also been found in an earlier study regarding late OHSS (Mathur et al., 2000).

Only a few studies (Quasim et al., 1997, Abramov et al., 1999b) have reported the frequency of OHSS after ovulation induction (OI) alone or compared it to the frequency after IVF. The present study, in accordance with earlier studies from the USA and Israel, shows serious OHSS to be more common after IVF than after OI.

The present study confirmed earlier results that thromboembolic events exist after IVF but are rare complications (Serour et al., 1998), and even rarer after OI. The frequency of bleeding after IVF was the same in the present study as in an Egyptian study with 3500 cycles (Serour et al., 1998), but it was much lower than the frequency found in a recent report from ESHRE (Nyboe Andersen et al., 2006) which covered all bleeding complications, even those not leading to hospitalization. The frequency of infections in the present study was similar to that reported earlier in the Nordic countries (Bergh and Lunkvist, 1992) and Egypt (Serour et al., 1998), but higher than the frequency reported by ESHRE (Nyboe Andersen et al., 2006). The finding of very low rates after OI suggests, that bleeding and infections may be complications of the IVF technique.

It was not possible to identify how many of the treated women had become pregnant, but the miscarriage ratio to 100 IVF births (23.0) suggests similar miscarriage rates as found earlier after IVF (15% to 21%, Serour et al., 1998, Kupka et al., 2003, Schieve et al., 2003, Wang et al., 2004). However, since all miscarriages do not lead to hospital care, the actual rate of miscarriages must have been higher. The miscarriage ratio to 100 OI births was lower than after IVF (15 vs. 23). Whether this was due to women's characteristics or to the procedure itself, could not be judged from this study. Previously, greatly varying rates after clomiphene-induced pregnancies have been reported (9–27%, Venn et al., 1994).

In the present study no pregnant controls were available, but, according to one Finnish study, 8% of women with spontaneous pregnancies needed hospital care due to a miscarriage (Hemminki and Meriläinen, 1996). In one study from the United States the miscarriage rate was similar (15%) among ART women and normal female population (Schieve et al., 2003). However, in another study from the United States, the risk of miscarriages was slightly increased after ART (Wang et al., 2004).

The ectopic pregnancy ratio to 100 IVF births (5.0) in this study was two-fold higher than found earlier in Finland (Hemminki and Heinonen, 1987, Mäkinen, 1996). Information of the reasons for infertility was not available in this study, and the number of women having tubal occlusion, which is considered to be one reason for the high frequency of ectopic pregnancies among IVF women, could not examined. In the case of OI, which requires open tubes in order to be effective, a possible reason for the high rate of ectopic pregnancies could be clomiphene citrate (Venn et al., 1994).

In one study from Australia, the maternal mortality of IVF women was higher than the national rate (Venn et al., 2001). The authors suggested that reasons for that can be advanced maternal age, a high proportion of multiple pregnancies, and a high Caesarean section rate. Due to the lack of a control group of spontaneously pregnant mothers or women aiming at pregnancy, the best control group for IVF women was in this study the group of OI women, though the IVF women were older than the OI women. The present overall mortality was lower than in the general female population (matched by age and municipality), which is in accordance with the Australian study. In particular, the cardiovascular deaths were rarer. It speaks for a "healthy patient effect" among IVF and OI women (Venn et al., 2001): sick women are less likely to be married or to receive infertility treatment than healthy women. The socioeconomic position of the IVF women in this study was slightly higher than that of the control women, which can partly explain the low mortality. Lower mortality among the women having received IVF compared to those who had registered for IVF but never received the treatment has been reported in Australia (Venn et al., 2001).

10.4 Health of IVF children (Papers III and IV)

10.4.1 Health of the newborn

In this study 4 559 children born after IVF and 4 467 after OI could be identified. Of the IVF children 34.7% were twins and 1.1% triplets. The corresponding rates of the OI children were 11% and 1.1%. Among the control children 2.2% were twins and only 13 sets were triplets (0.02%).

The health of the IVF infants was much worse than that of the other infants, which was partly explained by plurality (Table 10). The health of the multiple IVF infants was comparable to that of control multiples; only the risk of a very preterm birth was increased, but not statistically significantly. In the subanalysis of the first births the results were mainly similar to those of all children and no differences in the results of the two logit analyses (see Methods) were found.

Stillbirths were more common among the IVF infants in total compared to the other children in total (7.2/1000 vs. 3.9/1000, p-value < 0.001 in the test for relative proportions) as well as among the IVF singletons compared to the control singletons (6.5/1000 vs. 3.7/1000, p-value $= 0.014$ in the test for relative proportions), but not separately among the multiples.

Among the IVF and OI children 51% of the reported major CAs had been accepted by RCM, whereas the proportion was 46% among control children. The total risk of major CA for IVF singletons was statistically significantly increased (Table 10) and for multiples insignificantly decreased. The prevalence of a major

TABLE 10. Proportions (%) and odds ratios (and 95 % confidence intervals, CI) of infant outcomes as compared to other infants, adjusted to mothers' background variables [a]

	Total			Singletons			Multiples		
	IVF	Controls		IVF	Controls		IVF	Controls	
Number of children	4559	190 398		2930	186 216		1629	4182	
Outcome	%	%	OR (95% CI)	%	%	OR (95% CI)	%	%	OR (95% CI)
Very preterm (< 32 gw)	4.7	0.9	4.45 (3.80-5.21)	2.0	0.8	2.06 (1.56-2.71)	9.6	7.0	1.26 (0.99-1.60)
Preterm (< 37 gw)	23.6	5.5	4.43 (4.10-4.77)	9.5	4.7	1.72 (1.51-1.96)	49.2	42.2	1.06 (0.93-1.21)
Birth weight < 1500 g	4.2	0.8	4.19 (3.55-4.95)	1.9	0.7	2.17 (1.64-2.88)	8.2	7.4	0.95 (0.74-1.22)
Birth weight < 2500 g	19.8	4.0	4.77 (4.40-5.18)	6.5	3.2	1.60 (1.37-1.87)	43.7	39.2	0.92 (0.81-1.06)
Apgar score 0–6	8.8	4.4	1.68 (1.50-1.87)	5.6	4.2	1.07 (0.91-1.26)	14.5	12.5	1.10 (0.90-1.33)
Special care[b]	23.0	8.2	2.71 (2.52-2.92)	12.5	7.6	1.36 (1.21-1.53)	42.1	35.0	1.04 (0.91-1.19)
Respiratory treatment	4.3	1.1	3.61 (3.08-4.24)	2.0	0.9	1.76 (1.34-2.31)	8.4	6.7	1.19 (0.93-1.53)
Hospitalization ≥ 7 days	23.8	6.4	3.42 (3.08-4.24)	10.8	5.8	1.43 (1.26-1.61)	47.4	37.6	1.02 (0.88-1.17)
Perinatal mortality	1.3	0.6	1.85 (1.40-2.44)	0.9	0.5	1.32 (0.88-1.98)	2.0	2.9	0.73 (0.47-1.13)
Congenital anomaly [c]	4.3	2.9	1.31 (1.10-1.57)	4.3	2.9	1.30 (1.05-1.61)	4.3	5.3	0.80 (0.48-1.32)

[a] County, smoking, age, marital status, parity, socioeconomic position.
[b] Treatment in intensive care unit or in newborn surveillance unit.
[c] Total number of controls = 27 078, singleton controls = 26 489, and multiple controls = 589
Reference group (OR=1) = controls.

CA was the same for IVF singletons and IVF multiples but much higher for multiples than for singletons among the OI (Paper IV) and control children. The IVF boys, both singletons and multiples, had major CAs more often than the IVF girls (Paper IV). A significantly increased OR was found among the singleton IVF boys (OR 1.63, CI 1.23–2.15) and a significantly decreased OR among the multiple IVF girls (OR 0.45, CI 0.22–0.93). Furthermore, increased ORs for urogenital and musculoskeletal CAs were found among the singleton IVF boys (Paper IV). Hypospadia was the most common diagnosis of these major urogenital anomalies, and the control boys had more minor hypospadias than the IVF boys. Also the OI singleton boys had a higher risk of urogenital CAs (Paper IV). No risk of specific musculoskeletal CA among the IVF boys was found.

By definition, all IVF mothers were exposed to some infertility drugs, most commonly to progesterone (Paper IV). Most mothers were exposed to several drugs. Only estrogens were used more often by the mothers of malformed than by those of non-malformed IVF children, but the mothers of most malformed children had not received estrogen. Among the OI children no differences in the use of drugs between malformed and non-malformed children were found, neither in the use of a natural nor a synthetic progestin.

During the study period nine out of 9175 IVF women (19.7 per 10 000 IVF birth) and eight out of 10 270 OI women (17.9 per 10 000 OI birth) had an induced abortion due to the suspicion or detected foetal defect. The national rate per 10 000 births in 1996–1998 in Finland was 36.7 (the MBR).

This study confirms the earlier findings of poorer infant health of IVF singletons (Schieve et al., 2002, Helmerhorst et al., 2004, Jackson et al., 2004) compared to naturally conceived singletons. The IVF multiples had a worse health in infancy than the IVF singletons, but the IVF and control multiples were similar in regard to health in infancy, which is largely in accordance with an earlier study (except for the finding of an increased risk of admittance to a neonatal intensive care unit and more common longer hospitalizations after the birth, Pinborg et al., 2004c). In contrast, a recently published Belgian study reported an increased risk of preterm birth also among IVF twins compared to naturally conceived twins, which was, however, largely explainable by the first birth given by IVF women (Verstraelen et al., 2005).

The previous finding that twins have more CAs than singletons (Mastroiacovo et al., 1999) was also found among the control children in this study, but not among the IVF children. This is in accordance with Danish studies, in which no differences were found in the malformation rates between IVF/ ICSI and naturally conceived twins (Pinborg et al,. 2004c, Zhu et al., 2006), but contrary to a recent study from the United States (Olson et al., 2005).

The present study verified an earlier result of the overall risk of urogenital and musculoskeletal CAs among IVF children (Hansen et al., 2002, Zhu et al., 2006). The present study was, however, too small to examine the risk of individual diagnoses such as the previously reported hypospadia (Ericson and Källén, 2001, Silver et al., 1999) and could not verify the increased risk of heart anomalies found earlier (Koivurova, 2005).

Potential reasons for the poorer health of IVF infants include infertility itself (Draper et al., 1999, Brink Henriksen et al., 1997, Basso and Baird, 2003, Basso and Olsen, 2005, Zhu et al., 2006), infertility treatments, and varying health behaviour during pregnancy. In IVF treatments one cause for CAs might be the use of hormonal drugs (Silver et al., 1999, Hemminki et al., 1999, Zhu et al., 2006). Although the dangers of hormones in early pregnancy have been discussed for decades (Hemminki et al., 1999, Kruse et al., 2003), they have not been the focus

when the health effects of IVF have been discussed. Other potential causes may be bypassing the fertilization barriers in gametes especially in ICSI, culture media, freezing and thawing of embryos as well as timing of embryo transfer (Shiota and Yamada, 2005). Male genital anomalies have been suggested to have a link to the hereditary paternal subfertility associated with ICSI (Wennerholm et al., 2000). The advanced age of mothers, a lower fertility rate, and an increased reproductive loss rate characterizing women seeking for infertility treatment have all been associated with different foetal and neonatal abnormalities. However, the higher age of mothers did not explain the increased risk of major CAs in this study.

Among IVF singletons the main cause for poorer health has been suggested to be infertility itself due to the higher incidence of preterm birth and a low birth weight also among infertile women without treatment and women with other infertility treatment than IVF (Lambert, 2003). One the other hand, some modifications in the gestational process induced by IVF and ICSI have been suggested (de Geyter et al., 2006) as well as so-called vanishing twins (singletons originating from twin pregnancies, Pinborg et al., 2005, De Sutter et al., 2006).

Zygosity plays a significant role when the health of IVF multiples is compared to the health of other multiples. In general monozygotic twins have had poorer perinatal outcomes and more major CAs than dizygotic twins. Although IVF and OI increase monozygotic twinning (Ericson and Källén, 2001, Källén et al., 2002), transfer of several embryos causes the majority of IVF twins to be dizygotic (30%) compared to naturally conceived pregnancies (1%, Schachter et al., 2001). This can partly explain the results of the similar outcomes of multiples in studies unable to take zygosity into account. In this study 50% of the IVF and 30% the control twins were opposite-sex twins indicating that more IVF children were dizygotic. The fact that the CA rate was not smaller among the IVF twin boys could result from a higher risk of CA among IVF boys.

10.4.2 Health in early childhood

Up to the age of four years a larger proportion of the IVF children were hospitalized and the IVF children had more often long hospital episodes, the average length of their episodes being longer compared to the controls (detailed in Paper III). In all ages the IVF children had slightly more hospital episodes than the control children (the difference being clearest during infancy) and in almost every ICD-10 category the proportion of hospitalized children was higher among the multiples than among the singletons. Perinatal problems were the main single reason for hospitalizations.

When information from different data sources was combined until the age of two years, it was found that IVF children, singletons, and multiples together had a three-fold increased risk of cerebral palsy, and more often disorders in psy-

TABLE 11. Proportion (per 1000) of children and adjusted[a] odds ratios of having an allergic or chronic disorder or a common infection (ICD-10-codes) until the age of two years.

	Controls (n = 26 877) 1 / 1000	IVF (n = 4 527) 1 / 1000	OR (95% CI)
Cerebral Palsy (G80)	1.4	3.8	2.92 (1.63-5.26)
Epilepsy (G40-G41)	2.5	3.3	1.33 (0.76-2.34)
Behavioural disorders (F80-F98)	4.1	6.6	1.68 (1.11-2.53)
Diabetes (E10)	0.5	0.9	1.57 (0.51-4.84)
Asthma (J45-J46)	28.1	30.3	1.08 (0.90-1.30)
Allergy (L20-23, L27, L50)	53.8	59.9	1.07 (0.94-1.23)
Pneumonia (J12-J18)	11.4	9.9	0.85 (0.62-1.17)
Diarrhoea (A08-A09)	38.6	44.2	1.17 (1.00-1.37)

[a] Adjusted to mother's socioeconomic position

chological development or behavioural and emotional disorders than the control children (Table 11). This was not seen when the IVF singletons and multiples were considered separately (Paper III). Of the infants with cerebral palsy, 88% were preterm and 76% from multiple pregnancies. Of the children with developmental or behavioural problems, 60% were multiples.

Until the age of two years a larger proportion of the IVF children and of the IVF singletons had received child disability allowance compared to the controls, but no statistically significant differences in the use of long-term medication were found between the IVF and control children (Paper III).

In the subanalysis of the first births the results were mainly similar to those of all children and no differences in the results of the two logit analyses (see Methods) were found.

According to the Care Registry for Social Welfare Institutions, 2.2 IVF children per 1000 had experienced at least one period of institutional care in a social welfare institutions. For other children born in 1997–1998 the rate was 2.7 per 1000 children.

The total mortality up to the age of two years was two-fold higher among the IVF children compared to the controls (9.0/1000 and 4.1/1000); the main causes being congenital malformations and conditions originating in the perinatal period. Separately, between the mortality rates of the IVF and control singletons and the IVF and control multiples no significant differences were found.

The present study confirms earlier results of higher mortality (Koivurova, 2005), higher number of hospitalizations (Ericson et al., 2002, Källén et al., 2005c), increased risk of behavioural problems (Källén et al., 2005c), CP (Strömberg et al., 2002, Lidegaard et al., 2005, Hvintjørn et al., 2006), and infections (Ericson et al.,

2002) among IVF children. In accordance with an earlier Finnish study based on both outpatient and inpatient visits (Koivurova, 2005) a slightly, but not statistically significant, increased risk of diarrhea was found, but, contrary to that study, no increased risk of pneumonia was seen among the present IVF children.

Unlike previous studies (Strömberg et al., 2002, Lidegaard et al., 2005), no increased risk of CP or sleeping disturbances was found among the IVF singletons; in this study the excess risk of CP was mainly explained by multiplicity. Also in the studies by Strömberg et al. (2002) and Hvintjørn et al. (2006) the main reasons for the increased risk of CP were prematurity and the multiple pregnancy rate. A recent Swedish study could not confirm the increased risk of CP; the risk disappeared after adjustment to confounders (Källén et al., 2005c). Furthermore, contrary to an earlier Swedish study (Ericson et al., 2002), an increased risk for epilepsy, tumours, and asthma among the IVF children in total could not be found in this study. However, no increased risk of epilepsy was found in the recent Swedish study, either (Källén et al., 2005c).

A few previous studies have reported on childhood morbidity of IVF multiples. In two studies no differences in neurological sequelae were found (Strömberg et al., 2002, Pinborg et al., 2004a). In this study no increased risk of any specific disease among IVF multiples was found. However, the IVF multiples showed in general higher childhood morbidity than the IVF singletons.

To the knowledge of the present author, there are no other studies examining the use of long-term medication, child disability allowance, and utilization of institutional care among IVF children. A slightly increased risk of child disability allowance among the present IVF children was explained by multiplicity, while in the utilization of long-term medication and institutional care no statistically significant differences were found between the groups.

10.5 Costs and allocation of resources in IVF (Paper V)

The estimated mean cost of IVF treatment with embryo transfer was EUR 3750 (Paper V). Frozen embryo transfers were much cheaper, EUR 1100. Of the total IVF costs, 36% were due to drugs, 21% to interventions, and 42% to other direct costs.

During the mean 1.5-year follow-up, the total costs per treated woman were EUR 6500, of which EUR 40% was paid from private sources (by women themselves) and 60% from public sources. In the private sector, the share of private expenditure (out-of-pocket payment) was 49% and in the public sector 24% of the total expenditures. The unit costs of IVF did not vary much between the age groups, but the older the women were, the more they paid themselves. The women from the highest socioeconomic position spent more of their own money for IVF

treatment compared to the blue-collar women regardless of the age of the women. This was due to the more frequent use of private services.

The cost of a live birth was on average EUR 16 000 and increased by age (Table 12). Live-births were the most costly among the women using both sectors. The total expenditures of IVF per population were highest among the women aged 30–34 years and then decreased (Table 12) due to the lesser use of IVF among older women (Table 5). Because of the higher use of IVF, in every age group the total expenditure of IVF was approximately two-fold for upper white-collar women compared to blue-collar women (Table 12). No remarkable regional differences were found according to the urbanity of the living area.

In previous studies the cost calculations of the IVF cycles have included different components which vary between countries and therefore make the comparison of the calculations difficult. The cost estimates of a successful IVF cycle in this study are in accordance with an earlier Finnish study (Koivurova, 2005) as well as with earlier international cost calculations by age that have included the same components as used in this study (Broekmans and Klinkert, 2006).

In the present study only some of the actual costs were taken into account. Only routine radiological and laboratory tests were included, and all indirect costs, such as travel costs and sick leaves, were excluded. Furthermore, the costs of complications as well as the pregnancy and birth costs, which are known to be higher among older women, were not included. With the inclusion of all costs, the total costs may have been higher for the older women and possibly also for rural

TABLE 12. Total expenditure per live-birth and per female population in euros by age, socioeconomic position, and treatment sector.

	Total expenditure per live-birth					Total expenditure per population				
	Age					Age				
	20–29	30–34	35–39	40+	Total	20–29	30–34	35–39	40–49	Total
Socioeconomic position										
Upper white-collar	12133	13196	17785	38437	16126	97	200	167	49	113
Lower white-collar	12264	13496	16930	43308	15303	77	158	111	22	75
Blue-collar	14302	14694	20503	31840	16908	49	95	74	16	48
Others [a]	14082	14603	20392	59310	17342	14	33	20	8	16
Sector										
Public	13603	13373	17395	38766	14712	NA	NA	NA	NA	NA
Private	10588	11843	16170	40522	14877	NA	NA	NA	NA	NA
Both	20188	22581	26645	42832	23870	NA	NA	NA	NA	NA
Total	12851	13657	17828	40662	15941	44	116	88	21	55

[a] Entrepreneurs, students, pensioners, unemployed, and women with an unclassified or unknown position.

NA = not available

women due to the longer distances from care facilities. The impact on socioeconomic differences is unclear.

Among infertile women in the IVF care system, older women with poorer success rates (i.e. increased need) received more treatments, and the costs per live birth were much higher among them than among the younger women. The expenditures per population were lower among the older women, since fewer older women were treated. In this study no data of the population-based need for IVF and wish for a child by age were available, and therefore it is not certain whether all older women whishing to have a baby were in the IVF care system. It is also unknown how many of younger women wishing for a child did not receive IVF. In total, more resources were allocated to younger women, which is —due to the higher costs and an increased health risk of older women—a fairer solution than the provision according to the need by age. The women with a higher socioeconomic position had more often used IVF, and the total and societal costs per population were higher than among them compared to the women from lower socioeconomic positions, which indicates inequality.

11 General discussion

The present study was based on registers. In general, the utilization of existing health care registers in health research has several advantages. The total costs and time spent on data collection can be reduced, the collection of longitudinal data is technically easy, a large sample size is possible, no contact with the studied individuals is needed, participating problems can be abolished, and the reporting bias is reduced (Gissler, 1999), which leads to more reliable data than is received by questionnaire surveys. On the other hand, only health problems that are collected or registered can be studied. Furthermore, most of the health care registers are administrative registers, not planned for ad hoc epidemiological studies. Reporting and data collecting systems may vary, and no corrections can be made. Mostly the data of diagnoses are not exact, but crude estimates, and to adjust the register data to scientifically valid information demands a lot of pre-processing (Sund, 2003).

Originally the present study on the health of IVF women and their children was designed to be performed by using data from clinics, but the data could not be successfully collected (Hemminki, 2002). After that it was decided to collect all data of exposed women and children as well as their follow-up, from nationwide registers. This decision allowed a larger sample size, secure processing of high data, and easy follow-up.

The registries used in the present study are of high quality (Keskimäki and Aro, 1991, Teperi 1993, Gissler et al., 1995b). The identification of the cohorts of the IVF and OI women from the reimbursement records and of the IVF children from the MBR, including all infants born in Finland, was successful (Hemminki et al., 2003, Gissler et al., 2004).The existence of a unique personal identification number enables reliable linkages to other health care registers. The cohorts of the IVF and OI women and their children were large enough to study the frequency of even rare health problems after IVF and OI. The data on major congenital anomalies of all children were received from a routine nationwide register, of which information is collected and classified blindly in regard to the IVF status. In addition, reimbursed diseases for long-term medication are clearly defined, and both child disability allowance and support for long-term medication are based on recent medical documents. Therefore it can be assumed that the reimbursement records are relevant in estimating disease occurrence.

In the present study socioeconomic differences were found in the use of IVF services and in the allocation of resources, primarily due to the use of private services. In the identification process as well as in the follow-up several assumptions and estimations had to be made. It is possible that in 1996 some women who had received treatment in the public sector and had used drugs bought and reimbursed before 1996 were missed. Both the grouping of the IVF treatments into private and public sectors and the estimations of the costs were crude. However, the lack of data is estimated to be only about 4% of the IVF and 6% of the OI women (Hemminki et al., 2003), and it is not likely to be biased by age, socioeconomic position or region of residence. The socioeconomic position of the women was defined by using their occupation and classified automatically according to the national classification complied by Statistics Finland (Central Statistical Office of Finland, 1989). Thus, even though the data are not necessarily accurate for each individual, it seems that there was no systematic bias and the differences between the groups are correct.

In the present study the risk of complications for women after each IVF treatment cycle was low, but repeated attempts resulted in serious complications for many women and occurred much more often than after OI alone. Since the method of identification of serious complications and miscarriages was based on a register covering only hospital care, inpatient care, and operations in outpatient clinics, the identification of outcomes was dependent on the care practices and the style of the physicians to record the diagnosis. However, serious complications leading to hospital care could be collected extensively, but less serious cases—also cases needing special care but treated in private clinics or public outpatient clinics —are missing in this data. Thus, the results underestimate the actual complication risks. In addition, the effects on the psychosocial health of IVF and OI women could not be examined in this study.

Although the health of most IVF children in the present study was good, they had more health problems than the other children. The reason for not being able to estimate the occurrence of less serious diseases and cases was the same as among the women: the use of outpatient care is not registered. The results of the health of the children may be biased by different thresholds in hospital admissions between the IVF and control children. The IVF parents, who were more often first-time-parents, may have been more anxious, which can lead to more hospital admissions and longer duration of care. It might also be that IVF children are more carefully examined by physicians or their health problems are more conscientiously reported than those of naturally conceived children. However, several facts speak against this source of bias. Less rejected reports of congenital anomalies were found among the control children than among the IVF children. The rate of hospitalizations was not increased in all categories of diseases among the IVF children. In addition, the results after adjustment to parity and socioeconomic

position and the results in a subanalysis of the first births remained unchanged. Furthermore, informing and advising on the benefits are part of routine clinical practice. The higher frequency of hospitalizations and certain health problems very likely reflect higher morbidity among IVF children. In addition, almost every outcome studied was quite similar between the IVF and control multiples.

As Mooney (1994) pointed out, the first step in discussion on equity is to define the population in need. The need for infertility treatments derives from the wish for a child, the biological capacity to achieve a pregnancy, and the availability of technology, i.e. assisted fertilization. It is known that the biological capacity decreases by increasing age (Baird and Strassmann, 2000, Broekmans and Klinkert, 2004, ESHRE, 2005), and therefore the age-related biological need for IVF is be assumed to be higher among older women compared to younger ones. The need should not be affected by the socioeconomic position in Finland (Notkola, 1995, Klemetti et al., 2004), i.e. the biological need is assumed to be the same in the different socioeconomic positions. In this study no information of the wish for a child, neither by age nor by socioeconomic position, was available.

Despite the existing technology, all infertile couples do not seek medical care (Gunnell and Ewings, 1994, Schmidt and Münster, 1995, Stephen and Chandra, 2000, Malin et al., 2001, Klemetti et al., 2004), and the demand for infertility treatments may vary by age and socioeconomic position. It might be that older women and women from higher socioeconomic positions are more aware of the availability of treatments and more likely to demand them. In addition, recognition of fertility problems, attitudes towards health and medical treatment, social support, health status, and prior contacts and experiences with health care can vary between the groups (Tain, 2003, White et al., 2006). However, as Mooney (1994) pointed out, the need and demand for services should be distinguished in the equity analysis; access should be equal according to the need, not according to the demand, for services. In this study access could not be examined, but, instead, equity in the use of infertility treatments, i.e. among those who already were in the care system, was discussed among the present women.

The next step in the equity analysis is to ask to what extent priority should be given on infertility treatments. Although infertility treatments were not very highly prioritized by a multiprofessional group on the prioritization of medical care in Finland (STAKES report 161, 1994), infertility is considered a disease and defined as such by medical practitioners (CDBI, 2005). Since infertility is defined as a medical problem, a natural consequence—though not the only possibility—is to solve it with medical technology. After the first IVF birth in Finland in 1984, IVF technology was rapidly introduced into all Finnish university clinics (Malin Silverio and Hemminki, 1996). Also private clinics were founded by pioneer physicians. IVF has become a common practice in Finland, but prioritization has not been explicitly discussed. However, the utilization rate of IVF treatments in

Finland, being one of the highest in the Europe (Nyboe-Andersen et al., 2006), may indicate that infertility treatments are considered valuable and important. In addition, the Finnish system, in which infertility treatments are offered both in the private and public sector with some reservations (a couple with two biological children, risk of infections or either female or male partner sterilized) (STM, 2005) and with public funds, speaks on behalf of high prioritization of infertility treatments. However, it can be asked by whom (health care professionals, decision makers, health care consumers or the whole public) the priority of infertility treatments is set in Finland.

According to the present study, inequity in the use of IVF by the socioeconomic position was evident, mainly resulting from the use of the private sector. The services are not organised in an equal way if infertile women of lower socioeconomic position lack opportunity to use private IVF services despite their need (Whitehead, 1990). In Finland it has been traditionally considered unfair that people should have to utilise the private sector to obtain the health care services they need.

Inequality in resource allocation by socioeconomic position was also prevalent: more resources were allocated to the higher socioeconomic groups compared to the lower ones. In this study the personal preferences (Mooney, 1994) could not be studied. However, if fewer resources were allocated to blue-collar women, because they were not willing to use IVF services as often as white-collar women, this differentiated allocation cannot be considered an inequality. On the other hand, women form a higher socioeconomic position used more own money for treatments. It can, however, be argued that those who are able to pay should have the freedom to allocate their own resources as they like. But due to scarcer resources (the same resources i.e. the same physicians work both in the public and private clinics, and, for example, complications leading to hospital care are treated in public clinics regardless of the treatment sector) and the unique Finnish system, in which private treatments are also partly covered, it can be asked whether this argument is applicable—especially considering the treatment of the other women. On the other hand, in spite of the coverage, the private expenditure remains higher, i.e. more own money is needed for treatments in the private sector. According to the review by Dawson et al. (2005), the most common reasons for refusal of IVF treatment have been financial. In this study it was not possible to examine the reasons for the use or non-use of IVF. Neither was it possible to study whether the treatments or the quality of care varied with different socioeconomic positions. In France, despite equal use of IVF, a deeper analysis showed that women from lower positions faced greater risks and lower benefits (Tain, 2003). The author asked whether 'social inequality is being reinforced with the experimentation of new technologies'. Poorer success (benefit) among the blue-collar women in this study may be related to more serious infertility: infertility-related risk factors such

as smoking, obesity (Helakorpi et al., 2001), and probably increased likelihood of genital infections.

In the case of IVF, the differences in age are a more complex and non-traditional equity issue than those between the socioeconomic groups. Is it equitable that in IVF treatment, as in other health care services, the 'sickest' (older women) receive more care—or would it be more equitable to treat women with the best possibility of achieving pregnancy, for example younger women with specified causes of infertility (Mooney, 1994, Neumann, 1997)? In this study the older women of a higher socioeconomic position received more intensive treatment. In the private sector the number of treatments was not age-dependent, but in the public sector the women younger than 40 years of age received more cycles than the older women. This can be a sign of adequate resources and an ability to respond to the need and demand in the private sector, but it might also be a sign of growing commercialism. The success or effectiveness of IVF decreased by increasing age, which speaks against the option of concentrating on treating older women. On the other hand, concentrating on treating younger women can lead to over-treatment (Gnoth et al., 2005). Age-restrictions set in the public sector have reduced waiting lists and conserved public health care resources. It can also be argued that age should not be a reason to turn women away from IVF, because for older women IVF may offer the last chance to become pregnant (Klipstein et al., 2005). However, the costs of live-births among the older women were over three-fold compared to the younger women. Thus, it can be asked whether treating older women is replacing the treatment of younger women and the resources of their treatment, and, if so, whether it is equal.

When discussing access and equity in the use of services, health risks should also be taken into account (Blank, 1997). Pregnancy and birth complications as well as poorer foetal outcome increase by age (Nybo Andersen et al., 2000, Salihu et al., 2003). Furthermore, as shown in the present study, there are IVF-related risks for treated women (serious complications leading to hospitalization) and their children (more health problems), which have to be considered in equity discussion. Also the safety of the new technologies in assisted fertilization is an issue still under debate (Peters, 2004). The use of ovulation induction should be considered carefully. According to the unpublished data by the present author on OI children, ovulation induction contributes to some health problems among children born after OI. From a public health perspective it would be wise to concentrate on treating women in the usual childbearing age, equally in all socioeconomic positions respecting the women's own preferences and to offer IVF treatment for medical reasons only after careful patient selection. Treating sexually transmitted infections at an early stage and encouraging couples to have children at a younger age than nowadays (to avoid potential fertility problems) may, in the future, play a significant role in the prevention of infertility. In addition, treatment costs cannot be ignored in equity discussion.

IVF has offered hope for a number of infertility couples and fulfilled their wish for a child. In this study 40% of the treated IVF women received a child. Other potential benefits of IVF could not be examined in this study. An ideal situation would be the one with healthy singletons without serious health complications neither in child nor mother, or infertile couples satisfied after finding solution for their infertility, either infertility treatment (with or without child), a child via adoption or decision to live contently without children.

The advancement of assisted fertilization has aroused many other questions of the equity and resource allocation than those related to age and socioeconomic position or efficacy and safety of treatments. It has also created a doubtful "baby market" which is characterised by the limits of science, an unmet demand due to the high cost of IVF, and a political system lacking sufficient legalisation (Spar, 2006). Increased marketing can lead to the use of AF earlier than necessary (Mitchell, 2002). In Finland the number of IVF treatment cycles has grown (IVF statistics, http://www.stakes.info/2/1/2,1,4.asp.), there is an increased competition for clients, and IVF has become commercialised as in other countries. So-called reproductive tourism (Blyth and Farrand, 2005) from other countries to Finland has been claimed to be a natural consequence of the permitting situation without legislation. The coming Finnish law is the most permissive one in the Nordic countries, though with some exceptions (for example assisted reproduction allowed for single women in Finland) in line with the Swedish law (Legislation..., 2005). Thus, the reproductive tourism may still continue but will not play a significant role in the use of AF in Finland.

The present study has both clinical and political implications. To avoid overtreatment infertility should be defined in line with the WHO definition: two years without conception, especially among women under 35 years of age. In IVF, transferring only one embryo whenever possible and treating women in the usual childbearing age reduce health problems both in pregnant mothers and their children. Information of the potential health effects and of the chances of having a baby at a certain age are, should be useful for couples seeking medical help for infertility.

Policy implications are to encourage health promotion institutions and experts to give information of the declining fertility by age as well as the complexity of IVF, since IVF is not an equal option to natural conceiving. The policy makers should make resource allocation for high technology transparent and openly discuss the issue of equity.

Additional implications for further studies include examining the short- and long-term health of OI children and the long-term health of IVF children. Studies on puberty and own fertility of IVF and OI children are lacking. Furthermore, it is of importance to examine the long-term health of IVF and OI women (for example cancers and psychosocial health). A deeper analysis of the use and non-use of IVF by different women's background characteristics would be useful for discussing whether equity prevails in infertility services in Finland.

12 Conclusions

1. Although the health of most IVF children was good, they had more health problems than the other children. As this was partly explained by multiplicity, reducing the number of transferred embryos would improve the health of IVF children.
2. Further studies are needed to explain the poorer health of IVF singletons and to examine the long-term health of IVF children as well as the health of children born after ovulation induction alone.
3. The risk of complications for women after each IVF treatment cycle was low, but repeated attempts resulted in serious complications for many women, and the complications occurred much more often than after OI alone.
4. Further studies are needed to examine the long-term health of IVF and OI women.
5. The socioeconomic differences in the use of IVF were due to the use of private services.
6. More resources were used by women from a higher socioeconomic position, adjusting to age.
7. Older women were treated more intensively; the distribution by need could not be studied.
8. The live-births of older women were much more expensive than those of younger women.

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APPENDIX. Health outcomes of IVF and OI women and IVF children; definitions, follow-up times, and data sources.

Outcome	Definiton	Follow-up time	Data source
Women			
OHSS	Diagnoses in ICD-10 [a] and length of hospitalization	120 days [b]	HDR
Potential OHSS			
Bleeding			
Infection			
Other complications			
Misscarriage	Diagnoses in ICD-10 and operation codes	240 days	
Ectopic pregnancy			
Death	Date of death and cause of death (ICD-10)	Mean 3.7 years for IVF and 3.8 years for OI	Cause-of-Death Register
Children			
Preterm	< 37gestation weeks	until 7 days after birth	MBR
Very preterm	< 32 gestation weeks		
Low birth weight	< 2500 g		
Very low birth weight	< 1500 g		
Special care	Treatment in intensive care unit or in newborn surveillance unit.		
Respiratory treatment	Respiratory treatment used		
Apgar scores	One minit scores 0-10		
Hospitalization	7 or more days after birth		
Stillbirth	Death from the completed 22nd gestational week onwards or if birth weight is ≥ 500g.		
Perinatal mortality	Stillbirths and death < 7 days from birth / 1000 live births		
Major congenital anomaly	A major congenital structural anomaly, chromosomal defect, or congenital hypothyroidism	until 1 year	RCM
Use of hospital services	Hospital episodes in the HDR	until 4 years	HDR
Length of hospitalization	Days		
Long-term medication	Support for long-term mecdication received	until 2 years	SII
Child disablity allowance	Child disability allowance received		
Childhood mortality	Deaths after perinatal period and ≤ 2 years / 1000.		Cause-of-Death Register
Cerebral palsy	ICD-10: G80	until 2 years	HDR
Epilepsy	ICD-10: G40-G41		
Behavioural disorders	ICD-10: F80-F98		
Diabetes	ICD-10: E10		
Asthma	ICD-10: J45-J46		
Allergy	ICD-10: L20-L23, L27, L50		
Diarrhoea	ICD-10: A08-A09		
Pneumonia	ICD-10: J12-J18		

[a] ICD-10 codes in Paper II.
[b] Days after the last reimbursement.

Original Articles I–V

Paper I

ORIGINAL ARTICLE

Taylor&Francis healthsciences

Equity in the use of IVF in Finland in the late 1990s

Reija Klemetti, Mika Gissler and Elina Hemminki

STAKES, National Research and Development Centre for Welfare and Health, Health Services Research, Helsinki, Finland

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Aims: The purpose of this study was to describe equity in the use of *in vitro* fertilization (IVF; including micro-injections and frozen-embryo transfers), and compare its use with that of other assisted reproduction technologies (other ARTs; including ovulation inductions with or without inseminations). *Methods*: The women who received IVF ($n=9$, 175) and other ARTs ($n=10{,}254$) between 1996 and 1998 were identified from the reimbursement records of the Social Insurance Institution (SII) covering all Finns. Population controls, matched by age and municipality, were selected for IVF women ($n=9{,}175$). Information concerning background characteristics came from the Central Population Register and the SII's reimbursement files. The sector (public vs. private) was defined using prescribing physicians' codes. IVF use was studied by the proportions of women treated and the frequency of treatment. *Results*: The age-standardized IVF incidence per thousand 20-to-49-year-old women was 8.8 in urban and 7.3 in rural areas, but the use of other ARTs did not vary correspondingly (9.2, 9.3). The regional incidence of IVF and other ARTs varied considerably. In the private sector, women in the highest socioeconomic position were over-represented (29% private, 18% public, 16% controls). During the mean 1.5 years of the study period, the IVF women had somewhat more treatment cycles in the private than in the public sector (mean 3.3, 2.7), and those in the highest socioeconomic position had more cycles than others (3.5, 3.2); the frequency was not age-dependent. In the public sector the number of cycles did not differ by socioeconomic group (mean 2.7–2.8 per woman), and women aged 25 to 39 had more cycles than others. *Conclusion*: There were socioeconomic differences in use of IVF services, but they were small because of the equitable use of public services.

Key words: equity, infertility treatment, IVF, private sector, public sector.

Reija Klemetti, PO Box 220, 00531 Helsinki, Finland. Tel: 358-9-3967 2265, fax: 358-9-3967 2496. E-mail: reija.klemetti@stakes.fi

INTRODUCTION

Infertility is common (1), and IVF (including micro-injections and frozen-embryo transfers) has become a universal infertility treatment. According to statistics published by the European Society of Human Reproduction and Embryology, the greatest availability of IVF services among 18 European countries was reported in Finland and Denmark (2). In 2001, approximately 2.5% of all Finnish newborns were born as a result of IVF. The number of children born with the help of other assisted reproduction technologies (called here other ARTs) is unknown.

It is generally believed that IVF services are unevenly distributed, and that urban women from upper social classes use these services more than rural women from lower social classes. However, there are few reliable data on the use and users of IVF or other ARTs. In Finland, the 19 IVF clinics were situated in eight towns in 1999 (3). Three out of 12 of the pre-1995 provinces studied had no IVF clinic. Women in some areas had to make long trips (as much as 700 km) to obtain IVF treatment. Other ARTs services were available in all parts of Finland.

Unlike the rest of the health service system in Finland, the private sector is an important provider of IVF; about 60% of all IVF services are supplied by private clinics (3). In 1999, 12 of the 19 clinics were private. In the public sector, patients pay a small fee for their visits, and the rest of visit costs are covered by the tax-financed healthcare system. In the private sector, patients pay significantly more for their visits, but about 60% of the physician's charges are reimbursed by the Social Insurance Institution (SII). About 50% of the drugs used in infertility treatments are reimbursed by the SII in both the public and private sectors. Despite public financial support, IVF treatments are still costly for women, especially in private clinics (4). During 1996–98 on average five IVF cycles were needed to achieve one live birth (Mika Gissler, personal communication). Frozen-embryo transfers are cheaper but more cycles are needed to achieve one live birth.

The aim of this study was to investigate equity in

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the use of IVF in Finland in 1996–98, and to compare it with the use of other ARTs. The use of IVF was studied both by the percentages of women treated and the frequency of treatment (cycles per woman).

MATERIALS AND METHODS

In Finland, IVF, artificial insemination and ovulation inductions are performed in outpatient clinics but in most cases the treatment involves prescribed drugs. Using reimbursements for drugs and infertility interventions in private clinics in the SII files, a cohort of women who had had at least one IVF treatment (*in vitro* fertilization without embryo transfer, *in vitro* fertilization with embryo transfer, or preparations for frozen-embryo transfer, $n=9{,}175$), and women who had had other infertility treatments including drugs (ovulation inductions with or without artificial insemination, $n=10{,}254$) between 1996 and 1998 in Finland were identified, by means of a pre-designed algorithm. The algorithm was based on the fact that some drugs or their combinations, sequence, and dosages are specific to infertility treatments. With the patient advice of IVF clinics, scientific literature, Finnish drug catalogues, and discussions with infertility physicians, we created an algorithm for drugs used in different infertility treatments (unpublished data from Hemminki et al., STAKES, 2003).

If an intervention in the IVF cycle involved reimbursement by the SII, the cycle was defined as having taken place in the private sector. For the other IVF cycles the classification of cycles as private or public was made according to the main work place of physicians given in a catalogue of physicians (STAKES, 1998). The classification was crude because we were not always able to define the main work place. The other ARTs cycles could not be classified as private or public.

Population controls, matched by age and municipality, were randomly selected for IVF women ($n=9{,}175$) from the SII population record (covering the total Finnish population).

Information on the women's background characteristics was obtained from the Central Population Register (CPR) and from the reimbursement files of the SII. According to the municipality of residence, the women were divided into urban, semi-urban, and rural groups. To calculate the age-specific incidences, the number of women treated was divided by the number of all women in the same age group in the same area (SOTKA database 2001, STAKES). The age adjustment was made by using direct age-standardization.

The socioeconomic position of the women was defined by using their own occupation (5): unknown, upper white-collar workers, lower white-collar workers, blue-collar workers, entrepreneurs, students, pensioners, and others, including unemployed women and women with an unclassified position. In the analysis, the four last categories were combined. Marital status (from CPR) at the beginning of the treatment was defined by the starting and ending dates of marriages, and there were five categories: non-married, married, divorced, widowed, and unknown. There was no information on cohabitation.

To study the frequency per woman of IVF treatment, data on women with at least one IVF treatment in 1997 ("1997 IVF data", $n=4{,}909$) were analysed. All cycles of these women in the years 1996–98 were included, and the number of treatment cycles per woman during the study period (range 0.5–3.0 years, mean 1.5 years, assuming an even distribution of first cycles in 1996–98), was calculated.

Tests for relative proportions, *t*-tests, chi-square tests, and one-sided analysis of variance were used to measure statistical significance. A *p*-value of less than 0.05 was considered significant. The statistical analyses were mainly performed using SPSS, version 10.

RESULTS

Characteristics of IVF women, other ARTs women, and population control women are presented in Table I. The IVF women were older than the other ARTs women (mean age 33.4 vs. 31.1 years). Women who had received any infertility therapy were more often married than the population controls were. A fifth of the women treated were never married.

There were more women in the highest socioeconomic category among IVF women than among control women (Table I). The upper white-collar women underwent IVF treatments at older ages than the other women (34.5 years for upper white-collar vs. 33.3 for lower white collar vs. 32.3 for blue-collar), measured either by age distribution (data not shown) or by mean age.

The age-standardized incidence of IVF, calculated per thousand 20-to-49-year-old women varied by region from 6.5 (in eastern Finland) to 9.2 (in the capital area in southern Finland). The age-standardized incidence of other ARTs varied by region from 5.2 (in eastern Finland) to 12.7 (in northern Finland). Women from the capital area underwent IVF and other ARTs treatment at older ages than women in other parts of Finland. When the use rates of IVF and other ARTs were combined, infertility treatments were significantly more common in one region of northern Finland and in the capital area than in the

Table I. *Background characteristics of IVF women, Other ARTs women and population controls* in 1996–98 in Finland, (%)*

	IVF (n=9,175)	Other ARTs (n=10,254)		Controls (n=9,175)	
Age group					
20–24	3.5	11.0		3.5	
25–29	20.8	31.4		20.8	
30–34	35.2	31.5		35.2	
35–39	27.7	17.8		27.7	
40–44	10.8	6.9		10.8	
45+	2.0	1.4		2.0	
Unknown	0.0	0.0		0.0	
Total	100.0	100.0	*p<0.001*†	100.0	*p=1.000*§
Marital status					
Non-married‡	22.3	19.1		36.1	
Married	69.4	72.5		56.7	
Divorced	7.9	7.9		9.4	
Widowed	0.4	0.5		0.4	
Unknown	0.0	0.0		1.4	
Total	100.0	100.0	p<0.001†	100.0	p<0.001§
Socioeconomic position					
Upper white-collar	25.3	20.6		16.3	
Lower white-collar	48.5	48.7		45.7	
Blue-collar	16.2	18.0		19.3	
Others	7.9	10.0		12.3	
Unknown	2.1	2.7		6.4	
Total	100.0	100.0	p<0.001†	100.0	p<0.001§

*Population controls for IVF women, matched by age and muncipality.
†P-values for χ^2-tests (IVF women and Other ARTs women).
‡Includes cohabitation. Divorced and widowed women can also live in cohabitation.
§P-values for χ^2-tests (IVF women and controls).

country as a whole. The northern region had no IVF clinic, and the use of other ARTs was common.

There was a small but statistically significant difference in the total use of IVF between urban and rural women (test for relative propositions $p<0.001$, Table II). Adjustment by age did not change the result. When the data were examined by age group, the difference remained only among women over 35 years old ($p<0.001$). The total use of other ARTs was also more common among urban than rural women, but after age adjustment, the difference disappeared; the use was most common among semi-urban women. When the use of IVF and other ARTs was combined, infertility treatments were more common among urban ($p<0.001$) and semi-urban ($p<0.001$) women than among rural women.

Some 53% of IVF women received all their IVF treatments from private doctors (“private users”), 35% from public doctors (“public users”), and 12% from both private and public doctors (“both-sector users”, Table III). The private users were older (mean age 34.3 years) than public users (32.3 years) and both-sector users (32.8 years, $p<0.001$). Most women in both the private and the public sector category were

Table II. *Raw and age-standardized incidences per 1000 20-to-49-year-old women for IVF and Other ARTs women†, by urbanity*

	Raw rates		Age-standarised rates	
	IVF (n=9,136)	Other ARTs (n=10,207)	IVF (n=9,136)	Other ARTs (n=10,207)
Urban	8.7	9.4	8.8	9.2
Capital	9.7	8.8	8.9	8.5
Other	8.5	9.7	8.5	9.5
Semi-urban	7.9	9.9	8.2	10.4
Rural	7.0	8.7	7.3	9.3
Total	8.3	9.3	8.3	9.3

†Women over 49 years, women living abroad and women whose place of recidence is unknown are excluded.

Table III. *The distribution of IVF women by socioeconomic position and by care site (%)*

	Only private (n = 4,809)	Both sectors (n = 1,118)	Only public (n = 3,225)
Socioeconomic position			
Upper white-collar	29	29	18
Lower white-collar	48	48	50
Blue-collar	14	15	20
Others	7	6	9
Unknown	2	2	3
Total	100	100	100

For χ^2-test (socioeconomic position and sector) $p < 0.001$.

between 30 and 39 years old, but younger age groups were larger and older age groups smaller in the public than in the private sector; 19% of private sector users and 5% of public sector users were aged 40 years or more.

The private and both-sector users were more often women in the highest socioeconomic groups than were the public users (Table III). In the public sector, women in the highest socioeconomic position were not over-represented when compared with population controls (Table I).

The background characteristics of women in the "1997 IVF data" did not differ from that of IVF-treated women in total. During the examination period (estimated average 1.5 years), the mean number of IVF cycles was 3.3 (Table IV). The mode was two, and the maximum number was 14 cycles. A quarter of the women underwent five or more IVF cycles. In the private sector, the number of IVF cycles was higher than in the public sector, and in the private sector the number did not depend on a woman's age. In the public sector, the youngest and the oldest women did not undergo as many IVF cycles as other women. In all age groups, more women underwent five or more IVF cycles in the private than in the public sector. Both the number of IVF cycles and the number of women undergoing five or more cycles were highest among both-sector users.

Women in the highest socioeconomic group underwent more cycles than women in the other socioeconomic groups (mean 3.5 for upper white-collar vs. 3.3 for lower white-collar vs. 3.2 for blue-collar group). The number of cycles was age dependent only among the women from the highest socioeconomic position; 40-to-44-year-old women underwent more cycles than the other women (data not shown). In the private sector, women from every socioeconomic group had more IVF cycles than in the public sector but the users of both sectors had most IVF cycles. Socioeconomic position had no impact on whether women underwent five or more cycles in the public sector but it had some impact in the private sector.

Overall, the frequency per woman of IVF treatments was the same for urban, semi-urban, and rural women as well as in different regions (data not shown).

DISCUSSION

There are two main questions that are asked when one discusses equity in infertility: first, what priority

Table IV. *Mean number (standard deviation) of treatment cycles in 1996–98 of IVF-women† who had at least one treatment cycle in 1997 by care site, and the proportion of women with 5 or more cycles*

	Age in years						
	20–24 (n = 163)	25–29 (n = 1,048)	30–34 (n = 1,765)	35–39 (n = 1,308)	40–44 (n = 540)	45–49 (n = 77)	Total‡ (n = 4,901)
Care site							
Only private (n = 2,457)	2.8(1.9)	3.3(2.1)	3.3(2.1)	3.3(2.0)	3.4(2.2)	3.0(2.1)	3.3(2.1)
Only public (n = 1,620)	2.6(1.5)	2.8(1.6)	2.7(1.5)	2.7(1.6)	2.5(2.3)	1.4(0.6)	2.7(1.6)***
Both sectors (n = 824)	3.6(1.6)	4.6(1.9)	4.6(1.8)	4.5(2.0)	4.6(1.8)	3.3(1.0)	4.6(1.9)*
Total	2.7(2.0)	3.5(2.2)	3.3(2.0)	3.3(2.0)	3.3(2.0)	2.9(1.7)	3.3(2.0)**
≥5 cycles, %§							
Only private	19	26	24	25	26	18	24
Only public	0	9	15	13	12	15	13
Both sectors	0	46	44	48	48	19	46
Total	17	25	24	24	26	14	24

†Women living abroad and women whose place of recidence is unknown are excluded.
‡For one-sided analysis of variance *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
§For χ^2-test (age and care site of women undergone 5 or more cycles) $p < 0.001$.

should be given to infertility services; and second, how scarce healthcare resources can be distributed equitably and with maximum benefit to public health (6). In addition, issues of reproductive rights, safety, efficacy, and access to infertility services have been discussed (7). Access to services is linked to the funding of services. Economic status, information on available programs and morality (8), and geographical variations, age, marital status, and sexual orientation of women (7) have also been issues. Our study provides answers to some of these questions as they apply to equity in the use of IVF in Finland.

The first main finding of our study was that the differences between socioeconomic groups were relatively small. Additionally, the observed differences were mainly a consequence of the use of the private sector. The third finding was that although the IVF clinics were unevenly distributed geographically in Finland, the distribution of women receiving IVF treatment was less skewed. The finding that differences were due to use of the private sector suggests that the supply and cost of IVF treatments are likely to create inequalities.

Can these results be trusted? A potential weakness of our study lies in the accuracy of exposure, constructed from reimbursement files. Despite the complexity of the process, the identification went well, the high quality of register data and the existence of a unique personal identification number suggest that the identification of women was not biased by their social class or region of residence (unpublished data from Hemminki et al., STAKES, 2003, unpublished data from Gissler et al., STAKES, 2003).

Our findings concerning the over-representation of women from the highest socioeconomic group are in line with those of some earlier studies from Canada and Australia (6), the United States (9), the United Kingdom (10) and France (11). In the United States in 1995, college graduate women were more likely to have received infertility services – but not assisted reproductive technology – than other women; but the total number of women being treated by means of assisted reproductive technology was very small (12). A recent Swedish study found no clear trend with regard to the level of education of IVF mothers (13). However, the Swedish study included only successful treatments, whereas our study included all treatments, a fact which may explain the difference between the two studies. It is possible that treatments of women in the highest socioeconomic position are less successful, because these women resort to IVF services at an older age than others. However, it is also possible that widespread use of IVF eliminates socioeconomic differences in countries using public resources to provide IVF.

There are few reliable data concerning the need for infertility services in different socioeconomic groups or geographical areas. One Finnish study indicates no significant socioeconomic or regional differences in infertility rates but it suggests that secondary infertility could be more common among women from the highest socioeconomic group, and primary infertility in southern Finland (1). On the other hand, because smoking and obesity, which have been linked to infertility, are more common among women from lower socioeconomic groups (14), the need for infertility treatment may be greater among them.

Easy availability may increase the use of services, and the uneven geographic distribution of IVF clinics can create inequalities. Because the regional differences were not great, it seems that long distances are no object; women are prepared to travel to obtain IVF treatments. The use of all infertility services was common in the capital area, where many clinics are situated and distances to clinics are short. On the other hand, use was even more common in one region of northern Finland where long distances are involved. Reimbursement of travel expenses by the SII may somewhat decrease regional inequalities.

In our study, over-representation of women in the highest socioeconomic position was found only in the private sector. Furthermore, in the private sector, the IVF-treated women underwent more cycles than women in the public sector. The larger number of cycles cannot be explained solely by age, because the difference was also found in the age-specific analysis. Nor can it be explained by the type of cycle: equal proportions of frozen-embryo transfers and IVF cycles are performed in private clinics. A higher number of cycles in the private sector can be a sign of effectiveness and an ability to respond to demand but also a sign of growing commercialism. In the United States, the growing numbers of fertility specialists and clinics have increased competition for clients, and some consider the marketing of infertility services aggressive (15). Increased marketing can lead to the use of ARTs earlier than used to be the case – perhaps unnecessarily. Although in Finland the number of IVF clinics and the number of treatment cycles stabilized in the late 1990s after a growth period during that decade (3), there *is* competition for clients, and IVF has become commercialized in Finland as well as in other countries.

The public sector made the use of services more equitable for different socioeconomic groups, even though it could not compensate for socioeconomic differences created in the private sector. On the other hand, if the private sector did not offer IVF services, the social class differences might be smaller but

waiting lists might be longer, and the total number of treatments and women treated would be smaller.

"Both-sector users" were an interesting group in our study. They were not too old or "sick" to receive treatment in the public sector, and they evidently had enough money to purchase care in the private sector. We did not study the order of IVF treatments (private or public first), and we do not know the reasons for infertility among these women. It is possible that treatments were less successful, because these women underwent so many cycles. Some of these women may have little or no chance of becoming pregnant, but they do not stop trying to have a baby. The number of cycles did not depend on the socioeconomic position of women, which suggests that care was experienced as important and useful.

Differences in rates of utilization of healthcare services do not automatically mean that they are inequitable (16). However, if the over-representation of higher socioeconomic groups in our study is due to the fact that infertile women in the lower socioeconomic position do not have the opportunity to use IVF services, then services are not organized in an equitable way. In Finland it has also traditionally been considered unfair that people should have to use the private sector to obtain the healthcare services that they need.

It is a common ethical principle that access to care should not be affected by socioeconomic position or region of residence. In the case of IVF, differences involving marital status and age are a more complex and non-traditional equity issue. In many countries, infertility services are limited to married or heterosexual couples (17). In Finland, IVF is not legally restricted, and in our study a fifth of the women treated were not married. However, we do not know how many of the single, divorced, and widowed women in our study were cohabiting and how many were really single. If IVF services are offered to single or lesbian women who are not infertile, i.e. have no medical reasons to undergo IVF, and if equal access is understood to cover all persons who ask for treatment, we are no longer dealing with a health issue but a social issue.

Our study found that in the private sector older women were treated more than in the public sector. Some of the women treated were aged over 50 years but their number was very insignificant. The differences can be explained by an informal age limit that the public sector has introduced. Many other countries have legal age limits for IVF (7). Supporters of age limits base their arguments on the lower success rates and increased maternal and fetal morbidity and mortality among older women (17). However, it has also been argued that age limits are a violation of human rights (7), and that late motherhood means a higher level of financial and professional security and greater motivation in fulfilling the role of a parent (17). From the health perspective, it would be better to concentrate on treating women in their normal fertile age in order to minimize the adverse health effects for mothers and children due to advanced maternal age. Age restrictions also reduce waiting lists and conserve public health care resources.

With regard to equity in IVF use, many important questions remain open. Is it equitable that in IVF treatment, as in other health care services, the "sickest" (i.e. those for whom becoming pregnant is the most difficult) receive more care, as do the 40- to 44-year-old women in the highest socioeconomic position in our study? Or would it be more equitable to treat women with the best possibility of achieving success, for example younger women with specified causes of infertility (18)? How can the scarce health care resources be equitably distributed between IVF and other health care services? Currently it is difficult to estimate what is best and most equitable, since the health effects of IVF on women and children are largely unknown. As Svensson and Stephenson (6) have pointed out, it is important to study the safety and efficiency of IVF in order to help decide what constitutes equity in the use of IVF.

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Paper II

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Complications of IVF and ovulation induction

Reija Klemetti[1,3], Tiina Sevón[1], Mika Gissler[2] and Elina Hemminki[1]

[1]Research on Practices and [2]Information Unit, STAKES, National Research and Development Centre for Welfare and Health, Helsinki, Finland

[3]To whom correspondence should be addressed: STAKES, P.O.Box 220, 00531 Helsinki, Finland. E-mail: reija.klemetti@stakes.fi

BACKGROUND: The frequency and importance of complications of IVF and other ovulation induction (OI) are poorly known. We examined the occurrence of serious complications and miscarriages leading to hospitalization or operation after IVF (including microinjections and frozen embryo transfers) and OI treatment (with or without insemination). METHODS: Women who received IVF (*n* = 9175) or OI treatment (*n* = 10 254) 1996–1998 in Finland were followed by a register linkage study until 2000. RESULTS: After the first IVF treatment cycle, 14 per 1000 women had a serious case of OHSS (ovarian hyperstimulation syndrome), with 23 per 1000 throughout the study period (mean of 3.3 treatments). The corresponding values after OI were very low. The rates of registered ectopic pregnancies and miscarriages after IVF were nine and 42 respectively per 1000 women, with corresponding rates after OI of eight and 42. Infections and bleeding were not common after IVF and even rarer after OI. Overall, 15% of IVF and 8% of OI women had at least one hospital episode during the study period. CONCLUSIONS: Though there was a low risk of complications after each IVF treatment cycle, repeated attempts resulted in serious complications for many women, and these occurred much more often than after ovulation induction alone.

Key words: complications/IVF/OHSS/ovulation induction/register-based study

Introduction

Impaired fertility has increasingly become a health service issue because of the availability of new treatments, especially IVF and its related procedures, such as ICSI and frozen embryo transfer (FET) (called here IVF). Older treatments, including ovulation induction with or without insemination (OI), are still in wide use. In Finland, currently ~5% of infants are born as a result of IVF or ovulation induction (Gissler, 2003). According to our unpublished data, the estimated yearly number of treatment cycles between 1996 and 1998 was 8200 for IVF and 6550 for OI, compared to 1320 and 1360 resultant births per year.

The novelty of IVF has attracted a large number of studies on the health of the newborn (Helmerhorst *et al*., 2004), but less is known about the long-term health effects of IVF on children (Hampton, 2004) or about the health effects on the women. Complications can occur during the ovulation induction, the oocyte collection procedure, and post-operatively. The pregnancy achieved can be ectopic (embryo outside the uterus) or heterotopic (embryo both in and outside the uterus), and it can end in a miscarriage.

Ovarian hyperstimulation syndrome (OHSS) is considered the most serious complication of ovulation induction. It can vary from being a mild illness to a severe, life-threatening disease requiring hospitalization. OHSS can occur as soon as a few days after receiving HCG ('early OHSS') or later ('late OHSS'). Multiple pregnancy has been shown to be associated with a higher risk of late OHSS (Mathur *et al.*, 2000). The incidence of severe OHSS has been reported to vary from 0.7 to 1.7% per initiated cycle (Bergh and Lundkvist, 1992; Serour *et al.*, 1998; Westergaard *et al*., 2000; Nyboe Andersen *et al*., 2005). Some case reports (Cluroe and Synek, 1995; Koo *et al.*, 2002), studies (Bergh and Lundkvist, 1992; Serour *et al*., 1998; Abramov *et al.*, 1999a), and reviews (Whelan and Vlahos, 2000; Delvigne and Rozenberg, 2003; De Sutter, 2004) describe some serious aspects of OHSS, such as thromboembolic events, pulmonary manifestations, and death, but the magnitude of the risk is unclear.

The frequency of IVF complications other than OHSS has been only sporadically reported. For oocyte collection, bleeding has been reported in 0.03–0.5% and infections in 0.02–0.3% of embryo transfers (Bergh and Lundkvist, 1992; Nyboe Andersen *et al.*, 2005). Two to 5% of IVF pregnancies have been reported to be ectopic and 0.1–0.3% heterotopic, and estimates of IVF pregnancies ending in miscarriage have varied from 15 to 23% (Roest *et al.*, 1996; Serour *et al.*, 1998; Westergaard *et al.*, 2000; Kupka *et al.*, 2003; Schieve *et al.*, 2003; Bryant *et al*., 2004).

Most studies reporting complications after ovulation induction with or without insemination are based on old data (St Clair Stephenson, 1991; Venn *et al.*, 1994), and the frequency of OHSS after OI is unknown (Unkila-Kallio, 2001). In one small clinical study, the OHSS hospitalization rate per initiated cycle was 0.07% (Quasim *et al*., 1997).

Even though various adverse effects of IVF and OI on treated women have been identified, many of the published

studies and reports are deficient. They are based on old data, voluntary reporting, or a small number of cases or treatment cycles and concentrate on only one complication, or they lack information on the severity of the complications. The purpose of this study is to estimate the frequency of serious complications and miscarriages following IVF and OI. The criterion of seriousness is the need for hospital care, either in the form of hospitalization or an operation at a hospital outpatient clinic. This study is the first extensive study examining the different serious complications of both IVF and OI.

Materials and methods

The study is a historic cohort study based on prospectively collected register data on the following two exposed cohorts: 20–59 year old women having had IVF treatments (IVF, ICSI and FET, n = 9175) and women having had other infertility treatments including drug-based treatments (ovulation inductions with or without artificial insemination, OI, n = 10 254) between 1996 and 1998 in Finland. The women were identified with a pre-designed algorithm using the reimbursement files of the Finnish Social Insurance Institution (SII) (Hemminki *et al.*, 2003). Population controls, matched by age and municipality, were randomly selected for IVF women (n = 9175) from the SII population record (which covers the entire Finnish population).

The data included detailed information on the use of infertility drugs, including dates of prescription and purchase. The beginning of a cycle was defined by the date of the first purchase of the drug. All drugs bought within 35 days of the first purchase were considered part of the same treatment cycle with the exception of clomiphene citrate; a new prescription of clomiphene was considered the beginning of a new cycle regardless of the time interval. Consecutive cycles without a new prescription could not be separated.

The women's background characteristics were obtained from the Central Population Register, information about care episodes in hospitals from the Hospital Discharge Register (HDR), and dates and causes of death from the Cause-of-Death Register. The HDR collects information on inpatient care as well as on those visits to outpatient clinics that included an operation. It gathers information on diagnoses (10th revision of the International Classification of Diseases, ICD-10), operation codes, and dates of admission and discharge. The diagnoses include the main diagnosis (which can consist of separate diagnoses of the reasons and the symptoms leading to hospitalization) and two secondary diagnoses (which can also also consist of two separate diagnoses of the reasons and the symptoms) for each hospital episode. Miscarriages and ectopic pregnancies can be identified if they lead to inpatient care or an operation (such as laparoscopic surgery or curettage). From 1983 to 1995, operations were registered according to a national coding system; since 1996, according to the Finnish version of the NOMESCO classification system for surgical operations (Toimenpideluokitus, STAKES, 1996).

All hospital episodes due to OHSS, pelvic infections and abscesses, bleeding, other complications, miscarriages, and ectopic pregnancies were identified using the HDR (codes in Appendix); the dates for the start and end of the hospital stays were recorded. In cases of miscarriage and ectopic pregnancy, the hospitalization can be registered with an ICD-10 code and/or an operation code. A hospital outpatient visit is registered only when an operation has been carried out. By using ICD-10 codes, 71% of miscarriages after IVF and 74% after OI could be identified, and the rest were identified by using only operation codes. Almost all ectopic pregnancies were identified by using ICD-10 codes (98% of IVF and 97% of OI cases).

In addition to the diagnoses defined in the HDR to be OHSS-related, we searched for women having had symptoms or diseases potentially related to OHSS ('potential OHSS'). Our definition was based on one unpublished Finnish clinical study of women with diagnosed OHSS, on consultations with experienced clinicians, on symptoms and diseases described in the literature, and on diagnoses given to women in our data just before OHSS diagnosis (ICD-10 code N98.1). Five of the 48 women listed in the Finnish clinical OHSS data could be found in the HDR with the ICD-10 code N98.1. Two other women were hospitalized after IVF treatment with a diagnosis of pain localized in other parts of the lower abdomen (R10.3), and one due to other and unspecified ovarian cysts (N832). The diagnoses women received just before they were hospitalized due to OHSS were E15 (non-diabetic hypoglycaemic coma), R10.3, and J90 (pleural effusion, not elsewhere classified).Combining these diagnoses with those found in the literature, we made a list of diagnoses probably related to OHSS by consulting experienced clinicians (see Appendix).

Using all diagnoses and operation codes for all hospital episodes, we searched for those due to an IVF/OI complication (hereafter called a complication episode). To be eligible, the episode had to have occurred within 120 days from the beginning of the IVF/OI treatment in the case of OHSS, infections, abscesses, bleeding, and other complications. A time lag of 240 days was chosen in the case of miscarriages and ectopic pregnancies. These time lags were defined after studying the shapes of distribution curves of each complication to find a point when incidences clearly decreased. In addition, we consulted experienced clinicians in calculating the probable time lag from the start of treatment (first purchase date of the drug) to the occurrence of potential complications. If a woman had several treatments within this time frame, the latest was defined to be the treatment that led to the complication. If the same episode included different complications (e.g. OHSS and bleeding), they were all counted.

The complication risk was calculated in two ways. First, the proportion of women whose first complication occurred after the first treatment cycle (in our study window) was calculated separately for each type of complication (risk after the first treatment). Secondly, all treatment cycles were considered, but still only the first occurrence of each complication was taken into account, and the proportion of women having at least one complication (of each type) was calculated (risk of a complication after an average of 3.3 IVF and 2.7 OI treatment cycles). Furthermore, the risk of OHSS in each treatment cycle was calculated. In this calculation, individual women can appear more than once. The proportion of women having had any complication episode during the study period was calculated as well as the proportion of women whose hospital visit had lasted >5 days.

To calculate whether OHSS is more common in multiple than singleton pregnancies (among pregnancies ending in birth) and the rate of miscarriages and ectopic pregnancies per 100 births, we linked the data to the nationwide Medical Birth Register by using the women's personal identification numbers. For IVF and OI births, time limits of 44 and 48 weeks respectively were used to define whether births were the result of IVF or OI or spontaneous pregnancies; times were calculated from the beginning of treatment (the first purchase date of the drug) to the date of birth. In addition, to be able to estimate the risk of each complication per initiated cycle and to find comparable rates for earlier studies, the number of women having had each type of complication was divided by the total number of treatment cycles. This calculation produced only raw estimates because only the first occurrence of each complication was counted.

The numbers of deaths during and after the exposure to IVF and OI until the end of 2000 (after an average of 3.7 and 3.8 years for IVF and OI women respectively) were obtained from the Cause-of-Death Register. The follow-up time of the control group was as long as that of

the IVF women (from the first date of IVF exposure to the end of 2000). The causes of death were classified according to the following eight categories: reproductive mortality (Fortney *et al.*, 1986) including methods related to achieving pregnancy, diseases of the circulatory system, cancers, suicides, homicides, accidents, other, and unknown causes.

The differences were tested by using a χ^2-test or a test of relative proportions. The statistical analyses were performed in SAS, version 9.

Results

The background characteristics of the women are presented in Table I.

Depending on the definition of OHSS, the number of women having OHSS after the first treatment cycle varied from 14 to 19 per 1000 women and after all treatment cycles from 23 to 35 (Table II). As a specified (N98.1 in ICD-10) and potential diagnosis, OHSS was most common 1–2 and 2–3 months respectively after the beginning of IVF treatment. Depending on the definition of OHSS, the total rate of hospitalization due to OHSS per initiated IVF treatment cycle varied from 0.9% (210 cases/24 318 cycles) to 1.4% (330 cases/24 318 cycles). The mean length of hospitalization due to OHSS and potential OHSS was 4.1 and 3.3 bed days respectively.

After OI (94% of women treated with clomiphene citrate) hospitalization due to OHSS was rare (Table II). Depending on the definition of OHSS, the total rate of hospitalization per OI treatment cycle varied from 0.04% (eight patients/18 000 cycles) to 0.5% (100 patients/18 000 cycles). Most cases of OHSS occurred in the first month after the treatment cycle. Potential OHSS typically appeared 2–3 months after the treatment cycle.The mean length of hospitalization due to ICD-10 OHSS and potential OHSS was 2.4 and 1.9 bed days respectively.

The risk of OHSS was highest after the first and after the fifth or more IVF treatment cycles (Table III).

In our data, 21.2% of IVF pregnancies ending in birth (total of 3737 births) were twin births and 0.4% were triplets. The risk of OHSS (ICD-10 code) was more common among twin than among singleton pregnancies ending in birth (3.2 versus 1.4%, $P < 0.001$ for a test of relative proportions). In triplet pregnancies, no OHSS was registered.

After IVF treatment, OHSS (ICD-10) was much more common among younger than older women; 3.2% of women <35 years of age were hospitalized due to OHSS, but only 1% of older women. This was also the case when potential OHSS was taken into account.

Bleeding that necessitated hospital care was a rare complication (Table II). Most instances of bleeding occurred within 2 months of starting the treatment cycle. The total rate per initiated treatment cycle was 0.09%. Ten per 1000 IVF women were hospitalized due to infections; infections were diagnosed somewhat later than bleeding. The total rate per treatment cycle was 0.4%. The mean length of hospitalization after all treatment cycles was 2.1 bed days for bleeding and 3.7 for infections. After OI, hospitalizations due to bleeding and infections were even rarer than after IVF (Table II).

Only 17 IVF women were hospitalized due to complications other than OHSS, bleeding, and infections, and these mainly occurred 1–2 months after starting the treatment (Table II). Six women (four registered as pregnant) had a thromboembolic event. Three of these six cases were serious: one cerebral infarction and two pulmonary embolisms. None of the six women was registered as having OHSS in their thromboembolic episodes, but the cerebral infarction occurred just after hospitalization due to OHSS. One pulmonary embolism was registered as a complication of assisted reproduction (ICD-10 N98.8) that had included excision of the ovary and Fallopian tube.

After all OI treatment cycles, a total of five women had another complication. Four women (two registered as pregnant) had a thromboembolic event, but there was no information in the register about any of them possibly having OHSS. One was a serious case with a pulmonary embolism.

After the first IVF treatment cycle, 42 per 1000 women had received hospital care due to miscarriage; after all treatment cycles, the value was 93 per 1000 women (Table IV). The need for hospital care increased steadily until 4 months after IVF treatment, but the hospitalizations were short; the mean length of hospitalization was 1.2 bed days. The number of miscarriages per 100 births after all IVF treatment cycles was 23 (854/3737).

After the first IVF treatment cycle, nine per 1000 women, and after all IVF treatment cycles, 21 per 1000 women had needed hospital care due to an ectopic pregnancy (Table IV). Ectopic pregnancies had led to hospitalization most commonly during the first 3 months after the beginning of the IVF cycle, and the mean length of hospitalization was 2.1 bed days. The rate of ectopic pregnancies per 100 births after all IVF treatment cycles was 5.0 (187/3737).

Table I. Background characteristics of women in the IVF, ovulation induction (OI) and control[a] groups at the beginning of the 1996–98 follow-up in Finland

	IVF (n = 9175)	OI (n = 10 254)	Controls (n = 9175)
Age (years) (mean ± SD)	33.4 ± 5	31.1 ± 6	33.4 ± 5
Age group (years) (%)			
20–24	3.5	11.0	3.5
25–29	20.8	31.4	20.8
30–34	35.2	31.5	35.2
35–39	27.7	17.8	27.7
40–44	10.8	6.9	10.8
≥45	2.0	1.4	2.0
Total	100	100[c]	100
Marital status (%)			
Single[b]	22.3	19.1	36.1
Married	69.4	72.5	56.7
Divorced	7.9	7.9	9.4
Widow	0.4	0.5	0.4
Unknown	0.0	0.0	1.4
Total	100	100[c]	100[d]
Socioeconomic position (%)			
Upper white-collar	25.3	20.6	16.3
Lower white-collar	48.5	48.7	45.7
Blue-collar	16.2	18.0	19.3
Others	7.9	10.0	12.3
Unknown	2.1	2.7	6.4
Total	100	100[c]	100[d]

[a]Population controls for IVF women, matched by age and muncipality.
[b]Includes cohabitation.
[c]$P < 0.001$ for χ^2-tests (distributions of IVF women and OI women).
[d]$P < 0.001$ for χ^2-tests (distributions of IVF women and controls).

Table II. Serious complications in the first[a] IVF or ovulation induction (OI) treatment cycle, and including all[b] treatment cycles in the study period, according to the time lag from the start of the cycle to hospitalization, per 1000 women

	Time lag (days)[c]									
	First treatment cycle					All treatment cycles				
	≤30	31–60	61–90	91–120	Total	≤30	31–60	61–90	91–120	Total
IVF (*n* = 9175)										
OHSS, ICD-10[d]	2.4	10.7	0.3	0.7	14.1	6.3	14.4	1.0	1.2	22.9
Potential OHSS[e]	1.0	1.9	1.3	1.4	5.6	3.3	3.9	3.6	2.5	13.3
OHSS, ICD-10 or potential	3.4	12.2	1.4	2.0	19.0	9.4	17.6	4.1	3.6	34.7
Bleeding	0.3	0.5	0.0	0.1	1.0	0.9	1.0	0.3	0.2	2.4
Infection	0.9	1.4	1.9	1.0	5.1	2.1	3.3	3.4	2.2	10.9
Other[f]	0.0	0.9	0.1	0.1	1.1	0.2	1.4	0.1	0.1	1.9
OI (*n* = 10 254)										
OHSS, ICD-10[d]	0.1	0.1	0.0	0.1	0.3	0.4	0.1	0.1	0.2	0.8
Potential OHSS[e]	0.9	1.0	1.5	1.7	5.6	1.6	1.8	2.8	2.9	9.1
OHSS, ICD-10 or potential	1.0	1.1	1.5	1.6	5.7	2.0	1.9	2.9	3.0	9.8
Bleeding	0.1	0.1	0.1	0.0	0.3	0.1	0.1	0.1	0.0	0.3
Infection	0.4	0.2	0.4	0.4	1.5	0.6	0.7	0.9	1.0	3.1
Other[f]	0.1	0.0	0.0	0.0	0.1	0.2	0.0	0.2	0.1	0.5

[a]First treatment cycle in our study.
[b]With an average of 3.3 IVF and 2.7 OI treatment cycles. For each problem, the follow-up is truncated after the first problem.
[c]Number of days between first purchase of the drug in the cycle and the first day of hospitalization due to the complication.
[d]OHSS = ovarian hyperstimulation syndrome (N98.1, ICD-10 code).
[e]Symptoms potentially related to OHSS but not registered as OHSS (see Appendix).
[f]Other complication than OHSS related to IVF or OI (see Appendix) and thromboembolic events.
ICD-10 = International Classification of Diseases, 10th edition.

Table III. Proportion (%) of IVF women[a] having ovarian hyperstimulation syndrome (OHSS) leading to hospitalization and the proportion with long hospitalization in each treatment cycle

	n	OHSS		In hospital ≥5 days[b]			
		ICD-10[c]	Including potential	ICD-10	(*n*)	Including potential	(*n*)
Treatment cycle							
1st	9175	1.4	1.9	27.1	(129)	20.6	(175)
2nd	6066	0.6***	1.1	28.6	(35)	18.5	(65)
3rd	3844	0.7***	1.2	12.0	(25)	8.9	(45)
4th	2320	0.6**	0.9	7.7	(13)	4.8	(21)
≥5th	1318	1.2	2.1	25.0	(16)	14.3	(28)
Total	9175	2.4	3.6	24.3	(218)	17.1	(334)

[a]Includes the first OHSS episode in each treatment cycle, so individual woman can appear more than once.
[b]% of cases.
[c]For test of relative proportions: ***$P < 0.001$, **$P < 0.01$ compared to the first cycle.
ICD-10 = International Classification of Diseases, 10th edition.

The percentage of women having a miscarriage was similar after the first OI and IVF treatment cycle, but after all treatment cycles, miscarriage was 1.6 times more common among IVF women than among OI women (Table IV). The number of miscarriages per 100 births (15.0) after all OI treatment cycles (634/4188) was lower than the corresponding rate after IVF (23.0). Ectopic pregnancies were almost equally common after the first treatment cycle in both groups, but they were more common among IVF women than OI women after all cycles. The number of ectopic pregnancies per 100 births after all OI treatment cycles was 2.6 (107/4188).

Overall, after all treatment cycles, 1354 IVF (15%) and 824 OI (8%) women were hospitalized for complications. Of these hospital episodes, 10.5% of IVF and 1.6% of OI women's episodes lasted >5 days.

A total of 12, 15 and 37 women died in the IVF, OI and control groups respectively during the follow-up as a whole (after an average of 3.7 years (IVF) and 3.8 years (OI) from the time of exposure). The causes of deaths are presented in Table V. One death in both the IVF and the OI group was related to reproduction.

Discussion

The risk of complications after each IVF treatment cycle was low, but cumulatively repeated attempts led to hospital care in the case of many women. After ovulation induction (OI) treatment, there were far fewer complications. OHSS and miscarriages were the most common reasons for hospital care. OHSS occurred after IVF much more often than after OI alone, but

Table IV. Miscarriage or ectopic pregnancy leading to hospitalization or an operation after the first[a] IVF or ovulation induction (OI) treatment cycle, and including all[b] treatment cycles in the study period, according to the time lag from the start of the cycle to hospitalization, per 1000 women

	Time lag (days)[c]									
	First treatment cycles					All treatment cycles				
	≤60	61–120	121–180	181–240	Total	≤60	61–120	121–180	181–240	Total
IVF (n = 9175)										
Miscarriage	14.0	19.3	5.8	2.8	41.9	31.3	41.9	13.3	6.6	93.1
Ectopic pregnancy	3.0	4.1	0.9	1.3	9.3	9.1	7.9	2.3	1.6	20.9
OI (n = 10 254)										
Miscarriage	7.0	15.7	9.6	5.3	42.1	12.3	24.8	15.5	9.2	61.8
Ectopic pregnancy	2.1	2.7	1.4	1.3	8.2	3.4	3.6	1.9	1.8	10.7

[a]First treatment cycle in our study.
[b]An average of 3.3 IVF treatment cycles and 2.7 OI treatment cycles. For each problem, the follow-up is truncated after the first problem.
[c]Number of days between first purchase of the drug in the treatment cycle and the first day of hospitalization due to the complication.

Table V. Deaths by cause from 1996 to 2000 [after an average 3.7 years for women in IVF and control groups, and 3.8 for ovulation induction (OI) women after the first exposure]

	IVF (n = 9175)	OI (n = 10 254)	Controls (n = 9175)
Cause of death			
Reproductive-related[a]	1	1	0
Diseases of the circulatory system	1	2	10
All cancers	4	2	13
Breast cancer	1	0	3
Ovarian cancer	0	1	0
Suicide	4	5	4
Homicide	0	3	0
Accident	2	0	3
Other	0	0	6
Unknown (died abroad)	0	2	1
Total	12	15	37

[a]Includes causes attributable to IVF and OI treatment, pregnancy, and childbirth.

miscarriages and ectopic pregnancies were equally common after OI and IVF after the first treatment cycle. Other serious complications, infections, and instances of bleeding were quite rare, especially among OI women.

Are our estimates of complication risks reliable? The identification of IVF and OI cohorts from the reimbursement records went well (Hemminki *et al.*, 2003). We also believe that the data covered most Finnish women treated from 1996 to 1998. The cohorts are large enough to study the frequency of even rare complications caused by IVF and OI. However, our method of identification of serious complications and miscarriages was based on a register covering only hospital care, inpatient care, and operations in outpatient clinics; therefore our identification of outcomes depended on care practices and the diagnosis recording style of physicians.

Even though the validity of the HDR has been high (Keskimäki and Aro, 1991), it is a routine care register that does not have the accuracy of *ad hoc* epidemiological studies. For example, OHSS is not always easy to diagnose. Symptoms may be atypical, and there may be no questions about a history of IVF or OI treatments; or a physician may not enter the code for a specific form of OHSS and instead list its symptoms, such as abdominal pain, enlarged ovaries, or dyspnoea. Likewise, the identification of miscarriages using the register is difficult (Hemminki, 1998). The time lags (between the start of a cycle and hospitalization due to a complication) were defined on the basis of drug purchases, and the chosen thresholds were relative. We only had data on the purchase day, not the actual start of the cycle. There may have been intervals between drug purchases and use. On the other hand, due to the character of IVF treatment and the costs of the drugs, it is unlikely that women would have bought the drugs a long time before their use.

Overall, we think that our results underestimate the real complication risks. Mild (less serious) cases are missing in our data. To calculate how reliable our definition of OHSS is, we correlated our data with unpublished Finnish clinical data from the same time period. This showed that only 16% of OHSS cases are in the HDR (10% with the OHSS code and 6% with codes related to OHSS symptoms). Most likely the rest of the cases are missing because the women had had a less serious OHSS that did not lead to hospitalization or to an operation. Some cases may be missing because OHSS was not correctly diagnosed or registered. The overall frequency of OHSS, including mild forms, is no doubt much higher than our results show. On the other hand, some symptoms of OHSS such as abdominal pain are common and can relate to many other diseases. Thus some of our OHSS cases (‘potential OHSS’) may have actually been other diseases.

Our results cannot be extrapolated to countries with a less advanced health care system or less developed practices, in which treated women are less strictly screened or more risks are taken. For example, multiple pregnancies are suspected to entail a higher risk of late OHSS (Mathur *et al.*, 2000). In our population, plural births were lower than in many other countries (Bryant *et al.*, 2004; Nyboe Andersen *et al.*, 2005).

In our study, the hospitalization rates of OHSS per initiated IVF treatment cycle are somewhat higher and the length of hospital stays shorter than reported earlier (Quasim *et al.*, 1997; Serour *et al.*, 1999). Earlier studies are, however, based on less extensive or older data than ours (from 1980s to mid 1990s). It is possible that serious OHSS became more common from the 1980s to the late 1990s, when more potent treatments were used. At least in Israel, the incidence of severe OHSS

after IVF increased from 1987 to 1996 (Abramov *et al.*, 1999b). On the other hand, it might be that OHSS has become better known and more readily diagnosed. Shorter stays at hospital for OHSS may relate to the general trend towards shorter hospital stays.

As earlier reported (Schenker, 1999), women aged <35 years are at greater risk of developing OHSS. According to that study, the risk is also greater among women who receive only one treatment cycle or many cycles. It is generally assumed that a woman with a previous OHSS is at greater risk of OHSS in a following cycle (Whelan and Vlahos, 2000). For that reason, it may be assumed that women with previous OHSS are more carefully monitored during the next cycle to prevent OHSS. However, the women's first cycle was the first in our study window. We do not know how many cycles the women had received before 1996. After many repeated cycles, a woman may be at greater risk due to the repeated doses of drugs (especially gonadotrophin). This should be considered when many attempts are needed. Furthermore, the risk was also higher among twin pregnancies than among singleton pregnancies ending in birth. This was also found in an earlier study on late OHSS (Mathur *et al*., 2000). We were not able to classify the OHSS cases as late or early.

Only a few studies (Quasim *et al.*, 1997; Abramov *et al.*, 1999b) have reported the frequency of OHSS after ovulation induction (OI) alone or compared it to the frequency after IVF. Our study, as well as the older ones from the USA and Israel, shows serious OHSS to be more common after IVF than after OI. In addition, according to our study, the length of hospital stay was longer after IVF than after OI. This suggests that OHSS after IVF is more serious than after OI.

Our study confirmed earlier results that thromboembolic events exist after IVF but are rare complications, and even rarer after OI. In our study, the proportion of women reported as having a thromboembolic event leading to hospitalization (0.07%) was much lower than in an earlier Egyptian study (0.2%) (Serour *et al.*, 1998). The difference between the studies might be explained by different data collection methods (register/clinical study) and different time periods. In the Egyptian study, all cases were related to severe OHSS. In contrast, none of the women in our study were registered as having OHSS at the same time as thromboembolic complications. We do not know whether this is because thromboembolic events related to OHSS were not specifically recorded (but considered a part of OHSS), or whether OHSS was not diagnosed or not present. In one case report (Ulug *et al.*, 2003), a woman had venous thrombosis without OHSS after ovulation induction and ICSI. According to an extensive review, many studies have reported thromboembolic phenomena related to IVF or ovulation induction without any signs of OHSS (Delvigne and Rozenberg, 2003). However, severe OHSS was diagnosed in >76% of thromboembolic cases. Some case reports have described a cerebral infarction complicating OHSS (Koo *et al.*, 2002).

The frequency of bleeding per initiated IVF cycle was the same in our study as in an Egyptian study with 3500 cycles (Serour *et al.*, 1998). But it was much lower than in a recent report from the ESHRE (Nyboe Andersen *et al.*, 2005), covering all bleeding complications, even those not leading to hospitalization. The frequency of infections in our study was similar to that reported earlier in the Nordic countries (Bergh and Lunkvist, 1992) and Egypt (Serour *et al.*, 1998), but higher than reported by ESHRE (Nyboe Andersen *et al.*, 2005). The very low bleeding and infection rates after OI suggest that bleeding and infections were complications of IVF technique.

We found that >9% of IVF and >6% of OI women received hospital care due to miscarriages. We could not identify how many of the treated women had become pregnant, but the number of miscarriages per 100 IVF births (23.0) suggests similar miscarriage rates found earlier (15–23%; Serour *et al.*, 1998; Kupka *et al*., 2003; Schieve *et al.*, 2003; Wang *et al.*, 2004). However, the real miscarriage rate must have been higher, for not all miscarriages lead to hospital care. The miscarriage rate per 100 OI births was lower than the rate per 100 IVF births (15 versus 23). Whether this was due to characteristics of the individual women or the procedure itself could not be judged on the basis of this study. Previously, greatly varying miscarriage rates have been reported after clomiphene-induced pregnancies (9–27%; Venn *et al*., 1994).

Were the miscarriage rates after IVF higher than in natural pregnancies? We did not have a pregnant control group, but 8% of women with spontaneous pregnancies needed hospital care due to a miscarriage according to one Finnish study (Hemminki and Meriläinen, 1996). In one study from the USA, the miscarriage rate was similar (15%) among assisted reproduction treatment women and the rest of the female population (Schieve *et al*., 2003). However, in another study from the USA, the risk of miscarriage slightly increased after assisted reproductive treatment (Wang *et al*., 2004).

The rate of ectopic pregnancies per 100 IVF births (5.0) in our study is twice that of earlier studies in Finland (Hemminki and Heinonen, 1987; Mäkinen, 1996). The frequency per initiated IVF cycle (0.8%) is also somewhat higher than in earlier studies of IVF treatments (Bergh and Lundkvist, 1992; Serour *et al.*, 1998; Bryant *et al*., 2004). We do not have information on the reasons for infertility among the women in our study. We also could not examine how many of the women studied had tubal occlusion, which is considered to be one reason for the high frequency of ectopic pregnancies among IVF women. In the case of OI, which requires open tubes in order to be effective, clomiphene citrate could be a possible reason for the observed high rate of ectopic pregnancies (Venn *et al*., 1994).

Hardly any data have been published about maternal mortality or other deaths occurring as IVF complications. In one study from Australia, the maternal mortality of IVF women was higher than the national rate (Venn *et al.*, 2001). We did not have a control group consisting of spontaneously pregnant mothers or women trying to become pregnant. The best control group for IVF women that we had was OI women, although IVF women were older than OI women. Total mortality within an average of 3.7 years (IVF) and 3.8 years (OI) of follow-up was nearly equal among IVF and OI, and one death in both groups was connected with reproduction. The overall mortality in our study was lower than in the general female population (matched by age and municipality). In particular, the cardiovascular deaths were rarer. This indicates a 'healthy patient

effect' among IVF and OI women, i.e. sick women are less likely to be married or to receive infertility treatment than healthy women. The socioeconomic position of IVF women in our study was somewhat higher than that of the women in the control group, which can explain some of the lower mortality. Lower mortality has been reported in Australia among women who received IVF compared to women who had registered for IVF but never received the treatment (Venn *et al*., 2001).

Register-based studies with sufficiently large populations enable the examination of rare events. However, such studies have their limitations. Registers provide only limited information, and the coding of diagnoses are very likely to vary. Estimates of the frequencies of complications are needed to help clinicians in choosing safer methods, in applying new methods, and in informing women who contemplate IVF or OI treatment. It would be important to establish a routine follow-up system for IVF and OI treatments and their complications. This should also provide information on the duration and causes of infertility, the exact nature and duration of maternal drug exposure, and maternity background data. In countries with computerized health care and IVF registers, it would be easy to implement such a system. However, even before the possible establishment of such a new follow-up system, current estimates of the complication risk should be available both to women and physicians.

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Appendix. ICD-10 and operation codes and their explanations used in identifying the complications of IVF and ovulation induction (OI)

Ovarian hyperstimulation syndrome (OHSS)	
ICD-10	
N98.1	Hyperstimulation of ovaries
Potential OHSS	
ICD-10	
E15	Non-diabetic hypoglycaemic coma
J80	Adult respiratory distress syndrome
J90	Pleural effusion, not elsewhere classified
J94.8	Other specified pleural conditions (hydrothorax)
K65.0	Acute peritonitis
N17	Acute renal failure
N83.0	Follicular cyst of ovary
N83.1	Corpus luteum cyst
N83.2	Other and unspecified ovarian cysts
N99.0	Post-procedural renal failure
R06.0	Dyspnoea
R10.2	Pelvic and perineal pain
R10.3	Pain localized in other parts of lower abdomen
R10.4	Other and unspecified abdominal pain
R18	Ascites
R34	Anuria and oliguria
R60	Oedema, not elsewhere classified
Infections	
ICD-10	
N70	Salpingitis and oophoritis
N71	Inflammatory disease of uterus, except cervix
N73	Other female pelvic inflammatory diseases
N74.8	Female pelvic inflammatory disorders in other diseases classified elsewhere
N98.0	Infection associated with artificial insemination
Bleedings	
ICD-10	
N83.6	Haematosalpinx
N85.7	Haematometra
N93.8	Other specified abnormal uterine and vaginal bleeding
N93.9	Abnormal uterine and vaginal bleeding, unspecified
K66.1	Haemoperitoneum
T81.0	Haemorrhage and haematoma complicating a procedure, not elsewhere classified
Other	
ICD-10	
N98.2	Complications of attempted introduction of fertilized ovum following IVF
N98.3	Complications of attempted introduction of embryo in embryo transfer
N98.8	Other complications associated with artificial fertilization
N98.9	Complication associated with artificial fertilization, unspecified
I26	Pulmonary embolism
I63	Cerebral infarction
I74	Arterial embolism and thrombosis
I80	Phlebitis and thrombophlebitis
I82	Other venous embolism and thrombosis
Miscarriages	
ICD-10	
O02.1	Missed abortion
O03	Spontaneous abortion
O05	Other abortion
O06	Unspecified abortion
O08	Complications following abortion and ectopic and molar pregnancy
Operation codes	
1350	Other operation in uterus
8113	Curettage of body of uterus
8319	Destruction of endometrium
8501	Evacuation of uterus by aspiration
8502	Evacuation and abrasion
8509	Other operation related to miscarriage
LCA10	Curettage of body of uterus
LCA13	Curettage of cervix and body of uterus
LCA16	Destruction of endometrium
LCA96	Other intrauterine operation
LCA98	Other transluminal endoscopic operation on uterus
Ectopic pregnancies	
ICD-10	
O00	Ectopic pregnancy
O08	Complications following abortion and ectopic and molar pregnancy
Operation codes	
8231-8239	Operations related to ectopic pregnancy
LBC00-LBC98	Tube conserving operations for tubal pregnancy

Paper III

Health of Children Born as a Result of In Vitro Fertilization

Reija Klemetti, Tiina Sevón, Mika Gissler and Elina Hemminki

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ARTICLE

Health of Children Born as a Result of In Vitro Fertilization

Reija Klemetti, MHSc[a], Tiina Sevón[a], Mika Gissler, DrPhil, MSocSc[b], Elina Hemminki, MD[a]

[a]Health Services Research and [b]STAKES Information, STAKES, National Research and Development Centre for Welfare and Health, Helsinki, Finland

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ABSTRACT

OBJECTIVE. The purpose of this study was to use nationwide registries to examine the health of children up to 4 years of age who were born as a result of in vitro fertilization.

METHODS. Children born after in vitro fertilization (N = 4559) from 1996 to 1999 were monitored until 2003. Two control groups were selected from the Finnish Medical Birth Register as follows: all other children (excluding children born after ovulation induction) from the same period (N = 190 398, for study of perinatal health and hospitalizations) and a random sample of those children (n = 26 877, for study of health-related benefits). Mortality rates and odds ratios for perinatal outcomes, hospitalizations, health-related benefits, and long-term medication use were calculated.

RESULTS. Although the health of most in vitro fertilization children was good, such children had more health problems than other children. A total of 35.7% of in vitro fertilization children and 2.2% of control children were multiple births, and the health of multiple births was worse than that of singletons. Perinatal outcomes of in vitro fertilization children were worse and hospital episodes were more common than among control children. Risks for cerebral palsy and psychological and developmental disorders were increased. Among in vitro fertilization singletons, worse results for perinatal outcomes and hospitalizations, but no increased risk for specific diseases, were found. The health of in vitro fertilization multiple births was comparable to the health of control multiple births.

CONCLUSIONS. Reducing the number of transferred embryos would improve the health of in vitro fertilization children. Additional studies are needed to explain the poorer health of in vitro fertilization singletons, as well as follow-up studies to examine the health of in vitro fertilization children from 4 years onward.

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Key Words
in vitro fertilization, perinatal health, morbidity, multiplicity, registry-based study

Abbreviations
CP— cerebral palsy
IVF—in vitro fertilization
HDR—Hospital Discharge Register
MBR—Medical Birth Register
SII—Social Insurance Institution
OR— odds ratio
CI— confidence interval
ICD-10 —*International Classification of Diseases, 10th Revision*

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Address correspondence to Reija Klemetti, MHSc, PO Box 220, 00531, Helsinki, Finland.

In vitro fertilization (IVF) (including intracytoplasmic sperm injections and frozen embryo transfers) is a common infertility treatment. In Finland, currently ~2.5% of infants are born as a result of IVF,[1] with women <40 years of age being able to receive 2 to 5 IVF treatment cycles within the public sector[2] while paying a small fee for visits. Approximately 60% of all IVF services are supplied by private clinics, with no strict age limit. Private physicians' charges and drug costs are partly reimbursed by the Social Insurance Institution (SII). Usually, the pharmacies and IVF clinics take care of billing for the reimbursements. Approximately 76% of total IVF costs (visits, examinations, treatments, and drugs) are covered in the public sector and 50% in the private sector, with the rest being paid by women (R.K., T.S., M.G., and E.H., unpublished data, 2006).

The perinatal health of IVF singletons has been reported as being worse than that of naturally conceived singletons,[3–5] with more-recent studies also showing an increased risk for preterm birth and/or low birth weight for twins.[6,7] However, studies of the long-term health of IVF children are few, and their results are conflicting.

According to previous small cohort studies, the morbidity rates, growth, and development of IVF children are similar to those of control children (as reviewed by Koivurova[8]). Although the health of children is mainly good, large studies are needed to clarify potential health problems. Registry-based studies allow for large sample sizes and are published regularly from the Nordic countries.[9–17] In the case of IVF children, research has found an excess use of hospital services, long hospitalizations, and increased risk for infections, epilepsy, and tumors,[10] asthma,[10,17] cerebral palsy (CP),[10,11,14] sleep disturbances,[14] convulsions, behavioral problems, and accidents,[17] and congenital malformations.[9,10,15–17] However, some of those studies were based on early IVF experience and concentrated on specific diagnoses, hospital care utilization, or singletons/twins only or did not consider multiplicity.

Results on the perinatal health of IVF twins are controversial, whereas data on the long-term health of IVF children are sparse. For this reason, our aim was to perform a large, thorough, up-to-date, registry-based study of the health of IVF children up to 4 years of age, separately for singletons and multiple births, by using several population-based registries.

METHODS

Identification of IVF Children

The study is based on children born to women who received IVF between 1996 and 1998 in Finland. The women were identified, with a predesigned algorithm, from the reimbursement files of the SII.[18] Data on children born as a result of IVF treatment (N = 4559) and their perinatal health were obtained from the Finnish Medical Birth Register (MBR)[15,19] by using women's personal identification numbers and the children's dates of birth as the linkage keys. The MBR also includes the children's unique identification numbers. It contains information on maternal backgrounds and on infant outcomes until the age of 7 days for all infants born in Finland. The data are collected by delivery hospitals and are completed by linkage to the Central Population Register and cause-of-death statistics (compiled by Statistics Finland). The identified children were linked to 4 other nationwide registries through the children's identification numbers, namely, cause-of-death statistics, the Hospital Discharge Register (HDR) (hospital episodes, diagnoses, ie, *International Classification of Diseases, 10th Revision* [ICD-10] codes, and dates of admissions and discharges), the Care Register for Social Welfare (episodes in institutional care), and health-related social benefits from the SII (reimbursements for long-term medication use and child disability allowance).

Control Groups

As control groups, 2 groups of children were selected from the MBR. The first control group consisted of all children other than IVF children or those born as a result of ovulation induction (N = 190 398) who had been conceived during the same period (1996–1998). The second control group (n = 26 877) was a random sample of the first control group, selected to reduce the workload caused by large registry linkages in the SII, and was used to study the benefit payments from the SII and for the combined analysis.

Data Collection

The number of deaths of all children from 1996 to 2001 until the age of 2 years was obtained from cause-of-death statistics. We grouped the causes of deaths (given as ICD-10 codes) into 4 categories, namely, conditions originating from the perinatal period, congenital malformations, other medical causes, and deaths from external causes.

The HDR collects information on inpatient care and visits to outpatient clinics involving surgical or other procedures. The HDR gathers information on diagnoses (ICD-10 codes) and dates of admissions and discharges. The diagnoses include the main diagnosis and 2 secondary diagnoses for each episode. All hospitalizations until the children were 4 years of age were studied (1996–2003).

The Care Register for Social Welfare collects information on care episodes in social institutions, such as institutions for people with intellectual disabilities. For this study, we received information on the numbers of IVF children having ≥1 period of institutional care up until the end of 2004. We compared the rates of institutionalized children with the national rates for children born

in 1997 or 1998, excluding the numbers of children from IVF or ovulation induction.

The SII grants child disability allowances for families who have a disabled or chronically sick child needing continuous help and surveillance at home. A child's parents applying for benefits are required to supply recent medical documents. The register of child disability allowances contains information on start and end dates, type (temporary or permanent), level (normal, increased, or special), and diagnoses. The special refund category covers ~50 chronic diseases, entitling patients to receive higher reimbursements of long-term medication costs. Among children, the most common diseases in the special refund category are asthma, epilepsy, diabetes mellitus, and rheumatoid arthritis. The data on special refunds included the start and end dates of entitlement periods and the reasons. Information on both child disability allowance and long-term medication use was gathered from 1996 to 2001 (ie, until the children were 2 years of age).

Data Analyses

A comparison was made between control and IVF mothers in their utilization of health care services during the pregnancy and child birth (hospitalization during the pregnancy, cesarean section, and hospitalization of ≥7 days after delivery) and in infant outcomes, first including all children and then including first births only. As health outcomes, we used very low birth weight (<1500 g), low birth weight (<2500 g), very preterm birth (<32 weeks), preterm birth (<37 weeks), low 1-minute Apgar scores (scores of 0–6), treatment in an ICU or neonatal surveillance unit, need for respiratory treatment, hospitalization of the child for ≥7 days after birth, and perinatal death.

All inpatient hospital episodes until 2 years and 4 years of age were collected separately from the HDR. The total number of hospital episodes, the length of the episodes, and the number of hospitalized children were determined. We grouped diagnoses (ICD-10 codes) into 16 categories. The 2 categories of "symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified" (codes R00–R99) and "factors influencing health status and contact with health services" (codes Z00–Z99) were combined and renamed as "other." Both main and secondary diagnoses were taken into account. If the child was hospitalized more than once because of the same diagnosis, then only the first hospitalization was included.

We calculated the numbers of IVF and control children who had received ≥1 child disability allowance period or reimbursement for long-term medication. The most common reasons for child disability allowance and reimbursement were counted and IVF children were compared with naturally conceived children. Finally, we combined information from the different data sources and calculated the number of children who had used services, according to any of the data sources, because of an allergic and chronic disorder and common infection-like allergy (ICD-10 codes L20–L23, L27, and L50), asthma bronchial (ICD-10 codes J45 and J46), CP (ICD-10 code G80), epilepsy (ICD-10 codes G40 and G41), diabetes mellitus (ICD-10 code E10), diarrhea (ICD-10 codes A08–A09), pneumonia (ICD-10 codes J12–J18), or disorders of psychological development and behavioral and emotional disorders usually occurring in childhood and adolescence (ICD-10 codes F80–F98).

Statistical Analyses

The differences between the IVF and control groups were first tested with a χ^2 test and t test for relative proportions and with logistic regression analysis, adjusting for available background characteristics. For perinatal outcomes, these characteristics were county, smoking, maternal age, socioeconomic position, and previous births. The socioeconomic position of the women was defined by using their own occupation when delivering, which is collected routinely from maternity hospitals and classified automatically by the MBR into 5 categories according to the national classification compiled by Statistics Finland, that is, upper white-collar workers, lower white-collar workers, blue-collar workers, others (entrepreneurs, students, pensioners, unemployed women, and women with an unclassified position), and unknown position.[20] All analyses were made separately for singletons and multiple births. Two logit models were used, namely, an ordinary logit model in which all children were assumed to be independent and an additional model created by using the iterative, generalized, least-squares method, in which siblings born in the same delivery were assumed to be dependent.

Research Ethics and Data Protection

The study plan was approved by the National Research and Development Centre for Welfare and Health research ethics committee (September 18, 1998). For register linkages, the National Data Protection Authority was consulted, and permissions were obtained from the registry keepers.

RESULTS

Of the 4559 IVF children, 34.7% were twins and 1.1% were triplets. Among the 190 398 control children, 2.2% were twins and only 13 sets were triplets (<0.01%). IVF mothers were older, more often married, and from a higher socioeconomic position than other mothers (Table 1).

Compared with other mothers, IVF mothers received more hospital care during pregnancy and more cesarean sections (Table 2). Adjustment for mothers' background characteristics did not change the results. Inspection of singletons and multiple births separately showed that

TABLE 1 Mothers' Background Characteristics According to Group and Plurality for IVF and Control Mothers

	Total Births			Singleton Births			Multiple Births		
	IVF (n = 3737)	Control (n = 188 298)	P	IVF (n = 2930)	Control (n = 186 216)	P	IVF (n = 807)	Control (n = 2084)	P
Maternal age at delivery									
Mean ± SD, y[a]	33.9 ± 4.5	29.7 ± 5.3	<.001	34.1 ± 4.6	29.7 ± 5.3	<.001	33.1 ± 4.3	30.5 ± 5.2	<.001
Age group, %									
<25 y	2.9	22.4		2.6	22.4		4.1	17.4	
25–29 y	20.1	33.6		18.8	33.7		24.5	31.7	
30–34 y	41.2	29.4		41.2	29.4		41.5	33.2	
35–39 y	41.2	12.2		28.3	12.2		25.3	15.4	
≥40 y[b]	8.1	2.3	<.001	9.1	2.3	<.001	4.6	2.3	<.001
Marital status									
Married or cohabiting	95.3	87.5		95.4	87.5		94.9	86.4	
Single	3.9	10.6		3.9	10.6		4.0	11.3	
Missing information[b]	0.8	1.9	<.001	0.8	1.9	<.001	1.1	2.4	<.001
Socioeconomic position, %									
Upper white-collar	25.1	15.1		25.5	15.1		23.7	17.0	
Lower white-collar	48.5	40.6		48.2	40.6		49.9	40.3	
Blue-collar	13.0	17.0		13.0	17.0		12.6	16.1	
Others	8.0	18.5		8.0	18.5		8.1	18.2	
Unknown[b]	5.4	8.9	<.001	5.3	8.9	<.001	5.7	8.4	<.001
Smoked during pregnancy[c]	6.6	14.8	<.001	6.6	14.8	<.001	6.6	16.6	<.001
First birth[c]	72.2	39.5	<.001	72.0	39.5	<.001	72.9	35.6	<.001

The control group consisted of all other mothers whose children were fertilized in the same time period as IVF children.

[a] For t tests in comparisons between IVF and control subjects.

[b] For χ^2 tests in comparisons between IVF and control subjects.

[c] For tests for relative proportions in comparisons between IVF and control subjects.

TABLE 2 Raw Proportions and Adjusted ORs of Pregnancy and Birth Treatments and Infant Outcomes Among IVF Mothers and Infants, Compared With Other Mothers and Infants

	Total Births			Singleton Births			Multiple Births		
	No. or Proportion		OR (95% CI)	No. or Proportion		OR (95% CI)	No. or Proportion		OR (95% CI)
	IVF	Control		IVF	Control		IVF	Control	
Deliveries, n	3737	188 298		2930	186 216		807	2084	
Infants, n	4559	190 398		2930	186 216		1629	4182	
Mother, %									
Hospital treatment[a]	43.0	20.6	2.61 (2.43–2.79)	36.4	20.2	1.99 (1.84–2.16)	66.9	54.2	1.51 (1.24–1.85)
Hospitalization of ≥7 d[b]	16.8	4.5	2.33 (2.11–2.57)	9.6	4.2	1.23 (1.07–1.41)	46.8	31.7	1.04 (0.83–1.30)
Cesarean section	35.8	15.3	1.95 (1.81–2.10)	30.4	15.0	1.51 (1.39–1.65)	55.5	41.8	1.24 (1.03–1.50)
Infant, %									
Very preterm (<32 wk)	4.7	0.9	4.45 (3.80–5.21)	2.0	0.8	2.06 (1.56–2.71)	9.6	7.0	1.26 (0.99–1.60)
Preterm (<37 wk)	23.6	5.5	4.43 (4.10–4.77)	9.5	4.7	1.72 (1.51–1.96)	49.2	42.2	1.06 (0.93–1.21)
Birth weight of <1500 g	4.2	0.8	4.19 (3.55–4.95)	1.9	0.7	2.17 (1.64–2.88)	8.2	7.4	0.95 (0.74–1.22)
Birth weight of <2500 g	19.8	4.0	4.77 (4.40–5.18)	6.5	3.2	1.60 (1.37–1.87)	43.7	39.2	0.92 (0.81–1.06)
Apgar score of 0–6	8.8	4.4	1.68 (1.50–1.87)	5.6	4.2	1.07 (0.91–1.26)	14.5	12.5	1.10 (0.90–1.33)
Special care[c]	23.0	8.2	2.71 (2.52–2.92)	12.5	7.6	1.36 (1.21–1.53)	42.1	35.0	1.04 (0.91–1.19)
Respiratory treatment	4.3	1.1	3.61 (3.08–4.24)	2.0	0.9	1.76 (1.34–2.31)	8.4	6.7	1.19 (0.93–1.53)
Hospitalization of ≥7 d	23.8	6.4	3.42 (3.08–4.24)	10.8	5.8	1.43 (1.26–1.61)	47.4	37.6	1.02 (0.88–1.17)
Perinatal death	1.3	0.6	1.85 (1.40–2.44)	0.9	0.5	1.32 (0.88–1.98)	2.0	2.9	0.73 (0.47–1.13)

ORs were adjusted for mother's county, smoking, age, marital status, parity, and socioeconomic position. The reference group (OR = 1) was the control group.

[a] During pregnancy.

[b] After delivery.

[c] Treatment in ICU or in newborn surveillance unit.

this difference was partly, but not totally, explained by IVF children more often being twins.

Similarly, the indicators of perinatal health showed much worse health of IVF children, which was explained partly by plurality. The perinatal health of IVF multiple births was comparable to that of control multiple births; the risk for very preterm birth was increased but not statistically significantly.

Stillbirths were more common among IVF children in total, compared with other children in total (7.2 cases

per 1000 vs 3.9 cases per 1000; $P < .001$), and among IVF singletons, compared with control singletons (6.5 cases per 1000 vs 3.7 cases per 1000; $P = .014$ in a test for relative proportions), but not separately for multiple births. The main causes of stillbirths were conditions originating in the perinatal period (for example, placental infarction, extreme immaturity, and abruptio placentae).

The total mortality rate up to the age of 2 years was twofold higher among IVF children, compared with control children (9.0 deaths per 1000 and 4.1 deaths per 1000, respectively). Among singletons, rates of deaths after birth until the age of 2 years were similar in all groups of children; the main causes were congenital malformations (2.4 cases per 1000 among IVF children and 1.4 cases per 1000 among control children) and conditions originating in the perinatal period (for example, extremely low birth weight and respiratory distress syndrome; 1.4 cases per 1000 and 1.3 cases per 1000, respectively). The main causes among multiple births were the same as those among singletons (malformations: 11.2 cases per 1000 and 4.6 cases per 1000; perinatal causes: 11.2 cases per 1000 and 14.8 cases per 1000, respectively), and no significant differences between the groups were found.

According to the Care Registry for Social Welfare Institutions, 2.2 IVF children per 1000 had had ≥1 period of institutional care at a social welfare institution. For other children born in 1997 to 1998, the rate was 2.7 per 1000 children. Institutional care does not include children taken into children's homes or custody but refers mainly to mentally handicapped children who stayed in an institution for people with intellectual disabilities.

Until the age of 2 years, larger proportions of IVF children and IVF singletons received child disability allowances, compared with control children (Table 3). The most common reasons (according to ICD-10 classification) for receiving child disability allowances were the same for IVF and control singletons, namely, diseases of the skin and subcutaneous tissue, diseases of the respiratory system, and conditions involving the eyes and ears. For multiple births, the most common reasons included, in addition, certain conditions originating in the perinatal period. No statistically significant differences in long-term medication use were found between IVF and control children.

When information from different data sources until the age of 2 years was combined, it was found that IVF children, singletons and multiple births taken together, had a threefold increased risk of CP and more often had disorders of psychological development or behavioral and emotional disorders, compared with control children (Table 4). This was not the case when IVF singletons and multiple births were considered separately. Of the infants with CP, 88% were preterm.

Up to the age of 4 years, a larger proportion of IVF children were hospitalized, IVF children more often had long hospital episodes, and the average length of their episodes was greater, compared with control children (Table 5). IVF children had somewhat more hospital episodes than control children at all ages, but the difference was clearest during infancy.

Compared with control children, the risk of being hospitalized was increased among IVF children for many categories of diseases (according to ICD-10 grouping), even after adjustment for the mother's socioeconomic position (data not shown). The risk among IVF singletons was increased statistically significantly for perinatal problems (ICD-10 codes P00–P96; odds ratio [OR]: 1.76; 95% confidence interval [CI]: 1.54–2.01), congenital malformations (codes Q00–Q99; OR: 1.45; 95% CI: 1.20–1.75), and problems of the genitourinary system (codes N00–N99; OR: 1.40; 95% CI: 1.11–1.77) and decreased for diseases of the respiratory system (codes J00–J99; OR: 0.86; 95% CI: 0.76–0.97). IVF multiple births had increased risk for hospitalization because of diseases originating from the perinatal period (OR: 1.34; 95% CI: 1.18–1.53) and "other" diagnoses (codes R00–R99 and Z00-Z99; OR: 1.27; 95% CI: 1.09–1.48) and decreased risk for hospitalization because of diagnoses in the categories of eye and ear (codes H00–H95; OR: 0.77;

TABLE 3 Raw Proportions of Children and Crude and Adjusted ORs (and 95% CI) of Having Any Child Disability Allowance Period or Any Long-Term Medication Use Until the Age of 2 Years

	Total		Singleton		Multiple	
	IVF ($n = 4527$)	Control ($n = 26\,877$)	IVF ($n = 2911$)	Control ($n = 26\,296$)	IVF ($n = 1616$)	Control ($n = 581$)
Any child disability allowance						
Proportion, %	10.6	9.5	10.5	9.5	10.8	13.1
Crude OR (95% CI)	1.13 (1.02–1.25)	1.00	1.13 (0.99–1.28)	1.00	0.81 (0.61–1.08)	1.00
Adjusted OR (95% CI)	1.11 (1.00–1.23)	1.00	1.10 (0.97–1.25)	1.00	0.81 (0.62–1.10)	1.00
Any long-term medication use[a]						
Proportion, %	3.3	2.8	2.9	2.8	4.1	4.5
Crude OR (95% CI)	1.18 (0.98–1.41)	1.00	1.03 (0.82–1.29)	1.00	0.91 (0.57–1.45)	1.00
Adjusted OR (95% CI)	1.18 (0.98–1.41)	1.00	1.03 (0.82–1.30)	1.00	0.95 (0.59–1.52)	1.00

The ORs were adjusted for mother's socioeconomic position. The reference group (OR = 1) was the control group.

[a] Reimbursements for cow's milk or soy milk intolerance were excluded.

TABLE 4 **Raw Proportions of Children and Adjusted ORs of Having an Allergic or Chronic Disorder or a Common Infection (ICD-10 Codes) Until the Age of 2 Years, From Any Available Data Source**

	Total		Singleton		Multiple	
	IVF ($n = 4527$)	Control ($n = 26\,877$)	IVF ($n = 2911$)	Control ($n = 26\,296$)	IVF ($n = 1616$)	Control ($n = 581$)
CP (code G80)[a]						
Proportion, cases per 1000	3.8	1.4	1.4	1.3	8.0	5.2
OR (95% CI)	2.92 (1.63–5.26)	1.00	1.15 (0.40–3.27)	1.00	1.52 (0.43–5.40)	1.00
Epilepsy (code G40–G41)[b]						
Proportion, cases per 1000	3.3	2.5	3.4	2.5	3.1	3.4
OR (95% CI)	1.33 (0.76–2.34)	1.00	1.39 (0.71–2.71)	1.00	0.95 (0.18–5.01)	1.00
Behavioral disorders (code F80–F98)[a,c]						
Proportion, cases per 1000	6.6	4.1	4.1	4.1	11.1	3.4
OR (95% CI)	1.68 (1.11–2.53)	1.00	1.05 (0.57–1.91)	1.00	3.05 (0.70–13.29)	1.00
Diabetes mellitus (code E10)[b]						
Proportion, cases per 1000	0.9	0.5	1.0	0.5	0.6	1.7
OR (95% CI)	1.57 (0.51–4.84)	1.00	1.98 (0.56–7.07)	1.00	0.28 (0.02–4.50)	1.00
Asthma (code J45–J46)[b]						
Proportion, cases per 1000	30.3	28.1	26.5	27.8	37.1	43.0
OR (95% CI)	1.08 (0.90–1.30)	1.00	0.95 (0.74–1.20)	1.00	0.93 (0.57–1.51)	1.00
Allergy (code L20–L23, L27, L50)[b]						
Proportion, cases per 1000	59.9	53.8	61.8	54.0	56.3	46.5
OR (95% CI)	1.07 (0.94–1.23)	1.00	1.10 (0.94–1.30)	1.00	1.25 (0.80–1.96)	1.00
Pneumonia (code J12–J18)[a]						
Proportion, cases per 1000	9.9	11.4	9.6	11.4	10.5	8.6
OR (95% CI)	0.85 (0.62–1.17)	1.00	0.81 (0.55–1.20)	1.00	1.26 (0.46–3.49)	1.00
Diarrhea (code A08–A09)[a]						
Proportion, cases per 1000	44.2	38.6	35.4	38.1	60.0	60.2
OR (95% CI)	1.17 (1.00–1.37)	1.00	0.94 (0.76–1.15)	1.00	1.04 (0.69–1.56)	1.00

ORs were adjusted for mother's socioeconomic position.

[a] Data sources: the HDR and child-care support.

[b] Data sources: the HDR, long-term medication use, and child-disability allowance.

[c] Disorders of psychological development and behavioral and emotional disorders.

TABLE 5 **Use of Hospital Services Until the Age of 4 Years Among IVF and Control Children, According to Multiplicity**

Use of Hospital Services	Total		Singleton		Multiple	
	IVF ($n = 4527$)	Control ($n = 189\,656$)	IVF ($n = 2911$)	Control ($n = 185\,530$)	IVF ($n = 1616$)	Control ($n = 4126$)
Total no. of hospital episodes	4397	136 782	2281	131 459	2116	5323
Hospitalized children, %	40	33	34	32	50	49
OR (95% CI)	1.40 (1.31–1.48)	1.00	1.12 (1.04–1.21)	1.00	1.07 (0.95–1.20)	1.00
Time in hospital per child, d	6.3	2.7	3.8	2.6	10.8	9.8
Proportion of long hospital episodes (≥7 d), %	20	11	14	10	28	24

ORs were adjusted for mother's socioeconomic position. The reference group (OR = 1) was the control group.

95% CI: 0.63–0.95) and the respiratory system (OR: 0.74; 95% CI: 0.63–0.87). Otherwise, their outcomes were comparable to those of control multiple births. However, in almost every category the proportion of hospitalized children was higher among multiple births than among singletons.

In the subanalysis for first births, the results were mainly similar to the results for all children; although IVF children in total had increased risk for asthma (adjusted OR: 1.39; 95% CI: 1.08–1.79), the risk for mothers' long hospital stay for IVF singletons (OR: 1.17; 95% CI: 0.89–1.58) and the risk for cesarean sections for multiple births (OR: 1.19; 95% CI: 0.92–1.53) were not statistically significantly increased. In addition, IVF multiple births had statistically significantly decreased risk for low birth weight (adjusted OR: 0.78; 95% CI: 0.65–0.93).

There were no differences in the results of the 2 logit analyses (an ordinary logit model and an additional analysis using the iterative generalized least-squares method; see Methods). For some rare outcomes, adjustment for mother's socioeconomic position was not possible in the additional analysis because of small numbers.

DISCUSSION

We found an increased burden of disease associated with IVF, with poorer perinatal health, higher mortality rates, increased risk for hospitalization and CP, and longer

hospital episodes. This burden depended in part on higher twin rates among IVF children. However, the burden of disease resulted not only from the greater number of twins but also from the poorer health of singletons, compared with naturally conceived singletons. Increased morbidity was attributable not to any specific disease but rather to small increases in many groups of diseases. In general, the health of IVF multiple births was comparable to that of other multiple births.

Are the results reliable? IVF children were identified on the basis of drugs used, laboratory and radiologic examinations, and infertility treatment procedures. We might have missed some IVF children, who would therefore be included in the control group. However, the number of missing children cannot be large[18,19] and would not affect the results. The data on deaths and perinatal health received from the MBR[21,22] are reliable. However, other outcome measures depend on service utilization (seeking care or applying for benefits); technically, the registers are considered to be of good quality.[23]

The occurrence of less-serious diseases and cases cannot be estimated from these registries, because the use of outpatient care is not registered. Our results might be biased by different thresholds for hospital admissions between IVF and control children. IVF parents, who were more often first-time parents, might have been more worried, which might have led more easily to hospital care and also longer hospital stays. It might also be that IVF children were examined more carefully by physicians, compared with naturally conceived children, if the mode of conception was known to the physicians. However, because IVF children did not have an increased rate of hospitalizations in all categories of diseases and because adjustment for parity and socioeconomic position and a subanalysis of first births did not change our results, it is unlikely that the anxiousness of parents, more-careful examinations, or lower thresholds for hospitalization alone could explain the greater frequency of visits. Rather, the greater frequency likely reflects higher morbidity rates among singleton IVF children. Furthermore, rates of almost every outcome studied were quite similar between IVF multiple births and control multiple births.

In Finland, most health care is public, financed by taxes. Private health care is covered by the national social security system, but some children are covered by additional voluntary private insurance. No private hospitals for children exist but, in 2005, ~28% of children up to 4 years of age used private (outpatient) physicians (Social Insurance Institution of Finland, unpublished data, 2005). It is possible that, in the case of small surgical procedures, private specialist outpatient care competes with hospital outpatient clinics. If IVF children were treated more or less frequently in such private care, then a bias would result.

In Finland, health-related social benefits (child care allowance and reimbursement for long-term medication use) must be applied for. It might be that some parents are more capable of applying for the benefits. Because the adjustment for socioeconomic position did not change the results, however, there is no reason to assume that parents of IVF children with a higher socioeconomic position would receive benefits more easily than parents of control children. Informing and advising parents on these benefits is part of routine clinical practice. In addition, reimbursed diseases for long-term medication use are defined clearly, and recent medical documents are needed for receipt of both child disability allowance and support for long-term medication use. Child disability allowance is based on ICD-10 classifications and long-term medication support on defined diagnoses; therefore, it can be assumed that these are relevant in estimating disease occurrence.

Our study confirms earlier findings of poorer perinatal health,[3–5,8] greater numbers of hospitalizations,[9] and increased risk for congenital anomalies[15,16,24] for IVF singletons, compared with naturally conceived singletons. Perinatal problems had a significant role also in hospitalizations; diseases originating from the perinatal period represented one of the most common diagnoses leading to hospitalization, among both singletons and multiple births. IVF multiple births had worse perinatal health than did IVF singletons, but IVF and control multiple births were similar with respect to perinatal health, which is largely in accordance with an earlier study (except for the finding in that study of an increased risk of admittance to a NICU and more-common longer hospitalizations after the birth).[25] In contrast, a recently published Belgian study found an increased risk for preterm birth also among IVF twins, compared with naturally conceived twins, which was largely explainable by the first birth of IVF women.[7] In accordance with the study by Pinborg et al,[13] we did not find any excess use of hospital services among IVF multiple births.

In addition, our study confirms earlier results of higher mortality rates,[8] greater numbers of hospitalizations,[10,17] and increased risks for behavioral problems,[17] CP,[11,14] and infections[10] among IVF children overall. In accordance with an earlier Finnish study based on both outpatient and inpatient visits,[8] we found a slightly but not statistically significantly increased risk for diarrhea; contrary to that study, however, we did not find an increased risk for pneumonia.

Unlike previous studies,[11,14] we did not find an increased risk for CP or sleeping disturbances among IVF singletons. In our study, the excess risk for CP was mainly explainable by multiplicity. In the study by Strömberg et al,[11] the main reasons for the increased risk for CP were prematurity and the multiple pregnancy rate. A recent Swedish study could not confirm the increased risk for CP; the risk disappeared after adjust-

ment for confounders.[17] Furthermore, we could not find increased risk for epilepsy, tumors, or asthma among IVF children in total, as found earlier in Sweden.[10] However, increased risk for epilepsy was not found in the recent Swedish study.[17]

A few previous studies reported about childhood morbidity for IVF multiple births. In 2 studies, no differences in neurologic sequelae were found.[11,12] In our study, no increased risk for any disease among IVF multiple births was found. In general, however, IVF multiple births had higher childhood morbidity rates than did IVF singletons.

We could not find any other study examining long-term medication use, child disability allowance, and utilization of institutional care among IVF children. A slightly increased risk for child disability allowance among IVF children in our study was explainable by multiplicity, whereas no statistically significant differences in the utilization of long-term medication therapy and institutional care between the groups were found.

Potential reasons for the poorer perinatal health of IVF children include infertility itself,[26–29] infertility treatments, and varying health behavior during pregnancy. Among IVF singletons, the main cause of poorer perinatal health has been suggested to be infertility itself, because of the higher incidence of preterm birth and low birth weight also among infertile women without treatment and women with infertility treatments other than IVF.[30] Some modification in the gestational process induced by IVF and intracytoplasmic sperm injection has been suggested,[31] as well as so-called vanishing twins (singletons originating from twin pregnancies).[32] It has also been found that the risk for preterm birth increases with low-technology treatments, compared with natural pregnancy, and increases further with high-technology treatments.[33]

Zygosity plays a significant role when the health of IVF multiple births are compared with the health of other multiple births. In general, monozygotic twins have poorer perinatal outcomes than dizygotic twins. A larger proportion of twins are dizygotic among medically assisted pregnancies (30%), compared with naturally conceived pregnancies (1%).[34] This can partly explain the results of the similar outcomes of multiple births in studies unable to take zygosity into account. In our study, 50% of IVF twins and 30% of control twins were opposite-gender twins, which suggested that more IVF children were dizygotic.

During the 1990s, the perinatal health of IVF children improved in Finland, mainly because of a decrease in higher-order multiple births.[35,36] Because so many IVF pregnancies in the late 1990s were still multiple births, the health of IVF children in total was worse than that of naturally conceived children, with increased risks for CP and developmental and psychological problems. The best way to improve the health of IVF children is to favor single-embryo transfers. The way to improve the health of singletons is more problematic, because we do not know the reasons for the findings. Sufficiently large follow-up studies that consider the health of IVF children from 4 years onward are needed.

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Paper IV

Children born after assisted fertilization have an increased rate of major congenital anomalies

Reija Klemetti, M.H.Sc.,[a] *Mika Gissler, D.Phil.,*[b] *Tiina Sevón,*[a] *Sari Koivurova, M.D.,*[c] *Annukka Ritvanen, M.D.,*[b] *and Elina Hemminki, M.D. Dr. P.H.*[a]

[a] Health Services Research and [b] Information Unit, National Research and Development Centre for Welfare and Health (STAKES), Helsinki; and [c] Department of Obstetrics and Gynecology, University Hospital of Oulu, Oulu, Finland

Objective: To study the occurrence of major congenital anomalies (CAs) among children born after IVF (IVF, microinjections, and frozen embryo transfers) and after ovulation inductions with or without insemination (other assisted reproductive technologies [ART]).
Design: Register-based study.
Setting: Data regarding CAs were obtained from the Register of Congenital Malformations.
Patient(s): Children from IVF (n = 4,559), children from other ART (n = 4,467), and controls (n = 27,078, a random sample of naturally conceived children) from the Medical Birth Register.
Intervention(s): In vitro fertilization and other ART treatment in ordinary practice.
Main Outcome Measure(s): Rate of major CAs. Children from IVF and other ART were compared with control children, both overall and by plurality, controlling for confounding factors by logistic regression.
Result(s): For IVF children, the adjusted odds ratio (OR) was 1.3 (95% confidence interval [CI], 1.1–1.6). Stratifying by gender and plurality showed that the risk was only increased for boys, and the risk was decreased for multiple IVF girls (OR = 0.5, 95% CI 0.2–0.9). The crude OR of major CA for other ART children was 1.3 (95% CI 1.1–1.5), but adjusted differences by gender and plurality were statistically insignificant.
Conclusion(s): In vitro fertilization was associated with an increased risk for major CAs among singleton boys and a decreased risk among multiple girls. The risk after other ART was only slightly increased. (Fertil Steril® 2005;84:1300–7. ©2005 by American Society for Reproductive Medicine.)

Key Words: Major congenital anomaly, ART, register-based study

In vitro fertilization and its related procedures—intracytoplasmic sperm injection (ICSI)and frozen embryo transfer (FET)—have become common infertility treatments. For example, in Finland approximately 2.5% of all infants are born as a result of these therapies (1). The exact number of children born after other assisted reproduction technologies (ART), such as ovulation inductions and inseminations, is unknown, but according to our estimation during 1996–1999 2.4% of all infants were born after other ART in Finland.

Some studies (2–9) but not others (10–13) have shown an increase in some congenital anomalies (CAs) among IVF or ICSI children. Most published studies have had methodological problems, such as small sample sizes, lack of proper controls, and different definitions of CA among IVF and naturally conceived children. In a recent Australian study, the rate of musculoskeletal, cardiovascular, chromosomal, and urogenital defects was increased among IVF children (7). In a small Finnish study, the prevalence of heart malformations was fourfold among IVF infants compared with control infants (8). We found only one study on malformations of children born as a result of other ART (14). There were increased rates of congenital malformations, but these could be mainly explained by maternal characteristics.

In this study, we compared the prevalence of major CAs among IVF and other ART children with that among naturally conceived children, controlling for confounding factors. The data source of CAs was the same for all children—the Finnish Register of Congenital Malformations (RCM)—and we have information regarding the drugs used in the infertility therapy.

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Reprint requests: Reija Klemetti, M.H.Sc., STAKES, Health Services Research, P.O. Box 220, Helsinki 00531, Finland (FAX: 358-9-3967-2496; E-mail: reija.klemetti@stakes.fi).

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MATERIALS AND METHODS

The study is based on children born to women having received IVF (IVF, ICSI, and FET) and other ART between 1996 and 1998 in Finland. The women were identified with a predesigned algorithm from the reimbursement files of the Social Insurance Institution (15) and linked to the Finnish Medical Birth Register (MBR); the time difference between the beginning of the last treatment cycle and the birth of the child was used to estimate which infants resulted from IVF or other ART (16).

The MBR includes the mother's and child's unique personal identification numbers and contains information on maternal background and on the infant's outcome until the age of 7 days for all infants born in Finland. The duration and causes of infertility are not registered. The data are collected by delivery hospitals and completed by linkage to the Central Population Register and the Cause-of-Death Register. The quality of the MBR has been found to be high for the variables used in this study (17, 18).

We identified 4,559 IVF and 4,467 other ART children born between October 1996 and September 1999. As controls, 27,078 naturally conceived children (three times the number of cases) were selected randomly from the MBR, excluding children having a note of IVF or other ART in MBR. Children from ICSI (n = 861) could be distinguished from IVF children only if the treatment had been given in private clinics because a specific code for ICSI exists only there.

The identified children were linked to the RCM according to the mothers' identification numbers and the childrens' dates of birth. The RCM collects information on all infants with a CA or birth defect through several data sources, including a form completed by delivery hospitals, neonatal, pediatric, and pathology departments, and cytogenetic laboratories and by linkage to several other nationwide registers. More than 99% of the major CAs are registered before the age of 1 year.

In the RCM a CA has been defined as a major congenital structural anomaly, chromosomal defect, or congenital hypothyroidism involved in a birth. The register records all notified cases, but the physician responsible for RCM routinely classifies congenital anomalies into major, other, and rejected. Rejected anomalies include some minor congenital anomalies, as defined by the European Surveillance of Congenital Anomalies (European Concerted Action on Congenital Anomalies and Twins [EUROCAT]; http://www.eurocat.ulster.ac.uk) exclusion list (hereditary diseases, dysfunction of organs or tissues, developmental disabilities, congenital infections, isolated minor dysmorphic features, normal variations, and other less significant anomalies). For this study, the physician reviewed all diagnosis and inclusion criteria without knowing the mode of conception of the children.

The study plan was approved by the National Research and Development Centre for Welfare and Health (STAKES) research ethics committee. For register linkages, the National Data Protection Authority was consulted and permissions from the register keepers were obtained.

The differences were tested by *t*-test, a test for relative proportions, and a χ^2 test. The statistical analyses were performed in SAS, version 8 (SAS Institute, Cary, NC). The IVF and other ART children were compared with the control children according to odds ratios (OR) and 95% confidence intervals (CI), stratifying by gender and multiplicity. Twins and triplets were analyzed separately. Differences in age of the mother, parity, socioeconomic position (measured from maternal occupation), and the region of residence were controlled by logistic regression.

In the analysis by organ system, a child appeared more than once if (s)he had more than one major CA affecting different organ systems. Different CAs in the same organ system were calculated as one, but if the child had a major CA both in the urinary and genital system, only one was taken into account by combining these two groups as the "urogenital system." Only major CAs, as defined in the RCM, were included in the analysis, but minor urinary and genital CAs were separately compared between studied groups.

To investigate which of the infertility drugs used in the treatment were related to CAs, a nested case–control design in the IVF and other ART cohorts was used: mothers of children with CAs were compared with mothers of nonmalformed children. Drugs used during the last IVF cycle preceding the birth were classified into five groups: GnRH, FSH, hCG, progesterones (Ps) (among IVF women 99% and among other ART women 50% were natural Ps), and estrogens (Es), and the age-adjusted ORs for using at least one of the drugs from the category were calculated.

To estimate the total prevalence of major CAs, we linked the IVF and other ART women to the Register of Induced Abortions, specifying induced abortions performed because of a suspected or confirmed CA. The rates were compared with the national rates per 10,000 births.

RESULTS

In vitro fertilization and other ART mothers differed from control mothers, and IVF mothers from other ART mothers in regard to most characteristics (Table 1). Multiplicity was much higher in the IVF than in the other ART group, but the number of triplets was the same (16 vs. 17).

Among IVF and other ART children, 51% of reported major CAs had been accepted by the RCM, whereas among control children the proportion was 46%. In total, 195 IVF children (4.3%), 166 other ART children (3.7%), and 787 control children (2.9%) had at least one major CA. The prevalence of a major CA was the same for IVF singletons and IVF multiples but much higher for multiples than for singletons among other ART and control children (Table 2).

TABLE 1

Characteristics of IVF, other ART, and control mothers and children by multiplicity and gender.

	IVF	Other ART	Controls
Mothers	n = 3,737	n = 4,188	n = 27,022
Age (y) (mean ± SD)[a]	33.9 ± 4.5	31.2 ± 4.6	29.8 ± 5.3
Age (y)[b]			
<25	2.2	8.3	19.7
25–29	17.3	34.1	32.2
30–34	40.6	37.2	31.4
35–39	30.1	16.4	13.5
40+	9.8	4.0	3.1
Married[c]	76.1	74.8	60.5
Parity[b]			
0	71.7	54.3	38.7
1	21.1	32.4	33.4
2	4.2	9.3	16.4
3+	2.4	3.3	10.1
Missing	0.6	0.7	1.4
Socioeconomic position[b]			
Upper white-collar	26.1	21.2	15.7
Lower white-collar	48.8	47.8	41.3
Blue-collar	12.8	13.9	16.6
Other	12.3	17.2	26.4
Place of residence[b]			
Southern Finland	44.8	38.6	40.6
Western Finland	33.4	38.3	34.4
Eastern Finland	9.9	9.5	10.4
Northern Finland	11.6	13.3	13.9
Missing	0.3	0.3	0.7
Children	n = 4,459	n = 4,467	n = 27,078
Singletons	64.3	87.9	97.8
Girls	32.7	42.8	48.6
Boys	31.6	45.1	49.3
Multiples	35.7	12.1	2.2
Girls	17.6	6.0	1.2
Boys	18.1	6.0	1.0

Note: Values are percentages, unless otherwise noted.

[a] $P<.001$, *t*-test.

[b] $P<.001$ for all comparisons (IVF vs. other ART, IVF vs. controls, and other ART vs. controls), χ^2 test.

[c] $P<.001$ (IVF vs. controls and other ART vs. controls), test for relative proportions.

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Boys from IVF, both singletons and multiples, had major CAs more often than IVF girls (Table 3). The same was seen among multiples from other ART.

An increased OR for having any major CA was found in the crude analysis both for IVF and other ART children (Table 3). The adjustment for maternal age or other confounding factors somewhat decreased the ratio for IVF children but not for other ART children. The total risk for singletons was statistically significantly increased and for multiples insignificantly decreased. A significantly increased OR was found among singleton IVF boys, and a significantly decreased OR for multiple IVF girls. The result did not change after taking into account the confounding factors. In the separate analysis for twins, excluding triplets, the results for IVF girls remained similar (the adjusted OR was 0.31, 95% CI 0.11–0.88).

In the analysis by different organ system, compared with controls, IVF children had a higher risk for CA for most categories. Compared with other ART children, IVF children had more CAs in the categories of "eye, ear, face, and neck,"

TABLE 2

Prevalence of major congenital anomalies per 10,000 infant by the organ system affected.[a]

	Singletons								Multiples							
	IVF (n = 2,930)			Other ART (n = 3,926)			Controls (n = 26,489)		IVF (n = 1,629)			Other ART (n = 541)			Controls (n = 589)	
	n	/10,000	*P*[b]	n	/10,000	*P*[b]	n	/10,000	n	/10,000	*P*[b]	n	/10,000	*P*[b]	n	/10,000
Any	125	427	<.001	138	352	.022	756	285	70	430	.335	27	499	.836	31	526
Central nervous system	9	31	.008	12	31	.003	31	12	9	55	.071	7	129	.006	0	0
Eye, ear, face and neck	12	41	.009	6	15	.693	48	18	5	31	.583	1	18	.952	1	17
Heart	44	150	.042	59	150	.021	287	108	33	203	.791	11	203	.840	13	221
Other circulatory system	6	20	.740	12	31	.088	47	18	2	12	.790	0	0	.338	1	17
Respiratory system	5	17	.284	5	13	.647	27	10	3	18	.496	0	0	.175	2	34
Cleft palate and cleft lip	12	41	.034	14	36	.076	56	21	5	31	.904	0	0	.175	2	34
Digestive system	14	48	.028	16	41	.083	67	25	5	31	.093	4	74	.836	5	85
Urogenital system	35	119	<.001	26	66	.150	129	49	12	74	.789	4	74	.836	5	85
Musculoskeletal system	34	116	.004	30	76	.588	182	69	20	123	.270	6	111	.441	4	68
Skin, hair and nails	1	3	.533	2	5	.757	17	6	2	12	.395	0	0	NA	0	0
Chromosomal anomalies	8	27	.304	7	18	.927	49	18	3	18	.496	2	37	.932	2	34
Other congenital anomalies and the defects	12	41	.171	19	48	.020	71	27	9	55	.237	3	55	.381	6	102

Note: NA = not applicable.

[a] n = number of children. If a child had a major malformation in more than one organ system, the child appears several times in the table. If the malformations affect the same organ system, the child appears only once in the table.

[b] Test for relative proportions, control group as a reference group.

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TABLE 3

Total risk of major congenital anomalies and risk according to organ system affected[a] by gender and multiplicity.

		Risk								
		Girls			Boys			Total		
Multiplicity	Group	n[b]	OR (95% CI)	OR[c] (95% CI)	n[b]	OR (95% CI)	OR[c] (95% CI)	n[b]	OR (95% CI)	OR[c] (95% CI)
Singletons										
Total	Control	348	1.00	1.00	408	1.00	1.00	756	1.00	1.00
	IVF	48	1.23 (0.90–1.66)	0.97 (0.69–1.36)	77	1.79 (1.40–2.30)	1.63 (1.23–2.15)	125	1.52 (1.25–1.84)	1.30 (1.05–1.61)
	Other ART[d]	67	1.34 (1.02–1.74)	1.21 (0.98–1.67)	71	1.16 (0.90–1.50)	1.12 (0.86–1.46)	138	1.24 (1.03–1.49)	1.17 (0.97–1.41)
Heart	Control	128	1.00	1.00	136	1.00	1.00	264	1.00	1.00
	IVF	17	1.17 (0.71–1.95)	1.05 (0.62–1.78)	19	1.30 (0.80–2.11)	1.21 (0.73–2.00)	36	1.24 (0.87–1.75)	1.13 (0.79–1.62)
	Other ART	29	1.57 (1.04–2.35)	1.52 (1.01–2.28)	24	1.17 (0.76–1.81)	1.17 (0.75–1.81)	53	1.36 (1.01–1.83)	1.33 (0.99–1.80)
Urogenital	Control	52	1.00	1.00	80	1.00	1.00	26	1.00	1.00
	IVF	9	1.53 (0.75–3.11)	1.47 (0.70–3.07)	22	2.57 (1.60–4.14)	2.46 (1.49–4.07)	31	2.14 (1.44–3.17)	2.05 (1.36–3.10)
	Other ART	4	0.53 (0.19–1.46)	0.52 (0.19–1.45)	20	1.66 (1.02–2.72)	1.62 (0.99–2.65)	24	1.23 (0.79–1.90)	1.20 (0.78–1.87)
Musculosceletal	Control	72	1.00	1.00	110	1.00	1.00	182	1.00	1.00
	IVF	11	1.35 (0.72–2.55)	1.26 (0.65–2.44)	23	1.95 (1.24–3.07)	1.75 (1.09–2.81)	34	1.70 (1.17–2.45)	1.55 (1.05–2.27)
	Other ART	12	1.15 (0.62–2.12)	1.11 (0.60–2.05)	18	1.09 (0.66–1.79)	1.04 (0.63–1.72)	30	1.11 (0.76–1.64)	1.07 (0.73–1.58)
Multiples										
Total	Control	18	1.00	1.00	13	1.00	1.00	31	1.00	1.00
	IVF	26	0.55 (0.30–1.02)	0.45 (0.22–0.93)	44	1.13 (0.60–2.14)	1.31 (0.64–2.71)	70	0.81 (0.52–1.25)	0.80 (0.48–1.32)
	Other ART	7	0.44 (0.18–1.08)	0.41 (0.16–1.05)	20	1.59 (0.77–3.26)	1.56 (0.71–3.42)	27	0.95 (0.56–1.61)	0.91 (0.52–1.61)
Total	Control	366	1.00	1.00	421	1.00	1.00	787	1.00	1.00
	IVF	74	1.19 (0.93–1.54)	0.97 (0.73–1.28)	121	1.77 (1.44–2.17)	1.66 (1.31–2.10)	195	1.49 (1.27–1.75)	1.31 (1.10–1.57)
	Other ART	75	1.26 (0.98–1.62)	1.15 (0.89–1.50)	91	1.30 (1.03–1.64)	1.26 (0.99–1.59)	166	1.28 (1.08–1.52)	1.21 (1.02–1.44)

[a] Reference group (OR = 1) = control children. If a child had a major CA in more than one organ system, the child appears several times in the table. If the CAs affect the same organ system, the child appears only once in the table.

[b] n = number of malformed children.

[c] For all major CAs adjusted by age, parity, socioeconomic position, and region, and for some specific anomalies according to organ system adjusted only by age owing to the small number of cases.

[d] One other ART child excluded owing to missing gender status.

Klemetti. Assisted reproduction and congenital anomaly. Fertil Steril 2005.

TABLE 4

Major genital anomalies (and all hypospadias) among singleton boys: number and rate per 10,000.

	IVF (n = 1,440)	Other ART (n = 2,014)	Controls (n = 13,339)
Total			
No.	11	6	15
Rate	76	30	11
P[a]	<.001	.036	
Hypospadias			
No.	7	3	10
Rate	15	7	4
P[a]	<.001	.287	
All hypospadias[b]			
No.	11	8	38
Rate	76	40	29
P[a]	.003	.390	

[a] Test for relative proportions, compared with controls.
[b] Also includes glandular hypospadias.

Klemetti. Assisted reproduction and congenital anomaly. Fertil Steril 2005.

"respiratory system," "urogenital system," and "musculoskeletal system." When stratifying the analysis to singletons and multiples (Table 2), IVF singletons had statistically significantly more major CAs than control singletons in many categories. Among multiples the rates were the opposite: in most categories, IVF multiples had fewer major CAs than control multiples, and none of the differences were statistically significant. Among other ART children, singletons had more and multiples had fewer CAs in most organ systems than control singletons, but the differences were not as clear as that between IVF and control children.

When inspecting the risk according to the organ system affected, by gender and multiplicity, we found a slightly increased OR for major heart anomalies among singleton other ART girls and increased ORs for urogenital and musculoskeletal CAs among singleton IVF boys (Table 3). The results remained the same after adjustment for age. Among IVF singleton boys, major urogenital CAs were more severe than among controls. When we checked for minor urogenital CAs of singleton boys, no reported minor urinary CA was observed. In the separate analysis of urinary and genital CAs, it was found that the increased risk was mainly due to the genital CAs. Hypospadia was the most common diagnosis of these major genital anomalies, and control boys had more minor hypospadias than IVF boys (Table 4). In addition, other ART singleton boys had a higher risk for urogenital CAs. No specific musculoskeletal CA among IVF boys was found.

Out of 861 ICSI children, 40 (4.6%) had one or more CA. The frequency of major CAs was in general as among all IVF children. Because of the small number of cases, a more specific analysis of the ICSI group was not done.

By definition, all IVF mothers were exposed to some infertility drugs, most commonly to P (Table 5). Most mothers were exposed to several drugs. Only Es were used more often by the mothers of malformed than by the mothers of

TABLE 5

Drugs used by mothers of malformed and nonmalformed children.

Group	Malformed[a]	Non-malformed	*P*[b]
IVF[c]	n = 179	n = 4,088	
P	87	88	.736
FSH or hMG	59	63	.241
GnRH	55	62	.050
hCG	17	20	.286
E_2	20	12	.003
Other ART	n = 166	n = 4,301	
Clomiphene citrate	81	86	.056
P	30	30	.896
FSH or hMG	14	11	.250
hCG	5	4	.598

Note: Values are percentages.
[a] At least one major congenital anomaly.
[b] Comparisons of malformed and nonmalformed groups, test for relative proportions.
[c] Two hundred ninety-two IVF children are excluded owing to the lack of information on drugs used.

Klemetti. Assisted reproduction and congenital anomaly. Fertil Steril 2005.

nonmalformed IVF children, but mothers of most malformed children had not received it. Some 27% of the mothers of singleton boys with a genital CA had used Es (vs. 13% of mothers of nonmalformed singleton boys) and 82% P (vs. 82% of mothers of nonmalformed singleton boys). Among other ART children, no differences in the drugs used between malformed and nonmalformed children were found, neither in the use of a natural nor a synthetic progestin.

During the study period, 9 of the 9,175 IVF women (19.7 per 10,000 IVF births) and 8 of the 10,270 other ART women (17.9 per 10,000 other ART births) had an induced abortion owing to the suspected or detected fetal defect. The national rate per 10,000 births in 1996–1998 in Finland was 36.7 (The Finnish Medical Birth Register).

DISCUSSION

We found increased total rates of major CAs for IVF and other ART singletons. Singleton boys from IVF in particular had more major urogenital and musculoskeletal CAs, and other ART singleton girls had more major heart anomalies. Among multiples, the total risk for a major CA was not increased, and for multiple IVF girls the risk had even decreased.

Can our results be trusted? Our data include most infants born as a result of IVF and other ART in Finland during the study period. The identification was based on drugs used in infertility therapy and reimbursed treatments (only private clinics) (15, 16). It is possible that we missed some women who had received their treatment in the public sector and had used drugs bought and reimbursed before 1996. We have estimated that our data lack approximately 4% of IVF women and 6% of other ART women (15), but the identification of the women was made before pregnancy and is unlikely to relate to the occurrence of major CAs.

Data on major CAs in all three groups came from a routine nationwide register, the RCM, to which information is collected and classified blindly with regard to IVF or ART status. However, we do not know whether physicians who reported CA to the register knew the mode of conception. It could be that IVF children were more carefully examined and/or that CAs for them were more conscientiously reported than those for naturally conceived children. However, the fact that more reports that were rejected by the RCM occurred for control children than for IVF children speaks against this source of bias. Likewise, the checking of minor genital anomalies showed that the number of reported minor CAs of IVF children was smaller than that of controls. One could have expected it to be greater if the IVF and other ART children had been more carefully examined and reported. The types of genital anomalies suggest that classification into major CAs has been clear-cut.

We do not have information regarding induced abortions of the naturally conceived children's mothers or of major CAs among them. However, the rates of induced abortions due to CAs were so low that they are unlikely to bias the results.

According to previously published studies, twins have more CAs than singletons (19). That was also true among control children in our study but not among IVF children, which is in accordance with the results from a recent Danish study of IVF and ICSI twins, in which no differences in malformation rates between IVF/ICSI and naturally conceived twins were found (20). What, therefore, could explain this discrepancy between multiples and singletons? One explanation could be the fact that many singletons originated from multiple ET and from multiple pregnancy with a higher risk (during the study period 15% of ETs [IVF, ICSI, and FET] were single-embryo transfers, but 88% of live births were singleton births [21]). If two embryos succeed during implantation and develop in assisted reproduction, it can be assumed that conditions have to have been especially favorable.

Another possible explanation is zygocity: monozygotic twins have more malformations than dizygotic, and monozygosity is rarer among twins of assisted reproduction than among naturally conceived twins (1% vs. 30%) (22). Although IVF and other ART increase monozygotic twinning (6, 14), transfer of several embryos causes the majority of IVF twins to be dizygotic. The fact that the CA rate was not smaller among IVF twin boys could result from a higher risk of CA among IVF boys.

Most hormones in IVF treatment are used before pregnancy, and the half-life of most of these drugs is short. However, the duration of active drugs and metabolites in the body and their individual variations are not clear. Some drugs are also used as luteal-phase support during pregnancy. In addition to direct toxic effect, the drugs might have their effect through the mother's hormonal secretion balance. Although the dangers of hormones in early pregnancy have been discussed for decades (23, 24), this has not been the focus when the health effects of IVF have been discussed. We had information regarding fertility drugs (dosages and number of packages) bought, but the exact date and duration of their use was not known. Because the treated women received many and varied medicines during the last cycle, it was not possible to identify any specifically harmful drug.

Our study verified an earlier result of the overall risk for urogenital CAs (7), but ours was too small to study the risk of individual diagnoses, such as the hypospadia previously reported (6, 25). The use of P during IVF treatment has been offered as one explanation for the increased risk of one genital CA, hypospadia (25). Children exposed in utero to E and P or only P were found to have more male genital malformations than nonexposed children (23). However, in our study no difference in P use was found among boys with major genital anomalies and other IVF boys. Instead, E use was more frequent, but most boys with genital CAs were not exposed to it.

Another explanation for the higher rate of male genital anomalies might be the hereditary paternal subfertility associated with ICSI (5). Unfortunately, we could identify ICSI children only when the treatment was given in a private clinic. Because of the possible bias and the small number of children, we did not study specific CAs of ICSI children. Because the genital CAs were more severe among IVF than among control children, the risk for major urogenital CAs could be greater than our results show. The risk was also somewhat increased among other ART boys.

In another Finnish study, IVF children had more heart anomalies than control children (8). This was also true in our study, but the risk was not statistically significant. Rather, it was found among other ART children. This might relate to the use of clomiphene citrate (14). The increased risk for musculoskeletal CAs among IVF children is in accordance with a previous study from Australia (7).

Other than drugs, potential causes for congenital anomalies could include infertility itself, the advanced age of mothers, and factors related to the IVF procedure, such as the freezing and thawing of embryos. We did not have any information about the duration and causes of infertility and could not adjust data for them. The higher age of mothers did not explain the increased risk for major CAs.

In conclusion, our study verifies an increased risk for major CAs among IVF singleton boys and suggests that the risk after other ART is also slightly increased and not explained by those maternal characteristics available in the Finnish MBR. The actual risk is, however, quite small. Because our findings regarding different organ systems are based on small numbers of children, further studies are needed to explain them. It would be important to perform a large follow-up study of IVF and other ART births which includes information on the duration and causes of infertility, exact information regarding maternal drug exposure, and other maternal background characteristics. Meanwhile, the techniques used in IVF and other ART should be considered potentially teratogenic, thus requiring that information be given to the physicians and the public.

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Paper V

Equity in the resource allocation of in vitro fertilization

Klemetti R, Gissler M, Sevón T, Hemminki E.

Abstract

Background: The purpose of this study was to describe equity in the allocation of resources for in vitro fertilization (IVF) by women's age and socioeconomic position.
Methods: Women who received IVF between 1996 and 1998 (N=9175) were identified from the reimbursement records of the Social Insurance Institution (SII). Information on IVF women's background characteristics came from the Central Population Register and the SII, on treatment costs from IVF clinics and the SII, and on births from the Medical Birth Register.
Results: During a mean period of 1.5 years, older women received 1.4 times more IVF treatment cycles than younger women. The success rate—live births per cycle—decreased by age: from 22% among women aged below 30 to 6% among women aged 40 or older. The mean cost of a live birth increased by age from EUR 12 851 to EUR 40 662. Calculated by population, society contributed most to women from the highest socioeconomic position.
Conclusions: Our study suggests that women from higher socioeconomic position are favoured in resource allocation. Children of older women are more expensive, but equality of services cannot be judged because we have no information on need for IVF by age.

Key words: costs / equity / expenditures / in vitro fertilization / resource allocation

The Use of Assisted Fertilization in Finland: Health Effects and Equity

Reija Klemetti

Academic Dissertation

Research Reports 158

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Tutkimuksen taustaa: Koeputkihedelmöitys (IVF, joka sisältää mikroinjektion ja pakastetun alkion siirron) ja munasarjojen lääkkeellinen induktio (OI, johon voi sisältyä keinosiemennys) ovat yleisiä hedelmöityshoitoja Suomessa. Niiden käytöstä ja terveysvaikutuksista hoitoja saaneille naisille ja hoitojen jälkeen syntyneille lapsille ei kuitenkaan vielä tiedetä riittävästi. Oikeudenmukaisuus on suomalaisessa terveydenhuollossa määritelty siten, että samanlaisessa tarpeessa olevilla on samanlainen mahdollisuus päästä hoitoon ja saada hoitoa. Terveydenhuoltoon käytettävien resurssien tulisi jakautua oikeudenmukaisesti sukupuolen, iän, asuinalueen ja sosioekonomisen aseman suhteen. IVF on kallis hoito, jossa naisen iän lisääntymisen myötä onnistuminen laskee. Samoin äidin ja lapsen terveysongelmien riski kasvaa.

Tutkimuksen tarkoitus: Tämän tutkimuksen tarkoituksena on useita terveydenhuollon rekistereitä käyttäen selvittää IVF:n ja OI:n käyttöä, sairaalahoitoon johtaneita komplikaatioita ja keskenmenoja hoitoja saaneilla naisilla, hoitojen jälkeen syntyneiden lasten terveyttä ja kuvata IVF-hoitoihin käytettyjen resurssien jakautumista hoitoja saaneiden naisten iän ja sosioekonomisen aseman sekä hoitosektorin (yksityinen tai julkinen) mukaan sekä pohtia IVF:n käytön ja resurssien jaon oikeudenmukaisuutta.

Tutkimusaineisto ja menetelmät: Tässä rekisteripohjaisessa tutkimuksessa IVF-hoitoja (N = 9175) ja OI-hoitoja (N = 10 254) vuosina 1996–1998 saaneet naiset identifioitiin Kelan lääke- ja toimenpidekorvausrekistereistä ja heitä seurattiin vuoteen 2000 yhdistämällä aineisto hoitoilmoitus- ja kuolinsyyrekistereihin. IVF-naisille valittiin iän ja asuinpaikan suhteen kaltaistetut vertailunaiset (N = 9175). IVF:n (N = 4559) ja OI:n (N = 4467) jälkeen syntyneet lapset identifioitiin syntymärekisteristä, josta heille poimittiin vertailulapset (kaikki muut lapset, N=190 398, tutkittaessa vastasyntyneisyysajan terveyttä, sairaalahoitoja ja kuolleisuutta, ja satunnaisotos näistä lapsista, n = 26 877 tutkittaessa synnynnäisiä epämuodostumia ja pitkäaikaissairaiden lasten hoitotukia ja korvattuja lääkkeitä). Lapsia seurattiin vuoden 2003 loppuun yhdistämällä aineisto hoitoilmoitus-, epämuodostuma- ja kuolinsyyrekisteriin sekä Kelan rekistereihin. Naisten taustatiedot saatiin Kelasta ja Väestörekisteristä ja hoitojen korvaus- ja kustannustiedot Kelasta ja hoitoja antavilta klinikoilta.

Tulokset: Keskimääräisen 1,5 vuoden seurannan aikana vanhimmat, 40 vuotta täyttäneet naiset, saivat hieman enemmän IVF-hoitosyklejä kuin nuorimmat, alle 30-vuotiaat naiset (2,2 vrt. 3,0). Yksityissektorilla oli julkista sektoria enem-

män korkeammassa sosioekonomisessa asemassa olevia IVF-hoitoja saaneita naisia. Nämä naiset saivat muita enemmän IVF-syklejä. IVF-hoitojen onnistuminen – elävänä syntyneiden lasten lukumäärä IVF-syklejä kohti – laski naisen iän myötä: 22 % alle 30-vuotiailla ja 6 % yli 40-vuotiailla.

IVF:n jälkeen 23 ja OI:n jälkeen yksi tuhannesta naisesta joutui tutkimusajankohtana (keskimäärin 2,7 hoitoa) sairaalaan munasarjojen hyperstimulaatiosyndrooman (OHSS) takia. Sekä IVF:n että OI:n jälkeen sairaalahoitoon johtaneita keskenmenoja oli 42 tuhatta hoidettua naista kohti. Noin 15 % IVF-naisista ja 8 % OI-naisista joutui komplikaatioiden tai keskenmenon takia ainakin kerran sairaalahoitoon seurannan aikana.

IVF-lasten vastasyntyneisyysajan terveys oli huonompi ja sairaalahoito yleisempää kuin muilla lapsilla. IVF-lapsilla oli kohonnut riski CP-vammaisuuteen (OR-luku 2.9 ja 95 % luottamusväli 1.6–5.3), psykologisiin ja kehityksellisiin häiriöihin (1.7, 1.1–2.5) sekä synnynnäisiin merkittäviin epämuodostumiin (1.3, 1.1–1.6). Tulokset selittyivät osin monisikiöisten raskauksien suurella määrällä. IVF-yksösillä oli muita yksösiä huonompi vastasyntyneisyysajan terveys, enemmän sairaalahoitoja ja pojilla kohonnut synnynnäisten epämuodostumien riski. IVF-kaksosten ja -kolmosten terveys oli samanlainen kuin muilla kaksosilla ja kolmosilla.

Keskimääräiset kokonaiskustannukset elävänä syntynyttä IVF-lasta kohti lisääntyivät naisen iän myötä 12 851 eurosta (alle 30-vuotiaat) 40 662 euroon (40 vuotta täyttäneet). Väestökohtaisesti laskettuna (kutakin ikäluokkaa ja sosioekonomista asemaa kohti) yhteiskunnan resursseja käytettiin eniten 30–39-vuotiaiden naisten ja korkeimmassa sosioekonomisessa asemassa olevien naisten hoitamiseen. Alueelliset erot olivat pieniä.

Johtopäätökset: Vaikka suurin osa IVF-lapsista oli terveitä, heillä oli enemmän terveyteen liittyviä ongelmia kuin muilla lapsilla. Yksittäiseen IVF-sykliin liittyvien komplikaatioiden riski oli pieni, mutta useampien hoitosyklien antaminen johti vakaviin komplikaatioihin useilla naisilla; IVF:n jälkeen selvästi useammin kuin OI:n jälkeen. Lisätutkimuksia tarvitaan selvittämään IVF- ja OI-naisten ja heidän lastensa pidemmän ajan terveyttä. Tutkimuksessa ei ollut tietoa hoidon tarpeesta eli hedelmättömyyden yleisyydestä eikä toiveesta saada lapsi, joten ei voi varmasti sanoa, suositaanko hedelmöityshoidoissa tietyn ikäisiä naisia. Korkeammat kustannukset, suuremmat terveysriskit ja hoitojen huonompi onnistuminen vanhemmilla naisilla puoltavat keskittymistä nuorempien, hedelmällisessä iässä olevien naisten hoitamiseen. Erot sosioekonomisen aseman suhteen IVF:n käytössä ja resurssien jaossa voivat kertoa epäoikeudenmukaisuudesta.

Avainsanat: koeputkihedelmöitys, ovulaation induktio, rekisteritutkimus, terveysvaikutukset, komplikaatiot, OHSS, lasten terveys, synnynnäiset epämuodostumat, kustannukset, oikeudenmukaisuus

SAMMANFATTNING

Klemetti Reija. The Use of Assisted Fertilization in Finland: Health Effects and Equity [Användningen av assisterad befruktning i Finland: Hälsoeffekter och rättvisa.]STAKES, Research Reports, 158. Helsingfors, Finland, 2006. ISBN 951-

Bakgrund till undersökningen: In vitro fertilisering (IVF, som omfattar en mikroinjektion och överföring av ett fryst embryo) och medicinsk ovulationsinduktion (OI, som kan omfatta artificiell insemination) är vanliga fertilitetsbehandlingar i Finland. Om deras användning och hälsopåverkan på kvinnorna som fått behandling och på barnen som föds efter behandlingen vet man dock tillsvidare inte tillräckligt. Rättvisa har inom den finländska hälso- och sjukvården definierats så, att de som har samma behov har samma tillgång till vård och samma möjlighet att få vård. De resurser som används för hälso- och sjukvård borde fördelas rättvist i förhållande till kön, ålder, bostadsort och socioekonomisk ställning. IVF är en dyr behandling, och med ökad ålder hos kvinnan minskar behandlingens utfall. Samtidigt ökar risken för hälsoproblem hos modern och barnet.

Syftet med undersökningen: Syftet med denna undersökning är att med hjälp av flera av hälso- och sjukvårdens register utreda användningen av IVF och OI, komplikationer och missfall som lett till sjukhusvård hos kvinnor som erhållit behandlingar och hälsan hos barn som fötts efter behandlingarna samt att beskriva fördelningen av de resurser som använts för IVF-behandlingar i förhållande till de behandlade kvinnornas ålder och socioekonomiska ställning samt vårdsektor (privat eller offentlig). Syftet är även att bedöma användningen av IVF och rättvisan i fördelningen av resurserna.

Undersökningsmaterial och metoder: I denna registerbaserade undersökning identifierades kvinnor som fått IVF-behandling (N = 9175) och OI-behandling (N = 10 254) under åren 1996–1998 i Folkpensionsanstaltens (FPA) register över ersättningar för läkemedel och åtgärder, och kvinnorna följdes upp till år 2000 genom att materialet sammanställdes med vårdanmälnings- och dödsorsaksregistren. För IVF-kvinnorna valdes en kontrollgrupp av kvinnor (N = 9175) som matchades utifrån ålder och bostadsort. Barnen som fötts efter IVF (N = 4559) och OI (N = 4467) identifierades i födelseregistret, från vilket en jämförelsegrupp av barn valdes (alla övriga barn, N=190 398, vid undersökning av hälsan under perinataltiden, sjukhusvård och dödlighet, och ett slumpmässigt urval av barn, n = 26 877 vid undersökning av medfödda missbildningar och vårdstöd för långtidssjuka barn och ersättningar för läkemedel). Barnen följdes upp till slutet av år 2003 genom att materialet sammanställdes med vårdanmälnings-, missbildnings- och dödsorsaksregistren samt FPA:s register. Bakgrundsinformation om kvinnorna erhölls från FPA och Befolkningsregistret och uppgifterna om ersättningar och kostnader för behandlingarna från FPA och de kliniker som gav behandling.

Resultat: Under den i medeltal 1,5 år långa uppföljningstiden fick de äldsta kvinnorna, som fyllt 40 år, något fler IVF-behandlingscykler än de yngsta, under 30 år gamla kvinnorna (2,2 mot 3,0). Inom den privata sektorn fanns fler kvinnor med högre socioekonomisk ställning som fått IVF-behandling än inom den offentliga sektorn. Dessa kvinnor erhöll fler IVF-cykler än andra. Antalet lyckade IVF-behandlingar – antalet levande födda barn per IVF-cykel – minskade med kvinnans ålder: 22 % vid under 30 års ålder och 6 % vid över 40 års ålder.

Efter IVF togs 23 och efter OI en av tusen kvinnor under undersökningsperioden (i medeltal 2,7 behandlingar) in på sjukhus på grund av ovarialt överstimuleringssyndrom (OHSS). Efter både IVF och OI var frekvensen av missfall som ledde till sjukhusvård 42 per tusen behandlade kvinnor. Cirka 15 % av IVF-kvinnorna och 8 % av OI-kvinnorna togs minst en gång in på sjukhus på grund av komplikationer eller missfall under uppföljningen.

IVF-barnens hälsa under perinataltiden var sämre och sjukhusvård vanligare än för andra barn. IVF-barnen hade förhöjd risk för CP-skador (oddskvot 2,9 och 95 % konfidensintervall 1,6–5,3), psykologiska störningar och utvecklingsstörningar (1,7, 1,1–2,5) samt medfödda betydande missbildningar (1,3, 1,1–1,6). Resultaten förklaras delvis av det stora antalet flerbörder. IVF-enlingar hade sämre hälsa under perinataltiden än andra enlingar, mera sjukhusvård och pojkarna förhöjd risk för medfödda missbildningar. IVF-tvillingars och trillingars hälsa motsvarade andra tvillingars och trillingars.

De genomsnittliga totalkostnaderna per levande fött IVF-barn ökade med kvinnans ålder från 12 851 euro (under 30 år) till 40 662 euro (för 40 år fyllda). Beräknat i förhållande till befolkningen (för varje åldersgrupp och socioekonomisk grupp) användes mest av offentliga resurser för behandling av kvinnor i åldern 30–39 år och kvinnor i den högsta socioekonomiska ställningen. De regionala skillnaderna var små.

Slutsatser: Även om den största delen av IVF-barnen var friska, hade de fler hälsorelaterade problem än andra barn. Risken för komplikationer vid en enstaka IVF-cykel var liten, men flera behandlingscykler ledde till allvarliga komplikationer hos flera kvinnor; betydligt oftare efter IVF än efter OI. Ytterligare undersökningar krävs för att utreda hälsan för IVF- och OI-kvinnor och deras barn på längre sikt. I undersökningen fanns inte uppgifter om behovet av behandling, det vill säga hur allmän ofruktsamhet är, och inte heller om önskan att skaffa barn, varför man inte med säkerhet kan säga huruvida kvinnor av någon viss ålder favoriseras vid fertilitetsbehandlingar. De högre kostnaderna, de större hälsoriskerna och det sämre utfallet vid behandling av äldre kvinnor talar för koncentration på behandling av yngre kvinnor i fruktsam ålder. Skillnaderna i fråga om den socioekonomiska ställningen vid behandling med IVF och fördelningen av resurser kan vittna om orättvisa.

Nyckelord: Provrörsbefruktning, in vitro fertilisering, ovulationsinduktion, registerundersökning, hälsopåverkan, komplikationer, OHSS, barnens hälsa, medfödda missbildningar, kostnader, rättvisa

ABSTRACT

Klemetti Reija. **The Use of Assisted Fertilization in Finland: Health Effects and Equity,** STAKES, Research Reports, 158. Helsinki, Finland, 2006. ISBN 951-33-1912-1

Background: Though Assisted Fertilization (AF), consisting of in vitro fertilization (IVF, including intracytoplasmic sperm injection and frozen embryo transfer) and ovulation induction (OI with or without inseminations), is widely used as a treatment for infertility, not enough is known about its utilization and health effects. Equity in health care should mean equal access to care according to need and an equitable distribution of health care resources by gender, age, living area, and socioeconomic position. IVF is a costly treatment in which effectiveness and appropriateness decrease by women's age while need and complications increase.

Objective: The purpose of this study is to investigate via nationwide registers the use of AF, i.e. IVF and OI, the occurrence of serious complications and miscarriages of treated women, and the health of their children, as well as to describe equity in the allocation of resources to IVF by women's age and socioeconomic position and by the treatment sector (public vs. private). Finally, the aim is to discuss whether the usual criteria of equity apply to IVF.

Materials and methods: In this register-based study, women who received IVF (N=9175) and OI (N=10 254) between 1996 and 1998 were identified from the reimbursement records of the Social Insurance Institution (SII) that cover all Finns and were followed until 2000 by means of register linkages (The Hospital Discharge Register and The Cause-of-Death Register). Population controls, matched by age and municipality, were selected for IVF women (N = 9175). IVF women's children (N = 4559) and OI women's children (N = 4467) were identified from the Medical Birth Register (MBR) and followed until 2003 by using the Hospital Discharge Register, the Register of Congenital Malformations, the Cause-of-Death statistics, and reimbursements records of the SII. Two control groups were selected from the MBR: all other children from the same period (N = 190 398, for studying perinatal health, hospitalizations and mortality) and also a random sample of them (n = 26 877, for studying congenital anomalies (CAs) and health-related benefits). Information on treatment costs were received from IVF clinics and the SII.

Results: During a mean follow-up period of 1.5 years, older women received 1.4 times more IVF treatment cycles than younger women (2.2 vs. 3.0). In the private sector, women in the highest socioeconomic position were over-represented and had more cycles than other women. The success rate—live-births per cycle—decreased by women's age: from 22% among women aged below 30, to 6% among women aged 40 or older.

After IVF, 23 per 1000 and after OI, 1 per 1000 women had a serious case of OHSS (ovarian hyperstimulation syndrome) during the study period (mean of 2.7 treatments). The rates of registered miscarriages after both IVF and OI were 42 per 1000 treated women. Overall, 15% of IVF and 8 % of OI women had at least one hospital episode during the study period.

Perinatal outcomes of IVF children were worse and hospital episodes were more common than among control children; odds ratios (OR) for cerebral palsy (2.9, 95% CI 1.6–5.3) and psychological and developmental disorders (1.7, 1.1–2.5) were increased as well as OR for congenital anomalies (1.3, 1.1–1.6). These results were partly explainable by the great number of twins among IVF children. Among IVF singletons, poorer results were found for perinatal outcomes and hospitalizations, while for singleton IVF boys an increased risk of major CAs were also found. The health of IVF multiples was comparable to the health of control multiples.

The mean cost of a live birth after IVF increased by women's age from EUR 12 851 among women aged under 30 to EUR 40 662 among women aged 40 or older. Calculated per population, society contributed most to the women aged 30–39 years and women from the highest socioeconomic position. Regional differences were not remarkable.

Conclusion: Although the health of most IVF children was good, they had more health problems than other children. The risk of complications for women after each IVF treatment cycle was low, but repeated attempts resulted in serious complications for many women, and these occurred much more often than after OI alone. Further studies are needed to examine the long-term health of IVF and OI women and their children. No information on the need for IVF and OI treatments, i.e. infertility rates and the wish for a child, was available in the study. It is therefore uncertain whether women from a certain age-group are favoured in treatments in Finland. Due to the higher costs, increased health risks and decreased IVF success for older women, concentrating on the treatment of younger women is a fairer solution than provision solely based on need. Socioeconomic differences in the use of IVF services and the allocation of resources may indicate inequality.

Key words: IVF, ovulation induction, health effects, register-based study, complications, OHSS, child health, perinatal health, congenital anomaly, equity, costs

CONTENTS

List of original publications

The present thesis is based on the following articles, which are referred to in the text by their Roman numerals:

I Klemetti Reija, Gissler Mika, Hemminki Elina.
Equity in the use of IVF in Finland in the late 1990s.
Scandinavian Journal of Public Health 2004;32:203–209.

II Klemetti Reija, Sevón Tiina, Gissler Mika, Hemminki Elina.
Complications of IVF and ovulation induction.
Human Reproduction 2005;20:3293–3300.

III Klemetti Reija, Sevón Tiina, Gissler Mika, Hemminki Elina.
Health of Children Born as a Result of In Vitro Fertilization.
Pediatrics 2006;118:1819–1827.

IV Klemetti Reija, Gissler Mika, Sevón Tiina, Koivurova Sari, Ritvanen Annukka, Hemminki Elina.
Children born after assisted fertilization have an increased rate of major congenital malformation.
Fertility & Sterility 2005;84:1300–1307.

V Klemetti Reija, Gissler Mika, Sevón Tiina, Hemminki Elina.
Equity in the allocation of resources in IVF (Submitted).

Abbreviations

AF = Assisted fertilization
ART = Assisted reproductive technologies
CA = Congenital anomaly
CI = Confidence interval
CP = Cerebral palsy
CPR = Central Population Register
FET = Frozen embryo transfer
HDR = Hospital Discharge Register
ICD = International Classification of Diseases
ICSI = Intra cytoplasmic sperm injection
IUI = Intra uterine insemination
IVF = In vitro fertilization
MBR = Medical Birth Register
OI = Ovulation induction with or without insemination
OHSS = Ovarian hyperstimulation syndrome
OR = Odds ratio
RCM = Register of Congenital Malformations
SII = Social Insurance Institution

1 Introduction

Involuntary childlessness was earlier considered a social problem and accompanied by social solutions such as foster children, adoption, changing partners, or accepting a life without children. When knowledge of human reproduction developed and medical reasons for childlessness were found, childlessness became a medical problem defined as infertility or impaired fertility. Efforts then began to solve this issue by medical means.

Ovulation has been induced with hormonal drugs since the 1950s. Insemination is documented to have been made even earlier, during the 18th century (Hovatta, 1989). The greatest innovation in medicine in resolving the problem of childlessness was, however, the development of in vitro fertilization (IVF); the first baby was born in 1978 in the United Kingdom (Steptoe and Edwards, 1978) and the first in Finland in 1984 (Malin Silverio and Hemminki, 1996). During the past 30 years, IVF has become a common infertility treatment. In 2002, between approximately 2.4% (in Norway) and 4.2% (in Denmark) of all infants in the Nordic countries were born following IVF, with the figure being some 2.9% in Finland (Nyboe Andersen et al., 2006). In the United States the proportion is about 1 % (CDC report, 2003) and in the United Kingdom 1.4% (Nyboe Andersen et al., 2006). In addition, in Denmark 2.3% of all infants were born as a result of intra uterine insemination in 2002 (Nyboe Andersen and Erb, 2006). The number of children born with the help of ovulation induction and/or insemination (called in this study OI) in Finland is unknown.

Although OI has been used for many decades and IVF has rapidly become a normal clinical practice, the related health effects have not been properly studied. For example, in Finland only a few studies have been published on the health of IVF infants (Gissler et al., 1995a, Isaksson, 2002, Klemetti et al., 2002, Koivurova, 2005), with one study on the health of children born after intrauterine insemination (Nuojua-Huttunen, 1999), and no studies on the complications of women following IVF and OI (Jokimaa, 2006).

In spite of a large number of international studies on the health of IVF newborns (Helmerhorst et al., 2004), little is known about the long-term health effects on children (Hampton, 2004) or the short and long-term health of OI children. Even though various adverse effects of IVF and OI on treated women have been identified, many of the published studies and reports are insufficient. They are

based on voluntary reporting or on a small number of cases or treatment cycles. Others concentrate on only one complication, or lack information on the severity of the complications.

IVF is a costly treatment and much is debated about recipients' eligibility (age, sexual orientation, and marital status), how it should be funded (private or public resources) and how to allocate the scarce health care resources in a fair way. It is generally believed that IVF is unevenly distributed by socioeconomic position and urban–rural areas. However, there is not great deal of reliable data on the use or users of IVF or OI.

In the present study, first the use of IVF and OI in Finland is examined by considering the factors of age, socioeconomic position, and area of residence of those women who have used infertility treatments. Second, the safety of IVF and OI is studied by considering the complications and miscarriages of IVF and OI women as well as the health of IVF children. Hospitalization during pregnancy and childbirth as well as frequency of Caesarean sections could be studied, but data on other pregnancy outcomes were not available in this study. An identical study on the health of OI children has been done, but these results will be published separately and are not presented in this study. The results of congenital anomalies of OI children have already been published, while OI children are in this study also used as a control group—along with children born to infertile women treated with other infertility treatments than IVF—for IVF children; another control group was formed with naturally conceived children. Third, the success of IVF measured by live-births per number of cycles and per number of women is studied. Fourth, the costs of IVF treatment are estimated and the allocation of expenditures used in IVF is examined: how much is paid by Finnish society and how much by women themselves. Finally it is discussed how fairly the IVF resources are used in Finland.

2 Infertility and its treatment

2.1 Infertility

The prevalence of infertility is not easy to calculate due to the variable terminology used in reproductive medicine (Nguyen and Wilcox, 2005) and also the different definitions used in studies (Schimdt and Münster, 1995). It has been suggested that we avoid using the terms 'infertility, subfertility, and fecundity' and instead use the term 'reduced fertility' in different grades: from 0 (normal fertility) to grade 4 (sterility) (Habbema et al., 2004). Alternatively, it has been argued that the term 'subfertility' should be used and defined as any form of reduced fertility with prolonged time to successful conception (Gnoth et al., 2005). Because in this study it is not important to define different grades of reduced fertility, the term 'infertility' is used as a common term for involuntary childlessness. A common definition for infertility is an inability to achieve a pregnancy after regular unprotected intercourse within 12 months (Nguyen and Wilcox, 2005). The time limit in the definition was previously longer. In a guidebook for doctors (Therapia Fennica, 1975) the time limit was three years in 1975 and one year in the next edition in 1986 (Therapia Fennica, 1986). The World Health Organization still uses a definition of two years (WHO, 1997). It has been estimated that about 84–90% of couples conceive within one year (te Velde et al., 2000, Cahill and Wardle, 2002, Taylor, 2003, Habbema et al., 2004, Gnoth et al., 2005) and a half of the rest during the next year (te Velde et al., 2000). Thus, the definition has a great practical impact. About 5% of couples succeed in conceiving spontaneously "only sporadically" (Gnoth et al., 2005) or are "sterile couples" (Habbema et al., 2004). Furthermore, infertility is not only an inability to become pregnant but also a devastating personal experience (Greil, 1997). It can cause anxiety, stress and depression and affect the whole life spectrum: domestic and social lives as well as work.

According to population-based studies, infertility is common. In Finland, for example, 13–17% of women reported difficulties in trying to conceive within 12 months (Rantala and Koskimies, 1986, Notkola, 1995, Malin et al., 2001, Klemetti et al., 2004). Similar proportions have been reported from other industrialized countries (Gunnell and Ewings, 1994, Schmidt and Münster, 1995, Stephen and Chandra, 2000).

The most common causes of infertility are sperm dysfunction, ovulation disorder and fallopian tube damage (Cahill and Wardle, 2002). The suggested or discovered factors that underlie these causes are age, reproductive tract infections, obesity, anorexia, health-related behaviours like cigarette smoking, and too much exercise, as well as occupational exposures (Baird and Strassmann, 2000). About 15% of couples have more than one cause and 10–20% of couples suffer unexplained infertility, i.e. definite causes can not be found (Isaksson, 2002). Infertility can be primary: the failure ever to have achieved a pregnancy or secondary: inability to achieve pregnancy after having had a pregnancy (Nguyen and Wilcox, 2005).

Reproductive behaviour in our society has changed: Childbearing is delayed and births are planned (ESHRE, 2005). The mean age of motherhood has increased; for example in Finland the mean age of maternity was 27.0 years in 1977 and 30.0 in 2003 (Statistics of Finland and Stakes) and in France 26.5 in 1977 and 29.5 in 2000 (ESHRE, 2005). More importantly, postponing the first birth has become common. In Finland the mean age of the first birth increased from 25.4 in 1982 to 27.7 in 1996, but after that the age of first birth has only slightly increased; 28.0 in 2005 (Statistics of Finland and STAKES). Postponing childbearing increases the need for infertility treatments, because fecundity decreases with age.

Female fertility decreases with age due to several factors: the number of oocytes decreases, oocyte quality decreases, intercourse frequency declines (ESHRE, 2005) and unfavourable biological changes occur in the uterus (Baird and Strassmann, 2000). The monthly chance of achieving a pregnancy diminishes gradually after the age of 30 and more rapidly after age 36, being almost zero at the age of 41 (Broekmans and Klinkert, 2004). However, the age of losing fertility can vary according to the individual. How fertility changes by age among men is not well known, but time to pregnancy has been found to increase when the male partner is over 50 years old (ESHRE, 2005).

Strict planning of the timing of childbirth and taking the one-year definition of infertility as a strict rule can lead to impatience with waiting for a natural conception and result in premature use of infertility services (te Velde and Cohlen, 1999). It has been pointed out that appropriate timing for starting treatment is important to avoid over- and under-treatment (Brosens et al., 2004) and it is suggested that the general public has, in many countries, too optimistic a picture of childbearing in later life and of the success of infertility treatments (te Velde and Cohlen, 1999, Heffner, 2004, Cahill and Wardle, 2006). In 2004, the majority of female university students in Sweden would like to have children, but half of Swedish students planned to have children after the age of 35 years and did not know about decreased female fertility in the late 30s (Lampic et al., 2006). In Finland, 90% of university students desired children, but only 8% had a child, although the students were at the optimal childbearing age (Virtala et al., 2006). Leridon

(2004) pointed out that infertility treatments cannot compensate for all births not realised due to postponed childbearing.

2.2 Treatments

Medical treatments for infertility involve a treatment of physiological barriers (e.g. weight reduction or gaining weight), diseases causing infertility (e.g. acute infections) or damaging health habits (e.g. smoking, narcotic use), different surgical techniques (like opening blocked fallopian tubes), hormonal treatment (ovulation induction or ovarian stimulation) and assisted fertilization. In assisted fertilization (AF) the aim is to bring the egg and sperm close to each other to increase the chances of fertilization and achieve a pregnancy (Rowell and Braude, 2003). AF includes intrauterine insemination (IUI) and in vitro fertilization (IVF) with all its subtypes, such as intracytoplasmic sperm injection (ICSI) and frozen embryo transfer (FET), in which both eggs and sperm are handled outside the woman's body (Fig. 1). In IUI, prepared sperm are deposited in the uterus (Rowell and Braude, 2003). The term assisted reproductive technology (ART) has widely been used as a synonym for AF. However, in a recent publication ART has been suggested as including only procedures including in vitro handling of human oocytes and sperm or embryos but not insemination (Zegers-Hochshildt et al., 2006). This study uses the term AF, which here includes IVF with all its modifications including ICSI and FET, and hormonal treatment with or without insemination.

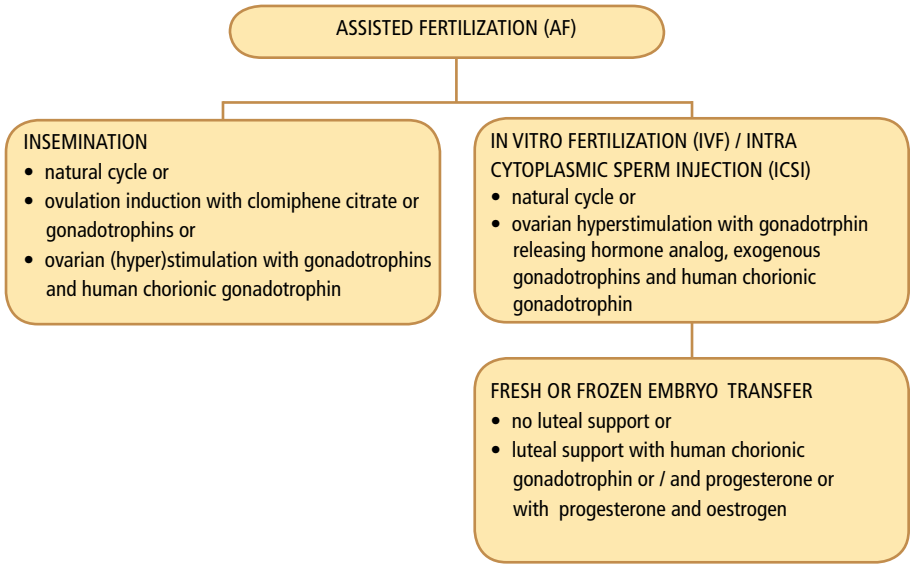

FIGURE 1. Different types of assisted fertilization (AF) and typical hormonal treatment used in AF.

In addition to medical treatments, psychological support is considered important for every couple as a part of infertility treatment (Bagshawe and Taylor, 2003). Counseling is suggested as helping couples in open communication, in clarifying their situation, needs and hopes, in adjusting to their circumstances, being supportive or therapeutic and in helping to understand what kind of effects treatment can have on couple's lives. It has been argued that the situation and experiences of infertile or involuntary childless people are culturally defined and that treatments and prevention of infertility should be seen in a cultural context (Bos et al., 2005).

IVF cannot cure or treat infertility, but it can help couples to conceive a child. This study concentrates on medical treatments, and in particular, hormonal treatment (with or without insemination) and IVF. The terms treatment and treatment cycle are used in spite the fact that AF is not curative.

2.2.1 Ovulation induction (OI)

Ovulation induction and ovarian (hyper)stimulation are two methods of hormonal treatment used in ovarian stimulation (Fauser et al., 2005). In ovulation induction, anovulatory women receive drugs (such as clomiphene citrate or gonadotrophins) to induce mono-ovulatory menstrual cycles. Ovarian (hyper)stimulation is used for women with normal menstrual cycles to induce development of multiple follicles. Both ovulation induction and ovarian (hyper)stimulation can be combined with intrauterine insemination (IUI) (Fig. 1). Particularly in ovarian (hyper)stimulation, the number of oocytes cannot be fully controlled. Multiple pregnancy rates after gonadotrophin ovulation induction have been reported to vary between 5 to 20% and after (hyper)stimulation from 10% to 40% per cycle. Hyperstimulation before IVF has a different aim than stimulation before the IUI. In IVF it is used to obtain a sufficient number of oocytes necessary to the procedure, and typically more drugs and higher dosages are used than in stimulation before the IUI. In this study, the term ovulation induction (OI) is used to describe both ovulation induction and low stimulation (lower dosages of drugs than in hyperstimulation) with or without insemination.

2.2.2 In vitro fertilization (IVF)

In vitro fertilization is the most famous type of AF. The first successful IVF treatment leading to the birth of Louise Brown in 1978 was done as part of a natural cycle without ovarian stimulation (Steptoe and Edwards, 1978). In the thirty years since, IVF has been modified and a current typical strategy includes six phases (Grainger and Tjaden, 2000, Unkila-Kallio, 2001, Fig. 1). However, there is varia-

tion in the drugs used and in their combinations. Firstly the natural function of ovaries is downregulated with various combinations of oral contraceptive pills, gonadotrophin releasing hormone analog, and progestins. Then ovaries are stimulated with exogenous gonadotrophins (follicle stimulating hormone and luteinizing hormone). After that oocytes are collected and fertilized. In this phase different micromanipulation techniques can be used: ICSI, assisted zona hatching or preimplantation genetic diagnosis. In ICSI one sperm is injected into one oocyte. Two to five days after retrieval, the embryo(s) is transferred to the uterus. The uterus is prepared for transfer (luteal support) with human chorionic gonadotrophin or progesterone, or both or with progesterone and oestrogen (Fig. 1).

If the embryo transfer is not possible or more embryos are fertilized than are needed, the embryos can be frozen and used later by thawing, called FET. If the hyperstimulation does not succeed, the procedure does not proceed to oocyte collection or thawed embryos can not be transferred, the treatment cycle is defined as a cancelled cycle (Zegers-Hochshildt et al., 2006). Both donated sperm and eggs can be used in IVF. If the woman has no uterus the embryo can be transferred to another woman's womb, called surrogacy.

3 IVF Success

IVF success can be calculated in many different ways, for example (clinical) pregnancy, delivery, live-birth or take-home baby rates per initiated cycles, per embryo retrievals or per embryo transfers. For most purposes, (one) live-birth or take-home baby rate per initiated cycle or cumulatively, is the best measure of success. The most important factors predicting good success in IVF have been women's young age (declining pregnancy and live-birth rates with increasing age), reasons of infertility (the highest live-birth rates being in male factor infertility and the lowest in respect of uterus-related reasons), the number of embryos transferred, good embryo quality, and previous live birth after IVF (Graigner and Tjaden, 2000).

Among younger women the live-birth rate increased by the number of embryos transferred up to three embryos and for older women up to four embryos, with the live-birth rate declining thereafter (Schieve et al., 1999). However, as the problems of multiplicity gained recognition, it was first recommended that two embryos were transferred and nowadays one embryo transfer is recommended (Tiitinen and Gissler, 2004, Kissin et al., 2005, Koivurova, 2005). According to Finnish experiences, the decreased number of transferred embryos has not led to a marked change in success rates (Tiitinen et al., 2003, Tiitinen and Gissler, 2004). In Finland success rate (live births per number of cycles) improved from 17% in 1994 to 19% in 2002, while the proportion of single embryo transfers has increased from 17% to 39%.

The success rates varied between the clinics and countries; in Europe deliveries per IVF cycle varied from 9.2% in Bulgaria to 25.2% in Norway, being mainly about 20% (Nyboe Andersen et al., 2006). Live-births per cycle and by female age were not reported. Of the register data on success rates found, the success rates and also the multiple birth-rates reported are highest in the United States (Table 1).

Calculations of success, both in terms of clinical pregnancy and live-births per cycle and per women's age showed that success decreased with increasing age (Table 1). It seems that success rates were somewhat improved between 1986 and 2004, but a comparison between earlier studies and currently available register data as well as between different countries have to be interpreted with reservations, due to the different definitions, data collection systems, and sample sizes.

TABLE 1. Success rates of IVF during different time-periods; pregnancy or live-births per initiated cycle, %

Document or Author	Country	Year(s)	Treatment	Multiplicity, %	Pregnancy	Live birth
Piette et al.1990	France	1986	IVF	NA		
<=24					15	
25–29					20	
30–34					19	
35–39					17	
>=40					13	
Devroye et al.1996	Belgium	1991–1993	ICSI	NA		
<40					23	
>=40					7	
Dew et al.1998	Australia	1987–1994	IVF			
<36				16	14	12
36-39				13	13	9
>=40				0	5	3
Meldrum et al.1998 [a]	USA	1994	IVF			
<40				NA	35	28
40–42				NA	21	14
>42				NA	10	5
Lass et al.1998	UK	1988–1995	IVF			
<40				NA	28	
>=40				5	11	
Klipstein et al. 2005	USA	1999–2002	IVF			
>=40				15		10
Waters et al. 2006	Australia and	2003	IVF			
Total	New Zealand			18		19
< 35				NA		25
35–39				NA		15
40+				NA		7
National summary of CDC [b]	USA	2003	IVF			
< 35				38		37
35–37				32		30
38–40				26		20
41–42				17		11
Swedish Statistics [a]	Sweden	2003	IVF+ICSI			
Total				12		23
< 35				NA		29
35–39				NA		20
40+				NA		10
Danish Statistics [a]	Denmark	2004	IVF+ICSI			
< 40				22		22–25
> 40				11		8-11
Statistics of HFEA [c]	UK	2003–2004	IVF			
< 35				28		28
35–37				23		24
38–39				19		18
40–42				12		11
>42				NS		3

[a] Deliveries per cycle started (%)
[b] CDC = Centers for Disease Control and Prevention, 99% is IVF and rest other types of assisted fertilization
[c] HFEA = Human Fertilisation & Embryology Authority, IVF includes fresh embryo transfers
NA = not avalable, NS = non-significant

Reported pregnancy and delivery rates have varied not only by woman's age but also by number of cycles; pregnancy rates have decreased after three or four cycles and delivery rates after four cycles (Meldrum et al., 1998, Lass et al., 1998). Cumulative live births rates per initiated cycles have varied from 3% to 71% by female age and number of cycles (Tan et al., 1994). Olivius et al. (2002) found that an overall cumulative live birth rate after three cycles varied from 56% to 66%. Wang (2006) has pointed out that calculating cumulative pregnancy rates can lead to an overestimation of treatment success. He suggests that the calculation should be limited only to the second or third cycle within one to two years to ensure that most women are included in the calculations.

4 Safety of infertility treatments

4.1 Women's health after IVF and OI

The safety issues related to infertility treatments for women include complications of the treatments and—following successful treatment—complications during pregnancy and delivery. The most common and serious consequence of infertility treatments is multiple pregnancy, which in the case of IVF often occurs with older age. IVF-pregnancies have been reported to be more complicated than natural pregnancies, with for example vaginal bleeding, pregnancy induced hypertension and Caesarean sections being more common (reviewed by Koivurova, 2005). This study concentrates on treatment complications, which have been studied less than pregnancy complications. They can occur during the ovulation induction (or stimulation), the oocyte collection procedure, and also post-operatively. The achieved pregnancy can be ectopic (embryo outside the uterus) or heterotopic (embryo both in and outside the uterus) and it can end up in a miscarriage. The frequency of miscarriages and ectopic pregnancies leading to hospital care is likewise covered in this study.

Ovarian hyperstimulation syndrome (OHSS) is considered the most serious complication of ovulation induction. It can vary from a mild illness to a critical, life-threatening disease requiring hospitalization (Table 2). Due to the various OHSS related symptoms and signs which can vary case by case, OHSS is typically not easy to diagnose. OHSS can occur within a few days of receiving of human chorion gonadotrophin ("early OHSS") or later ("late OHSS"). The multiple pregnancy has been associated with a higher risk of late OHSS (Mathur et al., 2000). The incidence of severe OHSS has been reported to vary from 0.7% to 1.7% per initiated cycle (Bergh and Lundkvist, 1992, Serour et al., 1998, Westergaard et al., 2000, Nyboe Andersen et al., 2006). OHSS has been estimated to lead to hospitalisation in 2.4% of IVF pregnancies (Källén et al., 2005a). Case reports (Cluroe and Synek, 1995, Koo et al., 2002), some studies (Bergh and Lundkvist 1992, Serour et al., 1998, Abramov et al., 1999a, Källén et al. 2005a) and reviews (Beerendonk et al., 1998, Whelan and Vlahos, 2000, Delvigne and Rozenberg, 2003, De Sutter, 2004, Jokimaa 2006) describe some serious aspects of OHSS, such as thromboembolic events, pulmonary manifestations, and death. However, the magnitude of the risk of OHSS is unclear. The frequency of OHSS after OI is unknown (Unkila-Kallio,

TABLE 2. Symptoms and signs related to different degrees of ovarian hyperstimulation syndrome (OHSS)

OHSS
Mild
Abdominal distension and discomfort
Nausea, vomiting and/or diarrhea
Enlarged ovaries
Moderate
Symptoms and signs of mild OHSS
Ascites
Severe
Symptoms and signs of moderate OHSS
Temperature of over 38 degrees
Ascites and / or hydrothorax or breathing difficulties
Weight increase
Hypovolemia
Hemoconcentration
Oligouria
Electrolyte imbalances
Critical
Symptoms and signs of severe OHSS
Impaired renal perfusion
Thromboembolism
Impending multiorgan failure

(Beerendonk et al.1998, Jokimaa 2006)

2001). In one small clinical study, the OHSS hospitalization rate per initiated cycle was 0.07% (Quasim et al., 1997).

The frequencies of IVF complications other than OHSS have been only sporadically reported. For oocyte collection, bleeding has been reported in 0.03 % to 0.5% and infections in 0.02% to 0.3% of embryo transfers (Bergh and Lundkvist, 1992, Nyboe Andersen et al., 2006). From 2% to 5% of IVF pregnancies have been reported to be ectopic and 0.1% to 1.0% heterotopic (Roest et al., 1995, Serour et al., 1998, Waters et al., 2006); both are higher than in naturally conceived pregnancies (Hemminki and Heinonen, 1987, Mäkinen, 1996, Roest et al., 1995). Estimates of IVF pregnancies ending in miscarriage have varied from 15% to 23% (Roest et al., 1995, Serour et al., 1998, Westergaard et al., 2000, Kupka et al., 2003, Schieve et al., 2003, Waters et al., 2006).

4.2 Health of IVF and OI children

Health of newborn

The most common health problems of IVF children are related to multiplicity (Schieve et al., 1999, Tiitinen et al., 2003, Kissin et al., 2005). Although IVF has been associated with an increased number of monozygotic twins (Ericson and Källén, 2001), the main reason for multiplicity is multiple embryo transfer and therefore IVF twins are much more often dizygotic compared to naturally conceived twins (99% vs. 70%, Schachter et al., 2001). Depending on the IVF practice, multiple birth rates have varied from 27% to 40%, being much higher in the United States than in Europe (Fauser et al., 2005): Single embryo transfer has become more common in Europe in recent years. With the preference for single embryo transfers, the multiple birth rate has decreased in Finland from 27% in 1992 to 13% in 2003 (calculated from IVF statistics, http://www.stakes.info/2/1/2,1,4.asp.). During the 1990s, an improved trend in the perinatal health of multiple IVF children was found in Finland, mainly due to a decrease in higher order multiple births (Klemetti et al., 2002).

IVF twins have had poorer perinatal health than IVF singletons but in previous publications no differences were found between the perinatal health of IVF and naturally conceived twins (reviewed by Ludwig et al., 2006). Contrary to these previous publications, recent studies show an increased risk of preterm birth and/or low birth weight for IVF twins (Verstraelen et al., 2005, Wang et al., 2005).

Poorer perinatal health in IVF children is however not only a consequence of multiplicity and a high frequency of twins: the perinatal health of IVF singletons has been found to be worse than that of naturally conceived singletons (Schieve et al., 2002, Helmerhorst et al., 2004, Jackson et al., 2004). Low birth weight and preterm birth were more common among IVF and ICSI singletons compared to naturally conceived singletons of previously infertile women (De Geyter et al., 2006).

Prematurity and low birth weight have been more common also among OI children than among naturally conceived children (Addor et al., 1998, Källén et al., 2002, Gaudoin et al., 2003, Wang et al., 2002, Verstraelen et al., 2006). Two small studies could not find any statistically significant differences between children conceived with intra uterine insemination (IUI) and spontaneously (Nuojua-Huttunen, 1999, De Geyter et al., 2006). In addition to low birth weight and prematurity, OI children have had a higher incidence of very low birth weight, treatment in the neonatal intensive care unit and of most neonatal morbidity parameters (Ombelet et al., 2006).

Some studies have shown an increase in congenital anomalies (CAs) among IVF or ICSI children (Bergh et al., 1999, Dohnt et al., 1999, Wennerholm et al.,

2000, Ericson and Källén, 2001, Anthony et al., 2002, Hansen et al., 2002, Koivurova, 2005, Katalinic et al., 2004), but other studies have not (Loft et al., 1999, Ritzk et al., 1991, Sutcliffe et al., 2001, Westergaard et al., 2000). The higher incidence of CAs among IVF children has involved musculoskeletal, cardiovascular, chromosomal and urogenital defects (Hansen et al., 2002, Koivurova, 2005).

Recently, sufficiently large studies on the CAs of IVF children have been published: two meta-analyses of earlier studies (Rimm et al., 2004, Hansen et al., 2005) and register-based studies from Sweden (Källén et al., 2005b) and Denmark (Zhu et al., 2006). According to the meta-analysis by Rimm et al. (2004), a 1.3-fold risk of major CAs was found among IVF and ICSI children and a 2.1-fold risk was found by Hansen et al. (2005). In the latter review the risk of CAs was increased also separately for singletons (OR 1.35, 1.20–1.51). Risk of specific malformations was not reported.

According to the Swedish study (Källén et al., 2005b) IVF children in total and singletons alone had a 1.3-fold risk of congenital anomalies. The risk was not increased among multiples. The risks for many specific malformations were increased, for example for neural tube defects, different gastrointestinal atresias, major cardiovascular defects, and hypospadias. No differences in the malformation rate by IVF method used were found with the exception of hypospadias after ICSI. In contrast, a meta-analysis comparing IVF children with ICSI children found no significantly increased risk after ICSI (Lie et al., 2005). A recent smaller study from the United States found the same 1.3-fold risk with a borderline significance among all IVF children and, contrary to earlier studies, an increased risk also for congenital anomalies among twins and triplets (Olson et al., 2005).

Olson et al. (2005) studied the risk of congenital anomalies among IUI children and could not find an increased risk. The number of IUI infants was however less than 100. Only one sufficiently large study on anomalies of children born as a result of ovarian stimulation could be found (Källén et al., 2002). There was an increased rate of congenital anomalies, but this could be mainly explained by maternal characteristics.

A Danish study found an increased risk among singletons born as a result of infertility treatments (IVF, ICSI, insemination and hormonal treatment) and interestingly also among naturally conceived children born to previously infertile couples (without treatments) (Zhu et al., 2006). Of the specific CAs, the risk of musculoskeletal and genital anomalies was increased for IVF children, but not the risk of genital anomalies among children born naturally to previously infertile couples. Risk among twins was not increased. The authors suggested that hormonal treatment might cause genital anomalies but otherwise the potential reason for anomalies could be infertility itself or its determinants.

Health in early childhood

According to previous small cohort studies, the morbidity, growth, and development of IVF children have been similar to that of control children (reviewed by Koivurova, 2005). A recent Finnish study found higher childhood morbidity and increased hospitalization (Koivurova et al., unpublished data). Large register-based studies having large sample sizes have been published from the Nordic countries (Ericson and Källén, 2001, Ericson et al., 2002, Strömberg et al., 2002, Pinborg et al., 2004a, Pinborg et al., 2004b, Lidegaard et al., 2005, Källén et al., 2005b, Källén et al., 2005c, Hvintjørn et al., 2006). These studies report an increased use of hospital services, long hospitalizations and an increased risk of infections, epilepsy and tumours (Ericson et al., 2002), asthma (Ericson et al., 2002, Källén et al., 2005c), cerebral palsy (Ericson et al., 2002, Strömberg et al., 2002, Lidegaard et al., 2005, Hvintjørn et al., 2006), sleep disturbances (Lidegaard et al., 2005), convulsions and behavioural problems and accidents (Källén et al., 2005c) among IVF children.

A review including both small cohort studies and some of these large register-based studies concluded that most studies did not find any differences in childhood morbidity, chronic illnesses, surgical interventions, physical development, mental health, and behavioural problems between IVF and naturally conceived singletons, but they found an increase in neurological problems among IVF singletons (Ludwig et al., 2006). Data on chronic illnesses, childhood morbidity, and surgical interventions were so contradictory that the authors could not draw a final conclusion. The data on IVF twins was limited and more data are needed to draw any conclusions on their childhood health. Long-term follow-up studies of OI children are lacking.

5 Use and service costs of infertility treatments

5.1 Human and reproductive rights

The Declaration of Human Rights of the United Nation from the 1948 (available at: www.un.org/Overview/rights.html) sets out the right to marry and establish a family without limitation due to race, nationality or religion. At the 1994 International Conference on Population and Development in Cairo, reproductive rights were defined as follows "…the basic right of all couples and individuals to decide freely and responsibly the number, spacing and timing of their children and to have the information and means to do so, and the right to attain the highest standard of sexual and reproductive health. They also include the right of all to make decisions concerning reproduction free of discrimination, coercion and violence." (available at: http://www.unfpa.org/icpd/summary.htm).

5.2 Right to infertility treatments

The question of whether a right exists for infertility treatments and if so who is eligible to treatments is problematic. Do the human and reproductive rights mean that everyone has the right to receive a child and a right to receive infertility treatments to fulfil these rights? McLean (1993) argued that the right to reproduce does not automatically mean the right to have a child. On the other hand, Blank (1997) pointed out that reproductive rights have different dimensions, for example the right to have a child or the right not to have a child. He continued that infertility treatments belong to the category of rights to have children i.e. positive rights. Positive rights include claims for society to offer services that are needed. If reproductive rights are understood as positive rights, an infertile couple can claim access to infertility services. According to McLean the last conclusion is right, but she argued that the declaration of human rights can be understood as a freedom to reproduce for those who have a capacity for that and not as a right for everyone. But she continued that because infertility technology is already available it is important to somehow control it. Furthermore, she pointed out that it would be necessary to asses how the technology is directed and developed taking into ac-

count related consequences. Daniels and Taylor (1993) argued that it is necessary to formulate selection policies for access to AF to be able to take into account the rights and needs of the child as well as to decide how much public funds are allocated to infertility services.

Daniels and Taylor (1993) pointed out that the criteria for eligibility for AF should be made through a public debate that asks whether access should be restricted, if so on what basis, and who should make the decisions. According to them, exclusion criteria could include for example previous children or females are beyond a certain age. They suggested that decisions should not be left to medical professionals alone but that some kind of expert committee should take into account public opinion.

5.3 Legislation on infertility treatments

Regulations of the eligibility for IVF of European countries, Canada and Israel were studied by a Steering Committee of Bioethics (CDBI), Council of Europe and published in 2005 (CDBI, 2005). They report that nowadays in most European countries, regulation governs who is eligible for IVF treatment, but that eligibility criteria vary between different countries. In 28 of the countries participating in the study, eligibility is regulated by the law. Two countries (Cyprus and Portugal) reported having no law and no regulations for assisted fertilization. The rest of the countries studied (7 including Finland) did not have a law at that time but drafting of legislation was in process or they have some kind of regulations for assisted fertilization. In the United States the criteria for eligibility have been found to vary also between clinics (Stern et al., 2001). AF was available only to heterosexual couples for example in Austria, Denmark, Norway, Germany and Italy, but allowed also for lesbian women in Sweden and for single or lesbian women in the United Kingdom, Israel and Canada.

In most countries, AF is given only for medical reasons but for example in the United Kingdom and Canada, AF could be received also for social reasons (i.e. without a diagnosed fertility problem, CDBI, 2005). Surrogacy was prohibited in most countries, but restrictively permitted for example in the United Kingdom, Canada, Israel, and Estonia. Sperm, oocyte and embryo donations were allowed in most countries but not in Italy, Lithuania and Turkey. In Croatia, Norway, Switzerland and Austria, sperm donation was permitted, but oocyte and embryo donations were not. Donations in studied countries were mostly anonymous, but not in the United Kingdom, Turkey, Sweden, Norway, Netherlands, Georgia and Germany.

Two Scandinavian countries have legally defined age-limits for AF: 45 years for women in Denmark and 42–45 for women and 50 for men in Iceland (Legislation

on biotechnology…, 2006). In Sweden women before their "normal age of menopause" and capable of "carrying out parental responsibilities throughout childhood" can receive AF. In the United Kingdom until the end of 2005 the infertile patient's suitability (family and social circumstances) to raise a child had to be examined by consulting the patient's general practitioner (Eaton, 2005). Nowadays, the examination of suitability is left to the fertility clinics.

In Finland, attempts to draw up a law on fertility treatments (insemination and IVF) have continued for twenty years. In October, 2006 a legislative proposal was accepted in the Finnish parliament. During the process, features that were problematic were the eligibility of single and lesbian women, children's right to know their biological origin, and surrogacy (Burrell, 2005). The law will be come into force in 2007. In the coming law, IVF and insemination will not be prohibited for single or lesbian women, children will have the right to know the identity of the donor at the age of 18, and surrogacy will not be allowed. Until now only heterosexual couples have been treated in the public sector, donations have been anonymous both in the public and private sector and about 20 pregnancies have been successful through surrogate mothers (CDBI, 2005). One quarter of parents of the first cases of using surrogacy in Finland has been foreign (Söderström-Anttila et al., 2002).

In the coming Finnish law on AF, no exact age-limit exists and the decision on the eligibility of women is left to medical doctors (Hallituksen esitys…, 2006). The doctor is not allowed to give AF if the achieved pregnancy were to be harmful to the health of the woman seeking AF or to the health of the newborn or if it is evident that the women cannot guarantee a balanced development for the child. Until now, the female age limit for public IVF services has varied between 38 and 42 years, but in the private sector no strict age limit has existed (Malin Silverio and Hemminki, 1996**,** CDBI 2005) and in practice there have been variations in the age of treated women between the clinics.

5.4 Funding of IVF services

It has been much debated whether health insurance should cover IVF. In some countries IVF is offered only in the private sector (for example in Canada and most states in the United States), where its use depends on a couple's ability to pay (Neumann, 1997, Stephen and Chandra, 2000). In the United States it has been found that insurance coverage of IVF increased utilization of IVF but on the other hand decreased the number of transferred embryos, i.e. making IVF more safe (Jain et al., 2002). In some countries IVF is offered both in the public and in the private sector (for example in Finland and Norway) and wealthy couples can shorten their waiting times by using services in both sectors (Svensson and

Stephenson, 1993). In the United Kingdom where 80% of IVF is given in the private sector, authorities have warned that IVF is becoming more commercial and people with insufficient income are in danger of remaining without treatments (Cole, 2006). In some countries IVF services are available mainly in the public sector (for example in France and Germany) (Jones and Cohen, 2004).

Criteria of coverage varied also between countries (Jones and Cohen, 2004, CDBI, 2005). For example in Austria, Switzerland, Turkey, and Poland, IVF is not covered by the social security system mainly because involuntary childlessness is not considered as a disease. Other limiting factors are age and number of cycles. Female age has been used as a criterion to cover IVF: from an age-limit of 35 years in the Ukraine to 45 years in Denmark and Israel (CDBI, 2005). The most common age-limit for coverage is 40 (in Austria, Cyprus, United Kingdom, Luxemburg and Germany). In Finland, the SII, in covering the infertility treatments, follows the limitations given by the Ministry of Social Affairs and Health (STM, 2005). In that document the suggested age-limit is 39 years, but if treatment is based on a specific disease and a medical certificate, treatment is covered regardless of the age of the woman. The advanced age of a male partner is a limitation for coverage in Austria and Germany (50 years) as well as in Norway ("reasonable difference in age" between partners). The coverage according to number of cycles varied: in Cyprus, coverage is for a single cycle, while Israel gives full coverage up until the birth of two children.

In Finland the private sector is an important provider of IVF: some 60% of all IVF cycles are offered by private clinics (IVF Statistics, http://www.stakes.info/2/1/2,1,4.asp.). In 1999, 12 of the 19 clinics were private, and in 2005 that figure was 12 of 18. In general, a woman can seek medical advice for infertility by visiting a general practitioner (GP) at a health care centre or a private gynaecologist at a private clinic. Simple diagnostic tests can be done in both places. After that the GP or gynaecologists can refer the woman to a public hospital for further diagnosis and infertility treatment or the woman can contact a private IVF specialist at a private clinic. About 70% of women who have sought help for infertility had visited private gynaecologists, 30% a gynaecologist at a hospital and 17% a GP in a health care centre (Malin et al., 2001).

In the public sector, women pay a small fee for their clinic visits, and the rest of visits costs are covered by taxes. Nevertheless, to receive IVF they often have to wait. In the private sector, IVF can be received quickly but patients pay more for their visits. However, up to about 60% of the private physician's charges and a part of the laboratory cost (75% of the standard fee) and interventions (60% of the standard fee) are reimbursed by the Social Insurance Institution (SII). Women both in the public and private sector pay for about half of the drug costs and the rest are reimbursed by the SII. If the individual's yearly upper limit of drug costs has been reached, all further costs are paid by the SII.

5.5 Use of IVF by age, socioeconomic position and area of residence

Not all infertile couples seek medical help for infertility in spite of growing number of fertility services and awareness of them. In population-based studies the proportion of infertile couples having sought medical advice (visit to general practitioner, private gynaecologist or hospital) varied from 22% to 95% (Gunnell and Ewings, 1994, Schmidt and Münster, 1995, Stephen and Chandra, 2000). Primarily infertile women sought help more often than secondarily infertile and younger generations more often than older generations. In population-based studies from Finland, 50–67% of infertile women had sought medical advice (examinations or treatments) for infertility (Malin et al., 2001, Klemetti et al., 2004).

There is little reliable data on the use or users of IVF. However, data on IVF treatments given—for example, number of cycles, transferred embryos, pregnancies, short term complications—are registered or collected voluntary in many countries. From these statistics and registers some aspects on the utilization of IVF can be estimated. The European Society for Human Reproduction and Embryology (ESHRE) has collected information on IVF in Europe since 1997 (Nyboe Andersen et al., 2006). Systems to collect the data are different across European countries and some data are lacking, especially from some Southern European countries. In the United States, the Department of Health and Human Services (Centres for Disease Control and Prevention, CDC) reports on the success rates and outcomes of assisted fertilization (http://www.cdc.gov/ART). Treatments given in Australia and New Zealand are registered and reported every year (Waters et al., 2006). In Finland statistical data on IVF treatments have been collected since 1992 as voluntary reporting (http://www.stakes.info/2/1/2,1,4.asp.).

The highest utilization of IVF services among the 25 European countries was reported in Finland and Denmark (Nyboe Andersen et al., 2006). In Finland the use of IVF increased during the 1990s, but has since levelled off (Gissler and Tiitinen, 2001). However, in 2004 the number of IVF cycles grew again (Table 3), with 7.0 cycles per 1000 women of reproductive age (15–49) resulting in increased number of IVF children (IVF Statistics, 2006, http://www.stakes.info/2/1/2,1,4.asp.). In a European context, the use of IVF in Finland is high, but for example in Australia the corresponding rate per 1000 women in 2003 was even higher, at 8.4 (Waters et al., 2006).

Age

According to the statistics of ESHRE (Nyboe Andersen et al., 2006) over 70% of women using IVF in Europe were aged 30 to 39. However, there was variation between the countries from 53% to 88%. About 13% (from 2 % to 25 %) were aged 40 or more. Almost the same proportions are reported from the United States (69% and 20%, http://www.cdc.gov/ART) and from Australia and New Zealand

TABLE 3. Number of IVF, ICSI and FET[a] cycles, pregnancies, life births and cycles per 1000 women aged 15–49 years in 1992–2004 in Finland.

	Year												
	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Cycles	2331	3189	4382	5043	6417	7336	7159	6968	6811	6766	7114	6990	8391
Pregnancies	502	670	840	1040	1496	1611	1663	1636	1536	1523	1662	1807	1848
Live births	392	489	612	763	1092	1205	1229	1191	1179	1147	1259	1353	1395
Cycles per 1000 women aged 15–49 years	1.8	2.5	3.4	4.0	5.1	5.8	5.7	5.6	5.5	5.6	5.9	5.8	7.0

[a] FET: the cycles with the embryo transfer.
Reference: IVF Statistics, 2006, http://www.stakes.info/2/1/2,1,4.asp.

(66% and 20%). In Finland the corresponding rates were 66% and 14% (Nyboe Andersen et al., 2006).

It is well known that complications during pregnancy and childbearing notably increase by female age (Nybo Anderssen et al., 2000, Salihu et al., 2003, Heffner, 2004. Furthermore, success in AF decreases by female age (Graigner and Tjaden, 2000, Table 1). However, the use of donated oocytes has made it possible to achieve occasional pregnancies and live births even among women aged over sixty. Treating older women—even post-menopausal women—raises many ethical questions, such as setting age-limits in the use of AF, the allocation of scarce health care resources, the shortage of donated eggs, and the risks for the child's and the woman's health (de Wert, 1998, Heffner, 2004). Raising children is hard work and it has been asked whether older women are fit enough for it (de Wert, 1998) or if there are too great risks for the child's later psychosocial development with old parents (or as orphan at an early age). On the other hand it has been discussed whether age-limits are violations of human rights (Blank, 1997), and it is assumed that older women have a good capability to raise their children, in that they may have a better education, better economical situation and better emotional preparedness compared to younger women (Eisenberg and Schenker, 1997).

Male partners' age is seldom reported (and limited), and the effect of paternal age on reproductive outcomes has almost been ignored. In Australia the oldest registered male partner in IVF was 87-years-old (Waters et al., 2006). The results of paternal age effects on the outcome of AF are conflicting (ESHRE, 2005). However, a recent study found increased failure to conceive following IVF among fathers over 40 years (De La Rochebrochard et al., 2006).

Socioeconomic position

The over-representation of women from the highest socioeconomic group among IVF users has been found in studies from Canada and Australia (Svensson and Stephenson, 1993), the United States (Wilcox and Mosher, 1993), and the United

Kingdom (Gunnell and Ewings, 1994). In the United States, women with higher levels of education and income were more likely to have received infertility services than women with a lower level of education and income (Stephen and Chandra 2000, CDC: National Survey of Family Growth 2005, Jain and Hornstein, 2005, Bitler and Schimdt, 2006). In France the use of IVF did not differ according to women's socioeconomic position (Tain, 2003).

In Finland, no differences in the education of women were found in those seeking help but those using infertility services more often had a longer education than non-users (Malin et al., 2001, Klemetti et al., 2004). IVF mothers have also been more educated or more often were of a higher socioeconomic position than other mothers (Gissler et al., 1995a, Malin Silverio and Hemminki, 1996, Bergh et al., 1999, Buitendijk, 2000, Klemetti et al., 2002).

Area of residence

It is generally believed that not only women from higher socioeconomic positions but also women in urban areas have easier access to infertility services and also use them more than women from rural areas. Rural women may live considerable distances from cities offering AF and long trips and a possible lack of social support (husbands, friends and relatives far away) needed during the treatment may affect the access and willingness to use AF services (Daniels and Taylor, 1993). So-called satellite clinics have been created at least in the United Kingdom, the United States and the Netherlands to make access easier outside the big cities (Kingsland et al., 1992, Kaplan et al., 1995, Roest et al., 1995).The experiences have been encouraging; success rates did not decline, but stress that was related to the treatment and the costs of treatments did so.

In Finland, IVF clinics have been unevenly distributed; all IVF clinics (19 clinics in 1999 and 18 in 2005) have been situated in eight towns (IVF Statistics, http://www.stakes.info/2/1/2,1,4.asp.). Three out of the 12 of the pre-1995 provinces have had no IVF clinic. Women in some areas have to make long trips (as much as 700 km) to obtain IVF treatments. OI services are available in all parts of Finland. With the exception of one previous study that found that IVF mothers came more often from southern Finland (Malin Silverio and Hemminki, 1996), no data on use by area existed before this study.

5.6 Costs of IVF treatments

The costs of IVF vary from country to country. Costs can be divided into direct and indirect costs. Direct costs include costs of medical consultations, personnel, equipment, drugs, complications, and monitoring, and indirect costs such

as women's travel, time off work, lost wages, long-term complications, multiple pregnancies, and obstetric and neonatal care (Fauser et al., 2002). Many studies on the cost and cost effectiveness of IVF have been published, as have a few studies on cost-effectiveness of IVF versus other AF, and so-called economic benefit studies (reviewed by Garceau et al., 2002). Most published studies have not included indirect costs. Economic-benefit studies have examined IVF couples' or potential child bearers' willingness to pay (WTP) for IVF or have had macroeconomic perspectives comparing costs of IVF to costs of other areas of health care. Problems in comparing these studies include for example different definitions for success in IVF and the high incidence of multiple births and its long-term costs.

Health care costs for IVF treatment by women's age have been previously described in a review by Broekmans and Klinkert (2004) that found that IVF costs EUR 13 000 (without sick-leave, cost of travelling, complications and pregnancy) for women up to the age of 40 and EUR 37 000 for women aged over 40. Based their own small data, the authors suggested that IVF is still cost-effective (cumulative pregnancy rate was 49% and the estimated IVF costs per one child were EUR 18 000) for a selected (tested to have a reasonable probability of ongoing pregnancy) group of women aged 41 to 42 years but not for women aged 43 or older.

Health care costs resulting from IVF have also been previously studied in Finland (Gissler et al., 1995a, Malin Silverio and Hemminki, 1996, Koivurova, 2005, unpublished data by Koivurova et al.). It was found that health care costs for an IVF newborn from pregnancy induction until the age of one week was 5.4-fold compared to that for other newborns (Gissler et al., 1995a), while costs for IVF singletons were higher compared to other singletons and multiple births increased the costs (Koivurova, 2005). Pre-school age health care costs are markedly higher among IVF children compared to other children (Koivurova et al., unpublished data).

The focus in these previous studies has not, however, been in the allocation of scarce health care resources. Empirical data that would quantify the question of equitable use of scarce resources have not been given, nor has the distribution of private and public expenditure been estimated.

6 Equity and infertility treatments

6.1 Equity as a principle in health care

Equity is a key objective of many health care systems and it is present in many policy documents (Mooney, 1994). The same is true also of Finland; many features in the Finnish health care system are intended to support social equity (Keskimäki, 1997). In health care, equity can be defined as equality of access, equality in health, or equality of use for equal need (Mooney, 1994). Equity has been chosen as the first regional target in the World Health Organization European Region and included also in many other targets of the WHO (Whitehead, 1990).

According to the WHO, equity in health care includes equal access to services for equal need, equal use for equal need and equal quality of care (Whitehead, 1990). Equal access does not come about if people are turned away from health care or are unable to use health services due to race, sex, age, religion, poor income or other factors not directly related to the need for care. According to Whitehead (1990) resources and facilities should not be unevenly distributed around the country, resources should not be used for specific services which benefit only a small population, services should not be organized in such a way that only a part of the population are capable of using them, while received care and its quality should be based on need and not on social factors. The different use of services by different social groups is not automatically unequal. But it is unequal if services are organized so that people in different social groups do not have the same possibility to use them.

Mooney (1994) has argued that the WHO's egalitarian view of equal use for equal need is problematic, because it requires people with the same need to use health care services without taking into account people's own preferences for their health and health care. People with the same need may not value their health equally and may not have the same willingness to use services. Mooney pointed out that equal access for equal need is not so problematic; it can be thought to include a desire for equal access. If equal access or use is required for equal need, it is also important to define the need. According to Mooney, a need can be defined as the extent of sickness (defined by a medical practitioner, health care system or some part of it) or the capacity to benefit. Definitions cause many problems, especially

the latter definition, as well as questions such as how different diseases or different grade of diseases will be taken into account, how to measure the benefit, and who will carry out such an assessment. However, the greater the capacity to benefit, the greater the need is, but Mooney reminds that not all diseases or conditions can be treated and that not all sufferers can be made healthier. Mooney commented that need and demand should be differentiated from each other; they are not the same. Need is defined by other people but demand is based on the person's own preferences. According to Mooney, use and consumption are not the same as demand or need. For example, due to factors such as prioritization, higher costs, or lack of services, people who would need services and who demand them have sometimes to wait. In other words, they cannot necessarily use or consume services in spite of a need or demand.

Equity in health care not only means that offering of services is based on need and that services are distributed equally. It has been argued that equity includes also the right to effective and safe treatments (Svensson and Stephensson, 1993). Because the health care system cannot afford to do everything, resources have to be allocated—according to priorities set by society—and in as equitably a way as possible (Svensson and Stephensson, 1993, Mooney, 1994). It has been argued that it would be useful if priorities are set—i.e. choices made—not only by health care professionals and decision makers but also by health care consumers and the public at large (STAKES report 161, 1994).

6.2 Equity in infertility treatments

What does equity mean in infertility treatments? Finding an adequate answer to this question is not easy (Daniels and Taylor, 1993, McLean, 1993, Svensson and Stephenson, 1993, Blank, 1997, Ashcroft, 2005). As in other health care, the first step is to define the need for infertility treatments in the population i.e. infertility prevalence and the wish for a child.

Secondly, it can be asked what priority should be given to infertility treatments compared to other treatments in health care. As in other countries (Daniels and Taylor, 1993, Nisker, 1996, Neumann, 1997), Finland has seen discussion on the following priority-related topics: Should infertility be considered a disease or not, should treatments be given only for medical reasons (infertility is diagnosed) or also for social reasons, and who should have the right to treatments or eligibility? Prioritization has not however been explicitly discussed. IVF is clearly prioritized only by women's age, as already explained in Chapter 5.

Thirdly, it can be discussed whether these treatments are efficacious and safe enough (Peters, 2004). The fourth significant question is how can scarce health care resources be distributed equitably (in terms of geographical variations as well

as variations by socioeconomic position, and age) and with maximum benefit to public health. The allocation of resources is linked to the funding of infertility treatments. If IVF services are available only in the private sector, access will depend on ability to pay.

7 Summary

Infertility is a common problem and IVF and OI are widely used infertility treatments, but not enough is known about their utilization and health effects. Data on the frequency of IVF complications for treated women are sparse and the number of studies reporting complications after OI is even rarer. In spite of the large number of studies on perinatal health of IVF children, some studies on the general health of IVF children are based on early experience of IVF. Some studies concentrate on specific diagnosis or hospital care utilization or singletons or twins only, or do not consider multiplicity. Results on the perinatal health of IVF twins are controversial. Studies on congenital anomalies of IVF children are also controversial and many of them have had methodological problems such as small sample sizes, lack of proper controls, and different definitions of congenital anomalies among IVF and naturally conceived children. Only a few studies have examined congenital anomalies among OI children.

Health care costs for a live-birth among IVF women by age have briefly been described previously but otherwise empirical data that would quantify the question of resource allocation have not been given, nor has the distribution of private and public expenditure been estimated. There are many general assumptions of inequalities in the use of infertility treatments (i.e. urban women and women from higher socioeconomic position use more IVF services than rural women or women from lower socioeconomic positions) but not enough data are available to verify these assumptions. Equity is considered an important principle in health care. To be able to discuss equity in assisted fertilization data on effectiveness or success, safety, costs and resource allocation as well as utilization of assisted fertilization are needed.

8 Aims of the study

8.1 General aims

The general aims of this study were to study the utilization of IVF and OI, the health effects of IVF and OI as well as the equity in the use and resource allocation of IVF by using nationwide Finnish health care registers.

8.2 Specific aims

The specific aims were to study

1. the use of IVF and OI in Finland in 1996–1998 by women's background characteristics.
2. the serious complications and miscarriages leading to women's hospitalization or operations after IVF or OI.
3. the health of IVF children until the age of four years.
4. the prevalence of major congenital anomalies among IVF children.
5. the treatment costs of IVF in Finland.
6. the equity in the resource allocation for IVF in Finland.

9 Methods

Six different nationwide registers were used in the present register-based longitudinal study: Reimbursement records of the Social Insurance Institution (SII), the Central Population Register, the Hospital Discharge Register (HDR), the Medical Birth Register (MBR), the Register of Congenital Malformations (RCM), and the Cause-of-Death Register.

The study plan was approved by the STAKES research ethics committee. For register linkages, the National Data Protection Authority was consulted and permissions from the register keepers were obtained.

9.1 Registers used in the study

9.1.1 Reimbursement records of the Social Insurance Institution

The reimbursements of medical expenses such, as drugs, doctor's fees, and treatment or examination fees, are available by the Finnish national sickness insurance provider, the Social Insurance Institution (SII, http://www.kela.fi/in/internet/English.nsf). Up to 60 % of the doctor's fees and part of the cost of examinations and treatments ordered by a physician in the private sector are covered according to a fixed scale of charges. The part exceeding the fixed charge is not reimbursed.

The reimbursements are filed in electronic registers with personal identification (ID) numbers. The register of reimbursed examinations and treatments also includes the code of the physician, the codes of the examinations or treatments, dates, costs, and the amounts of reimbursements. The register of reimbursed drugs includes the municipality of recipients, the name and class of the drug, the size and numbers of packages, the dose recommended, the dates prescribed and bought, and the code of the physician.

In Finland, patients with certain long-term illnesses are entitled to a higher reimbursement of their costs of medication and clinical nutrients. This so-called Special Refund Category consists of approximately 50 diseases. Among children, the most common special refunded diseases are asthma, epilepsy, diabetes, rheumatoid arthritis, and allergy to cow's milk and/or soya milk. For the present study, information of reimbursements of long-term medication was also available and

the reimbursed medications were taken into account (excluding reimbursements of the clinical nutrients). The data on Special Refunds included the start and end dates of an entitlement period, the types, and the reasons.

The SII also grants child disability allowance for families who have a disabled or a chronically sick child needing continuous help and surveillance at home. The parents applying for benefits are required to supply recent medical documents. The register of the child disability allowance contains information of the start and end dates, the nature of benefit (temporary and permanent), the level of benefit (normal, increased and special), and the diagnoses for the support.

9.1.2 The Central Population Register

The information of marital status and occupation of the women was received from the Central Population Register (http://www.vaestorekisterikeskus.fi). The socioeconomic position was defined by using their occupation and classified into five categories: upper white-collar workers, lower white-collar workers, blue-collar workers, other (entrepreneurs, students, pensioners, unemployed women, and women with an unclassified position), and unknown position (Central Statistical Office, 1989).

9.1.3 The Hospital Discharge Register and the Care Register for Social Welfare

The HDR (http://www.stakes.info/2/9/index.asp) and the Care Register for Social Welfare (http://www.stakes.info/2/10/index.asp) are maintained by STAKES. The HDR collects information of inpatient care as well as of visits to outpatient clinics involving surgical or other procedures. It gathers information of diagnoses (the tenth revision of the International Classification of Diseases, ICD-10 since 1996), operation codes, and dates of admission and discharge. The diagnoses include the main diagnosis (which can consist of separate diagnoses of the reasons and symptoms leading to hospitalization) and two secondary diagnoses (which can also consist of two separate diagnoses of the reasons and symptoms) for each hospital episode. From 1983 to 1995, operations were registered according to a national coding system and, since 1996, according to the Finnish version of the NOMESCO classification system for surgical operations (Toimenpideluokitus, STAKES, 1996). The Care Register for Social Welfare collects information of care episodes in social institutions. Institutional care does not include children taken into children's homes or custody but refers mainly to mentally handicapped children who have stayed in institutions for intellectually disabled persons.

9.1.4 The Medical Birth Register

The MBR (http://www.stakes.info/2/1/2,1,1.asp) includes the unique ID numbers of the mother and the child and contains information of maternal background and on the outcome of all infants born in Finland until the age of seven days. The duration and causes of infertility are not registered. The data are collected by the delivery hospitals and completed by linkage to the Central Population Register and the Cause-of-Death Register. The socioeconomic position of the mothers was defined by using their occupation when delivering, which is collected routinely from maternity hospitals and classified automatically by the MBR into five categories (Central Statistical Office, 1989, Statistics Finland).

9.1.5 The Register of Congenital Malformations

The RCM (http://www.stakes.info/2/1/2,1,5.asp) collects information of all infants with a congenital anomaly (CA) or birth defect through several data sources, including a notification completed by the delivery hospitals, neonatal, pediatric and pathology departments, and cytogenetic laboratories as well as by linkage to several other nationwide registers. In the RCM a CA has been defined as a major congenital structural anomaly, chromosomal defect or congenital hypothyroidism involved in a birth. The CAs reported to the RCM, which do not qualify the criteria of major CA, are not accepted to the register (rejected, not registered cases).The physician responsible for RCM routinely classifies CAs into major, other, and rejected. Other anomalies reported to the register can, for example, be minor anomalies related to major CAs. Rejected anomalies include some minor CAs as defined by the European Surveillance of Congenital Anomalies EUROCAT (http://www.eurocat.ulster.ac.uk) exclusion list (hereditary diseases, dysfunction of organs or tissues, developmental disabilities, congenital infections, isolated minor dysmorphic features, normal variations, and other less significant anomalies).

9.1.6 The Cause-of-Death Register

The Cause-of-Death Register is maintained by Statistics in Finland and it includes personal ID numbers, causes of death (diagnoses according to the ICD-10 since 1996), and dates of death. The data is obtained from the death certificates, which are supplemented with the data from the population information system of the Central Population Register. The data in the Cause-of-Death Register covers the persons who have died in Finland or abroad and who at the time of death were domiciled in Finland.

9.2 Identification of IVF and OI women and their children

The study includes two exposed cohorts: 20–59-year-old women having had IVF treatments (IVF, ICSI and FET, N = 9175) and women having had other infertility treatments including drugs (ovulation inductions or low stimulation with or without artificial insemination, OI, N = 10 254) between 1996 and 1998 in Finland, and their children (Fig. 2). The population controls, matched by age and municipality, were randomly selected for IVF women (N = 9175) from the SII population record (covering the total Finnish population).

The basis for the data collection was that all infertility treatment cycles (not natural cycles and a part of frozen embryo transfers) start with drugs, and some drugs and their combinations are specific to infertility treatments as such. The bought and reimbursement drugs can be found from the reimbursement files of the SII. An algorithm about which drug combination indicates each infertility treatment was created (detailed in Hemminki et al., 2003). The beginning of a treatment cycle was defined by the date of buying the first infertility drug. The cycles were classified as ovulation induction (with or without insemination), IVF without embryo transfer (cancelled cycles and cycles for ovum pick-up), IVF with embryo transfer, and frozen embryo transfer. IVF interventions done in the private sector (over 60%) which are covered and registered by the SII were added to the cycles. The functioning of the algorithm was checked manually 18 times (with the sample sizes between 200 and 2000 women), and the algorithm was improved with the received information. As a whole the algorithm worked well (Hemminki et al., 2003), and a total 24 318 IVF cycles could be identified, which was slightly higher than the number of cycles registered in IVF statistics (21 424). This can be partly explained by the cancelled cycles which were also included in this study and partly by incorrect classification. The number of identified OI cycles was 24 611, which could not be compared to any other number of cycles, since OI cycles are not collected in any statistics. The data on IVF and OI women were created from the women who had received IVF and OI treatment cycles.

To identify the children born after IVF or OI the data were linked to the nationwide MBR by using the personal identification numbers of the women and the dates of birth of the children as the linkage keys. For IVF births the time limit of 44 weeks after the beginning of treatment (the purchase of the first drug) to the date of birth was used as a standard and for OI births it was 48 weeks.

As controls for the children, two groups of children were selected from the MBR. The first control group consisted of all children other than IVF and OI children (N = 190 398) who had been conceived during the same time-period (1996–1998). The second control group (n = 26 877) was a random sample of the first control group and was selected to reduce the workload caused by large register linkages in the SII and the RCM; it was used to study the benefit payments from the SII, CAs from the RCM, and in the combined analysis.

9.3 Register linkages

The data on the identified women who had used IVF and OI were linked to the CPR to receive information of women's background characteristics. The data on the costs and reimbursements were received partly from the SII and partly from the clinics: Helsinki University Central Hospital and the biggest private IVF clinic recommended by other clinics (Paper V). The costs taken into account were direct costs, such as medications, visits, routine examinations, interventions, and costs of equipment and trained staff. Indirect costs, such as costs for travel and sick-leave, were not included. The expenditures were partly based on the average costs in clinics, partly on estimations, and partly on exact paid and reimbursed costs. Private expenditures include costs paid by the patient and public expenditures costs paid by the health care system. All costs and reimbursements have been inflated to correspond to 2005 prices (in euros) using a consumer price index compiled by Statistics Finland.

The data on care episodes at hospital were collected by register linkages to the HDR, and dates and causes of death (during the mean of 3.7-years of follow-up for IVF and control women and 3.8 years for OI women) from the Cause-of-Death Register by using personal ID numbers (Fig. 2).

The data on perinatal health of the IVF children and the ID numbers of the children were obtained from the MBR. To receive data on the health of early childhood the identified children were linked to five other nationwide registers by the ID numbers of the children: the Cause-of-Death Register, the HDR, the Care Register for Social Welfare, the RCM (without knowing the mode of conception of the children), and the health-related social benefits from the SII (Fig. 2).

9.4 Data analysis

Use and costs

To calculate the age-specific incidences of the use of IVF and OI, the number of women treated was divided by the number of all women in the same age group in the same area (SOTKA database 2001, STAKES). The age-adjustment was made by using direct age-standardisation. The mean price of different types of IVF cycles by the care sector were calculated as well as the private, public, and total expenditures by women's background characteristics and by live births. The mean population of females aged 20–49 years in Finland by socioeconomic position and area of residence according to census information for 1995 and 2000 available from Statistics Finland was used to count the expenditure by population groups.

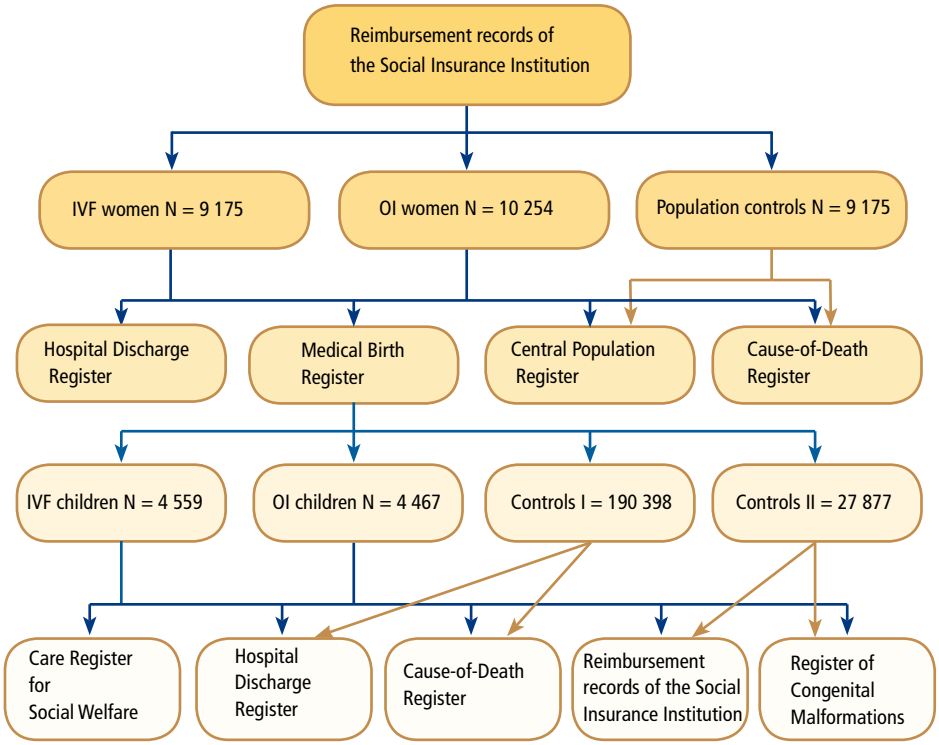

FIGURE 2. Registers, study population, and register-linkages used in the study.

The cycle was defined as having taken place in the private sector in cases where an intervention in the IVF cycle involved reimbursement by the SII. For the other IVF cycles the classification of cycles as private or public was made according to the main work place of the physicians given in a catalogue of physicians (STAKES, 1998). The catalogue is based on the register of health care personnel (TERHIKKI) which receives information of certificate doctors from the Finnish Medical Association. The classification for private and public cycles was crude, since the main work place could not always be defined. The OI cycles could not be classified as private or public.

Complications and miscarriages after IVF and OI and pregnancy and birth treatments

The proportion of the IVF and OI women with a complication (the first occurrence) after the first cycle and after all treatment cycles (in the study window) was calculated separately for each type of complication (risk for a complication after an average of 2.7 treatment cycles). The studied outcomes, follow-up times, and data sources are presented in the Appendix, and the ICD-10 codes of complications are detailed in the Appendix of Paper II. In addition, the diagnoses defined

in the HDR as OHSS (ICD-10 code) as well as symptoms or diseases potentially related to OHSS ("potential OHSS") were searched from the HDR. Some women had both the diagnosed OHSS (with the specific ICD-10 code) and the "potential OHSS".

The causes of death were classified into eight categories: reproductive mortality as defined by Fortney et al. (1986) with the addition of causes related to achieving the pregnancy, diseases of the circulatory system, cancers, suicides, homicides, accidents, other, and unknown causes.

The IVF mothers were compared to the mothers of the control children in their utilization of health care services during the pregnancy and child birth (hospitalization during the pregnancy, Caesarean section, and the hospitalization of seven or more days after the delivery). The same variables were studied also for OI women but were not reported in Paper IV for space reasons as suggested by the referees of the journal.

Health of IVF children

The IVF children were compared to the control children. The studied outcomes, follow-up times, and data sources are presented in the Appendix. The follow-up times varied, because the data were first collected until two years of age and then completed by the data on hospitalizations until the children were four years of age. Information of specific diseases was received by combining the different data sources and by calculating the number of children who had used the services—according to any of the data sources—due to an allergic or chronic disorder or common infection until two years of age. If the child was hospitalized more than once due to the same diagnosis, only the first hospitalization was included. The same variables were studied also for the OI children, but they were not reported in Paper IV for space reasons as suggested by the referees of the journal.

The occurrence of major CAs both among the IVF and OI children was reported (detailed in Paper III). Only major CAs, as defined in the RCM, were included in the analysis. In the analysis of the CAs by the organ system, a child appeared more than once if (s)he had more than one major CA affecting different organ systems. The IVF and OI women were linked to the Register of Induced Abortions to specify induced abortions performed due to a suspected or confirmed CA. The rates were compared to the national rates per 10 000 births.

Statistical analysis

The differences between the IVF and control groups as well as those between the OI and control groups were examined by using tests for relative proportions, t-tests, chi-square tests, and the one-sided analysis of variance. A P-value of less than 0.05 was considered significant.

The IVF mothers were compared to the mothers of the control children and the IVF and OI children were compared to the control children using odds ratios (OR) and 95 % confidence intervals (CI). When the health of the IVF children in the early childhood was studied, two logit models were made: an ordinary logit model where all the children were assumed to be independent and an additional analysis using the iterative generalized least squares method where siblings born in the same delivery were assumed to be dependent.

The singletons and multiples were analysed separately. When the ORs for congenital anomalies were studied, the children were stratified also by sex and multiplicity. For perinatal outcomes adjustment was made by the age of the mother, previous births, smoking, marital status, socioeconomic position, and the residence of region, for congenital anomalies by the age of the mother, parity, socioeconomic position, and the residence of region, and for other childhood outcomes by socioeconomic position using logistic regression.

10 Results and comments

10.1 Use of IVF and OI (Papers I and V)

The background characteristics of IVF, OI, and control women are presented in Table 4. The IVF women were more often married and from the higher socioeconomic position compared to the OI and control women.

TABLE 4. Background characteristics of IVF, OI, and control women[a] in 1996–1998.

	IVF (n=9 175)	OI (n=10 254)		Controls (n=9 175)	
Age group					
20–24	3.5	11.0		3.5	
25–29	20.8	31.4		20.8	
30–34	35.2	31.5		35.2	
35–39	27.7	17.8		27.7	
40–44	10.8	6.9		10.8	
45+	2.0	1.4		2.0	
Total	100.0	100.0	p<0.001[b]	100.0	p=1.000[d]
Marital status					
Non-married [c]	22.3	19.1		36.1	
Married	69.4	72.5		56.7	
Divorced	7.9	7.9		9.4	
Widow	0.4	0.5		0.4	
Unknown	0.0	0.0		1.4	
Total	100.0	100.0	p<0.001[b]	100.0	p<0.001[d]
Socioeconomic position					
Upper white-collar	25.3	20.6		16.3	
Lower white-collar	48.5	48.7		45.7	
Blue-collar	16.2	18.0		19.3	
Others	7.9	10.0		12.3	
Unknown	2.1	2.7		6.4	
Total	100.0	100.0	p<0.001[b]	100.0	p<0.001[d]

[a] Population controls for IVF women, matched by age and muncipality.

[b] P-values for chi square tests (IVF women and OI women).

[c] Includes cohabitation. Divorced and widowed women can also live in cohabitation.

[d] P-values for chi-square tests (IVF women and controls).

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TABLE 5. Number of IVF cycles per treated women by age, socioeconomic position and treatment sector in the study period (mean 1.5 years).

	Age					
	20–29	30–34	35–39	40+	Total	P-value[b]
Socioeconomic position						
Upper white-collar	2.28	2.83	2.91	3.14	2.82	< 0.001
Lower white-collar	2.16	2.69	2.77	2.98	2.62	< 0.001
Blue-collar	2.27	2.56	2.74	2.96	2.56	< 0.001
Others [a]	2.23	2.69	2.59	2.83	2.52	0.003
Sector						
Public	1.93	2.21	2.36	2.18	2.17	< 0.001
Private	2.21	2.65	2.66	2.92	2.61	0.573
Both	3.09	4.43	4.59	5.30	4.19	0.055
Total	2.21	2.71	2.79	3.01	2.65	0.066

[a] Entrepreneurs, students, pensioners, unemployed, and women with an unclassified or unknown position.

[b] P-values for one-sided analysis of variance.

The age-standardised IVF incidence per thousand 20–49-year-old women was 8.8 in the urban and 7.3 in the rural areas. The use of OI was highest in the semi-urban area (10.4) and lowest (8.5) in the capital area. The regional incidence of IVF varied from 6.5 (in eastern Finland) to 9.2 (in the capital area in southern Finland) and of OI from 5.2 (in eastern Finland) to 12.7 (in northern Finland). The northern region had no IVF clinic, and the use of OI was common.

Approximately 53% of IVF women received all IVF treatments from private doctors ('private users'), 35% from public doctors ('public users'), and 12% from both private and public doctors ('both-sector users'). The private users were older (mean age 34.3 years) than the public (32.3 years) and both-sector users (32.8 years, $p<0.001$). In the private sector, the women in the highest socioeconomic position were over-represented (29% private, 18% public, 16% controls). During the mean 1.5-years study period, the IVF women had received a total of 24 318 cycles; the minimum number was one and the maximum 14 cycles. The IVF women

TABLE 6. Rates (per 1000 female population) of women having received IVF by age and socioeconomic position in the study period.

	Age				
	20–29	30–34	35–39	40+	Total
Socioeconomic position					
Upper white-collar	14	30	24	4	13
Lower white-collar	13	25	17	2	9
Blue-collar	8	16	12	1	6
Others [a]	2	5	3	1	2
Total	7	18	14	2	7

[a] Entrepreneurs, students, pensioners, unemployed, and women with an unclassified or unknown position.

received slightly more treatment cycles in the private sector compared to the public sector (p-value for one-sided analysis of variance < 0.001); the frequency was not age-dependent, and the women in the highest socioeconomic position had slightly more cycles than the others (p-value < 0.001, Table 5). In the public sector the number of cycles did not differ by socioeconomic group, and the women aged from 30 to 39 years had more cycles than the others. In the population-based examination it was found that the women from the highest socioeconomic-group used IVF twice as much as the blue-collar women in every age-group.

The over-representation of women in the highest socioeconomic position among the IVF women is in accordance with previous studies (Svensson and Stephenson, 1993, Wilcox and Mosher, 1993, Gunnell and Ewings, 1994, Bachelot and Mouzon, 2002), but in the present study it was found only in the private sector. The higher number of cycles in the private sector cannot be explained solely by age, because the difference was also found in the age-specific analysis. It may indicate effectiveness and an ability to respond to demand, but also a sign of growing commercialism. In the United States, the growing numbers of fertility specialists and clinics have increased competition for clients, and some authors consider the marketing of infertility services aggressive (Mitchell 2002, Spar 2006). The older age of the treated IVF women in the private sector found in the present study can be explained by an informal age limit within the public sector. Some of the women treated were over 50 years of age, but their number was very insignificant.

It is possible that a widespread use of IVF eliminates socioeconomic differences in countries using public resources to provide IVF. In the present study, the public sector made the use of services more equitable for different socioeconomic groups, though it could not compensate for socioeconomic differences created in the private sector. On the other hand, if the private sector did not offer IVF services, the social class differences might be smaller but waiting lists might be longer, and the total number of treatments and women treated would be smaller. Since the regional differences were not great, it seems that long distances are no object; women are prepared to travel to obtain IVF treatments.

10.2 Success of IVF (Papers I and V)

The numbers and rates of women having received IVF was the highest among women aged 30–39 years (Tables 4 and 6), but the treatment was more intense for older women (number of cycles per woman, Table 5). The efficacy of IVF measured by the success rate per cycle and per woman decreased by age (Tables 7 and 8). The higher treatment intensity among the older women did not compensate for the lowered success rate, and approximately 47% of the women aged under 30 years and only 17% of those aged 40 years or older succeeded in achieving a live birth after the treatment period (mean 1.5 years).

TABLE 7. Live-births per number of IVF cycles[a] by age, socioeconomic position, and treatment sector.

	Age				
	20–29	30–34	35–39	40+	Total
Socioeconomic position					
Upper white-collar	0.25	0.18	0.13	0.06	0.15
Lower white-collar	0.23	0.17	0.14	0.05	0.16
Blue-collar	0.19	0.16	0.11	0.07	0.14
Others [b]	0.19	0.16	0.11	0.04	0.14
Sector					
Public	0.20	0.18	0.13	0.04	0.16
Private	0.26	0.20	0.15	0.06	0.17
Both	0.15	0.10	0.08	0.04	0.10
Total	0.22	0.17	0.13	0.06	0.15

[a] All live births and all cycles during the mean 1.5 years treatment period.

[b] Entrepreneurs, students, pensioners, unemployed, and women with an unclassified or unknown position.

The success of the IVF treatment was also dependant on the socioeconomic position: live-births per cycle were more common among the white-collar women than among the blue-collar ones aged less than 30 years (Table 7). Furthermore, the white-collar women in total achieved a live-birth more often than the blue-collar women (Table 8). The success per cycle did not vary much by the treatment sector, being the poorest among the both-sector users (Table 7), but the women treated in the private sector received more often a live-birth than those treated in public sector or in both (Table 8).

TABLE 8. Live-births per IVF women[a] by age, socioeconomic position, and treatment sector.

	Age				
	20–29	30–34	35–39	40+	Total
Socioeconomic position					
Upper white-collar	0.55	0.49	0.38	0.20	0.42
Lower white-collar	0.49	0.46	0.37	0.15	0.40
Blue-collar	0.42	0.40	0.30	0.21	0.36
Others [b]	0.42	0.41	0.29	0.12	0.35
Sector					
Public	0.39	0.40	0.31	0.08	0.35
Private	0.56	0.50	0.39	0.19	0.42
Both	0.44	0.44	0.36	0.23	0.40
Total	0.47	0.45	0.36	0.17	0.40

[a] One live birth per woman during the mean 1.5 years treatment period.

[b] Entrepreneurs, students, pensioners, unemployed, and women with an unclassified or unknown position.

The success rates in this study were age-dependent as also found earlier, but slightly lower than especially in recent publications (Table 1). This can be due to the improved success rates in the course of time or to the different ways to calculate the number of cycles; cancelled cycles were included in this study. The better success of the women from the higher socioeconomic position compared to the other women in the present study can be a consequence of seeking for medical advice after a shorter period of infertility, of more intense treatments or of more serious infertility among women from the lower socioeconomic position. On the other hand, the greater number of cycles received by women in the highest socioeconomic position can be a consequence of seeking for IVF services at an older age as well of a capability to pay for or to request more treatments. The both-sector users were not too old or 'sick' to receive treatment in the public sector and they had evidently enough money to purchase care in the private sector. Since they needed many treatment cycles, it can be assumed that their treatments were less successful. Some of these women may have little or no chance of becoming pregnant, but they did not want to stop trying. However, 40 % of them received a child as a result of the treatments; finally they succeeded as well as the women in this study on average. The number of cycles among the both-sector users was not dependent on the socioeconomic position, which suggests that the care itself was experienced as important and useful.

10.3 Complications after IVF and OI, and pregnancy and childbirth treatments (Papers II and III)

Only a few IVF women were hospitalized due to the OHSS after the first treatment cycle but more after repeated attempts and particularly when the 'potential OHSS' was taken into account (Table 9). After OI the hospitalization due to the OHSS was rare. The risk of having OHSS was highest after the first and the fifth or more IVF treatment cycles (Paper II) and it was more common among twin than among singleton pregnancies ending in birth (3.2% vs. 1.4%, p-value < 0.001 for a test of relative proportions). After IVF treatment, OHSS (ICD-10) was much more common among younger than older women: 3.2% of the women under the age of 35 years were hospitalized due to the OHSS compared to 1% of the older women.

Bleeding and infections necessitating hospital care were rare and even rarer after OI than after IVF (Table 9). Miscarriage was the most common reason for hospital care. The percentage of women that had miscarriage was similar after the first OI and IVF treatment cycle, but after all treatment cycles, miscarriage was 1.6 times more common among the IVF women than among the OI women. The number of miscarriages per 100 births was 23.0 after IVF and 15.0 after OI. Ectopic pregnancies were also more common among the IVF women compared to

TABLE 9. Health problems leading to hospitalization after the first and all IVF or OI treatment cycles in the study period, per 1000 women.

	IVF (N = 9175)		OI (N= 10 254)	
	First	All	First	All
Outcomes				
OHSS, ICD-10 [a]	14.1	22.9	0.3	0.8
Potential OHSS [b]	5.6	13.3	5.6	9.1
OHSS, ICD-10 or potential	19.0	34.7	5.7	9.8
Bleeding	1.0	2.4	0.3	0.3
Infection	5.1	10.9	1.5	3.1
Other [c]	1.1	1.9	0.1	0.5
Ectopic pregnancy	9.3	20.9	8.2	10.7
Miscarriage	41.9	93.1	42.1	61.8

[a] OHSS = Ovarian hyperstimulation syndrome (N98.1, ICD code).

[b] Symptoms potentially related to OHSS (see Paper II).

[c] Other complication than OHSS related to IVF or OI (see Paper II) and thromboembolic events.

the OI women. The ratio per 100 births after IVF was 5.0 and that after OI 0.03. Six IVF women (four registered as pregnant) and four OI women had a thromboembolic event (two registered as pregnant).

After all treatment cycles, 15% IVF and 8% OI women were hospitalized for complications. During the whole follow-up (mean 3.7 years for IVF women and 3.8 years for OI women from the exposure) one death in both the IVF and OI group was related to reproduction (Paper II).

The IVF mothers were older, more often married, and from a higher socioeconomic position than the other mothers (Paper III). They were seldom smokers, the child was more often their first, and they received more hospital care during the pregnancy and Caesarean sections compared to the other mothers. Adjustment to mothers' background characteristics did not change the results. The inspection of singletons and multiples separately showed that this difference was partly, but not totally, explained by IVF children being more often twins.

As reported earlier (Schenker, 1999), women under 35 years of age were at a greater risk of OHSS. The risk was also greater among the women with only one cycle and those with many cycles. In this study it is not known how many cycles the women had received before the year 1996. After many repeated cycles a woman may be in a greater risk due to the repeated doses of drugs (especially gonadotrophin). This should be considered when many attempts are needed. Furthermore, the risk was also higher among twin pregnancies than among singleton pregnancies ending in birth, which has also been found in an earlier study regarding late OHSS (Mathur et al., 2000).

Only a few studies (Quasim et al., 1997, Abramov et al., 1999b) have reported the frequency of OHSS after ovulation induction (OI) alone or compared it to the frequency after IVF. The present study, in accordance with earlier studies from the USA and Israel, shows serious OHSS to be more common after IVF than after OI.

The present study confirmed earlier results that thromboembolic events exist after IVF but are rare complications (Serour et al., 1998), and even rarer after OI. The frequency of bleeding after IVF was the same in the present study as in an Egyptian study with 3500 cycles (Serour et al., 1998), but it was much lower than the frequency found in a recent report from ESHRE (Nyboe Andersen et al., 2006) which covered all bleeding complications, even those not leading to hospitalization. The frequency of infections in the present study was similar to that reported earlier in the Nordic countries (Bergh and Lunkvist, 1992) and Egypt (Serour et al., 1998), but higher than the frequency reported by ESHRE (Nyboe Andersen et al., 2006). The finding of very low rates after OI suggests, that bleeding and infections may be complications of the IVF technique.

It was not possible to identify how many of the treated women had become pregnant, but the miscarriage ratio to 100 IVF births (23.0) suggests similar miscarriage rates as found earlier after IVF (15% to 21%, Serour et al., 1998, Kupka et al., 2003, Schieve et al., 2003, Wang et al., 2004). However, since all miscarriages do not lead to hospital care, the actual rate of miscarriages must have been higher. The miscarriage ratio to 100 OI births was lower than after IVF (15 vs. 23). Whether this was due to women's characteristics or to the procedure itself, could not be judged from this study. Previously, greatly varying rates after clomiphene-induced pregnancies have been reported (9–27%, Venn et al., 1994).

In the present study no pregnant controls were available, but, according to one Finnish study, 8% of women with spontaneous pregnancies needed hospital care due to a miscarriage (Hemminki and Meriläinen, 1996). In one study from the United States the miscarriage rate was similar (15%) among ART women and normal female population (Schieve et al., 2003). However, in another study from the United States, the risk of miscarriages was slightly increased after ART (Wang et al., 2004).

The ectopic pregnancy ratio to 100 IVF births (5.0) in this study was two-fold higher than found earlier in Finland (Hemminki and Heinonen, 1987, Mäkinen, 1996). Information of the reasons for infertility was not available in this study, and the number of women having tubal occlusion, which is considered to be one reason for the high frequency of ectopic pregnancies among IVF women, could not examined. In the case of OI, which requires open tubes in order to be effective, a possible reason for the high rate of ectopic pregnancies could be clomiphene citrate (Venn et al., 1994).

In one study from Australia, the maternal mortality of IVF women was higher than the national rate (Venn et al., 2001). The authors suggested that reasons for that can be advanced maternal age, a high proportion of multiple pregnancies, and a high Caesarean section rate. Due to the lack of a control group of spontaneously pregnant mothers or women aiming at pregnancy, the best control group for IVF women was in this study the group of OI women, though the IVF women were older than the OI women. The present overall mortality was lower than in the general female population (matched by age and municipality), which is in accordance with the Australian study. In particular, the cardiovascular deaths were rarer. It speaks for a "healthy patient effect" among IVF and OI women (Venn et al., 2001): sick women are less likely to be married or to receive infertility treatment than healthy women. The socioeconomic position of the IVF women in this study was slightly higher than that of the control women, which can partly explain the low mortality. Lower mortality among the women having received IVF compared to those who had registered for IVF but never received the treatment has been reported in Australia (Venn et al., 2001).

10.4 Health of IVF children (Papers III and IV)

10.4.1 Health of the newborn

In this study 4 559 children born after IVF and 4 467 after OI could be identified. Of the IVF children 34.7% were twins and 1.1% triplets. The corresponding rates of the OI children were 11% and 1.1%. Among the control children 2.2% were twins and only 13 sets were triplets (0.02%).

The health of the IVF infants was much worse than that of the other infants, which was partly explained by plurality (Table 10). The health of the multiple IVF infants was comparable to that of control multiples; only the risk of a very preterm birth was increased, but not statistically significantly. In the subanalysis of the first births the results were mainly similar to those of all children and no differences in the results of the two logit analyses (see Methods) were found.

Stillbirths were more common among the IVF infants in total compared to the other children in total (7.2/1000 vs. 3.9/1000, p-value < 0.001 in the test for relative proportions) as well as among the IVF singletons compared to the control singletons (6.5/1000 vs. 3.7/1000, p-value $= 0.014$ in the test for relative proportions), but not separately among the multiples.

Among the IVF and OI children 51% of the reported major CAs had been accepted by RCM, whereas the proportion was 46% among control children. The total risk of major CA for IVF singletons was statistically significantly increased (Table 10) and for multiples insignificantly decreased. The prevalence of a major

TABLE 10. Proportions (%) and odds ratios (and 95 % confidence intervals, CI) of infant outcomes as compared to other infants, adjusted to mothers' background variables [a]

	Total			Singletons			Multiples		
	IVF	Controls		IVF	Controls		IVF	Controls	
Number of children	4559	190 398		2930	186 216		1629	4182	
Outcome	%	%	OR (95% CI)	%	%	OR (95% CI)	%	%	OR (95% CI)
Very preterm (< 32 gw)	4.7	0.9	4.45 (3.80-5.21)	2.0	0.8	2.06 (1.56-2.71)	9.6	7.0	1.26 (0.99-1.60)
Preterm (< 37 gw)	23.6	5.5	4.43 (4.10-4.77)	9.5	4.7	1.72 (1.51-1.96)	49.2	42.2	1.06 (0.93-1.21)
Birth weight < 1500 g	4.2	0.8	4.19 (3.55-4.95)	1.9	0.7	2.17 (1.64-2.88)	8.2	7.4	0.95 (0.74-1.22)
Birth weight < 2500 g	19.8	4.0	4.77 (4.40-5.18)	6.5	3.2	1.60 (1.37-1.87)	43.7	39.2	0.92 (0.81-1.06)
Apgar score 0–6	8.8	4.4	1.68 (1.50-1.87)	5.6	4.2	1.07 (0.91-1.26)	14.5	12.5	1.10 (0.90-1.33)
Special care[b]	23.0	8.2	2.71 (2.52-2.92)	12.5	7.6	1.36 (1.21-1.53)	42.1	35.0	1.04 (0.91-1.19)
Respiratory treatment	4.3	1.1	3.61 (3.08-4.24)	2.0	0.9	1.76 (1.34-2.31)	8.4	6.7	1.19 (0.93-1.53)
Hospitalization ≥ 7 days	23.8	6.4	3.42 (3.08-4.24)	10.8	5.8	1.43 (1.26-1.61)	47.4	37.6	1.02 (0.88-1.17)
Perinatal mortality	1.3	0.6	1.85 (1.40-2.44)	0.9	0.5	1.32 (0.88-1.98)	2.0	2.9	0.73 (0.47-1.13)
Congenital anomaly [c]	4.3	2.9	1.31 (1.10-1.57)	4.3	2.9	1.30 (1.05-1.61)	4.3	5.3	0.80 (0.48-1.32)

[a] County, smoking, age, marital status, parity, socioeconomic position.
[b] Treatment in intensive care unit or in newborn surveillance unit.
[c] Total number of controls = 27 078, singleton controls = 26 489, and multiple controls = 589
Reference group (OR=1) = controls.

CA was the same for IVF singletons and IVF multiples but much higher for multiples than for singletons among the OI (Paper IV) and control children. The IVF boys, both singletons and multiples, had major CAs more often than the IVF girls (Paper IV). A significantly increased OR was found among the singleton IVF boys (OR 1.63, CI 1.23–2.15) and a significantly decreased OR among the multiple IVF girls (OR 0.45, CI 0.22–0.93). Furthermore, increased ORs for urogenital and musculoskeletal CAs were found among the singleton IVF boys (Paper IV). Hypospadia was the most common diagnosis of these major urogenital anomalies, and the control boys had more minor hypospadias than the IVF boys. Also the OI singleton boys had a higher risk of urogenital CAs (Paper IV). No risk of specific musculoskeletal CA among the IVF boys was found.

By definition, all IVF mothers were exposed to some infertility drugs, most commonly to progesterone (Paper IV). Most mothers were exposed to several drugs. Only estrogens were used more often by the mothers of malformed than by those of non-malformed IVF children, but the mothers of most malformed children had not received estrogen. Among the OI children no differences in the use of drugs between malformed and non-malformed children were found, neither in the use of a natural nor a synthetic progestin.

During the study period nine out of 9175 IVF women (19.7 per 10 000 IVF birth) and eight out of 10 270 OI women (17.9 per 10 000 OI birth) had an induced abortion due to the suspicion or detected foetal defect. The national rate per 10 000 births in 1996–1998 in Finland was 36.7 (the MBR).

This study confirms the earlier findings of poorer infant health of IVF singletons (Schieve et al., 2002, Helmerhorst et al., 2004, Jackson et al., 2004) compared to naturally conceived singletons. The IVF multiples had a worse health in infancy than the IVF singletons, but the IVF and control multiples were similar in regard to health in infancy, which is largely in accordance with an earlier study (except for the finding of an increased risk of admittance to a neonatal intensive care unit and more common longer hospitalizations after the birth, Pinborg et al., 2004c). In contrast, a recently published Belgian study reported an increased risk of preterm birth also among IVF twins compared to naturally conceived twins, which was, however, largely explainable by the first birth given by IVF women (Verstraelen et al., 2005).

The previous finding that twins have more CAs than singletons (Mastroiacovo et al., 1999) was also found among the control children in this study, but not among the IVF children. This is in accordance with Danish studies, in which no differences were found in the malformation rates between IVF/ ICSI and naturally conceived twins (Pinborg et al,. 2004c, Zhu et al., 2006), but contrary to a recent study from the United States (Olson et al., 2005).

The present study verified an earlier result of the overall risk of urogenital and musculoskeletal CAs among IVF children (Hansen et al., 2002, Zhu et al., 2006). The present study was, however, too small to examine the risk of individual diagnoses such as the previously reported hypospadia (Ericson and Källén, 2001, Silver et al., 1999) and could not verify the increased risk of heart anomalies found earlier (Koivurova, 2005).

Potential reasons for the poorer health of IVF infants include infertility itself (Draper et al., 1999, Brink Henriksen et al., 1997, Basso and Baird, 2003, Basso and Olsen, 2005, Zhu et al., 2006), infertility treatments, and varying health behaviour during pregnancy. In IVF treatments one cause for CAs might be the use of hormonal drugs (Silver et al., 1999, Hemminki et al., 1999, Zhu et al., 2006). Although the dangers of hormones in early pregnancy have been discussed for decades (Hemminki et al., 1999, Kruse et al., 2003), they have not been the focus

when the health effects of IVF have been discussed. Other potential causes may be bypassing the fertilization barriers in gametes especially in ICSI, culture media, freezing and thawing of embryos as well as timing of embryo transfer (Shiota and Yamada, 2005). Male genital anomalies have been suggested to have a link to the hereditary paternal subfertility associated with ICSI (Wennerholm et al., 2000). The advanced age of mothers, a lower fertility rate, and an increased reproductive loss rate characterizing women seeking for infertility treatment have all been associated with different foetal and neonatal abnormalities. However, the higher age of mothers did not explain the increased risk of major CAs in this study.

Among IVF singletons the main cause for poorer health has been suggested to be infertility itself due to the higher incidence of preterm birth and a low birth weight also among infertile women without treatment and women with other infertility treatment than IVF (Lambert, 2003). One the other hand, some modifications in the gestational process induced by IVF and ICSI have been suggested (de Geyter et al., 2006) as well as so-called vanishing twins (singletons originating from twin pregnancies, Pinborg et al., 2005, De Sutter et al., 2006).

Zygosity plays a significant role when the health of IVF multiples is compared to the health of other multiples. In general monozygotic twins have had poorer perinatal outcomes and more major CAs than dizygotic twins. Although IVF and OI increase monozygotic twinning (Ericson and Källén, 2001, Källén et al., 2002), transfer of several embryos causes the majority of IVF twins to be dizygotic (30%) compared to naturally conceived pregnancies (1%, Schachter et al., 2001). This can partly explain the results of the similar outcomes of multiples in studies unable to take zygosity into account. In this study 50% of the IVF and 30% the control twins were opposite-sex twins indicating that more IVF children were dizygotic. The fact that the CA rate was not smaller among the IVF twin boys could result from a higher risk of CA among IVF boys.

10.4.2 Health in early childhood

Up to the age of four years a larger proportion of the IVF children were hospitalized and the IVF children had more often long hospital episodes, the average length of their episodes being longer compared to the controls (detailed in Paper III). In all ages the IVF children had slightly more hospital episodes than the control children (the difference being clearest during infancy) and in almost every ICD-10 category the proportion of hospitalized children was higher among the multiples than among the singletons. Perinatal problems were the main single reason for hospitalizations.

When information from different data sources was combined until the age of two years, it was found that IVF children, singletons, and multiples together had a three-fold increased risk of cerebral palsy, and more often disorders in psy-

TABLE 11. Proportion (per 1000) of children and adjusted[a] odds ratios of having an allergic or chronic disorder or a common infection (ICD-10-codes) until the age of two years.

	Controls (n = 26 877) 1 / 1000	IVF (n = 4 527) 1 / 1000	OR (95% CI)
Cerebral Palsy (G80)	1.4	3.8	2.92 (1.63-5.26)
Epilepsy (G40-G41)	2.5	3.3	1.33 (0.76-2.34)
Behavioural disorders (F80-F98)	4.1	6.6	1.68 (1.11-2.53)
Diabetes (E10)	0.5	0.9	1.57 (0.51-4.84)
Asthma (J45-J46)	28.1	30.3	1.08 (0.90-1.30)
Allergy (L20-23, L27, L50)	53.8	59.9	1.07 (0.94-1.23)
Pneumonia (J12-J18)	11.4	9.9	0.85 (0.62-1.17)
Diarrhoea (A08-A09)	38.6	44.2	1.17 (1.00-1.37)

[a] Adjusted to mother's socioeconomic position

chological development or behavioural and emotional disorders than the control children (Table 11). This was not seen when the IVF singletons and multiples were considered separately (Paper III). Of the infants with cerebral palsy, 88% were preterm and 76% from multiple pregnancies. Of the children with developmental or behavioural problems, 60% were multiples.

Until the age of two years a larger proportion of the IVF children and of the IVF singletons had received child disability allowance compared to the controls, but no statistically significant differences in the use of long-term medication were found between the IVF and control children (Paper III).

In the subanalysis of the first births the results were mainly similar to those of all children and no differences in the results of the two logit analyses (see Methods) were found.

According to the Care Registry for Social Welfare Institutions, 2.2 IVF children per 1000 had experienced at least one period of institutional care in a social welfare institutions. For other children born in 1997–1998 the rate was 2.7 per 1000 children.

The total mortality up to the age of two years was two-fold higher among the IVF children compared to the controls (9.0/1000 and 4.1/1000); the main causes being congenital malformations and conditions originating in the perinatal period. Separately, between the mortality rates of the IVF and control singletons and the IVF and control multiples no significant differences were found.

The present study confirms earlier results of higher mortality (Koivurova, 2005), higher number of hospitalizations (Ericson et al., 2002, Källén et al., 2005c), increased risk of behavioural problems (Källén et al., 2005c), CP (Strömberg et al., 2002, Lidegaard et al., 2005, Hvintjørn et al., 2006), and infections (Ericson et al.,

2002) among IVF children. In accordance with an earlier Finnish study based on both outpatient and inpatient visits (Koivurova, 2005) a slightly, but not statistically significant, increased risk of diarrhea was found, but, contrary to that study, no increased risk of pneumonia was seen among the present IVF children.

Unlike previous studies (Strömberg et al., 2002, Lidegaard et al., 2005), no increased risk of CP or sleeping disturbances was found among the IVF singletons; in this study the excess risk of CP was mainly explained by multiplicity. Also in the studies by Strömberg et al. (2002) and Hvintjørn et al. (2006) the main reasons for the increased risk of CP were prematurity and the multiple pregnancy rate. A recent Swedish study could not confirm the increased risk of CP; the risk disappeared after adjustment to confounders (Källén et al., 2005c). Furthermore, contrary to an earlier Swedish study (Ericson et al., 2002), an increased risk for epilepsy, tumours, and asthma among the IVF children in total could not be found in this study. However, no increased risk of epilepsy was found in the recent Swedish study, either (Källén et al., 2005c).

A few previous studies have reported on childhood morbidity of IVF multiples. In two studies no differences in neurological sequelae were found (Strömberg et al., 2002, Pinborg et al., 2004a). In this study no increased risk of any specific disease among IVF multiples was found. However, the IVF multiples showed in general higher childhood morbidity than the IVF singletons.

To the knowledge of the present author, there are no other studies examining the use of long-term medication, child disability allowance, and utilization of institutional care among IVF children. A slightly increased risk of child disability allowance among the present IVF children was explained by multiplicity, while in the utilization of long-term medication and institutional care no statistically significant differences were found between the groups.

10.5 Costs and allocation of resources in IVF (Paper V)

The estimated mean cost of IVF treatment with embryo transfer was EUR 3750 (Paper V). Frozen embryo transfers were much cheaper, EUR 1100. Of the total IVF costs, 36% were due to drugs, 21% to interventions, and 42% to other direct costs.

During the mean 1.5-year follow-up, the total costs per treated woman were EUR 6500, of which EUR 40% was paid from private sources (by women themselves) and 60% from public sources. In the private sector, the share of private expenditure (out-of-pocket payment) was 49% and in the public sector 24% of the total expenditures. The unit costs of IVF did not vary much between the age groups, but the older the women were, the more they paid themselves. The women from the highest socioeconomic position spent more of their own money for IVF

treatment compared to the blue-collar women regardless of the age of the women. This was due to the more frequent use of private services.

The cost of a live birth was on average EUR 16 000 and increased by age (Table 12). Live-births were the most costly among the women using both sectors. The total expenditures of IVF per population were highest among the women aged 30–34 years and then decreased (Table 12) due to the lesser use of IVF among older women (Table 5). Because of the higher use of IVF, in every age group the total expenditure of IVF was approximately two-fold for upper white-collar women compared to blue-collar women (Table 12). No remarkable regional differences were found according to the urbanity of the living area.

In previous studies the cost calculations of the IVF cycles have included different components which vary between countries and therefore make the comparison of the calculations difficult. The cost estimates of a successful IVF cycle in this study are in accordance with an earlier Finnish study (Koivurova, 2005) as well as with earlier international cost calculations by age that have included the same components as used in this study (Broekmans and Klinkert, 2006).

In the present study only some of the actual costs were taken into account. Only routine radiological and laboratory tests were included, and all indirect costs, such as travel costs and sick leaves, were excluded. Furthermore, the costs of complications as well as the pregnancy and birth costs, which are known to be higher among older women, were not included. With the inclusion of all costs, the total costs may have been higher for the older women and possibly also for rural

TABLE 12. Total expenditure per live-birth and per female population in euros by age, socioeconomic position, and treatment sector.

	Total expenditure per live-birth					Total expenditure per population				
	Age					Age				
	20–29	30–34	35–39	40+	Total	20–29	30–34	35–39	40–49	Total
Socioeconomic position										
Upper white-collar	12133	13196	17785	38437	16126	97	200	167	49	113
Lower white-collar	12264	13496	16930	43308	15303	77	158	111	22	75
Blue-collar	14302	14694	20503	31840	16908	49	95	74	16	48
Others [a]	14082	14603	20392	59310	17342	14	33	20	8	16
Sector										
Public	13603	13373	17395	38766	14712	NA	NA	NA	NA	NA
Private	10588	11843	16170	40522	14877	NA	NA	NA	NA	NA
Both	20188	22581	26645	42832	23870	NA	NA	NA	NA	NA
Total	12851	13657	17828	40662	15941	44	116	88	21	55

[a] Entrepreneurs, students, pensioners, unemployed, and women with an unclassified or unknown position.

NA = not available

women due to the longer distances from care facilities. The impact on socioeconomic differences is unclear.

Among infertile women in the IVF care system, older women with poorer success rates (i.e. increased need) received more treatments, and the costs per live birth were much higher among them than among the younger women. The expenditures per population were lower among the older women, since fewer older women were treated. In this study no data of the population-based need for IVF and wish for a child by age were available, and therefore it is not certain whether all older women whishing to have a baby were in the IVF care system. It is also unknown how many of younger women wishing for a child did not receive IVF. In total, more resources were allocated to younger women, which is —due to the higher costs and an increased health risk of older women—a fairer solution than the provision according to the need by age. The women with a higher socioeconomic position had more often used IVF, and the total and societal costs per population were higher than among them compared to the women from lower socioeconomic positions, which indicates inequality.

11 General discussion

The present study was based on registers. In general, the utilization of existing health care registers in health research has several advantages. The total costs and time spent on data collection can be reduced, the collection of longitudinal data is technically easy, a large sample size is possible, no contact with the studied individuals is needed, participating problems can be abolished, and the reporting bias is reduced (Gissler, 1999), which leads to more reliable data than is received by questionnaire surveys. On the other hand, only health problems that are collected or registered can be studied. Furthermore, most of the health care registers are administrative registers, not planned for ad hoc epidemiological studies. Reporting and data collecting systems may vary, and no corrections can be made. Mostly the data of diagnoses are not exact, but crude estimates, and to adjust the register data to scientifically valid information demands a lot of pre-processing (Sund, 2003).

Originally the present study on the health of IVF women and their children was designed to be performed by using data from clinics, but the data could not be successfully collected (Hemminki, 2002). After that it was decided to collect all data of exposed women and children as well as their follow-up, from nationwide registers. This decision allowed a larger sample size, secure processing of high data, and easy follow-up.

The registries used in the present study are of high quality (Keskimäki and Aro, 1991, Teperi 1993, Gissler et al., 1995b). The identification of the cohorts of the IVF and OI women from the reimbursement records and of the IVF children from the MBR, including all infants born in Finland, was successful (Hemminki et al., 2003, Gissler et al., 2004).The existence of a unique personal identification number enables reliable linkages to other health care registers. The cohorts of the IVF and OI women and their children were large enough to study the frequency of even rare health problems after IVF and OI. The data on major congenital anomalies of all children were received from a routine nationwide register, of which information is collected and classified blindly in regard to the IVF status. In addition, reimbursed diseases for long-term medication are clearly defined, and both child disability allowance and support for long-term medication are based on recent medical documents. Therefore it can be assumed that the reimbursement records are relevant in estimating disease occurrence.

In the present study socioeconomic differences were found in the use of IVF services and in the allocation of resources, primarily due to the use of private services. In the identification process as well as in the follow-up several assumptions and estimations had to be made. It is possible that in 1996 some women who had received treatment in the public sector and had used drugs bought and reimbursed before 1996 were missed. Both the grouping of the IVF treatments into private and public sectors and the estimations of the costs were crude. However, the lack of data is estimated to be only about 4% of the IVF and 6% of the OI women (Hemminki et al., 2003), and it is not likely to be biased by age, socioeconomic position or region of residence. The socioeconomic position of the women was defined by using their occupation and classified automatically according to the national classification complied by Statistics Finland (Central Statistical Office of Finland, 1989). Thus, even though the data are not necessarily accurate for each individual, it seems that there was no systematic bias and the differences between the groups are correct.

In the present study the risk of complications for women after each IVF treatment cycle was low, but repeated attempts resulted in serious complications for many women and occurred much more often than after OI alone. Since the method of identification of serious complications and miscarriages was based on a register covering only hospital care, inpatient care, and operations in outpatient clinics, the identification of outcomes was dependent on the care practices and the style of the physicians to record the diagnosis. However, serious complications leading to hospital care could be collected extensively, but less serious cases—also cases needing special care but treated in private clinics or public outpatient clinics —are missing in this data. Thus, the results underestimate the actual complication risks. In addition, the effects on the psychosocial health of IVF and OI women could not be examined in this study.

Although the health of most IVF children in the present study was good, they had more health problems than the other children. The reason for not being able to estimate the occurrence of less serious diseases and cases was the same as among the women: the use of outpatient care is not registered. The results of the health of the children may be biased by different thresholds in hospital admissions between the IVF and control children. The IVF parents, who were more often first-time-parents, may have been more anxious, which can lead to more hospital admissions and longer duration of care. It might also be that IVF children are more carefully examined by physicians or their health problems are more conscientiously reported than those of naturally conceived children. However, several facts speak against this source of bias. Less rejected reports of congenital anomalies were found among the control children than among the IVF children. The rate of hospitalizations was not increased in all categories of diseases among the IVF children. In addition, the results after adjustment to parity and socioeconomic

position and the results in a subanalysis of the first births remained unchanged. Furthermore, informing and advising on the benefits are part of routine clinical practice. The higher frequency of hospitalizations and certain health problems very likely reflect higher morbidity among IVF children. In addition, almost every outcome studied was quite similar between the IVF and control multiples.

As Mooney (1994) pointed out, the first step in discussion on equity is to define the population in need. The need for infertility treatments derives from the wish for a child, the biological capacity to achieve a pregnancy, and the availability of technology, i.e. assisted fertilization. It is known that the biological capacity decreases by increasing age (Baird and Strassmann, 2000, Broekmans and Klinkert, 2004, ESHRE, 2005), and therefore the age-related biological need for IVF is be assumed to be higher among older women compared to younger ones. The need should not be affected by the socioeconomic position in Finland (Notkola, 1995, Klemetti et al., 2004), i.e. the biological need is assumed to be the same in the different socioeconomic positions. In this study no information of the wish for a child, neither by age nor by socioeconomic position, was available.

Despite the existing technology, all infertile couples do not seek medical care (Gunnell and Ewings, 1994, Schmidt and Münster, 1995, Stephen and Chandra, 2000, Malin et al., 2001, Klemetti et al., 2004), and the demand for infertility treatments may vary by age and socioeconomic position. It might be that older women and women from higher socioeconomic positions are more aware of the availability of treatments and more likely to demand them. In addition, recognition of fertility problems, attitudes towards health and medical treatment, social support, health status, and prior contacts and experiences with health care can vary between the groups (Tain, 2003, White et al., 2006). However, as Mooney (1994) pointed out, the need and demand for services should be distinguished in the equity analysis; access should be equal according to the need, not according to the demand, for services. In this study access could not be examined, but, instead, equity in the use of infertility treatments, i.e. among those who already were in the care system, was discussed among the present women.

The next step in the equity analysis is to ask to what extent priority should be given on infertility treatments. Although infertility treatments were not very highly prioritized by a multiprofessional group on the prioritization of medical care in Finland (STAKES report 161, 1994), infertility is considered a disease and defined as such by medical practitioners (CDBI, 2005). Since infertility is defined as a medical problem, a natural consequence—though not the only possibility—is to solve it with medical technology. After the first IVF birth in Finland in 1984, IVF technology was rapidly introduced into all Finnish university clinics (Malin Silverio and Hemminki, 1996). Also private clinics were founded by pioneer physicians. IVF has become a common practice in Finland, but prioritization has not been explicitly discussed. However, the utilization rate of IVF treatments in

Finland, being one of the highest in the Europe (Nyboe-Andersen et al., 2006), may indicate that infertility treatments are considered valuable and important. In addition, the Finnish system, in which infertility treatments are offered both in the private and public sector with some reservations (a couple with two biological children, risk of infections or either female or male partner sterilized) (STM, 2005) and with public funds, speaks on behalf of high prioritization of infertility treatments. However, it can be asked by whom (health care professionals, decision makers, health care consumers or the whole public) the priority of infertility treatments is set in Finland.

According to the present study, inequity in the use of IVF by the socioeconomic position was evident, mainly resulting from the use of the private sector. The services are not organised in an equal way if infertile women of lower socioeconomic position lack opportunity to use private IVF services despite their need (Whitehead, 1990). In Finland it has been traditionally considered unfair that people should have to utilise the private sector to obtain the health care services they need.

Inequality in resource allocation by socioeconomic position was also prevalent: more resources were allocated to the higher socioeconomic groups compared to the lower ones. In this study the personal preferences (Mooney, 1994) could not be studied. However, if fewer resources were allocated to blue-collar women, because they were not willing to use IVF services as often as white-collar women, this differentiated allocation cannot be considered an inequality. On the other hand, women form a higher socioeconomic position used more own money for treatments. It can, however, be argued that those who are able to pay should have the freedom to allocate their own resources as they like. But due to scarcer resources (the same resources i.e. the same physicians work both in the public and private clinics, and, for example, complications leading to hospital care are treated in public clinics regardless of the treatment sector) and the unique Finnish system, in which private treatments are also partly covered, it can be asked whether this argument is applicable—especially considering the treatment of the other women. On the other hand, in spite of the coverage, the private expenditure remains higher, i.e. more own money is needed for treatments in the private sector. According to the review by Dawson et al. (2005), the most common reasons for refusal of IVF treatment have been financial. In this study it was not possible to examine the reasons for the use or non-use of IVF. Neither was it possible to study whether the treatments or the quality of care varied with different socioeconomic positions. In France, despite equal use of IVF, a deeper analysis showed that women from lower positions faced greater risks and lower benefits (Tain, 2003). The author asked whether 'social inequality is being reinforced with the experimentation of new technologies'. Poorer success (benefit) among the blue-collar women in this study may be related to more serious infertility: infertility-related risk factors such

as smoking, obesity (Helakorpi et al., 2001), and probably increased likelihood of genital infections.

In the case of IVF, the differences in age are a more complex and non-traditional equity issue than those between the socioeconomic groups. Is it equitable that in IVF treatment, as in other health care services, the 'sickest' (older women) receive more care—or would it be more equitable to treat women with the best possibility of achieving pregnancy, for example younger women with specified causes of infertility (Mooney, 1994, Neumann, 1997)? In this study the older women of a higher socioeconomic position received more intensive treatment. In the private sector the number of treatments was not age-dependent, but in the public sector the women younger than 40 years of age received more cycles than the older women. This can be a sign of adequate resources and an ability to respond to the need and demand in the private sector, but it might also be a sign of growing commercialism. The success or effectiveness of IVF decreased by increasing age, which speaks against the option of concentrating on treating older women. On the other hand, concentrating on treating younger women can lead to over-treatment (Gnoth et al., 2005). Age-restrictions set in the public sector have reduced waiting lists and conserved public health care resources. It can also be argued that age should not be a reason to turn women away from IVF, because for older women IVF may offer the last chance to become pregnant (Klipstein et al., 2005). However, the costs of live-births among the older women were over three-fold compared to the younger women. Thus, it can be asked whether treating older women is replacing the treatment of younger women and the resources of their treatment, and, if so, whether it is equal.

When discussing access and equity in the use of services, health risks should also be taken into account (Blank, 1997). Pregnancy and birth complications as well as poorer foetal outcome increase by age (Nybo Andersen et al., 2000, Salihu et al., 2003). Furthermore, as shown in the present study, there are IVF-related risks for treated women (serious complications leading to hospitalization) and their children (more health problems), which have to be considered in equity discussion. Also the safety of the new technologies in assisted fertilization is an issue still under debate (Peters, 2004). The use of ovulation induction should be considered carefully. According to the unpublished data by the present author on OI children, ovulation induction contributes to some health problems among children born after OI. From a public health perspective it would be wise to concentrate on treating women in the usual childbearing age, equally in all socioeconomic positions respecting the women's own preferences and to offer IVF treatment for medical reasons only after careful patient selection. Treating sexually transmitted infections at an early stage and encouraging couples to have children at a younger age than nowadays (to avoid potential fertility problems) may, in the future, play a significant role in the prevention of infertility. In addition, treatment costs cannot be ignored in equity discussion.

IVF has offered hope for a number of infertility couples and fulfilled their wish for a child. In this study 40% of the treated IVF women received a child. Other potential benefits of IVF could not be examined in this study. An ideal situation would be the one with healthy singletons without serious health complications neither in child nor mother, or infertile couples satisfied after finding solution for their infertility, either infertility treatment (with or without child), a child via adoption or decision to live contently without children.

The advancement of assisted fertilization has aroused many other questions of the equity and resource allocation than those related to age and socioeconomic position or efficacy and safety of treatments. It has also created a doubtful "baby market" which is characterised by the limits of science, an unmet demand due to the high cost of IVF, and a political system lacking sufficient legalisation (Spar, 2006). Increased marketing can lead to the use of AF earlier than necessary (Mitchell, 2002). In Finland the number of IVF treatment cycles has grown (IVF statistics, http://www.stakes.info/2/1/2,1,4.asp.), there is an increased competition for clients, and IVF has become commercialised as in other countries. So-called reproductive tourism (Blyth and Farrand, 2005) from other countries to Finland has been claimed to be a natural consequence of the permitting situation without legislation. The coming Finnish law is the most permissive one in the Nordic countries, though with some exceptions (for example assisted reproduction allowed for single women in Finland) in line with the Swedish law (Legislation..., 2005). Thus, the reproductive tourism may still continue but will not play a significant role in the use of AF in Finland.

The present study has both clinical and political implications. To avoid overtreatment infertility should be defined in line with the WHO definition: two years without conception, especially among women under 35 years of age. In IVF, transferring only one embryo whenever possible and treating women in the usual childbearing age reduce health problems both in pregnant mothers and their children. Information of the potential health effects and of the chances of having a baby at a certain age are, should be useful for couples seeking medical help for infertility.

Policy implications are to encourage health promotion institutions and experts to give information of the declining fertility by age as well as the complexity of IVF, since IVF is not an equal option to natural conceiving. The policy makers should make resource allocation for high technology transparent and openly discuss the issue of equity.

Additional implications for further studies include examining the short- and long-term health of OI children and the long-term health of IVF children. Studies on puberty and own fertility of IVF and OI children are lacking. Furthermore, it is of importance to examine the long-term health of IVF and OI women (for example cancers and psychosocial health). A deeper analysis of the use and non-use of IVF by different women's background characteristics would be useful for discussing whether equity prevails in infertility services in Finland.

12 Conclusions

1. Although the health of most IVF children was good, they had more health problems than the other children. As this was partly explained by multiplicity, reducing the number of transferred embryos would improve the health of IVF children.
2. Further studies are needed to explain the poorer health of IVF singletons and to examine the long-term health of IVF children as well as the health of children born after ovulation induction alone.
3. The risk of complications for women after each IVF treatment cycle was low, but repeated attempts resulted in serious complications for many women, and the complications occurred much more often than after OI alone.
4. Further studies are needed to examine the long-term health of IVF and OI women.
5. The socioeconomic differences in the use of IVF were due to the use of private services.
6. More resources were used by women from a higher socioeconomic position, adjusting to age.
7. Older women were treated more intensively; the distribution by need could not be studied.
8. The live-births of older women were much more expensive than those of younger women.

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APPENDIX. Health outcomes of IVF and OI women and IVF children; definitions, follow-up times, and data sources.

Outcome	Definiton	Follow-up time	Data source
Women			
OHSS	Diagnoses in ICD-10 [a] and length of hospitalization	120 days [b]	HDR
Potential OHSS			
Bleeding			
Infection			
Other complications			
Misscarriage	Diagnoses in ICD-10 and operation codes	240 days	
Ectopic pregnancy			
Death	Date of death and cause of death (ICD-10)	Mean 3.7 years for IVF and 3.8 years for OI	Cause-of-Death Register
Children			
Preterm	< 37gestation weeks	until 7 days after birth	MBR
Very preterm	< 32 gestation weeks		
Low birth weight	< 2500 g		
Very low birth weight	< 1500 g		
Special care	Treatment in intensive care unit or in newborn surveillance unit.		
Respiratory treatment	Respiratory treatment used		
Apgar scores	One minit scores 0-10		
Hospitalization	7 or more days after birth		
Stillbirth	Death from the completed 22nd gestational week onwards or if birth weight is ≥ 500g.		
Perinatal mortality	Stillbirths and death < 7 days from birth / 1000 live births		
Major congenital anomaly	A major congenital structural anomaly, chromosomal defect, or congenital hypothyroidism	until 1 year	RCM
Use of hospital services	Hospital episodes in the HDR	until 4 years	HDR
Length of hospitalization	Days		
Long-term medication	Support for long-term mecdication received	until 2 years	SII
Child disablity allowance	Child disability allowance received		
Childhood mortality	Deaths after perinatal period and ≤ 2 years / 1000.		Cause-of-Death Register
Cerebral palsy	ICD-10: G80	until 2 years	HDR
Epilepsy	ICD-10: G40-G41		
Behavioural disorders	ICD-10: F80-F98		
Diabetes	ICD-10: E10		
Asthma	ICD-10: J45-J46		
Allergy	ICD-10: L20-L23, L27, L50		
Diarrhoea	ICD-10: A08-A09		
Pneumonia	ICD-10: J12-J18		

[a] ICD-10 codes in Paper II.
[b] Days after the last reimbursement.

Original Articles I–V

Paper I

ORIGINAL ARTICLE

Taylor&Francis healthsciences

Equity in the use of IVF in Finland in the late 1990s

Reija Klemetti, Mika Gissler and Elina Hemminki

STAKES, National Research and Development Centre for Welfare and Health, Health Services Research, Helsinki, Finland

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Aims: The purpose of this study was to describe equity in the use of *in vitro* fertilization (IVF; including micro-injections and frozen-embryo transfers), and compare its use with that of other assisted reproduction technologies (other ARTs; including ovulation inductions with or without inseminations). *Methods*: The women who received IVF ($n=9$, 175) and other ARTs ($n=10{,}254$) between 1996 and 1998 were identified from the reimbursement records of the Social Insurance Institution (SII) covering all Finns. Population controls, matched by age and municipality, were selected for IVF women ($n=9{,}175$). Information concerning background characteristics came from the Central Population Register and the SII's reimbursement files. The sector (public vs. private) was defined using prescribing physicians' codes. IVF use was studied by the proportions of women treated and the frequency of treatment. *Results*: The age-standardized IVF incidence per thousand 20-to-49-year-old women was 8.8 in urban and 7.3 in rural areas, but the use of other ARTs did not vary correspondingly (9.2, 9.3). The regional incidence of IVF and other ARTs varied considerably. In the private sector, women in the highest socioeconomic position were over-represented (29% private, 18% public, 16% controls). During the mean 1.5 years of the study period, the IVF women had somewhat more treatment cycles in the private than in the public sector (mean 3.3, 2.7), and those in the highest socioeconomic position had more cycles than others (3.5, 3.2); the frequency was not age-dependent. In the public sector the number of cycles did not differ by socioeconomic group (mean 2.7–2.8 per woman), and women aged 25 to 39 had more cycles than others. *Conclusion*: There were socioeconomic differences in use of IVF services, but they were small because of the equitable use of public services.

Key words: equity, infertility treatment, IVF, private sector, public sector.

Reija Klemetti, PO Box 220, 00531 Helsinki, Finland. Tel: 358-9-3967 2265, fax: 358-9-3967 2496. E-mail: reija.klemetti@stakes.fi

INTRODUCTION

Infertility is common (1), and IVF (including micro-injections and frozen-embryo transfers) has become a universal infertility treatment. According to statistics published by the European Society of Human Reproduction and Embryology, the greatest availability of IVF services among 18 European countries was reported in Finland and Denmark (2). In 2001, approximately 2.5% of all Finnish newborns were born as a result of IVF. The number of children born with the help of other assisted reproduction technologies (called here other ARTs) is unknown.

It is generally believed that IVF services are unevenly distributed, and that urban women from upper social classes use these services more than rural women from lower social classes. However, there are few reliable data on the use and users of IVF or other ARTs. In Finland, the 19 IVF clinics were situated in eight towns in 1999 (3). Three out of 12 of the pre-1995 provinces studied had no IVF clinic. Women in some areas had to make long trips (as much as 700 km) to obtain IVF treatment. Other ARTs services were available in all parts of Finland.

Unlike the rest of the health service system in Finland, the private sector is an important provider of IVF; about 60% of all IVF services are supplied by private clinics (3). In 1999, 12 of the 19 clinics were private. In the public sector, patients pay a small fee for their visits, and the rest of visit costs are covered by the tax-financed healthcare system. In the private sector, patients pay significantly more for their visits, but about 60% of the physician's charges are reimbursed by the Social Insurance Institution (SII). About 50% of the drugs used in infertility treatments are reimbursed by the SII in both the public and private sectors. Despite public financial support, IVF treatments are still costly for women, especially in private clinics (4). During 1996–98 on average five IVF cycles were needed to achieve one live birth (Mika Gissler, personal communication). Frozen-embryo transfers are cheaper but more cycles are needed to achieve one live birth.

The aim of this study was to investigate equity in

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the use of IVF in Finland in 1996–98, and to compare it with the use of other ARTs. The use of IVF was studied both by the percentages of women treated and the frequency of treatment (cycles per woman).

MATERIALS AND METHODS

In Finland, IVF, artificial insemination and ovulation inductions are performed in outpatient clinics but in most cases the treatment involves prescribed drugs. Using reimbursements for drugs and infertility interventions in private clinics in the SII files, a cohort of women who had had at least one IVF treatment (*in vitro* fertilization without embryo transfer, *in vitro* fertilization with embryo transfer, or preparations for frozen-embryo transfer, $n=9{,}175$), and women who had had other infertility treatments including drugs (ovulation inductions with or without artificial insemination, $n=10{,}254$) between 1996 and 1998 in Finland were identified, by means of a pre-designed algorithm. The algorithm was based on the fact that some drugs or their combinations, sequence, and dosages are specific to infertility treatments. With the patient advice of IVF clinics, scientific literature, Finnish drug catalogues, and discussions with infertility physicians, we created an algorithm for drugs used in different infertility treatments (unpublished data from Hemminki et al., STAKES, 2003).

If an intervention in the IVF cycle involved reimbursement by the SII, the cycle was defined as having taken place in the private sector. For the other IVF cycles the classification of cycles as private or public was made according to the main work place of physicians given in a catalogue of physicians (STAKES, 1998). The classification was crude because we were not always able to define the main work place. The other ARTs cycles could not be classified as private or public.

Population controls, matched by age and municipality, were randomly selected for IVF women ($n=9{,}175$) from the SII population record (covering the total Finnish population).

Information on the women's background characteristics was obtained from the Central Population Register (CPR) and from the reimbursement files of the SII. According to the municipality of residence, the women were divided into urban, semi-urban, and rural groups. To calculate the age-specific incidences, the number of women treated was divided by the number of all women in the same age group in the same area (SOTKA database 2001, STAKES). The age adjustment was made by using direct age-standardization.

The socioeconomic position of the women was defined by using their own occupation (5): unknown, upper white-collar workers, lower white-collar workers, blue-collar workers, entrepreneurs, students, pensioners, and others, including unemployed women and women with an unclassified position. In the analysis, the four last categories were combined. Marital status (from CPR) at the beginning of the treatment was defined by the starting and ending dates of marriages, and there were five categories: non-married, married, divorced, widowed, and unknown. There was no information on cohabitation.

To study the frequency per woman of IVF treatment, data on women with at least one IVF treatment in 1997 ("1997 IVF data", $n=4{,}909$) were analysed. All cycles of these women in the years 1996–98 were included, and the number of treatment cycles per woman during the study period (range 0.5–3.0 years, mean 1.5 years, assuming an even distribution of first cycles in 1996–98), was calculated.

Tests for relative proportions, *t*-tests, chi-square tests, and one-sided analysis of variance were used to measure statistical significance. A *p*-value of less than 0.05 was considered significant. The statistical analyses were mainly performed using SPSS, version 10.

RESULTS

Characteristics of IVF women, other ARTs women, and population control women are presented in Table I. The IVF women were older than the other ARTs women (mean age 33.4 vs. 31.1 years). Women who had received any infertility therapy were more often married than the population controls were. A fifth of the women treated were never married.

There were more women in the highest socioeconomic category among IVF women than among control women (Table I). The upper white-collar women underwent IVF treatments at older ages than the other women (34.5 years for upper white-collar vs. 33.3 for lower white collar vs. 32.3 for blue-collar), measured either by age distribution (data not shown) or by mean age.

The age-standardized incidence of IVF, calculated per thousand 20-to-49-year-old women varied by region from 6.5 (in eastern Finland) to 9.2 (in the capital area in southern Finland). The age-standardized incidence of other ARTs varied by region from 5.2 (in eastern Finland) to 12.7 (in northern Finland). Women from the capital area underwent IVF and other ARTs treatment at older ages than women in other parts of Finland. When the use rates of IVF and other ARTs were combined, infertility treatments were significantly more common in one region of northern Finland and in the capital area than in the

Table I. *Background characteristics of IVF women, Other ARTs women and population controls* in 1996–98 in Finland, (%)*

	IVF (n=9,175)	Other ARTs (n=10,254)		Controls (n=9,175)	
Age group					
20–24	3.5	11.0		3.5	
25–29	20.8	31.4		20.8	
30–34	35.2	31.5		35.2	
35–39	27.7	17.8		27.7	
40–44	10.8	6.9		10.8	
45+	2.0	1.4		2.0	
Unknown	0.0	0.0		0.0	
Total	100.0	100.0	*p<0.001*†	100.0	*p=1.000*§
Marital status					
Non-married‡	22.3	19.1		36.1	
Married	69.4	72.5		56.7	
Divorced	7.9	7.9		9.4	
Widowed	0.4	0.5		0.4	
Unknown	0.0	0.0		1.4	
Total	100.0	100.0	p<0.001†	100.0	p<0.001§
Socioeconomic position					
Upper white-collar	25.3	20.6		16.3	
Lower white-collar	48.5	48.7		45.7	
Blue-collar	16.2	18.0		19.3	
Others	7.9	10.0		12.3	
Unknown	2.1	2.7		6.4	
Total	100.0	100.0	p<0.001†	100.0	p<0.001§

*Population controls for IVF women, matched by age and muncipality.
†P-values for χ^2-tests (IVF women and Other ARTs women).
‡Includes cohabitation. Divorced and widowed women can also live in cohabitation.
§P-values for χ^2-tests (IVF women and controls).

country as a whole. The northern region had no IVF clinic, and the use of other ARTs was common.

There was a small but statistically significant difference in the total use of IVF between urban and rural women (test for relative propositions $p<0.001$, Table II). Adjustment by age did not change the result. When the data were examined by age group, the difference remained only among women over 35 years old ($p<0.001$). The total use of other ARTs was also more common among urban than rural women, but after age adjustment, the difference disappeared; the use was most common among semi-urban women. When the use of IVF and other ARTs was combined, infertility treatments were more common among urban ($p<0.001$) and semi-urban ($p<0.001$) women than among rural women.

Some 53% of IVF women received all their IVF treatments from private doctors (“private users”), 35% from public doctors (“public users”), and 12% from both private and public doctors (“both-sector users”, Table III). The private users were older (mean age 34.3 years) than public users (32.3 years) and both-sector users (32.8 years, $p<0.001$). Most women in both the private and the public sector category were

Table II. *Raw and age-standardized incidences per 1000 20-to-49-year-old women for IVF and Other ARTs women†, by urbanity*

	Raw rates		Age-standarised rates	
	IVF (n=9,136)	Other ARTs (n=10,207)	IVF (n=9,136)	Other ARTs (n=10,207)
Urban	8.7	9.4	8.8	9.2
Capital	9.7	8.8	8.9	8.5
Other	8.5	9.7	8.5	9.5
Semi-urban	7.9	9.9	8.2	10.4
Rural	7.0	8.7	7.3	9.3
Total	8.3	9.3	8.3	9.3

†Women over 49 years, women living abroad and women whose place of recidence is unknown are excluded.

Table III. *The distribution of IVF women by socioeconomic position and by care site (%)*

	Only private (n = 4,809)	Both sectors (n = 1,118)	Only public (n = 3,225)
Socioeconomic position			
Upper white-collar	29	29	18
Lower white-collar	48	48	50
Blue-collar	14	15	20
Others	7	6	9
Unknown	2	2	3
Total	100	100	100

For χ^2-test (socioeconomic position and sector) $p < 0.001$.

between 30 and 39 years old, but younger age groups were larger and older age groups smaller in the public than in the private sector; 19% of private sector users and 5% of public sector users were aged 40 years or more.

The private and both-sector users were more often women in the highest socioeconomic groups than were the public users (Table III). In the public sector, women in the highest socioeconomic position were not over-represented when compared with population controls (Table I).

The background characteristics of women in the "1997 IVF data" did not differ from that of IVF-treated women in total. During the examination period (estimated average 1.5 years), the mean number of IVF cycles was 3.3 (Table IV). The mode was two, and the maximum number was 14 cycles. A quarter of the women underwent five or more IVF cycles. In the private sector, the number of IVF cycles was higher than in the public sector, and in the private sector the number did not depend on a woman's age. In the public sector, the youngest and the oldest women did not undergo as many IVF cycles as other women. In all age groups, more women underwent five or more IVF cycles in the private than in the public sector. Both the number of IVF cycles and the number of women undergoing five or more cycles were highest among both-sector users.

Women in the highest socioeconomic group underwent more cycles than women in the other socioeconomic groups (mean 3.5 for upper white-collar vs. 3.3 for lower white-collar vs. 3.2 for blue-collar group). The number of cycles was age dependent only among the women from the highest socioeconomic position; 40-to-44-year-old women underwent more cycles than the other women (data not shown). In the private sector, women from every socioeconomic group had more IVF cycles than in the public sector but the users of both sectors had most IVF cycles. Socioeconomic position had no impact on whether women underwent five or more cycles in the public sector but it had some impact in the private sector.

Overall, the frequency per woman of IVF treatments was the same for urban, semi-urban, and rural women as well as in different regions (data not shown).

DISCUSSION

There are two main questions that are asked when one discusses equity in infertility: first, what priority

Table IV. *Mean number (standard deviation) of treatment cycles in 1996–98 of IVF-women† who had at least one treatment cycle in 1997 by care site, and the proportion of women with 5 or more cycles*

	Age in years						
	20–24 (n = 163)	25–29 (n = 1,048)	30–34 (n = 1,765)	35–39 (n = 1,308)	40–44 (n = 540)	45–49 (n = 77)	Total‡ (n = 4,901)
Care site							
Only private (n = 2,457)	2.8(1.9)	3.3(2.1)	3.3(2.1)	3.3(2.0)	3.4(2.2)	3.0(2.1)	3.3(2.1)
Only public (n = 1,620)	2.6(1.5)	2.8(1.6)	2.7(1.5)	2.7(1.6)	2.5(2.3)	1.4(0.6)	2.7(1.6)***
Both sectors (n = 824)	3.6(1.6)	4.6(1.9)	4.6(1.8)	4.5(2.0)	4.6(1.8)	3.3(1.0)	4.6(1.9)*
Total	2.7(2.0)	3.5(2.2)	3.3(2.0)	3.3(2.0)	3.3(2.0)	2.9(1.7)	3.3(2.0)**
≥5 cycles, %§							
Only private	19	26	24	25	26	18	24
Only public	0	9	15	13	12	15	13
Both sectors	0	46	44	48	48	19	46
Total	17	25	24	24	26	14	24

†Women living abroad and women whose place of recidence is unknown are excluded.
‡For one-sided analysis of variance *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
§For χ^2-test (age and care site of women undergone 5 or more cycles) $p < 0.001$.

should be given to infertility services; and second, how scarce healthcare resources can be distributed equitably and with maximum benefit to public health (6). In addition, issues of reproductive rights, safety, efficacy, and access to infertility services have been discussed (7). Access to services is linked to the funding of services. Economic status, information on available programs and morality (8), and geographical variations, age, marital status, and sexual orientation of women (7) have also been issues. Our study provides answers to some of these questions as they apply to equity in the use of IVF in Finland.

The first main finding of our study was that the differences between socioeconomic groups were relatively small. Additionally, the observed differences were mainly a consequence of the use of the private sector. The third finding was that although the IVF clinics were unevenly distributed geographically in Finland, the distribution of women receiving IVF treatment was less skewed. The finding that differences were due to use of the private sector suggests that the supply and cost of IVF treatments are likely to create inequalities.

Can these results be trusted? A potential weakness of our study lies in the accuracy of exposure, constructed from reimbursement files. Despite the complexity of the process, the identification went well, the high quality of register data and the existence of a unique personal identification number suggest that the identification of women was not biased by their social class or region of residence (unpublished data from Hemminki et al., STAKES, 2003, unpublished data from Gissler et al., STAKES, 2003).

Our findings concerning the over-representation of women from the highest socioeconomic group are in line with those of some earlier studies from Canada and Australia (6), the United States (9), the United Kingdom (10) and France (11). In the United States in 1995, college graduate women were more likely to have received infertility services – but not assisted reproductive technology – than other women; but the total number of women being treated by means of assisted reproductive technology was very small (12). A recent Swedish study found no clear trend with regard to the level of education of IVF mothers (13). However, the Swedish study included only successful treatments, whereas our study included all treatments, a fact which may explain the difference between the two studies. It is possible that treatments of women in the highest socioeconomic position are less successful, because these women resort to IVF services at an older age than others. However, it is also possible that widespread use of IVF eliminates socioeconomic differences in countries using public resources to provide IVF.

There are few reliable data concerning the need for infertility services in different socioeconomic groups or geographical areas. One Finnish study indicates no significant socioeconomic or regional differences in infertility rates but it suggests that secondary infertility could be more common among women from the highest socioeconomic group, and primary infertility in southern Finland (1). On the other hand, because smoking and obesity, which have been linked to infertility, are more common among women from lower socioeconomic groups (14), the need for infertility treatment may be greater among them.

Easy availability may increase the use of services, and the uneven geographic distribution of IVF clinics can create inequalities. Because the regional differences were not great, it seems that long distances are no object; women are prepared to travel to obtain IVF treatments. The use of all infertility services was common in the capital area, where many clinics are situated and distances to clinics are short. On the other hand, use was even more common in one region of northern Finland where long distances are involved. Reimbursement of travel expenses by the SII may somewhat decrease regional inequalities.

In our study, over-representation of women in the highest socioeconomic position was found only in the private sector. Furthermore, in the private sector, the IVF-treated women underwent more cycles than women in the public sector. The larger number of cycles cannot be explained solely by age, because the difference was also found in the age-specific analysis. Nor can it be explained by the type of cycle: equal proportions of frozen-embryo transfers and IVF cycles are performed in private clinics. A higher number of cycles in the private sector can be a sign of effectiveness and an ability to respond to demand but also a sign of growing commercialism. In the United States, the growing numbers of fertility specialists and clinics have increased competition for clients, and some consider the marketing of infertility services aggressive (15). Increased marketing can lead to the use of ARTs earlier than used to be the case – perhaps unnecessarily. Although in Finland the number of IVF clinics and the number of treatment cycles stabilized in the late 1990s after a growth period during that decade (3), there *is* competition for clients, and IVF has become commercialized in Finland as well as in other countries.

The public sector made the use of services more equitable for different socioeconomic groups, even though it could not compensate for socioeconomic differences created in the private sector. On the other hand, if the private sector did not offer IVF services, the social class differences might be smaller but

waiting lists might be longer, and the total number of treatments and women treated would be smaller.

"Both-sector users" were an interesting group in our study. They were not too old or "sick" to receive treatment in the public sector, and they evidently had enough money to purchase care in the private sector. We did not study the order of IVF treatments (private or public first), and we do not know the reasons for infertility among these women. It is possible that treatments were less successful, because these women underwent so many cycles. Some of these women may have little or no chance of becoming pregnant, but they do not stop trying to have a baby. The number of cycles did not depend on the socioeconomic position of women, which suggests that care was experienced as important and useful.

Differences in rates of utilization of healthcare services do not automatically mean that they are inequitable (16). However, if the over-representation of higher socioeconomic groups in our study is due to the fact that infertile women in the lower socioeconomic position do not have the opportunity to use IVF services, then services are not organized in an equitable way. In Finland it has also traditionally been considered unfair that people should have to use the private sector to obtain the healthcare services that they need.

It is a common ethical principle that access to care should not be affected by socioeconomic position or region of residence. In the case of IVF, differences involving marital status and age are a more complex and non-traditional equity issue. In many countries, infertility services are limited to married or heterosexual couples (17). In Finland, IVF is not legally restricted, and in our study a fifth of the women treated were not married. However, we do not know how many of the single, divorced, and widowed women in our study were cohabiting and how many were really single. If IVF services are offered to single or lesbian women who are not infertile, i.e. have no medical reasons to undergo IVF, and if equal access is understood to cover all persons who ask for treatment, we are no longer dealing with a health issue but a social issue.

Our study found that in the private sector older women were treated more than in the public sector. Some of the women treated were aged over 50 years but their number was very insignificant. The differences can be explained by an informal age limit that the public sector has introduced. Many other countries have legal age limits for IVF (7). Supporters of age limits base their arguments on the lower success rates and increased maternal and fetal morbidity and mortality among older women (17). However, it has also been argued that age limits are a violation of human rights (7), and that late motherhood means a higher level of financial and professional security and greater motivation in fulfilling the role of a parent (17). From the health perspective, it would be better to concentrate on treating women in their normal fertile age in order to minimize the adverse health effects for mothers and children due to advanced maternal age. Age restrictions also reduce waiting lists and conserve public health care resources.

With regard to equity in IVF use, many important questions remain open. Is it equitable that in IVF treatment, as in other health care services, the "sickest" (i.e. those for whom becoming pregnant is the most difficult) receive more care, as do the 40- to 44-year-old women in the highest socioeconomic position in our study? Or would it be more equitable to treat women with the best possibility of achieving success, for example younger women with specified causes of infertility (18)? How can the scarce health care resources be equitably distributed between IVF and other health care services? Currently it is difficult to estimate what is best and most equitable, since the health effects of IVF on women and children are largely unknown. As Svensson and Stephenson (6) have pointed out, it is important to study the safety and efficiency of IVF in order to help decide what constitutes equity in the use of IVF.

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Paper II

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Complications of IVF and ovulation induction

Reija Klemetti[1,3], Tiina Sevón[1], Mika Gissler[2] and Elina Hemminki[1]

[1]Research on Practices and [2]Information Unit, STAKES, National Research and Development Centre for Welfare and Health, Helsinki, Finland

[3]To whom correspondence should be addressed: STAKES, P.O.Box 220, 00531 Helsinki, Finland. E-mail: reija.klemetti@stakes.fi

BACKGROUND: The frequency and importance of complications of IVF and other ovulation induction (OI) are poorly known. We examined the occurrence of serious complications and miscarriages leading to hospitalization or operation after IVF (including microinjections and frozen embryo transfers) and OI treatment (with or without insemination). METHODS: Women who received IVF (*n* = 9175) or OI treatment (*n* = 10 254) 1996–1998 in Finland were followed by a register linkage study until 2000. RESULTS: After the first IVF treatment cycle, 14 per 1000 women had a serious case of OHSS (ovarian hyperstimulation syndrome), with 23 per 1000 throughout the study period (mean of 3.3 treatments). The corresponding values after OI were very low. The rates of registered ectopic pregnancies and miscarriages after IVF were nine and 42 respectively per 1000 women, with corresponding rates after OI of eight and 42. Infections and bleeding were not common after IVF and even rarer after OI. Overall, 15% of IVF and 8% of OI women had at least one hospital episode during the study period. CONCLUSIONS: Though there was a low risk of complications after each IVF treatment cycle, repeated attempts resulted in serious complications for many women, and these occurred much more often than after ovulation induction alone.

Key words: complications/IVF/OHSS/ovulation induction/register-based study

Introduction

Impaired fertility has increasingly become a health service issue because of the availability of new treatments, especially IVF and its related procedures, such as ICSI and frozen embryo transfer (FET) (called here IVF). Older treatments, including ovulation induction with or without insemination (OI), are still in wide use. In Finland, currently ~5% of infants are born as a result of IVF or ovulation induction (Gissler, 2003). According to our unpublished data, the estimated yearly number of treatment cycles between 1996 and 1998 was 8200 for IVF and 6550 for OI, compared to 1320 and 1360 resultant births per year.

The novelty of IVF has attracted a large number of studies on the health of the newborn (Helmerhorst *et al*., 2004), but less is known about the long-term health effects of IVF on children (Hampton, 2004) or about the health effects on the women. Complications can occur during the ovulation induction, the oocyte collection procedure, and post-operatively. The pregnancy achieved can be ectopic (embryo outside the uterus) or heterotopic (embryo both in and outside the uterus), and it can end in a miscarriage.

Ovarian hyperstimulation syndrome (OHSS) is considered the most serious complication of ovulation induction. It can vary from being a mild illness to a severe, life-threatening disease requiring hospitalization. OHSS can occur as soon as a few days after receiving HCG ('early OHSS') or later ('late OHSS'). Multiple pregnancy has been shown to be associated with a higher risk of late OHSS (Mathur *et al.*, 2000). The incidence of severe OHSS has been reported to vary from 0.7 to 1.7% per initiated cycle (Bergh and Lundkvist, 1992; Serour *et al.*, 1998; Westergaard *et al*., 2000; Nyboe Andersen *et al*., 2005). Some case reports (Cluroe and Synek, 1995; Koo *et al.*, 2002), studies (Bergh and Lundkvist, 1992; Serour *et al*., 1998; Abramov *et al.*, 1999a), and reviews (Whelan and Vlahos, 2000; Delvigne and Rozenberg, 2003; De Sutter, 2004) describe some serious aspects of OHSS, such as thromboembolic events, pulmonary manifestations, and death, but the magnitude of the risk is unclear.

The frequency of IVF complications other than OHSS has been only sporadically reported. For oocyte collection, bleeding has been reported in 0.03–0.5% and infections in 0.02–0.3% of embryo transfers (Bergh and Lundkvist, 1992; Nyboe Andersen *et al.*, 2005). Two to 5% of IVF pregnancies have been reported to be ectopic and 0.1–0.3% heterotopic, and estimates of IVF pregnancies ending in miscarriage have varied from 15 to 23% (Roest *et al.*, 1996; Serour *et al.*, 1998; Westergaard *et al.*, 2000; Kupka *et al.*, 2003; Schieve *et al.*, 2003; Bryant *et al*., 2004).

Most studies reporting complications after ovulation induction with or without insemination are based on old data (St Clair Stephenson, 1991; Venn *et al.*, 1994), and the frequency of OHSS after OI is unknown (Unkila-Kallio, 2001). In one small clinical study, the OHSS hospitalization rate per initiated cycle was 0.07% (Quasim *et al*., 1997).

Even though various adverse effects of IVF and OI on treated women have been identified, many of the published

studies and reports are deficient. They are based on old data, voluntary reporting, or a small number of cases or treatment cycles and concentrate on only one complication, or they lack information on the severity of the complications. The purpose of this study is to estimate the frequency of serious complications and miscarriages following IVF and OI. The criterion of seriousness is the need for hospital care, either in the form of hospitalization or an operation at a hospital outpatient clinic. This study is the first extensive study examining the different serious complications of both IVF and OI.

Materials and methods

The study is a historic cohort study based on prospectively collected register data on the following two exposed cohorts: 20–59 year old women having had IVF treatments (IVF, ICSI and FET, n = 9175) and women having had other infertility treatments including drug-based treatments (ovulation inductions with or without artificial insemination, OI, n = 10 254) between 1996 and 1998 in Finland. The women were identified with a pre-designed algorithm using the reimbursement files of the Finnish Social Insurance Institution (SII) (Hemminki *et al.*, 2003). Population controls, matched by age and municipality, were randomly selected for IVF women (n = 9175) from the SII population record (which covers the entire Finnish population).

The data included detailed information on the use of infertility drugs, including dates of prescription and purchase. The beginning of a cycle was defined by the date of the first purchase of the drug. All drugs bought within 35 days of the first purchase were considered part of the same treatment cycle with the exception of clomiphene citrate; a new prescription of clomiphene was considered the beginning of a new cycle regardless of the time interval. Consecutive cycles without a new prescription could not be separated.

The women's background characteristics were obtained from the Central Population Register, information about care episodes in hospitals from the Hospital Discharge Register (HDR), and dates and causes of death from the Cause-of-Death Register. The HDR collects information on inpatient care as well as on those visits to outpatient clinics that included an operation. It gathers information on diagnoses (10th revision of the International Classification of Diseases, ICD-10), operation codes, and dates of admission and discharge. The diagnoses include the main diagnosis (which can consist of separate diagnoses of the reasons and the symptoms leading to hospitalization) and two secondary diagnoses (which can also also consist of two separate diagnoses of the reasons and the symptoms) for each hospital episode. Miscarriages and ectopic pregnancies can be identified if they lead to inpatient care or an operation (such as laparoscopic surgery or curettage). From 1983 to 1995, operations were registered according to a national coding system; since 1996, according to the Finnish version of the NOMESCO classification system for surgical operations (Toimenpideluokitus, STAKES, 1996).

All hospital episodes due to OHSS, pelvic infections and abscesses, bleeding, other complications, miscarriages, and ectopic pregnancies were identified using the HDR (codes in Appendix); the dates for the start and end of the hospital stays were recorded. In cases of miscarriage and ectopic pregnancy, the hospitalization can be registered with an ICD-10 code and/or an operation code. A hospital outpatient visit is registered only when an operation has been carried out. By using ICD-10 codes, 71% of miscarriages after IVF and 74% after OI could be identified, and the rest were identified by using only operation codes. Almost all ectopic pregnancies were identified by using ICD-10 codes (98% of IVF and 97% of OI cases).

In addition to the diagnoses defined in the HDR to be OHSS-related, we searched for women having had symptoms or diseases potentially related to OHSS ('potential OHSS'). Our definition was based on one unpublished Finnish clinical study of women with diagnosed OHSS, on consultations with experienced clinicians, on symptoms and diseases described in the literature, and on diagnoses given to women in our data just before OHSS diagnosis (ICD-10 code N98.1). Five of the 48 women listed in the Finnish clinical OHSS data could be found in the HDR with the ICD-10 code N98.1. Two other women were hospitalized after IVF treatment with a diagnosis of pain localized in other parts of the lower abdomen (R10.3), and one due to other and unspecified ovarian cysts (N832). The diagnoses women received just before they were hospitalized due to OHSS were E15 (non-diabetic hypoglycaemic coma), R10.3, and J90 (pleural effusion, not elsewhere classified).Combining these diagnoses with those found in the literature, we made a list of diagnoses probably related to OHSS by consulting experienced clinicians (see Appendix).

Using all diagnoses and operation codes for all hospital episodes, we searched for those due to an IVF/OI complication (hereafter called a complication episode). To be eligible, the episode had to have occurred within 120 days from the beginning of the IVF/OI treatment in the case of OHSS, infections, abscesses, bleeding, and other complications. A time lag of 240 days was chosen in the case of miscarriages and ectopic pregnancies. These time lags were defined after studying the shapes of distribution curves of each complication to find a point when incidences clearly decreased. In addition, we consulted experienced clinicians in calculating the probable time lag from the start of treatment (first purchase date of the drug) to the occurrence of potential complications. If a woman had several treatments within this time frame, the latest was defined to be the treatment that led to the complication. If the same episode included different complications (e.g. OHSS and bleeding), they were all counted.

The complication risk was calculated in two ways. First, the proportion of women whose first complication occurred after the first treatment cycle (in our study window) was calculated separately for each type of complication (risk after the first treatment). Secondly, all treatment cycles were considered, but still only the first occurrence of each complication was taken into account, and the proportion of women having at least one complication (of each type) was calculated (risk of a complication after an average of 3.3 IVF and 2.7 OI treatment cycles). Furthermore, the risk of OHSS in each treatment cycle was calculated. In this calculation, individual women can appear more than once. The proportion of women having had any complication episode during the study period was calculated as well as the proportion of women whose hospital visit had lasted >5 days.

To calculate whether OHSS is more common in multiple than singleton pregnancies (among pregnancies ending in birth) and the rate of miscarriages and ectopic pregnancies per 100 births, we linked the data to the nationwide Medical Birth Register by using the women's personal identification numbers. For IVF and OI births, time limits of 44 and 48 weeks respectively were used to define whether births were the result of IVF or OI or spontaneous pregnancies; times were calculated from the beginning of treatment (the first purchase date of the drug) to the date of birth. In addition, to be able to estimate the risk of each complication per initiated cycle and to find comparable rates for earlier studies, the number of women having had each type of complication was divided by the total number of treatment cycles. This calculation produced only raw estimates because only the first occurrence of each complication was counted.

The numbers of deaths during and after the exposure to IVF and OI until the end of 2000 (after an average of 3.7 and 3.8 years for IVF and OI women respectively) were obtained from the Cause-of-Death Register. The follow-up time of the control group was as long as that of

the IVF women (from the first date of IVF exposure to the end of 2000). The causes of death were classified according to the following eight categories: reproductive mortality (Fortney *et al.*, 1986) including methods related to achieving pregnancy, diseases of the circulatory system, cancers, suicides, homicides, accidents, other, and unknown causes.

The differences were tested by using a χ^2-test or a test of relative proportions. The statistical analyses were performed in SAS, version 9.

Results

The background characteristics of the women are presented in Table I.

Depending on the definition of OHSS, the number of women having OHSS after the first treatment cycle varied from 14 to 19 per 1000 women and after all treatment cycles from 23 to 35 (Table II). As a specified (N98.1 in ICD-10) and potential diagnosis, OHSS was most common 1–2 and 2–3 months respectively after the beginning of IVF treatment. Depending on the definition of OHSS, the total rate of hospitalization due to OHSS per initiated IVF treatment cycle varied from 0.9% (210 cases/24 318 cycles) to 1.4% (330 cases/24 318 cycles). The mean length of hospitalization due to OHSS and potential OHSS was 4.1 and 3.3 bed days respectively.

After OI (94% of women treated with clomiphene citrate) hospitalization due to OHSS was rare (Table II). Depending on the definition of OHSS, the total rate of hospitalization per OI treatment cycle varied from 0.04% (eight patients/18 000 cycles) to 0.5% (100 patients/18 000 cycles). Most cases of OHSS occurred in the first month after the treatment cycle. Potential OHSS typically appeared 2–3 months after the treatment cycle.The mean length of hospitalization due to ICD-10 OHSS and potential OHSS was 2.4 and 1.9 bed days respectively.

The risk of OHSS was highest after the first and after the fifth or more IVF treatment cycles (Table III).

In our data, 21.2% of IVF pregnancies ending in birth (total of 3737 births) were twin births and 0.4% were triplets. The risk of OHSS (ICD-10 code) was more common among twin than among singleton pregnancies ending in birth (3.2 versus 1.4%, $P < 0.001$ for a test of relative proportions). In triplet pregnancies, no OHSS was registered.

After IVF treatment, OHSS (ICD-10) was much more common among younger than older women; 3.2% of women <35 years of age were hospitalized due to OHSS, but only 1% of older women. This was also the case when potential OHSS was taken into account.

Bleeding that necessitated hospital care was a rare complication (Table II). Most instances of bleeding occurred within 2 months of starting the treatment cycle. The total rate per initiated treatment cycle was 0.09%. Ten per 1000 IVF women were hospitalized due to infections; infections were diagnosed somewhat later than bleeding. The total rate per treatment cycle was 0.4%. The mean length of hospitalization after all treatment cycles was 2.1 bed days for bleeding and 3.7 for infections. After OI, hospitalizations due to bleeding and infections were even rarer than after IVF (Table II).

Only 17 IVF women were hospitalized due to complications other than OHSS, bleeding, and infections, and these mainly occurred 1–2 months after starting the treatment (Table II). Six women (four registered as pregnant) had a thromboembolic event. Three of these six cases were serious: one cerebral infarction and two pulmonary embolisms. None of the six women was registered as having OHSS in their thromboembolic episodes, but the cerebral infarction occurred just after hospitalization due to OHSS. One pulmonary embolism was registered as a complication of assisted reproduction (ICD-10 N98.8) that had included excision of the ovary and Fallopian tube.

After all OI treatment cycles, a total of five women had another complication. Four women (two registered as pregnant) had a thromboembolic event, but there was no information in the register about any of them possibly having OHSS. One was a serious case with a pulmonary embolism.

After the first IVF treatment cycle, 42 per 1000 women had received hospital care due to miscarriage; after all treatment cycles, the value was 93 per 1000 women (Table IV). The need for hospital care increased steadily until 4 months after IVF treatment, but the hospitalizations were short; the mean length of hospitalization was 1.2 bed days. The number of miscarriages per 100 births after all IVF treatment cycles was 23 (854/3737).

After the first IVF treatment cycle, nine per 1000 women, and after all IVF treatment cycles, 21 per 1000 women had needed hospital care due to an ectopic pregnancy (Table IV). Ectopic pregnancies had led to hospitalization most commonly during the first 3 months after the beginning of the IVF cycle, and the mean length of hospitalization was 2.1 bed days. The rate of ectopic pregnancies per 100 births after all IVF treatment cycles was 5.0 (187/3737).

Table I. Background characteristics of women in the IVF, ovulation induction (OI) and control[a] groups at the beginning of the 1996–98 follow-up in Finland

	IVF (n = 9175)	OI (n = 10 254)	Controls (n = 9175)
Age (years) (mean ± SD)	33.4 ± 5	31.1 ± 6	33.4 ± 5
Age group (years) (%)			
20–24	3.5	11.0	3.5
25–29	20.8	31.4	20.8
30–34	35.2	31.5	35.2
35–39	27.7	17.8	27.7
40–44	10.8	6.9	10.8
≥45	2.0	1.4	2.0
Total	100	100[c]	100
Marital status (%)			
Single[b]	22.3	19.1	36.1
Married	69.4	72.5	56.7
Divorced	7.9	7.9	9.4
Widow	0.4	0.5	0.4
Unknown	0.0	0.0	1.4
Total	100	100[c]	100[d]
Socioeconomic position (%)			
Upper white-collar	25.3	20.6	16.3
Lower white-collar	48.5	48.7	45.7
Blue-collar	16.2	18.0	19.3
Others	7.9	10.0	12.3
Unknown	2.1	2.7	6.4
Total	100	100[c]	100[d]

[a]Population controls for IVF women, matched by age and muncipality.
[b]Includes cohabitation.
[c]$P < 0.001$ for χ^2-tests (distributions of IVF women and OI women).
[d]$P < 0.001$ for χ^2-tests (distributions of IVF women and controls).

Table II. Serious complications in the first[a] IVF or ovulation induction (OI) treatment cycle, and including all[b] treatment cycles in the study period, according to the time lag from the start of the cycle to hospitalization, per 1000 women

	Time lag (days)[c]									
	First treatment cycle					All treatment cycles				
	≤30	31–60	61–90	91–120	Total	≤30	31–60	61–90	91–120	Total
IVF (*n* = 9175)										
OHSS, ICD-10[d]	2.4	10.7	0.3	0.7	14.1	6.3	14.4	1.0	1.2	22.9
Potential OHSS[e]	1.0	1.9	1.3	1.4	5.6	3.3	3.9	3.6	2.5	13.3
OHSS, ICD-10 or potential	3.4	12.2	1.4	2.0	19.0	9.4	17.6	4.1	3.6	34.7
Bleeding	0.3	0.5	0.0	0.1	1.0	0.9	1.0	0.3	0.2	2.4
Infection	0.9	1.4	1.9	1.0	5.1	2.1	3.3	3.4	2.2	10.9
Other[f]	0.0	0.9	0.1	0.1	1.1	0.2	1.4	0.1	0.1	1.9
OI (*n* = 10 254)										
OHSS, ICD-10[d]	0.1	0.1	0.0	0.1	0.3	0.4	0.1	0.1	0.2	0.8
Potential OHSS[e]	0.9	1.0	1.5	1.7	5.6	1.6	1.8	2.8	2.9	9.1
OHSS, ICD-10 or potential	1.0	1.1	1.5	1.6	5.7	2.0	1.9	2.9	3.0	9.8
Bleeding	0.1	0.1	0.1	0.0	0.3	0.1	0.1	0.1	0.0	0.3
Infection	0.4	0.2	0.4	0.4	1.5	0.6	0.7	0.9	1.0	3.1
Other[f]	0.1	0.0	0.0	0.0	0.1	0.2	0.0	0.2	0.1	0.5

[a]First treatment cycle in our study.
[b]With an average of 3.3 IVF and 2.7 OI treatment cycles. For each problem, the follow-up is truncated after the first problem.
[c]Number of days between first purchase of the drug in the cycle and the first day of hospitalization due to the complication.
[d]OHSS = ovarian hyperstimulation syndrome (N98.1, ICD-10 code).
[e]Symptoms potentially related to OHSS but not registered as OHSS (see Appendix).
[f]Other complication than OHSS related to IVF or OI (see Appendix) and thromboembolic events.
ICD-10 = International Classification of Diseases, 10th edition.

Table III. Proportion (%) of IVF women[a] having ovarian hyperstimulation syndrome (OHSS) leading to hospitalization and the proportion with long hospitalization in each treatment cycle

	n	OHSS		In hospital ≥5 days[b]			
		ICD-10[c]	Including potential	ICD-10	(*n*)	Including potential	(*n*)
Treatment cycle							
1st	9175	1.4	1.9	27.1	(129)	20.6	(175)
2nd	6066	0.6***	1.1	28.6	(35)	18.5	(65)
3rd	3844	0.7***	1.2	12.0	(25)	8.9	(45)
4th	2320	0.6**	0.9	7.7	(13)	4.8	(21)
≥5th	1318	1.2	2.1	25.0	(16)	14.3	(28)
Total	9175	2.4	3.6	24.3	(218)	17.1	(334)

[a]Includes the first OHSS episode in each treatment cycle, so individual woman can appear more than once.
[b]% of cases.
[c]For test of relative proportions: ***$P < 0.001$, **$P < 0.01$ compared to the first cycle.
ICD-10 = International Classification of Diseases, 10th edition.

The percentage of women having a miscarriage was similar after the first OI and IVF treatment cycle, but after all treatment cycles, miscarriage was 1.6 times more common among IVF women than among OI women (Table IV). The number of miscarriages per 100 births (15.0) after all OI treatment cycles (634/4188) was lower than the corresponding rate after IVF (23.0). Ectopic pregnancies were almost equally common after the first treatment cycle in both groups, but they were more common among IVF women than OI women after all cycles. The number of ectopic pregnancies per 100 births after all OI treatment cycles was 2.6 (107/4188).

Overall, after all treatment cycles, 1354 IVF (15%) and 824 OI (8%) women were hospitalized for complications. Of these hospital episodes, 10.5% of IVF and 1.6% of OI women's episodes lasted >5 days.

A total of 12, 15 and 37 women died in the IVF, OI and control groups respectively during the follow-up as a whole (after an average of 3.7 years (IVF) and 3.8 years (OI) from the time of exposure). The causes of deaths are presented in Table V. One death in both the IVF and the OI group was related to reproduction.

Discussion

The risk of complications after each IVF treatment cycle was low, but cumulatively repeated attempts led to hospital care in the case of many women. After ovulation induction (OI) treatment, there were far fewer complications. OHSS and miscarriages were the most common reasons for hospital care. OHSS occurred after IVF much more often than after OI alone, but

Table IV. Miscarriage or ectopic pregnancy leading to hospitalization or an operation after the first[a] IVF or ovulation induction (OI) treatment cycle, and including all[b] treatment cycles in the study period, according to the time lag from the start of the cycle to hospitalization, per 1000 women

	Time lag (days)[c]									
	First treatment cycles					All treatment cycles				
	≤60	61–120	121–180	181–240	Total	≤60	61–120	121–180	181–240	Total
IVF (n = 9175)										
Miscarriage	14.0	19.3	5.8	2.8	41.9	31.3	41.9	13.3	6.6	93.1
Ectopic pregnancy	3.0	4.1	0.9	1.3	9.3	9.1	7.9	2.3	1.6	20.9
OI (n = 10 254)										
Miscarriage	7.0	15.7	9.6	5.3	42.1	12.3	24.8	15.5	9.2	61.8
Ectopic pregnancy	2.1	2.7	1.4	1.3	8.2	3.4	3.6	1.9	1.8	10.7

[a]First treatment cycle in our study.
[b]An average of 3.3 IVF treatment cycles and 2.7 OI treatment cycles. For each problem, the follow-up is truncated after the first problem.
[c]Number of days between first purchase of the drug in the treatment cycle and the first day of hospitalization due to the complication.

Table V. Deaths by cause from 1996 to 2000 [after an average 3.7 years for women in IVF and control groups, and 3.8 for ovulation induction (OI) women after the first exposure]

	IVF (n = 9175)	OI (n = 10 254)	Controls (n = 9175)
Cause of death			
Reproductive-related[a]	1	1	0
Diseases of the circulatory system	1	2	10
All cancers	4	2	13
Breast cancer	1	0	3
Ovarian cancer	0	1	0
Suicide	4	5	4
Homicide	0	3	0
Accident	2	0	3
Other	0	0	6
Unknown (died abroad)	0	2	1
Total	12	15	37

[a]Includes causes attributable to IVF and OI treatment, pregnancy, and childbirth.

miscarriages and ectopic pregnancies were equally common after OI and IVF after the first treatment cycle. Other serious complications, infections, and instances of bleeding were quite rare, especially among OI women.

Are our estimates of complication risks reliable? The identification of IVF and OI cohorts from the reimbursement records went well (Hemminki *et al.*, 2003). We also believe that the data covered most Finnish women treated from 1996 to 1998. The cohorts are large enough to study the frequency of even rare complications caused by IVF and OI. However, our method of identification of serious complications and miscarriages was based on a register covering only hospital care, inpatient care, and operations in outpatient clinics; therefore our identification of outcomes depended on care practices and the diagnosis recording style of physicians.

Even though the validity of the HDR has been high (Keskimäki and Aro, 1991), it is a routine care register that does not have the accuracy of *ad hoc* epidemiological studies. For example, OHSS is not always easy to diagnose. Symptoms may be atypical, and there may be no questions about a history of IVF or OI treatments; or a physician may not enter the code for a specific form of OHSS and instead list its symptoms, such as abdominal pain, enlarged ovaries, or dyspnoea. Likewise, the identification of miscarriages using the register is difficult (Hemminki, 1998). The time lags (between the start of a cycle and hospitalization due to a complication) were defined on the basis of drug purchases, and the chosen thresholds were relative. We only had data on the purchase day, not the actual start of the cycle. There may have been intervals between drug purchases and use. On the other hand, due to the character of IVF treatment and the costs of the drugs, it is unlikely that women would have bought the drugs a long time before their use.

Overall, we think that our results underestimate the real complication risks. Mild (less serious) cases are missing in our data. To calculate how reliable our definition of OHSS is, we correlated our data with unpublished Finnish clinical data from the same time period. This showed that only 16% of OHSS cases are in the HDR (10% with the OHSS code and 6% with codes related to OHSS symptoms). Most likely the rest of the cases are missing because the women had had a less serious OHSS that did not lead to hospitalization or to an operation. Some cases may be missing because OHSS was not correctly diagnosed or registered. The overall frequency of OHSS, including mild forms, is no doubt much higher than our results show. On the other hand, some symptoms of OHSS such as abdominal pain are common and can relate to many other diseases. Thus some of our OHSS cases (‘potential OHSS’) may have actually been other diseases.

Our results cannot be extrapolated to countries with a less advanced health care system or less developed practices, in which treated women are less strictly screened or more risks are taken. For example, multiple pregnancies are suspected to entail a higher risk of late OHSS (Mathur *et al.*, 2000). In our population, plural births were lower than in many other countries (Bryant *et al.*, 2004; Nyboe Andersen *et al.*, 2005).

In our study, the hospitalization rates of OHSS per initiated IVF treatment cycle are somewhat higher and the length of hospital stays shorter than reported earlier (Quasim *et al.*, 1997; Serour *et al.*, 1999). Earlier studies are, however, based on less extensive or older data than ours (from 1980s to mid 1990s). It is possible that serious OHSS became more common from the 1980s to the late 1990s, when more potent treatments were used. At least in Israel, the incidence of severe OHSS

after IVF increased from 1987 to 1996 (Abramov *et al.*, 1999b). On the other hand, it might be that OHSS has become better known and more readily diagnosed. Shorter stays at hospital for OHSS may relate to the general trend towards shorter hospital stays.

As earlier reported (Schenker, 1999), women aged <35 years are at greater risk of developing OHSS. According to that study, the risk is also greater among women who receive only one treatment cycle or many cycles. It is generally assumed that a woman with a previous OHSS is at greater risk of OHSS in a following cycle (Whelan and Vlahos, 2000). For that reason, it may be assumed that women with previous OHSS are more carefully monitored during the next cycle to prevent OHSS. However, the women's first cycle was the first in our study window. We do not know how many cycles the women had received before 1996. After many repeated cycles, a woman may be at greater risk due to the repeated doses of drugs (especially gonadotrophin). This should be considered when many attempts are needed. Furthermore, the risk was also higher among twin pregnancies than among singleton pregnancies ending in birth. This was also found in an earlier study on late OHSS (Mathur *et al*., 2000). We were not able to classify the OHSS cases as late or early.

Only a few studies (Quasim *et al.*, 1997; Abramov *et al.*, 1999b) have reported the frequency of OHSS after ovulation induction (OI) alone or compared it to the frequency after IVF. Our study, as well as the older ones from the USA and Israel, shows serious OHSS to be more common after IVF than after OI. In addition, according to our study, the length of hospital stay was longer after IVF than after OI. This suggests that OHSS after IVF is more serious than after OI.

Our study confirmed earlier results that thromboembolic events exist after IVF but are rare complications, and even rarer after OI. In our study, the proportion of women reported as having a thromboembolic event leading to hospitalization (0.07%) was much lower than in an earlier Egyptian study (0.2%) (Serour *et al.*, 1998). The difference between the studies might be explained by different data collection methods (register/clinical study) and different time periods. In the Egyptian study, all cases were related to severe OHSS. In contrast, none of the women in our study were registered as having OHSS at the same time as thromboembolic complications. We do not know whether this is because thromboembolic events related to OHSS were not specifically recorded (but considered a part of OHSS), or whether OHSS was not diagnosed or not present. In one case report (Ulug *et al.*, 2003), a woman had venous thrombosis without OHSS after ovulation induction and ICSI. According to an extensive review, many studies have reported thromboembolic phenomena related to IVF or ovulation induction without any signs of OHSS (Delvigne and Rozenberg, 2003). However, severe OHSS was diagnosed in >76% of thromboembolic cases. Some case reports have described a cerebral infarction complicating OHSS (Koo *et al.*, 2002).

The frequency of bleeding per initiated IVF cycle was the same in our study as in an Egyptian study with 3500 cycles (Serour *et al.*, 1998). But it was much lower than in a recent report from the ESHRE (Nyboe Andersen *et al.*, 2005), covering all bleeding complications, even those not leading to hospitalization. The frequency of infections in our study was similar to that reported earlier in the Nordic countries (Bergh and Lunkvist, 1992) and Egypt (Serour *et al.*, 1998), but higher than reported by ESHRE (Nyboe Andersen *et al.*, 2005). The very low bleeding and infection rates after OI suggest that bleeding and infections were complications of IVF technique.

We found that >9% of IVF and >6% of OI women received hospital care due to miscarriages. We could not identify how many of the treated women had become pregnant, but the number of miscarriages per 100 IVF births (23.0) suggests similar miscarriage rates found earlier (15–23%; Serour *et al.*, 1998; Kupka *et al*., 2003; Schieve *et al.*, 2003; Wang *et al.*, 2004). However, the real miscarriage rate must have been higher, for not all miscarriages lead to hospital care. The miscarriage rate per 100 OI births was lower than the rate per 100 IVF births (15 versus 23). Whether this was due to characteristics of the individual women or the procedure itself could not be judged on the basis of this study. Previously, greatly varying miscarriage rates have been reported after clomiphene-induced pregnancies (9–27%; Venn *et al*., 1994).

Were the miscarriage rates after IVF higher than in natural pregnancies? We did not have a pregnant control group, but 8% of women with spontaneous pregnancies needed hospital care due to a miscarriage according to one Finnish study (Hemminki and Meriläinen, 1996). In one study from the USA, the miscarriage rate was similar (15%) among assisted reproduction treatment women and the rest of the female population (Schieve *et al*., 2003). However, in another study from the USA, the risk of miscarriage slightly increased after assisted reproductive treatment (Wang *et al*., 2004).

The rate of ectopic pregnancies per 100 IVF births (5.0) in our study is twice that of earlier studies in Finland (Hemminki and Heinonen, 1987; Mäkinen, 1996). The frequency per initiated IVF cycle (0.8%) is also somewhat higher than in earlier studies of IVF treatments (Bergh and Lundkvist, 1992; Serour *et al.*, 1998; Bryant *et al*., 2004). We do not have information on the reasons for infertility among the women in our study. We also could not examine how many of the women studied had tubal occlusion, which is considered to be one reason for the high frequency of ectopic pregnancies among IVF women. In the case of OI, which requires open tubes in order to be effective, clomiphene citrate could be a possible reason for the observed high rate of ectopic pregnancies (Venn *et al*., 1994).

Hardly any data have been published about maternal mortality or other deaths occurring as IVF complications. In one study from Australia, the maternal mortality of IVF women was higher than the national rate (Venn *et al.*, 2001). We did not have a control group consisting of spontaneously pregnant mothers or women trying to become pregnant. The best control group for IVF women that we had was OI women, although IVF women were older than OI women. Total mortality within an average of 3.7 years (IVF) and 3.8 years (OI) of follow-up was nearly equal among IVF and OI, and one death in both groups was connected with reproduction. The overall mortality in our study was lower than in the general female population (matched by age and municipality). In particular, the cardiovascular deaths were rarer. This indicates a 'healthy patient

effect' among IVF and OI women, i.e. sick women are less likely to be married or to receive infertility treatment than healthy women. The socioeconomic position of IVF women in our study was somewhat higher than that of the women in the control group, which can explain some of the lower mortality. Lower mortality has been reported in Australia among women who received IVF compared to women who had registered for IVF but never received the treatment (Venn *et al*., 2001).

Register-based studies with sufficiently large populations enable the examination of rare events. However, such studies have their limitations. Registers provide only limited information, and the coding of diagnoses are very likely to vary. Estimates of the frequencies of complications are needed to help clinicians in choosing safer methods, in applying new methods, and in informing women who contemplate IVF or OI treatment. It would be important to establish a routine follow-up system for IVF and OI treatments and their complications. This should also provide information on the duration and causes of infertility, the exact nature and duration of maternal drug exposure, and maternity background data. In countries with computerized health care and IVF registers, it would be easy to implement such a system. However, even before the possible establishment of such a new follow-up system, current estimates of the complication risk should be available both to women and physicians.

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Appendix. ICD-10 and operation codes and their explanations used in identifying the complications of IVF and ovulation induction (OI)

Ovarian hyperstimulation syndrome (OHSS)	
ICD-10	
N98.1	Hyperstimulation of ovaries
Potential OHSS	
ICD-10	
E15	Non-diabetic hypoglycaemic coma
J80	Adult respiratory distress syndrome
J90	Pleural effusion, not elsewhere classified
J94.8	Other specified pleural conditions (hydrothorax)
K65.0	Acute peritonitis
N17	Acute renal failure
N83.0	Follicular cyst of ovary
N83.1	Corpus luteum cyst
N83.2	Other and unspecified ovarian cysts
N99.0	Post-procedural renal failure
R06.0	Dyspnoea
R10.2	Pelvic and perineal pain
R10.3	Pain localized in other parts of lower abdomen
R10.4	Other and unspecified abdominal pain
R18	Ascites
R34	Anuria and oliguria
R60	Oedema, not elsewhere classified
Infections	
ICD-10	
N70	Salpingitis and oophoritis
N71	Inflammatory disease of uterus, except cervix
N73	Other female pelvic inflammatory diseases
N74.8	Female pelvic inflammatory disorders in other diseases classified elsewhere
N98.0	Infection associated with artificial insemination
Bleedings	
ICD-10	
N83.6	Haematosalpinx
N85.7	Haematometra
N93.8	Other specified abnormal uterine and vaginal bleeding
N93.9	Abnormal uterine and vaginal bleeding, unspecified
K66.1	Haemoperitoneum
T81.0	Haemorrhage and haematoma complicating a procedure, not elsewhere classified
Other	
ICD-10	
N98.2	Complications of attempted introduction of fertilized ovum following IVF
N98.3	Complications of attempted introduction of embryo in embryo transfer
N98.8	Other complications associated with artificial fertilization
N98.9	Complication associated with artificial fertilization, unspecified
I26	Pulmonary embolism
I63	Cerebral infarction
I74	Arterial embolism and thrombosis
I80	Phlebitis and thrombophlebitis
I82	Other venous embolism and thrombosis
Miscarriages	
ICD-10	
O02.1	Missed abortion
O03	Spontaneous abortion
O05	Other abortion
O06	Unspecified abortion
O08	Complications following abortion and ectopic and molar pregnancy
Operation codes	
1350	Other operation in uterus
8113	Curettage of body of uterus
8319	Destruction of endometrium
8501	Evacuation of uterus by aspiration
8502	Evacuation and abrasion
8509	Other operation related to miscarriage
LCA10	Curettage of body of uterus
LCA13	Curettage of cervix and body of uterus
LCA16	Destruction of endometrium
LCA96	Other intrauterine operation
LCA98	Other transluminal endoscopic operation on uterus
Ectopic pregnancies	
ICD-10	
O00	Ectopic pregnancy
O08	Complications following abortion and ectopic and molar pregnancy
Operation codes	
8231-8239	Operations related to ectopic pregnancy
LBC00-LBC98	Tube conserving operations for tubal pregnancy

Paper III

Health of Children Born as a Result of In Vitro Fertilization

Reija Klemetti, Tiina Sevón, Mika Gissler and Elina Hemminki

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ARTICLE

Health of Children Born as a Result of In Vitro Fertilization

Reija Klemetti, MHSc[a], Tiina Sevón[a], Mika Gissler, DrPhil, MSocSc[b], Elina Hemminki, MD[a]

[a]Health Services Research and [b]STAKES Information, STAKES, National Research and Development Centre for Welfare and Health, Helsinki, Finland

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ABSTRACT

OBJECTIVE. The purpose of this study was to use nationwide registries to examine the health of children up to 4 years of age who were born as a result of in vitro fertilization.

METHODS. Children born after in vitro fertilization (N = 4559) from 1996 to 1999 were monitored until 2003. Two control groups were selected from the Finnish Medical Birth Register as follows: all other children (excluding children born after ovulation induction) from the same period (N = 190 398, for study of perinatal health and hospitalizations) and a random sample of those children (n = 26 877, for study of health-related benefits). Mortality rates and odds ratios for perinatal outcomes, hospitalizations, health-related benefits, and long-term medication use were calculated.

RESULTS. Although the health of most in vitro fertilization children was good, such children had more health problems than other children. A total of 35.7% of in vitro fertilization children and 2.2% of control children were multiple births, and the health of multiple births was worse than that of singletons. Perinatal outcomes of in vitro fertilization children were worse and hospital episodes were more common than among control children. Risks for cerebral palsy and psychological and developmental disorders were increased. Among in vitro fertilization singletons, worse results for perinatal outcomes and hospitalizations, but no increased risk for specific diseases, were found. The health of in vitro fertilization multiple births was comparable to the health of control multiple births.

CONCLUSIONS. Reducing the number of transferred embryos would improve the health of in vitro fertilization children. Additional studies are needed to explain the poorer health of in vitro fertilization singletons, as well as follow-up studies to examine the health of in vitro fertilization children from 4 years onward.

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Key Words
in vitro fertilization, perinatal health, morbidity, multiplicity, registry-based study

Abbreviations
CP— cerebral palsy
IVF—in vitro fertilization
HDR—Hospital Discharge Register
MBR—Medical Birth Register
SII—Social Insurance Institution
OR— odds ratio
CI— confidence interval
ICD-10 —*International Classification of Diseases, 10th Revision*

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Address correspondence to Reija Klemetti, MHSc, PO Box 220, 00531, Helsinki, Finland.

In vitro fertilization (IVF) (including intracytoplasmic sperm injections and frozen embryo transfers) is a common infertility treatment. In Finland, currently ~2.5% of infants are born as a result of IVF,[1] with women <40 years of age being able to receive 2 to 5 IVF treatment cycles within the public sector[2] while paying a small fee for visits. Approximately 60% of all IVF services are supplied by private clinics, with no strict age limit. Private physicians' charges and drug costs are partly reimbursed by the Social Insurance Institution (SII). Usually, the pharmacies and IVF clinics take care of billing for the reimbursements. Approximately 76% of total IVF costs (visits, examinations, treatments, and drugs) are covered in the public sector and 50% in the private sector, with the rest being paid by women (R.K., T.S., M.G., and E.H., unpublished data, 2006).

The perinatal health of IVF singletons has been reported as being worse than that of naturally conceived singletons,[3–5] with more-recent studies also showing an increased risk for preterm birth and/or low birth weight for twins.[6,7] However, studies of the long-term health of IVF children are few, and their results are conflicting.

According to previous small cohort studies, the morbidity rates, growth, and development of IVF children are similar to those of control children (as reviewed by Koivurova[8]). Although the health of children is mainly good, large studies are needed to clarify potential health problems. Registry-based studies allow for large sample sizes and are published regularly from the Nordic countries.[9–17] In the case of IVF children, research has found an excess use of hospital services, long hospitalizations, and increased risk for infections, epilepsy, and tumors,[10] asthma,[10,17] cerebral palsy (CP),[10,11,14] sleep disturbances,[14] convulsions, behavioral problems, and accidents,[17] and congenital malformations.[9,10,15–17] However, some of those studies were based on early IVF experience and concentrated on specific diagnoses, hospital care utilization, or singletons/twins only or did not consider multiplicity.

Results on the perinatal health of IVF twins are controversial, whereas data on the long-term health of IVF children are sparse. For this reason, our aim was to perform a large, thorough, up-to-date, registry-based study of the health of IVF children up to 4 years of age, separately for singletons and multiple births, by using several population-based registries.

METHODS

Identification of IVF Children

The study is based on children born to women who received IVF between 1996 and 1998 in Finland. The women were identified, with a predesigned algorithm, from the reimbursement files of the SII.[18] Data on children born as a result of IVF treatment (N = 4559) and their perinatal health were obtained from the Finnish Medical Birth Register (MBR)[15,19] by using women's personal identification numbers and the children's dates of birth as the linkage keys. The MBR also includes the children's unique identification numbers. It contains information on maternal backgrounds and on infant outcomes until the age of 7 days for all infants born in Finland. The data are collected by delivery hospitals and are completed by linkage to the Central Population Register and cause-of-death statistics (compiled by Statistics Finland). The identified children were linked to 4 other nationwide registries through the children's identification numbers, namely, cause-of-death statistics, the Hospital Discharge Register (HDR) (hospital episodes, diagnoses, ie, *International Classification of Diseases, 10th Revision* [ICD-10] codes, and dates of admissions and discharges), the Care Register for Social Welfare (episodes in institutional care), and health-related social benefits from the SII (reimbursements for long-term medication use and child disability allowance).

Control Groups

As control groups, 2 groups of children were selected from the MBR. The first control group consisted of all children other than IVF children or those born as a result of ovulation induction (N = 190 398) who had been conceived during the same period (1996–1998). The second control group (n = 26 877) was a random sample of the first control group, selected to reduce the workload caused by large registry linkages in the SII, and was used to study the benefit payments from the SII and for the combined analysis.

Data Collection

The number of deaths of all children from 1996 to 2001 until the age of 2 years was obtained from cause-of-death statistics. We grouped the causes of deaths (given as ICD-10 codes) into 4 categories, namely, conditions originating from the perinatal period, congenital malformations, other medical causes, and deaths from external causes.

The HDR collects information on inpatient care and visits to outpatient clinics involving surgical or other procedures. The HDR gathers information on diagnoses (ICD-10 codes) and dates of admissions and discharges. The diagnoses include the main diagnosis and 2 secondary diagnoses for each episode. All hospitalizations until the children were 4 years of age were studied (1996–2003).

The Care Register for Social Welfare collects information on care episodes in social institutions, such as institutions for people with intellectual disabilities. For this study, we received information on the numbers of IVF children having ≥1 period of institutional care up until the end of 2004. We compared the rates of institutionalized children with the national rates for children born

in 1997 or 1998, excluding the numbers of children from IVF or ovulation induction.

The SII grants child disability allowances for families who have a disabled or chronically sick child needing continuous help and surveillance at home. A child's parents applying for benefits are required to supply recent medical documents. The register of child disability allowances contains information on start and end dates, type (temporary or permanent), level (normal, increased, or special), and diagnoses. The special refund category covers ~50 chronic diseases, entitling patients to receive higher reimbursements of long-term medication costs. Among children, the most common diseases in the special refund category are asthma, epilepsy, diabetes mellitus, and rheumatoid arthritis. The data on special refunds included the start and end dates of entitlement periods and the reasons. Information on both child disability allowance and long-term medication use was gathered from 1996 to 2001 (ie, until the children were 2 years of age).

Data Analyses

A comparison was made between control and IVF mothers in their utilization of health care services during the pregnancy and child birth (hospitalization during the pregnancy, cesarean section, and hospitalization of ≥7 days after delivery) and in infant outcomes, first including all children and then including first births only. As health outcomes, we used very low birth weight (<1500 g), low birth weight (<2500 g), very preterm birth (<32 weeks), preterm birth (<37 weeks), low 1-minute Apgar scores (scores of 0–6), treatment in an ICU or neonatal surveillance unit, need for respiratory treatment, hospitalization of the child for ≥7 days after birth, and perinatal death.

All inpatient hospital episodes until 2 years and 4 years of age were collected separately from the HDR. The total number of hospital episodes, the length of the episodes, and the number of hospitalized children were determined. We grouped diagnoses (ICD-10 codes) into 16 categories. The 2 categories of "symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified" (codes R00–R99) and "factors influencing health status and contact with health services" (codes Z00–Z99) were combined and renamed as "other." Both main and secondary diagnoses were taken into account. If the child was hospitalized more than once because of the same diagnosis, then only the first hospitalization was included.

We calculated the numbers of IVF and control children who had received ≥1 child disability allowance period or reimbursement for long-term medication. The most common reasons for child disability allowance and reimbursement were counted and IVF children were compared with naturally conceived children. Finally, we combined information from the different data sources and calculated the number of children who had used services, according to any of the data sources, because of an allergic and chronic disorder and common infection-like allergy (ICD-10 codes L20–L23, L27, and L50), asthma bronchial (ICD-10 codes J45 and J46), CP (ICD-10 code G80), epilepsy (ICD-10 codes G40 and G41), diabetes mellitus (ICD-10 code E10), diarrhea (ICD-10 codes A08–A09), pneumonia (ICD-10 codes J12–J18), or disorders of psychological development and behavioral and emotional disorders usually occurring in childhood and adolescence (ICD-10 codes F80–F98).

Statistical Analyses

The differences between the IVF and control groups were first tested with a χ^2 test and t test for relative proportions and with logistic regression analysis, adjusting for available background characteristics. For perinatal outcomes, these characteristics were county, smoking, maternal age, socioeconomic position, and previous births. The socioeconomic position of the women was defined by using their own occupation when delivering, which is collected routinely from maternity hospitals and classified automatically by the MBR into 5 categories according to the national classification compiled by Statistics Finland, that is, upper white-collar workers, lower white-collar workers, blue-collar workers, others (entrepreneurs, students, pensioners, unemployed women, and women with an unclassified position), and unknown position.[20] All analyses were made separately for singletons and multiple births. Two logit models were used, namely, an ordinary logit model in which all children were assumed to be independent and an additional model created by using the iterative, generalized, least-squares method, in which siblings born in the same delivery were assumed to be dependent.

Research Ethics and Data Protection

The study plan was approved by the National Research and Development Centre for Welfare and Health research ethics committee (September 18, 1998). For register linkages, the National Data Protection Authority was consulted, and permissions were obtained from the registry keepers.

RESULTS

Of the 4559 IVF children, 34.7% were twins and 1.1% were triplets. Among the 190 398 control children, 2.2% were twins and only 13 sets were triplets (<0.01%). IVF mothers were older, more often married, and from a higher socioeconomic position than other mothers (Table 1).

Compared with other mothers, IVF mothers received more hospital care during pregnancy and more cesarean sections (Table 2). Adjustment for mothers' background characteristics did not change the results. Inspection of singletons and multiple births separately showed that

TABLE 1 Mothers' Background Characteristics According to Group and Plurality for IVF and Control Mothers

	Total Births			Singleton Births			Multiple Births		
	IVF (n = 3737)	Control (n = 188 298)	P	IVF (n = 2930)	Control (n = 186 216)	P	IVF (n = 807)	Control (n = 2084)	P
Maternal age at delivery									
Mean ± SD, y[a]	33.9 ± 4.5	29.7 ± 5.3	<.001	34.1 ± 4.6	29.7 ± 5.3	<.001	33.1 ± 4.3	30.5 ± 5.2	<.001
Age group, %									
<25 y	2.9	22.4		2.6	22.4		4.1	17.4	
25–29 y	20.1	33.6		18.8	33.7		24.5	31.7	
30–34 y	41.2	29.4		41.2	29.4		41.5	33.2	
35–39 y	41.2	12.2		28.3	12.2		25.3	15.4	
≥40 y[b]	8.1	2.3	<.001	9.1	2.3	<.001	4.6	2.3	<.001
Marital status									
Married or cohabiting	95.3	87.5		95.4	87.5		94.9	86.4	
Single	3.9	10.6		3.9	10.6		4.0	11.3	
Missing information[b]	0.8	1.9	<.001	0.8	1.9	<.001	1.1	2.4	<.001
Socioeconomic position, %									
Upper white-collar	25.1	15.1		25.5	15.1		23.7	17.0	
Lower white-collar	48.5	40.6		48.2	40.6		49.9	40.3	
Blue-collar	13.0	17.0		13.0	17.0		12.6	16.1	
Others	8.0	18.5		8.0	18.5		8.1	18.2	
Unknown[b]	5.4	8.9	<.001	5.3	8.9	<.001	5.7	8.4	<.001
Smoked during pregnancy[c]	6.6	14.8	<.001	6.6	14.8	<.001	6.6	16.6	<.001
First birth[c]	72.2	39.5	<.001	72.0	39.5	<.001	72.9	35.6	<.001

The control group consisted of all other mothers whose children were fertilized in the same time period as IVF children.

[a] For t tests in comparisons between IVF and control subjects.

[b] For χ^2 tests in comparisons between IVF and control subjects.

[c] For tests for relative proportions in comparisons between IVF and control subjects.

TABLE 2 Raw Proportions and Adjusted ORs of Pregnancy and Birth Treatments and Infant Outcomes Among IVF Mothers and Infants, Compared With Other Mothers and Infants

	Total Births			Singleton Births			Multiple Births		
	No. or Proportion		OR (95% CI)	No. or Proportion		OR (95% CI)	No. or Proportion		OR (95% CI)
	IVF	Control		IVF	Control		IVF	Control	
Deliveries, n	3737	188 298		2930	186 216		807	2084	
Infants, n	4559	190 398		2930	186 216		1629	4182	
Mother, %									
Hospital treatment[a]	43.0	20.6	2.61 (2.43–2.79)	36.4	20.2	1.99 (1.84–2.16)	66.9	54.2	1.51 (1.24–1.85)
Hospitalization of ≥7 d[b]	16.8	4.5	2.33 (2.11–2.57)	9.6	4.2	1.23 (1.07–1.41)	46.8	31.7	1.04 (0.83–1.30)
Cesarean section	35.8	15.3	1.95 (1.81–2.10)	30.4	15.0	1.51 (1.39–1.65)	55.5	41.8	1.24 (1.03–1.50)
Infant, %									
Very preterm (<32 wk)	4.7	0.9	4.45 (3.80–5.21)	2.0	0.8	2.06 (1.56–2.71)	9.6	7.0	1.26 (0.99–1.60)
Preterm (<37 wk)	23.6	5.5	4.43 (4.10–4.77)	9.5	4.7	1.72 (1.51–1.96)	49.2	42.2	1.06 (0.93–1.21)
Birth weight of <1500 g	4.2	0.8	4.19 (3.55–4.95)	1.9	0.7	2.17 (1.64–2.88)	8.2	7.4	0.95 (0.74–1.22)
Birth weight of <2500 g	19.8	4.0	4.77 (4.40–5.18)	6.5	3.2	1.60 (1.37–1.87)	43.7	39.2	0.92 (0.81–1.06)
Apgar score of 0–6	8.8	4.4	1.68 (1.50–1.87)	5.6	4.2	1.07 (0.91–1.26)	14.5	12.5	1.10 (0.90–1.33)
Special care[c]	23.0	8.2	2.71 (2.52–2.92)	12.5	7.6	1.36 (1.21–1.53)	42.1	35.0	1.04 (0.91–1.19)
Respiratory treatment	4.3	1.1	3.61 (3.08–4.24)	2.0	0.9	1.76 (1.34–2.31)	8.4	6.7	1.19 (0.93–1.53)
Hospitalization of ≥7 d	23.8	6.4	3.42 (3.08–4.24)	10.8	5.8	1.43 (1.26–1.61)	47.4	37.6	1.02 (0.88–1.17)
Perinatal death	1.3	0.6	1.85 (1.40–2.44)	0.9	0.5	1.32 (0.88–1.98)	2.0	2.9	0.73 (0.47–1.13)

ORs were adjusted for mother's county, smoking, age, marital status, parity, and socioeconomic position. The reference group (OR = 1) was the control group.

[a] During pregnancy.

[b] After delivery.

[c] Treatment in ICU or in newborn surveillance unit.

this difference was partly, but not totally, explained by IVF children more often being twins.

Similarly, the indicators of perinatal health showed much worse health of IVF children, which was explained partly by plurality. The perinatal health of IVF multiple births was comparable to that of control multiple births; the risk for very preterm birth was increased but not statistically significantly.

Stillbirths were more common among IVF children in total, compared with other children in total (7.2 cases

per 1000 vs 3.9 cases per 1000; $P < .001$), and among IVF singletons, compared with control singletons (6.5 cases per 1000 vs 3.7 cases per 1000; $P = .014$ in a test for relative proportions), but not separately for multiple births. The main causes of stillbirths were conditions originating in the perinatal period (for example, placental infarction, extreme immaturity, and abruptio placentae).

The total mortality rate up to the age of 2 years was twofold higher among IVF children, compared with control children (9.0 deaths per 1000 and 4.1 deaths per 1000, respectively). Among singletons, rates of deaths after birth until the age of 2 years were similar in all groups of children; the main causes were congenital malformations (2.4 cases per 1000 among IVF children and 1.4 cases per 1000 among control children) and conditions originating in the perinatal period (for example, extremely low birth weight and respiratory distress syndrome; 1.4 cases per 1000 and 1.3 cases per 1000, respectively). The main causes among multiple births were the same as those among singletons (malformations: 11.2 cases per 1000 and 4.6 cases per 1000; perinatal causes: 11.2 cases per 1000 and 14.8 cases per 1000, respectively), and no significant differences between the groups were found.

According to the Care Registry for Social Welfare Institutions, 2.2 IVF children per 1000 had had ≥1 period of institutional care at a social welfare institution. For other children born in 1997 to 1998, the rate was 2.7 per 1000 children. Institutional care does not include children taken into children's homes or custody but refers mainly to mentally handicapped children who stayed in an institution for people with intellectual disabilities.

Until the age of 2 years, larger proportions of IVF children and IVF singletons received child disability allowances, compared with control children (Table 3). The most common reasons (according to ICD-10 classification) for receiving child disability allowances were the same for IVF and control singletons, namely, diseases of the skin and subcutaneous tissue, diseases of the respiratory system, and conditions involving the eyes and ears. For multiple births, the most common reasons included, in addition, certain conditions originating in the perinatal period. No statistically significant differences in long-term medication use were found between IVF and control children.

When information from different data sources until the age of 2 years was combined, it was found that IVF children, singletons and multiple births taken together, had a threefold increased risk of CP and more often had disorders of psychological development or behavioral and emotional disorders, compared with control children (Table 4). This was not the case when IVF singletons and multiple births were considered separately. Of the infants with CP, 88% were preterm.

Up to the age of 4 years, a larger proportion of IVF children were hospitalized, IVF children more often had long hospital episodes, and the average length of their episodes was greater, compared with control children (Table 5). IVF children had somewhat more hospital episodes than control children at all ages, but the difference was clearest during infancy.

Compared with control children, the risk of being hospitalized was increased among IVF children for many categories of diseases (according to ICD-10 grouping), even after adjustment for the mother's socioeconomic position (data not shown). The risk among IVF singletons was increased statistically significantly for perinatal problems (ICD-10 codes P00–P96; odds ratio [OR]: 1.76; 95% confidence interval [CI]: 1.54–2.01), congenital malformations (codes Q00–Q99; OR: 1.45; 95% CI: 1.20–1.75), and problems of the genitourinary system (codes N00–N99; OR: 1.40; 95% CI: 1.11–1.77) and decreased for diseases of the respiratory system (codes J00–J99; OR: 0.86; 95% CI: 0.76–0.97). IVF multiple births had increased risk for hospitalization because of diseases originating from the perinatal period (OR: 1.34; 95% CI: 1.18–1.53) and "other" diagnoses (codes R00–R99 and Z00-Z99; OR: 1.27; 95% CI: 1.09–1.48) and decreased risk for hospitalization because of diagnoses in the categories of eye and ear (codes H00–H95; OR: 0.77;

TABLE 3 Raw Proportions of Children and Crude and Adjusted ORs (and 95% CI) of Having Any Child Disability Allowance Period or Any Long-Term Medication Use Until the Age of 2 Years

	Total		Singleton		Multiple	
	IVF ($n = 4527$)	Control ($n = 26\,877$)	IVF ($n = 2911$)	Control ($n = 26\,296$)	IVF ($n = 1616$)	Control ($n = 581$)
Any child disability allowance						
Proportion, %	10.6	9.5	10.5	9.5	10.8	13.1
Crude OR (95% CI)	1.13 (1.02–1.25)	1.00	1.13 (0.99–1.28)	1.00	0.81 (0.61–1.08)	1.00
Adjusted OR (95% CI)	1.11 (1.00–1.23)	1.00	1.10 (0.97–1.25)	1.00	0.81 (0.62–1.10)	1.00
Any long-term medication use[a]						
Proportion, %	3.3	2.8	2.9	2.8	4.1	4.5
Crude OR (95% CI)	1.18 (0.98–1.41)	1.00	1.03 (0.82–1.29)	1.00	0.91 (0.57–1.45)	1.00
Adjusted OR (95% CI)	1.18 (0.98–1.41)	1.00	1.03 (0.82–1.30)	1.00	0.95 (0.59–1.52)	1.00

The ORs were adjusted for mother's socioeconomic position. The reference group (OR = 1) was the control group.

[a] Reimbursements for cow's milk or soy milk intolerance were excluded.

TABLE 4 **Raw Proportions of Children and Adjusted ORs of Having an Allergic or Chronic Disorder or a Common Infection (ICD-10 Codes) Until the Age of 2 Years, From Any Available Data Source**

	Total		Singleton		Multiple	
	IVF ($n = 4527$)	Control ($n = 26\,877$)	IVF ($n = 2911$)	Control ($n = 26\,296$)	IVF ($n = 1616$)	Control ($n = 581$)
CP (code G80)[a]						
Proportion, cases per 1000	3.8	1.4	1.4	1.3	8.0	5.2
OR (95% CI)	2.92 (1.63–5.26)	1.00	1.15 (0.40–3.27)	1.00	1.52 (0.43–5.40)	1.00
Epilepsy (code G40–G41)[b]						
Proportion, cases per 1000	3.3	2.5	3.4	2.5	3.1	3.4
OR (95% CI)	1.33 (0.76–2.34)	1.00	1.39 (0.71–2.71)	1.00	0.95 (0.18–5.01)	1.00
Behavioral disorders (code F80–F98)[a,c]						
Proportion, cases per 1000	6.6	4.1	4.1	4.1	11.1	3.4
OR (95% CI)	1.68 (1.11–2.53)	1.00	1.05 (0.57–1.91)	1.00	3.05 (0.70–13.29)	1.00
Diabetes mellitus (code E10)[b]						
Proportion, cases per 1000	0.9	0.5	1.0	0.5	0.6	1.7
OR (95% CI)	1.57 (0.51–4.84)	1.00	1.98 (0.56–7.07)	1.00	0.28 (0.02–4.50)	1.00
Asthma (code J45–J46)[b]						
Proportion, cases per 1000	30.3	28.1	26.5	27.8	37.1	43.0
OR (95% CI)	1.08 (0.90–1.30)	1.00	0.95 (0.74–1.20)	1.00	0.93 (0.57–1.51)	1.00
Allergy (code L20–L23, L27, L50)[b]						
Proportion, cases per 1000	59.9	53.8	61.8	54.0	56.3	46.5
OR (95% CI)	1.07 (0.94–1.23)	1.00	1.10 (0.94–1.30)	1.00	1.25 (0.80–1.96)	1.00
Pneumonia (code J12–J18)[a]						
Proportion, cases per 1000	9.9	11.4	9.6	11.4	10.5	8.6
OR (95% CI)	0.85 (0.62–1.17)	1.00	0.81 (0.55–1.20)	1.00	1.26 (0.46–3.49)	1.00
Diarrhea (code A08–A09)[a]						
Proportion, cases per 1000	44.2	38.6	35.4	38.1	60.0	60.2
OR (95% CI)	1.17 (1.00–1.37)	1.00	0.94 (0.76–1.15)	1.00	1.04 (0.69–1.56)	1.00

ORs were adjusted for mother's socioeconomic position.

[a] Data sources: the HDR and child-care support.

[b] Data sources: the HDR, long-term medication use, and child-disability allowance.

[c] Disorders of psychological development and behavioral and emotional disorders.

TABLE 5 **Use of Hospital Services Until the Age of 4 Years Among IVF and Control Children, According to Multiplicity**

Use of Hospital Services	Total		Singleton		Multiple	
	IVF ($n = 4527$)	Control ($n = 189\,656$)	IVF ($n = 2911$)	Control ($n = 185\,530$)	IVF ($n = 1616$)	Control ($n = 4126$)
Total no. of hospital episodes	4397	136 782	2281	131 459	2116	5323
Hospitalized children, %	40	33	34	32	50	49
OR (95% CI)	1.40 (1.31–1.48)	1.00	1.12 (1.04–1.21)	1.00	1.07 (0.95–1.20)	1.00
Time in hospital per child, d	6.3	2.7	3.8	2.6	10.8	9.8
Proportion of long hospital episodes (≥7 d), %	20	11	14	10	28	24

ORs were adjusted for mother's socioeconomic position. The reference group (OR = 1) was the control group.

95% CI: 0.63–0.95) and the respiratory system (OR: 0.74; 95% CI: 0.63–0.87). Otherwise, their outcomes were comparable to those of control multiple births. However, in almost every category the proportion of hospitalized children was higher among multiple births than among singletons.

In the subanalysis for first births, the results were mainly similar to the results for all children; although IVF children in total had increased risk for asthma (adjusted OR: 1.39; 95% CI: 1.08–1.79), the risk for mothers' long hospital stay for IVF singletons (OR: 1.17; 95% CI: 0.89–1.58) and the risk for cesarean sections for multiple births (OR: 1.19; 95% CI: 0.92–1.53) were not statistically significantly increased. In addition, IVF multiple births had statistically significantly decreased risk for low birth weight (adjusted OR: 0.78; 95% CI: 0.65–0.93).

There were no differences in the results of the 2 logit analyses (an ordinary logit model and an additional analysis using the iterative generalized least-squares method; see Methods). For some rare outcomes, adjustment for mother's socioeconomic position was not possible in the additional analysis because of small numbers.

DISCUSSION

We found an increased burden of disease associated with IVF, with poorer perinatal health, higher mortality rates, increased risk for hospitalization and CP, and longer

hospital episodes. This burden depended in part on higher twin rates among IVF children. However, the burden of disease resulted not only from the greater number of twins but also from the poorer health of singletons, compared with naturally conceived singletons. Increased morbidity was attributable not to any specific disease but rather to small increases in many groups of diseases. In general, the health of IVF multiple births was comparable to that of other multiple births.

Are the results reliable? IVF children were identified on the basis of drugs used, laboratory and radiologic examinations, and infertility treatment procedures. We might have missed some IVF children, who would therefore be included in the control group. However, the number of missing children cannot be large[18,19] and would not affect the results. The data on deaths and perinatal health received from the MBR[21,22] are reliable. However, other outcome measures depend on service utilization (seeking care or applying for benefits); technically, the registers are considered to be of good quality.[23]

The occurrence of less-serious diseases and cases cannot be estimated from these registries, because the use of outpatient care is not registered. Our results might be biased by different thresholds for hospital admissions between IVF and control children. IVF parents, who were more often first-time parents, might have been more worried, which might have led more easily to hospital care and also longer hospital stays. It might also be that IVF children were examined more carefully by physicians, compared with naturally conceived children, if the mode of conception was known to the physicians. However, because IVF children did not have an increased rate of hospitalizations in all categories of diseases and because adjustment for parity and socioeconomic position and a subanalysis of first births did not change our results, it is unlikely that the anxiousness of parents, more-careful examinations, or lower thresholds for hospitalization alone could explain the greater frequency of visits. Rather, the greater frequency likely reflects higher morbidity rates among singleton IVF children. Furthermore, rates of almost every outcome studied were quite similar between IVF multiple births and control multiple births.

In Finland, most health care is public, financed by taxes. Private health care is covered by the national social security system, but some children are covered by additional voluntary private insurance. No private hospitals for children exist but, in 2005, ~28% of children up to 4 years of age used private (outpatient) physicians (Social Insurance Institution of Finland, unpublished data, 2005). It is possible that, in the case of small surgical procedures, private specialist outpatient care competes with hospital outpatient clinics. If IVF children were treated more or less frequently in such private care, then a bias would result.

In Finland, health-related social benefits (child care allowance and reimbursement for long-term medication use) must be applied for. It might be that some parents are more capable of applying for the benefits. Because the adjustment for socioeconomic position did not change the results, however, there is no reason to assume that parents of IVF children with a higher socioeconomic position would receive benefits more easily than parents of control children. Informing and advising parents on these benefits is part of routine clinical practice. In addition, reimbursed diseases for long-term medication use are defined clearly, and recent medical documents are needed for receipt of both child disability allowance and support for long-term medication use. Child disability allowance is based on ICD-10 classifications and long-term medication support on defined diagnoses; therefore, it can be assumed that these are relevant in estimating disease occurrence.

Our study confirms earlier findings of poorer perinatal health,[3–5,8] greater numbers of hospitalizations,[9] and increased risk for congenital anomalies[15,16,24] for IVF singletons, compared with naturally conceived singletons. Perinatal problems had a significant role also in hospitalizations; diseases originating from the perinatal period represented one of the most common diagnoses leading to hospitalization, among both singletons and multiple births. IVF multiple births had worse perinatal health than did IVF singletons, but IVF and control multiple births were similar with respect to perinatal health, which is largely in accordance with an earlier study (except for the finding in that study of an increased risk of admittance to a NICU and more-common longer hospitalizations after the birth).[25] In contrast, a recently published Belgian study found an increased risk for preterm birth also among IVF twins, compared with naturally conceived twins, which was largely explainable by the first birth of IVF women.[7] In accordance with the study by Pinborg et al,[13] we did not find any excess use of hospital services among IVF multiple births.

In addition, our study confirms earlier results of higher mortality rates,[8] greater numbers of hospitalizations,[10,17] and increased risks for behavioral problems,[17] CP,[11,14] and infections[10] among IVF children overall. In accordance with an earlier Finnish study based on both outpatient and inpatient visits,[8] we found a slightly but not statistically significantly increased risk for diarrhea; contrary to that study, however, we did not find an increased risk for pneumonia.

Unlike previous studies,[11,14] we did not find an increased risk for CP or sleeping disturbances among IVF singletons. In our study, the excess risk for CP was mainly explainable by multiplicity. In the study by Strömberg et al,[11] the main reasons for the increased risk for CP were prematurity and the multiple pregnancy rate. A recent Swedish study could not confirm the increased risk for CP; the risk disappeared after adjust-

ment for confounders.[17] Furthermore, we could not find increased risk for epilepsy, tumors, or asthma among IVF children in total, as found earlier in Sweden.[10] However, increased risk for epilepsy was not found in the recent Swedish study.[17]

A few previous studies reported about childhood morbidity for IVF multiple births. In 2 studies, no differences in neurologic sequelae were found.[11,12] In our study, no increased risk for any disease among IVF multiple births was found. In general, however, IVF multiple births had higher childhood morbidity rates than did IVF singletons.

We could not find any other study examining long-term medication use, child disability allowance, and utilization of institutional care among IVF children. A slightly increased risk for child disability allowance among IVF children in our study was explainable by multiplicity, whereas no statistically significant differences in the utilization of long-term medication therapy and institutional care between the groups were found.

Potential reasons for the poorer perinatal health of IVF children include infertility itself,[26–29] infertility treatments, and varying health behavior during pregnancy. Among IVF singletons, the main cause of poorer perinatal health has been suggested to be infertility itself, because of the higher incidence of preterm birth and low birth weight also among infertile women without treatment and women with infertility treatments other than IVF.[30] Some modification in the gestational process induced by IVF and intracytoplasmic sperm injection has been suggested,[31] as well as so-called vanishing twins (singletons originating from twin pregnancies).[32] It has also been found that the risk for preterm birth increases with low-technology treatments, compared with natural pregnancy, and increases further with high-technology treatments.[33]

Zygosity plays a significant role when the health of IVF multiple births are compared with the health of other multiple births. In general, monozygotic twins have poorer perinatal outcomes than dizygotic twins. A larger proportion of twins are dizygotic among medically assisted pregnancies (30%), compared with naturally conceived pregnancies (1%).[34] This can partly explain the results of the similar outcomes of multiple births in studies unable to take zygosity into account. In our study, 50% of IVF twins and 30% of control twins were opposite-gender twins, which suggested that more IVF children were dizygotic.

During the 1990s, the perinatal health of IVF children improved in Finland, mainly because of a decrease in higher-order multiple births.[35,36] Because so many IVF pregnancies in the late 1990s were still multiple births, the health of IVF children in total was worse than that of naturally conceived children, with increased risks for CP and developmental and psychological problems. The best way to improve the health of IVF children is to favor single-embryo transfers. The way to improve the health of singletons is more problematic, because we do not know the reasons for the findings. Sufficiently large follow-up studies that consider the health of IVF children from 4 years onward are needed.

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Paper IV

Children born after assisted fertilization have an increased rate of major congenital anomalies

Reija Klemetti, M.H.Sc.,[a] *Mika Gissler, D.Phil.,*[b] *Tiina Sevón,*[a] *Sari Koivurova, M.D.,*[c] *Annukka Ritvanen, M.D.,*[b] *and Elina Hemminki, M.D. Dr. P.H.*[a]

[a] Health Services Research and [b] Information Unit, National Research and Development Centre for Welfare and Health (STAKES), Helsinki; and [c] Department of Obstetrics and Gynecology, University Hospital of Oulu, Oulu, Finland

Objective: To study the occurrence of major congenital anomalies (CAs) among children born after IVF (IVF, microinjections, and frozen embryo transfers) and after ovulation inductions with or without insemination (other assisted reproductive technologies [ART]).
Design: Register-based study.
Setting: Data regarding CAs were obtained from the Register of Congenital Malformations.
Patient(s): Children from IVF (n = 4,559), children from other ART (n = 4,467), and controls (n = 27,078, a random sample of naturally conceived children) from the Medical Birth Register.
Intervention(s): In vitro fertilization and other ART treatment in ordinary practice.
Main Outcome Measure(s): Rate of major CAs. Children from IVF and other ART were compared with control children, both overall and by plurality, controlling for confounding factors by logistic regression.
Result(s): For IVF children, the adjusted odds ratio (OR) was 1.3 (95% confidence interval [CI], 1.1–1.6). Stratifying by gender and plurality showed that the risk was only increased for boys, and the risk was decreased for multiple IVF girls (OR = 0.5, 95% CI 0.2–0.9). The crude OR of major CA for other ART children was 1.3 (95% CI 1.1–1.5), but adjusted differences by gender and plurality were statistically insignificant.
Conclusion(s): In vitro fertilization was associated with an increased risk for major CAs among singleton boys and a decreased risk among multiple girls. The risk after other ART was only slightly increased. (Fertil Steril® 2005;84:1300–7. ©2005 by American Society for Reproductive Medicine.)

Key Words: Major congenital anomaly, ART, register-based study

In vitro fertilization and its related procedures—intracytoplasmic sperm injection (ICSI)and frozen embryo transfer (FET)—have become common infertility treatments. For example, in Finland approximately 2.5% of all infants are born as a result of these therapies (1). The exact number of children born after other assisted reproduction technologies (ART), such as ovulation inductions and inseminations, is unknown, but according to our estimation during 1996–1999 2.4% of all infants were born after other ART in Finland.

Some studies (2–9) but not others (10–13) have shown an increase in some congenital anomalies (CAs) among IVF or ICSI children. Most published studies have had methodological problems, such as small sample sizes, lack of proper controls, and different definitions of CA among IVF and naturally conceived children. In a recent Australian study, the rate of musculoskeletal, cardiovascular, chromosomal, and urogenital defects was increased among IVF children (7). In a small Finnish study, the prevalence of heart malformations was fourfold among IVF infants compared with control infants (8). We found only one study on malformations of children born as a result of other ART (14). There were increased rates of congenital malformations, but these could be mainly explained by maternal characteristics.

In this study, we compared the prevalence of major CAs among IVF and other ART children with that among naturally conceived children, controlling for confounding factors. The data source of CAs was the same for all children—the Finnish Register of Congenital Malformations (RCM)—and we have information regarding the drugs used in the infertility therapy.

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Reprint requests: Reija Klemetti, M.H.Sc., STAKES, Health Services Research, P.O. Box 220, Helsinki 00531, Finland (FAX: 358-9-3967-2496; E-mail: reija.klemetti@stakes.fi).

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MATERIALS AND METHODS

The study is based on children born to women having received IVF (IVF, ICSI, and FET) and other ART between 1996 and 1998 in Finland. The women were identified with a predesigned algorithm from the reimbursement files of the Social Insurance Institution (15) and linked to the Finnish Medical Birth Register (MBR); the time difference between the beginning of the last treatment cycle and the birth of the child was used to estimate which infants resulted from IVF or other ART (16).

The MBR includes the mother's and child's unique personal identification numbers and contains information on maternal background and on the infant's outcome until the age of 7 days for all infants born in Finland. The duration and causes of infertility are not registered. The data are collected by delivery hospitals and completed by linkage to the Central Population Register and the Cause-of-Death Register. The quality of the MBR has been found to be high for the variables used in this study (17, 18).

We identified 4,559 IVF and 4,467 other ART children born between October 1996 and September 1999. As controls, 27,078 naturally conceived children (three times the number of cases) were selected randomly from the MBR, excluding children having a note of IVF or other ART in MBR. Children from ICSI (n = 861) could be distinguished from IVF children only if the treatment had been given in private clinics because a specific code for ICSI exists only there.

The identified children were linked to the RCM according to the mothers' identification numbers and the childrens' dates of birth. The RCM collects information on all infants with a CA or birth defect through several data sources, including a form completed by delivery hospitals, neonatal, pediatric, and pathology departments, and cytogenetic laboratories and by linkage to several other nationwide registers. More than 99% of the major CAs are registered before the age of 1 year.

In the RCM a CA has been defined as a major congenital structural anomaly, chromosomal defect, or congenital hypothyroidism involved in a birth. The register records all notified cases, but the physician responsible for RCM routinely classifies congenital anomalies into major, other, and rejected. Rejected anomalies include some minor congenital anomalies, as defined by the European Surveillance of Congenital Anomalies (European Concerted Action on Congenital Anomalies and Twins [EUROCAT]; http://www.eurocat.ulster.ac.uk) exclusion list (hereditary diseases, dysfunction of organs or tissues, developmental disabilities, congenital infections, isolated minor dysmorphic features, normal variations, and other less significant anomalies). For this study, the physician reviewed all diagnosis and inclusion criteria without knowing the mode of conception of the children.

The study plan was approved by the National Research and Development Centre for Welfare and Health (STAKES) research ethics committee. For register linkages, the National Data Protection Authority was consulted and permissions from the register keepers were obtained.

The differences were tested by *t*-test, a test for relative proportions, and a χ^2 test. The statistical analyses were performed in SAS, version 8 (SAS Institute, Cary, NC). The IVF and other ART children were compared with the control children according to odds ratios (OR) and 95% confidence intervals (CI), stratifying by gender and multiplicity. Twins and triplets were analyzed separately. Differences in age of the mother, parity, socioeconomic position (measured from maternal occupation), and the region of residence were controlled by logistic regression.

In the analysis by organ system, a child appeared more than once if (s)he had more than one major CA affecting different organ systems. Different CAs in the same organ system were calculated as one, but if the child had a major CA both in the urinary and genital system, only one was taken into account by combining these two groups as the "urogenital system." Only major CAs, as defined in the RCM, were included in the analysis, but minor urinary and genital CAs were separately compared between studied groups.

To investigate which of the infertility drugs used in the treatment were related to CAs, a nested case–control design in the IVF and other ART cohorts was used: mothers of children with CAs were compared with mothers of nonmalformed children. Drugs used during the last IVF cycle preceding the birth were classified into five groups: GnRH, FSH, hCG, progesterones (Ps) (among IVF women 99% and among other ART women 50% were natural Ps), and estrogens (Es), and the age-adjusted ORs for using at least one of the drugs from the category were calculated.

To estimate the total prevalence of major CAs, we linked the IVF and other ART women to the Register of Induced Abortions, specifying induced abortions performed because of a suspected or confirmed CA. The rates were compared with the national rates per 10,000 births.

RESULTS

In vitro fertilization and other ART mothers differed from control mothers, and IVF mothers from other ART mothers in regard to most characteristics (Table 1). Multiplicity was much higher in the IVF than in the other ART group, but the number of triplets was the same (16 vs. 17).

Among IVF and other ART children, 51% of reported major CAs had been accepted by the RCM, whereas among control children the proportion was 46%. In total, 195 IVF children (4.3%), 166 other ART children (3.7%), and 787 control children (2.9%) had at least one major CA. The prevalence of a major CA was the same for IVF singletons and IVF multiples but much higher for multiples than for singletons among other ART and control children (Table 2).

TABLE 1

Characteristics of IVF, other ART, and control mothers and children by multiplicity and gender.

	IVF	Other ART	Controls
Mothers	n = 3,737	n = 4,188	n = 27,022
Age (y) (mean ± SD)[a]	33.9 ± 4.5	31.2 ± 4.6	29.8 ± 5.3
Age (y)[b]			
<25	2.2	8.3	19.7
25–29	17.3	34.1	32.2
30–34	40.6	37.2	31.4
35–39	30.1	16.4	13.5
40+	9.8	4.0	3.1
Married[c]	76.1	74.8	60.5
Parity[b]			
0	71.7	54.3	38.7
1	21.1	32.4	33.4
2	4.2	9.3	16.4
3+	2.4	3.3	10.1
Missing	0.6	0.7	1.4
Socioeconomic position[b]			
Upper white-collar	26.1	21.2	15.7
Lower white-collar	48.8	47.8	41.3
Blue-collar	12.8	13.9	16.6
Other	12.3	17.2	26.4
Place of residence[b]			
Southern Finland	44.8	38.6	40.6
Western Finland	33.4	38.3	34.4
Eastern Finland	9.9	9.5	10.4
Northern Finland	11.6	13.3	13.9
Missing	0.3	0.3	0.7
Children	n = 4,459	n = 4,467	n = 27,078
Singletons	64.3	87.9	97.8
Girls	32.7	42.8	48.6
Boys	31.6	45.1	49.3
Multiples	35.7	12.1	2.2
Girls	17.6	6.0	1.2
Boys	18.1	6.0	1.0

Note: Values are percentages, unless otherwise noted.

[a] $P<.001$, *t*-test.

[b] $P<.001$ for all comparisons (IVF vs. other ART, IVF vs. controls, and other ART vs. controls), χ^2 test.

[c] $P<.001$ (IVF vs. controls and other ART vs. controls), test for relative proportions.

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Boys from IVF, both singletons and multiples, had major CAs more often than IVF girls (Table 3). The same was seen among multiples from other ART.

An increased OR for having any major CA was found in the crude analysis both for IVF and other ART children (Table 3). The adjustment for maternal age or other confounding factors somewhat decreased the ratio for IVF children but not for other ART children. The total risk for singletons was statistically significantly increased and for multiples insignificantly decreased. A significantly increased OR was found among singleton IVF boys, and a significantly decreased OR for multiple IVF girls. The result did not change after taking into account the confounding factors. In the separate analysis for twins, excluding triplets, the results for IVF girls remained similar (the adjusted OR was 0.31, 95% CI 0.11–0.88).

In the analysis by different organ system, compared with controls, IVF children had a higher risk for CA for most categories. Compared with other ART children, IVF children had more CAs in the categories of "eye, ear, face, and neck,"

TABLE 2

Prevalence of major congenital anomalies per 10,000 infant by the organ system affected.[a]

	Singletons								Multiples							
	IVF (n = 2,930)			Other ART (n = 3,926)			Controls (n = 26,489)		IVF (n = 1,629)			Other ART (n = 541)			Controls (n = 589)	
	n	/10,000	*P*[b]	n	/10,000	*P*[b]	n	/10,000	n	/10,000	*P*[b]	n	/10,000	*P*[b]	n	/10,000
Any	125	427	<.001	138	352	.022	756	285	70	430	.335	27	499	.836	31	526
Central nervous system	9	31	.008	12	31	.003	31	12	9	55	.071	7	129	.006	0	0
Eye, ear, face and neck	12	41	.009	6	15	.693	48	18	5	31	.583	1	18	.952	1	17
Heart	44	150	.042	59	150	.021	287	108	33	203	.791	11	203	.840	13	221
Other circulatory system	6	20	.740	12	31	.088	47	18	2	12	.790	0	0	.338	1	17
Respiratory system	5	17	.284	5	13	.647	27	10	3	18	.496	0	0	.175	2	34
Cleft palate and cleft lip	12	41	.034	14	36	.076	56	21	5	31	.904	0	0	.175	2	34
Digestive system	14	48	.028	16	41	.083	67	25	5	31	.093	4	74	.836	5	85
Urogenital system	35	119	<.001	26	66	.150	129	49	12	74	.789	4	74	.836	5	85
Musculoskeletal system	34	116	.004	30	76	.588	182	69	20	123	.270	6	111	.441	4	68
Skin, hair and nails	1	3	.533	2	5	.757	17	6	2	12	.395	0	0	NA	0	0
Chromosomal anomalies	8	27	.304	7	18	.927	49	18	3	18	.496	2	37	.932	2	34
Other congenital anomalies and the defects	12	41	.171	19	48	.020	71	27	9	55	.237	3	55	.381	6	102

Note: NA = not applicable.

[a] n = number of children. If a child had a major malformation in more than one organ system, the child appears several times in the table. If the malformations affect the same organ system, the child appears only once in the table.

[b] Test for relative proportions, control group as a reference group.

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TABLE 3

Total risk of major congenital anomalies and risk according to organ system affected[a] by gender and multiplicity.

		Risk								
		Girls			Boys			Total		
Multiplicity	Group	n[b]	OR (95% CI)	OR[c] (95% CI)	n[b]	OR (95% CI)	OR[c] (95% CI)	n[b]	OR (95% CI)	OR[c] (95% CI)
Singletons										
Total	Control	348	1.00	1.00	408	1.00	1.00	756	1.00	1.00
	IVF	48	1.23 (0.90–1.66)	0.97 (0.69–1.36)	77	1.79 (1.40–2.30)	1.63 (1.23–2.15)	125	1.52 (1.25–1.84)	1.30 (1.05–1.61)
	Other ART[d]	67	1.34 (1.02–1.74)	1.21 (0.98–1.67)	71	1.16 (0.90–1.50)	1.12 (0.86–1.46)	138	1.24 (1.03–1.49)	1.17 (0.97–1.41)
Heart	Control	128	1.00	1.00	136	1.00	1.00	264	1.00	1.00
	IVF	17	1.17 (0.71–1.95)	1.05 (0.62–1.78)	19	1.30 (0.80–2.11)	1.21 (0.73–2.00)	36	1.24 (0.87–1.75)	1.13 (0.79–1.62)
	Other ART	29	1.57 (1.04–2.35)	1.52 (1.01–2.28)	24	1.17 (0.76–1.81)	1.17 (0.75–1.81)	53	1.36 (1.01–1.83)	1.33 (0.99–1.80)
Urogenital	Control	52	1.00	1.00	80	1.00	1.00	26	1.00	1.00
	IVF	9	1.53 (0.75–3.11)	1.47 (0.70–3.07)	22	2.57 (1.60–4.14)	2.46 (1.49–4.07)	31	2.14 (1.44–3.17)	2.05 (1.36–3.10)
	Other ART	4	0.53 (0.19–1.46)	0.52 (0.19–1.45)	20	1.66 (1.02–2.72)	1.62 (0.99–2.65)	24	1.23 (0.79–1.90)	1.20 (0.78–1.87)
Musculosceletal	Control	72	1.00	1.00	110	1.00	1.00	182	1.00	1.00
	IVF	11	1.35 (0.72–2.55)	1.26 (0.65–2.44)	23	1.95 (1.24–3.07)	1.75 (1.09–2.81)	34	1.70 (1.17–2.45)	1.55 (1.05–2.27)
	Other ART	12	1.15 (0.62–2.12)	1.11 (0.60–2.05)	18	1.09 (0.66–1.79)	1.04 (0.63–1.72)	30	1.11 (0.76–1.64)	1.07 (0.73–1.58)
Multiples										
Total	Control	18	1.00	1.00	13	1.00	1.00	31	1.00	1.00
	IVF	26	0.55 (0.30–1.02)	0.45 (0.22–0.93)	44	1.13 (0.60–2.14)	1.31 (0.64–2.71)	70	0.81 (0.52–1.25)	0.80 (0.48–1.32)
	Other ART	7	0.44 (0.18–1.08)	0.41 (0.16–1.05)	20	1.59 (0.77–3.26)	1.56 (0.71–3.42)	27	0.95 (0.56–1.61)	0.91 (0.52–1.61)
Total	Control	366	1.00	1.00	421	1.00	1.00	787	1.00	1.00
	IVF	74	1.19 (0.93–1.54)	0.97 (0.73–1.28)	121	1.77 (1.44–2.17)	1.66 (1.31–2.10)	195	1.49 (1.27–1.75)	1.31 (1.10–1.57)
	Other ART	75	1.26 (0.98–1.62)	1.15 (0.89–1.50)	91	1.30 (1.03–1.64)	1.26 (0.99–1.59)	166	1.28 (1.08–1.52)	1.21 (1.02–1.44)

[a] Reference group (OR = 1) = control children. If a child had a major CA in more than one organ system, the child appears several times in the table. If the CAs affect the same organ system, the child appears only once in the table.

[b] n = number of malformed children.

[c] For all major CAs adjusted by age, parity, socioeconomic position, and region, and for some specific anomalies according to organ system adjusted only by age owing to the small number of cases.

[d] One other ART child excluded owing to missing gender status.

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TABLE 4

Major genital anomalies (and all hypospadias) among singleton boys: number and rate per 10,000.

	IVF (n = 1,440)	Other ART (n = 2,014)	Controls (n = 13,339)
Total			
No.	11	6	15
Rate	76	30	11
P[a]	<.001	.036	
Hypospadias			
No.	7	3	10
Rate	15	7	4
P[a]	<.001	.287	
All hypospadias[b]			
No.	11	8	38
Rate	76	40	29
P[a]	.003	.390	

[a] Test for relative proportions, compared with controls.
[b] Also includes glandular hypospadias.

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"respiratory system," "urogenital system," and "musculoskeletal system." When stratifying the analysis to singletons and multiples (Table 2), IVF singletons had statistically significantly more major CAs than control singletons in many categories. Among multiples the rates were the opposite: in most categories, IVF multiples had fewer major CAs than control multiples, and none of the differences were statistically significant. Among other ART children, singletons had more and multiples had fewer CAs in most organ systems than control singletons, but the differences were not as clear as that between IVF and control children.

When inspecting the risk according to the organ system affected, by gender and multiplicity, we found a slightly increased OR for major heart anomalies among singleton other ART girls and increased ORs for urogenital and musculoskeletal CAs among singleton IVF boys (Table 3). The results remained the same after adjustment for age. Among IVF singleton boys, major urogenital CAs were more severe than among controls. When we checked for minor urogenital CAs of singleton boys, no reported minor urinary CA was observed. In the separate analysis of urinary and genital CAs, it was found that the increased risk was mainly due to the genital CAs. Hypospadia was the most common diagnosis of these major genital anomalies, and control boys had more minor hypospadias than IVF boys (Table 4). In addition, other ART singleton boys had a higher risk for urogenital CAs. No specific musculoskeletal CA among IVF boys was found.

Out of 861 ICSI children, 40 (4.6%) had one or more CA. The frequency of major CAs was in general as among all IVF children. Because of the small number of cases, a more specific analysis of the ICSI group was not done.

By definition, all IVF mothers were exposed to some infertility drugs, most commonly to P (Table 5). Most mothers were exposed to several drugs. Only Es were used more often by the mothers of malformed than by the mothers of

TABLE 5

Drugs used by mothers of malformed and nonmalformed children.

Group	Malformed[a]	Non-malformed	*P*[b]
IVF[c]	n = 179	n = 4,088	
P	87	88	.736
FSH or hMG	59	63	.241
GnRH	55	62	.050
hCG	17	20	.286
E_2	20	12	.003
Other ART	n = 166	n = 4,301	
Clomiphene citrate	81	86	.056
P	30	30	.896
FSH or hMG	14	11	.250
hCG	5	4	.598

Note: Values are percentages.
[a] At least one major congenital anomaly.
[b] Comparisons of malformed and nonmalformed groups, test for relative proportions.
[c] Two hundred ninety-two IVF children are excluded owing to the lack of information on drugs used.

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nonmalformed IVF children, but mothers of most malformed children had not received it. Some 27% of the mothers of singleton boys with a genital CA had used Es (vs. 13% of mothers of nonmalformed singleton boys) and 82% P (vs. 82% of mothers of nonmalformed singleton boys). Among other ART children, no differences in the drugs used between malformed and nonmalformed children were found, neither in the use of a natural nor a synthetic progestin.

During the study period, 9 of the 9,175 IVF women (19.7 per 10,000 IVF births) and 8 of the 10,270 other ART women (17.9 per 10,000 other ART births) had an induced abortion owing to the suspected or detected fetal defect. The national rate per 10,000 births in 1996–1998 in Finland was 36.7 (The Finnish Medical Birth Register).

DISCUSSION

We found increased total rates of major CAs for IVF and other ART singletons. Singleton boys from IVF in particular had more major urogenital and musculoskeletal CAs, and other ART singleton girls had more major heart anomalies. Among multiples, the total risk for a major CA was not increased, and for multiple IVF girls the risk had even decreased.

Can our results be trusted? Our data include most infants born as a result of IVF and other ART in Finland during the study period. The identification was based on drugs used in infertility therapy and reimbursed treatments (only private clinics) (15, 16). It is possible that we missed some women who had received their treatment in the public sector and had used drugs bought and reimbursed before 1996. We have estimated that our data lack approximately 4% of IVF women and 6% of other ART women (15), but the identification of the women was made before pregnancy and is unlikely to relate to the occurrence of major CAs.

Data on major CAs in all three groups came from a routine nationwide register, the RCM, to which information is collected and classified blindly with regard to IVF or ART status. However, we do not know whether physicians who reported CA to the register knew the mode of conception. It could be that IVF children were more carefully examined and/or that CAs for them were more conscientiously reported than those for naturally conceived children. However, the fact that more reports that were rejected by the RCM occurred for control children than for IVF children speaks against this source of bias. Likewise, the checking of minor genital anomalies showed that the number of reported minor CAs of IVF children was smaller than that of controls. One could have expected it to be greater if the IVF and other ART children had been more carefully examined and reported. The types of genital anomalies suggest that classification into major CAs has been clear-cut.

We do not have information regarding induced abortions of the naturally conceived children's mothers or of major CAs among them. However, the rates of induced abortions due to CAs were so low that they are unlikely to bias the results.

According to previously published studies, twins have more CAs than singletons (19). That was also true among control children in our study but not among IVF children, which is in accordance with the results from a recent Danish study of IVF and ICSI twins, in which no differences in malformation rates between IVF/ICSI and naturally conceived twins were found (20). What, therefore, could explain this discrepancy between multiples and singletons? One explanation could be the fact that many singletons originated from multiple ET and from multiple pregnancy with a higher risk (during the study period 15% of ETs [IVF, ICSI, and FET] were single-embryo transfers, but 88% of live births were singleton births [21]). If two embryos succeed during implantation and develop in assisted reproduction, it can be assumed that conditions have to have been especially favorable.

Another possible explanation is zygocity: monozygotic twins have more malformations than dizygotic, and monozygosity is rarer among twins of assisted reproduction than among naturally conceived twins (1% vs. 30%) (22). Although IVF and other ART increase monozygotic twinning (6, 14), transfer of several embryos causes the majority of IVF twins to be dizygotic. The fact that the CA rate was not smaller among IVF twin boys could result from a higher risk of CA among IVF boys.

Most hormones in IVF treatment are used before pregnancy, and the half-life of most of these drugs is short. However, the duration of active drugs and metabolites in the body and their individual variations are not clear. Some drugs are also used as luteal-phase support during pregnancy. In addition to direct toxic effect, the drugs might have their effect through the mother's hormonal secretion balance. Although the dangers of hormones in early pregnancy have been discussed for decades (23, 24), this has not been the focus when the health effects of IVF have been discussed. We had information regarding fertility drugs (dosages and number of packages) bought, but the exact date and duration of their use was not known. Because the treated women received many and varied medicines during the last cycle, it was not possible to identify any specifically harmful drug.

Our study verified an earlier result of the overall risk for urogenital CAs (7), but ours was too small to study the risk of individual diagnoses, such as the hypospadia previously reported (6, 25). The use of P during IVF treatment has been offered as one explanation for the increased risk of one genital CA, hypospadia (25). Children exposed in utero to E and P or only P were found to have more male genital malformations than nonexposed children (23). However, in our study no difference in P use was found among boys with major genital anomalies and other IVF boys. Instead, E use was more frequent, but most boys with genital CAs were not exposed to it.

Another explanation for the higher rate of male genital anomalies might be the hereditary paternal subfertility associated with ICSI (5). Unfortunately, we could identify ICSI children only when the treatment was given in a private clinic. Because of the possible bias and the small number of children, we did not study specific CAs of ICSI children. Because the genital CAs were more severe among IVF than among control children, the risk for major urogenital CAs could be greater than our results show. The risk was also somewhat increased among other ART boys.

In another Finnish study, IVF children had more heart anomalies than control children (8). This was also true in our study, but the risk was not statistically significant. Rather, it was found among other ART children. This might relate to the use of clomiphene citrate (14). The increased risk for musculoskeletal CAs among IVF children is in accordance with a previous study from Australia (7).

Other than drugs, potential causes for congenital anomalies could include infertility itself, the advanced age of mothers, and factors related to the IVF procedure, such as the freezing and thawing of embryos. We did not have any information about the duration and causes of infertility and could not adjust data for them. The higher age of mothers did not explain the increased risk for major CAs.

In conclusion, our study verifies an increased risk for major CAs among IVF singleton boys and suggests that the risk after other ART is also slightly increased and not explained by those maternal characteristics available in the Finnish MBR. The actual risk is, however, quite small. Because our findings regarding different organ systems are based on small numbers of children, further studies are needed to explain them. It would be important to perform a large follow-up study of IVF and other ART births which includes information on the duration and causes of infertility, exact information regarding maternal drug exposure, and other maternal background characteristics. Meanwhile, the techniques used in IVF and other ART should be considered potentially teratogenic, thus requiring that information be given to the physicians and the public.

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Paper V

Equity in the resource allocation of in vitro fertilization

Klemetti R, Gissler M, Sevón T, Hemminki E.

Abstract

Background: The purpose of this study was to describe equity in the allocation of resources for in vitro fertilization (IVF) by women's age and socioeconomic position.
Methods: Women who received IVF between 1996 and 1998 (N=9175) were identified from the reimbursement records of the Social Insurance Institution (SII). Information on IVF women's background characteristics came from the Central Population Register and the SII, on treatment costs from IVF clinics and the SII, and on births from the Medical Birth Register.
Results: During a mean period of 1.5 years, older women received 1.4 times more IVF treatment cycles than younger women. The success rate—live births per cycle—decreased by age: from 22% among women aged below 30 to 6% among women aged 40 or older. The mean cost of a live birth increased by age from EUR 12 851 to EUR 40 662. Calculated by population, society contributed most to women from the highest socioeconomic position.
Conclusions: Our study suggests that women from higher socioeconomic position are favoured in resource allocation. Children of older women are more expensive, but equality of services cannot be judged because we have no information on need for IVF by age.

Key words: costs / equity / expenditures / in vitro fertilization / resource allocation

The research presented in this series has been approved
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Klemetti Reija. The Use of Assisted Fertilization in Finland: Health Effects and Equity [Hedelmöityshoitojen käyttö Suomessa: Terveysvaikutukset ja oikeudenmukaisuus] STAKES, Research Reports, 158. Helsinki, 2006. ISBN 951-33-1912-1

Tutkimuksen taustaa: Koeputkihedelmöitys (IVF, joka sisältää mikroinjektion ja pakastetun alkion siirron) ja munasarjojen lääkkeellinen induktio (OI, johon voi sisältyä keinosiemennys) ovat yleisiä hedelmöityshoitoja Suomessa. Niiden käytöstä ja terveysvaikutuksista hoitoja saaneille naisille ja hoitojen jälkeen syntyneille lapsille ei kuitenkaan vielä tiedetä riittävästi. Oikeudenmukaisuus on suomalaisessa terveydenhuollossa määritelty siten, että samanlaisessa tarpeessa olevilla on samanlainen mahdollisuus päästä hoitoon ja saada hoitoa. Terveydenhuoltoon käytettävien resurssien tulisi jakautua oikeudenmukaisesti sukupuolen, iän, asuinalueen ja sosioekonomisen aseman suhteen. IVF on kallis hoito, jossa naisen iän lisääntymisen myötä onnistuminen laskee. Samoin äidin ja lapsen terveysongelmien riski kasvaa.

Tutkimuksen tarkoitus: Tämän tutkimuksen tarkoituksena on useita terveydenhuollon rekistereitä käyttäen selvittää IVF:n ja OI:n käyttöä, sairaalahoitoon johtaneita komplikaatioita ja keskenmenoja hoitoja saaneilla naisilla, hoitojen jälkeen syntyneiden lasten terveyttä ja kuvata IVF-hoitoihin käytettyjen resurssien jakautumista hoitoja saaneiden naisten iän ja sosioekonomisen aseman sekä hoitosektorin (yksityinen tai julkinen) mukaan sekä pohtia IVF:n käytön ja resurssien jaon oikeudenmukaisuutta.

Tutkimusaineisto ja menetelmät: Tässä rekisteripohjaisessa tutkimuksessa IVF-hoitoja (N = 9175) ja OI-hoitoja (N = 10 254) vuosina 1996–1998 saaneet naiset identifioitiin Kelan lääke- ja toimenpidekorvausrekistereistä ja heitä seurattiin vuoteen 2000 yhdistämällä aineisto hoitoilmoitus- ja kuolinsyyrekistereihin. IVF-naisille valittiin iän ja asuinpaikan suhteen kaltaistetut vertailunaiset (N = 9175). IVF:n (N = 4559) ja OI:n (N = 4467) jälkeen syntyneet lapset identifioitiin syntymärekisteristä, josta heille poimittiin vertailulapset (kaikki muut lapset, N=190 398, tutkittaessa vastasyntyneisyysajan terveyttä, sairaalahoitoja ja kuolleisuutta, ja satunnaisotos näistä lapsista, n = 26 877 tutkittaessa synnynnäisiä epämuodostumia ja pitkäaikaissairaiden lasten hoitotukia ja korvattuja lääkkeitä). Lapsia seurattiin vuoden 2003 loppuun yhdistämällä aineisto hoitoilmoitus-, epämuodostuma- ja kuolinsyyrekisteriin sekä Kelan rekistereihin. Naisten taustatiedot saatiin Kelasta ja Väestörekisteristä ja hoitojen korvaus- ja kustannustiedot Kelasta ja hoitoja antavilta klinikoilta.

Tulokset: Keskimääräisen 1,5 vuoden seurannan aikana vanhimmat, 40 vuotta täyttäneet naiset, saivat hieman enemmän IVF-hoitosyklejä kuin nuorimmat, alle 30-vuotiaat naiset (2,2 vrt. 3,0). Yksityissektorilla oli julkista sektoria enem-

män korkeammassa sosioekonomisessa asemassa olevia IVF-hoitoja saaneita naisia. Nämä naiset saivat muita enemmän IVF-syklejä. IVF-hoitojen onnistuminen – elävänä syntyneiden lasten lukumäärä IVF-syklejä kohti – laski naisen iän myötä: 22 % alle 30-vuotiailla ja 6 % yli 40-vuotiailla.

IVF:n jälkeen 23 ja OI:n jälkeen yksi tuhannesta naisesta joutui tutkimusajankohtana (keskimäärin 2,7 hoitoa) sairaalaan munasarjojen hyperstimulaatiosyndrooman (OHSS) takia. Sekä IVF:n että OI:n jälkeen sairaalahoitoon johtaneita keskenmenoja oli 42 tuhatta hoidettua naista kohti. Noin 15 % IVF-naisista ja 8 % OI-naisista joutui komplikaatioiden tai keskenmenon takia ainakin kerran sairaalahoitoon seurannan aikana.

IVF-lasten vastasyntyneisyysajan terveys oli huonompi ja sairaalahoito yleisempää kuin muilla lapsilla. IVF-lapsilla oli kohonnut riski CP-vammaisuuteen (OR-luku 2.9 ja 95 % luottamusväli 1.6–5.3), psykologisiin ja kehityksellisiin häiriöihin (1.7, 1.1–2.5) sekä synnynnäisiin merkittäviin epämuodostumiin (1.3, 1.1–1.6). Tulokset selittyivät osin monisikiöisten raskauksien suurella määrällä. IVF-yksösillä oli muita yksösiä huonompi vastasyntyneisyysajan terveys, enemmän sairaalahoitoja ja pojilla kohonnut synnynnäisten epämuodostumien riski. IVF-kaksosten ja -kolmosten terveys oli samanlainen kuin muilla kaksosilla ja kolmosilla.

Keskimääräiset kokonaiskustannukset elävänä syntynyttä IVF-lasta kohti lisääntyivät naisen iän myötä 12 851 eurosta (alle 30-vuotiaat) 40 662 euroon (40 vuotta täyttäneet). Väestökohtaisesti laskettuna (kutakin ikäluokkaa ja sosioekonomista asemaa kohti) yhteiskunnan resursseja käytettiin eniten 30–39-vuotiaiden naisten ja korkeimmassa sosioekonomisessa asemassa olevien naisten hoitamiseen. Alueelliset erot olivat pieniä.

Johtopäätökset: Vaikka suurin osa IVF-lapsista oli terveitä, heillä oli enemmän terveyteen liittyviä ongelmia kuin muilla lapsilla. Yksittäiseen IVF-sykliin liittyvien komplikaatioiden riski oli pieni, mutta useampien hoitosyklien antaminen johti vakaviin komplikaatioihin useilla naisilla; IVF:n jälkeen selvästi useammin kuin OI:n jälkeen. Lisätutkimuksia tarvitaan selvittämään IVF- ja OI-naisten ja heidän lastensa pidemmän ajan terveyttä. Tutkimuksessa ei ollut tietoa hoidon tarpeesta eli hedelmättömyyden yleisyydestä eikä toiveesta saada lapsi, joten ei voi varmasti sanoa, suositaanko hedelmöityshoidoissa tietyn ikäisiä naisia. Korkeammat kustannukset, suuremmat terveysriskit ja hoitojen huonompi onnistuminen vanhemmilla naisilla puoltavat keskittymistä nuorempien, hedelmällisessä iässä olevien naisten hoitamiseen. Erot sosioekonomisen aseman suhteen IVF:n käytössä ja resurssien jaossa voivat kertoa epäoikeudenmukaisuudesta.

Avainsanat: koeputkihedelmöitys, ovulaation induktio, rekisteritutkimus, terveysvaikutukset, komplikaatiot, OHSS, lasten terveys, synnynnäiset epämuodostumat, kustannukset, oikeudenmukaisuus

SAMMANFATTNING

Klemetti Reija. The Use of Assisted Fertilization in Finland: Health Effects and Equity [Användningen av assisterad befruktning i Finland: Hälsoeffekter och rättvisa.]STAKES, Research Reports, 158. Helsingfors, Finland, 2006. ISBN 951-

Bakgrund till undersökningen: In vitro fertilisering (IVF, som omfattar en mikroinjektion och överföring av ett fryst embryo) och medicinsk ovulationsinduktion (OI, som kan omfatta artificiell insemination) är vanliga fertilitetsbehandlingar i Finland. Om deras användning och hälsopåverkan på kvinnorna som fått behandling och på barnen som föds efter behandlingen vet man dock tillsvidare inte tillräckligt. Rättvisa har inom den finländska hälso- och sjukvården definierats så, att de som har samma behov har samma tillgång till vård och samma möjlighet att få vård. De resurser som används för hälso- och sjukvård borde fördelas rättvist i förhållande till kön, ålder, bostadsort och socioekonomisk ställning. IVF är en dyr behandling, och med ökad ålder hos kvinnan minskar behandlingens utfall. Samtidigt ökar risken för hälsoproblem hos modern och barnet.

Syftet med undersökningen: Syftet med denna undersökning är att med hjälp av flera av hälso- och sjukvårdens register utreda användningen av IVF och OI, komplikationer och missfall som lett till sjukhusvård hos kvinnor som erhållit behandlingar och hälsan hos barn som fötts efter behandlingarna samt att beskriva fördelningen av de resurser som använts för IVF-behandlingar i förhållande till de behandlade kvinnornas ålder och socioekonomiska ställning samt vårdsektor (privat eller offentlig). Syftet är även att bedöma användningen av IVF och rättvisan i fördelningen av resurserna.

Undersökningsmaterial och metoder: I denna registerbaserade undersökning identifierades kvinnor som fått IVF-behandling (N = 9175) och OI-behandling (N = 10 254) under åren 1996–1998 i Folkpensionsanstaltens (FPA) register över ersättningar för läkemedel och åtgärder, och kvinnorna följdes upp till år 2000 genom att materialet sammanställdes med vårdanmälnings- och dödsorsaksregistren. För IVF-kvinnorna valdes en kontrollgrupp av kvinnor (N = 9175) som matchades utifrån ålder och bostadsort. Barnen som fötts efter IVF (N = 4559) och OI (N = 4467) identifierades i födelseregistret, från vilket en jämförelsegrupp av barn valdes (alla övriga barn, N=190 398, vid undersökning av hälsan under perinataltiden, sjukhusvård och dödlighet, och ett slumpmässigt urval av barn, n = 26 877 vid undersökning av medfödda missbildningar och vårdstöd för långtidssjuka barn och ersättningar för läkemedel). Barnen följdes upp till slutet av år 2003 genom att materialet sammanställdes med vårdanmälnings-, missbildnings- och dödsorsaksregistren samt FPA:s register. Bakgrundsinformation om kvinnorna erhölls från FPA och Befolkningsregistret och uppgifterna om ersättningar och kostnader för behandlingarna från FPA och de kliniker som gav behandling.

Resultat: Under den i medeltal 1,5 år långa uppföljningstiden fick de äldsta kvinnorna, som fyllt 40 år, något fler IVF-behandlingscykler än de yngsta, under 30 år gamla kvinnorna (2,2 mot 3,0). Inom den privata sektorn fanns fler kvinnor med högre socioekonomisk ställning som fått IVF-behandling än inom den offentliga sektorn. Dessa kvinnor erhöll fler IVF-cykler än andra. Antalet lyckade IVF-behandlingar – antalet levande födda barn per IVF-cykel – minskade med kvinnans ålder: 22 % vid under 30 års ålder och 6 % vid över 40 års ålder.

Efter IVF togs 23 och efter OI en av tusen kvinnor under undersökningsperioden (i medeltal 2,7 behandlingar) in på sjukhus på grund av ovarialt överstimuleringssyndrom (OHSS). Efter både IVF och OI var frekvensen av missfall som ledde till sjukhusvård 42 per tusen behandlade kvinnor. Cirka 15 % av IVF-kvinnorna och 8 % av OI-kvinnorna togs minst en gång in på sjukhus på grund av komplikationer eller missfall under uppföljningen.

IVF-barnens hälsa under perinataltiden var sämre och sjukhusvård vanligare än för andra barn. IVF-barnen hade förhöjd risk för CP-skador (oddskvot 2,9 och 95 % konfidensintervall 1,6–5,3), psykologiska störningar och utvecklingsstörningar (1,7, 1,1–2,5) samt medfödda betydande missbildningar (1,3, 1,1–1,6). Resultaten förklaras delvis av det stora antalet flerbörder. IVF-enlingar hade sämre hälsa under perinataltiden än andra enlingar, mera sjukhusvård och pojkarna förhöjd risk för medfödda missbildningar. IVF-tvillingars och trillingars hälsa motsvarade andra tvillingars och trillingars.

De genomsnittliga totalkostnaderna per levande fött IVF-barn ökade med kvinnans ålder från 12 851 euro (under 30 år) till 40 662 euro (för 40 år fyllda). Beräknat i förhållande till befolkningen (för varje åldersgrupp och socioekonomisk grupp) användes mest av offentliga resurser för behandling av kvinnor i åldern 30–39 år och kvinnor i den högsta socioekonomiska ställningen. De regionala skillnaderna var små.

Slutsatser: Även om den största delen av IVF-barnen var friska, hade de fler hälsorelaterade problem än andra barn. Risken för komplikationer vid en enstaka IVF-cykel var liten, men flera behandlingscykler ledde till allvarliga komplikationer hos flera kvinnor; betydligt oftare efter IVF än efter OI. Ytterligare undersökningar krävs för att utreda hälsan för IVF- och OI-kvinnor och deras barn på längre sikt. I undersökningen fanns inte uppgifter om behovet av behandling, det vill säga hur allmän ofruktsamhet är, och inte heller om önskan att skaffa barn, varför man inte med säkerhet kan säga huruvida kvinnor av någon viss ålder favoriseras vid fertilitetsbehandlingar. De högre kostnaderna, de större hälsoriskerna och det sämre utfallet vid behandling av äldre kvinnor talar för koncentration på behandling av yngre kvinnor i fruktsam ålder. Skillnaderna i fråga om den socioekonomiska ställningen vid behandling med IVF och fördelningen av resurser kan vittna om orättvisa.

Nyckelord: Provrörsbefruktning, in vitro fertilisering, ovulationsinduktion, registerundersökning, hälsopåverkan, komplikationer, OHSS, barnens hälsa, medfödda missbildningar, kostnader, rättvisa

ABSTRACT

Klemetti Reija. **The Use of Assisted Fertilization in Finland: Health Effects and Equity,** STAKES, Research Reports, 158. Helsinki, Finland, 2006. ISBN 951-33-1912-1

Background: Though Assisted Fertilization (AF), consisting of in vitro fertilization (IVF, including intracytoplasmic sperm injection and frozen embryo transfer) and ovulation induction (OI with or without inseminations), is widely used as a treatment for infertility, not enough is known about its utilization and health effects. Equity in health care should mean equal access to care according to need and an equitable distribution of health care resources by gender, age, living area, and socioeconomic position. IVF is a costly treatment in which effectiveness and appropriateness decrease by women's age while need and complications increase.

Objective: The purpose of this study is to investigate via nationwide registers the use of AF, i.e. IVF and OI, the occurrence of serious complications and miscarriages of treated women, and the health of their children, as well as to describe equity in the allocation of resources to IVF by women's age and socioeconomic position and by the treatment sector (public vs. private). Finally, the aim is to discuss whether the usual criteria of equity apply to IVF.

Materials and methods: In this register-based study, women who received IVF (N=9175) and OI (N=10 254) between 1996 and 1998 were identified from the reimbursement records of the Social Insurance Institution (SII) that cover all Finns and were followed until 2000 by means of register linkages (The Hospital Discharge Register and The Cause-of-Death Register). Population controls, matched by age and municipality, were selected for IVF women (N = 9175). IVF women's children (N = 4559) and OI women's children (N = 4467) were identified from the Medical Birth Register (MBR) and followed until 2003 by using the Hospital Discharge Register, the Register of Congenital Malformations, the Cause-of-Death statistics, and reimbursements records of the SII. Two control groups were selected from the MBR: all other children from the same period (N = 190 398, for studying perinatal health, hospitalizations and mortality) and also a random sample of them (n = 26 877, for studying congenital anomalies (CAs) and health-related benefits). Information on treatment costs were received from IVF clinics and the SII.

Results: During a mean follow-up period of 1.5 years, older women received 1.4 times more IVF treatment cycles than younger women (2.2 vs. 3.0). In the private sector, women in the highest socioeconomic position were over-represented and had more cycles than other women. The success rate—live-births per cycle—decreased by women's age: from 22% among women aged below 30, to 6% among women aged 40 or older.

After IVF, 23 per 1000 and after OI, 1 per 1000 women had a serious case of OHSS (ovarian hyperstimulation syndrome) during the study period (mean of 2.7 treatments). The rates of registered miscarriages after both IVF and OI were 42 per 1000 treated women. Overall, 15% of IVF and 8 % of OI women had at least one hospital episode during the study period.

Perinatal outcomes of IVF children were worse and hospital episodes were more common than among control children; odds ratios (OR) for cerebral palsy (2.9, 95% CI 1.6–5.3) and psychological and developmental disorders (1.7, 1.1–2.5) were increased as well as OR for congenital anomalies (1.3, 1.1–1.6). These results were partly explainable by the great number of twins among IVF children. Among IVF singletons, poorer results were found for perinatal outcomes and hospitalizations, while for singleton IVF boys an increased risk of major CAs were also found. The health of IVF multiples was comparable to the health of control multiples.

The mean cost of a live birth after IVF increased by women's age from EUR 12 851 among women aged under 30 to EUR 40 662 among women aged 40 or older. Calculated per population, society contributed most to the women aged 30–39 years and women from the highest socioeconomic position. Regional differences were not remarkable.

Conclusion: Although the health of most IVF children was good, they had more health problems than other children. The risk of complications for women after each IVF treatment cycle was low, but repeated attempts resulted in serious complications for many women, and these occurred much more often than after OI alone. Further studies are needed to examine the long-term health of IVF and OI women and their children. No information on the need for IVF and OI treatments, i.e. infertility rates and the wish for a child, was available in the study. It is therefore uncertain whether women from a certain age-group are favoured in treatments in Finland. Due to the higher costs, increased health risks and decreased IVF success for older women, concentrating on the treatment of younger women is a fairer solution than provision solely based on need. Socioeconomic differences in the use of IVF services and the allocation of resources may indicate inequality.

Key words: IVF, ovulation induction, health effects, register-based study, complications, OHSS, child health, perinatal health, congenital anomaly, equity, costs

CONTENTS

List of original publications

The present thesis is based on the following articles, which are referred to in the text by their Roman numerals:

I Klemetti Reija, Gissler Mika, Hemminki Elina.
Equity in the use of IVF in Finland in the late 1990s.
Scandinavian Journal of Public Health 2004;32:203–209.

II Klemetti Reija, Sevón Tiina, Gissler Mika, Hemminki Elina.
Complications of IVF and ovulation induction.
Human Reproduction 2005;20:3293–3300.

III Klemetti Reija, Sevón Tiina, Gissler Mika, Hemminki Elina.
Health of Children Born as a Result of In Vitro Fertilization.
Pediatrics 2006;118:1819–1827.

IV Klemetti Reija, Gissler Mika, Sevón Tiina, Koivurova Sari, Ritvanen Annukka, Hemminki Elina.
Children born after assisted fertilization have an increased rate of major congenital malformation.
Fertility & Sterility 2005;84:1300–1307.

V Klemetti Reija, Gissler Mika, Sevón Tiina, Hemminki Elina.
Equity in the allocation of resources in IVF (Submitted).

Abbreviations

AF = Assisted fertilization
ART = Assisted reproductive technologies
CA = Congenital anomaly
CI = Confidence interval
CP = Cerebral palsy
CPR = Central Population Register
FET = Frozen embryo transfer
HDR = Hospital Discharge Register
ICD = International Classification of Diseases
ICSI = Intra cytoplasmic sperm injection
IUI = Intra uterine insemination
IVF = In vitro fertilization
MBR = Medical Birth Register
OI = Ovulation induction with or without insemination
OHSS = Ovarian hyperstimulation syndrome
OR = Odds ratio
RCM = Register of Congenital Malformations
SII = Social Insurance Institution

1 Introduction

Involuntary childlessness was earlier considered a social problem and accompanied by social solutions such as foster children, adoption, changing partners, or accepting a life without children. When knowledge of human reproduction developed and medical reasons for childlessness were found, childlessness became a medical problem defined as infertility or impaired fertility. Efforts then began to solve this issue by medical means.

Ovulation has been induced with hormonal drugs since the 1950s. Insemination is documented to have been made even earlier, during the 18th century (Hovatta, 1989). The greatest innovation in medicine in resolving the problem of childlessness was, however, the development of in vitro fertilization (IVF); the first baby was born in 1978 in the United Kingdom (Steptoe and Edwards, 1978) and the first in Finland in 1984 (Malin Silverio and Hemminki, 1996). During the past 30 years, IVF has become a common infertility treatment. In 2002, between approximately 2.4% (in Norway) and 4.2% (in Denmark) of all infants in the Nordic countries were born following IVF, with the figure being some 2.9% in Finland (Nyboe Andersen et al., 2006). In the United States the proportion is about 1 % (CDC report, 2003) and in the United Kingdom 1.4% (Nyboe Andersen et al., 2006). In addition, in Denmark 2.3% of all infants were born as a result of intra uterine insemination in 2002 (Nyboe Andersen and Erb, 2006). The number of children born with the help of ovulation induction and/or insemination (called in this study OI) in Finland is unknown.

Although OI has been used for many decades and IVF has rapidly become a normal clinical practice, the related health effects have not been properly studied. For example, in Finland only a few studies have been published on the health of IVF infants (Gissler et al., 1995a, Isaksson, 2002, Klemetti et al., 2002, Koivurova, 2005), with one study on the health of children born after intrauterine insemination (Nuojua-Huttunen, 1999), and no studies on the complications of women following IVF and OI (Jokimaa, 2006).

In spite of a large number of international studies on the health of IVF newborns (Helmerhorst et al., 2004), little is known about the long-term health effects on children (Hampton, 2004) or the short and long-term health of OI children. Even though various adverse effects of IVF and OI on treated women have been identified, many of the published studies and reports are insufficient. They are

based on voluntary reporting or on a small number of cases or treatment cycles. Others concentrate on only one complication, or lack information on the severity of the complications.

IVF is a costly treatment and much is debated about recipients' eligibility (age, sexual orientation, and marital status), how it should be funded (private or public resources) and how to allocate the scarce health care resources in a fair way. It is generally believed that IVF is unevenly distributed by socioeconomic position and urban–rural areas. However, there is not great deal of reliable data on the use or users of IVF or OI.

In the present study, first the use of IVF and OI in Finland is examined by considering the factors of age, socioeconomic position, and area of residence of those women who have used infertility treatments. Second, the safety of IVF and OI is studied by considering the complications and miscarriages of IVF and OI women as well as the health of IVF children. Hospitalization during pregnancy and childbirth as well as frequency of Caesarean sections could be studied, but data on other pregnancy outcomes were not available in this study. An identical study on the health of OI children has been done, but these results will be published separately and are not presented in this study. The results of congenital anomalies of OI children have already been published, while OI children are in this study also used as a control group—along with children born to infertile women treated with other infertility treatments than IVF—for IVF children; another control group was formed with naturally conceived children. Third, the success of IVF measured by live-births per number of cycles and per number of women is studied. Fourth, the costs of IVF treatment are estimated and the allocation of expenditures used in IVF is examined: how much is paid by Finnish society and how much by women themselves. Finally it is discussed how fairly the IVF resources are used in Finland.

2 Infertility and its treatment

2.1 Infertility

The prevalence of infertility is not easy to calculate due to the variable terminology used in reproductive medicine (Nguyen and Wilcox, 2005) and also the different definitions used in studies (Schimdt and Münster, 1995). It has been suggested that we avoid using the terms 'infertility, subfertility, and fecundity' and instead use the term 'reduced fertility' in different grades: from 0 (normal fertility) to grade 4 (sterility) (Habbema et al., 2004). Alternatively, it has been argued that the term 'subfertility' should be used and defined as any form of reduced fertility with prolonged time to successful conception (Gnoth et al., 2005). Because in this study it is not important to define different grades of reduced fertility, the term 'infertility' is used as a common term for involuntary childlessness. A common definition for infertility is an inability to achieve a pregnancy after regular unprotected intercourse within 12 months (Nguyen and Wilcox, 2005). The time limit in the definition was previously longer. In a guidebook for doctors (Therapia Fennica, 1975) the time limit was three years in 1975 and one year in the next edition in 1986 (Therapia Fennica, 1986). The World Health Organization still uses a definition of two years (WHO, 1997). It has been estimated that about 84–90% of couples conceive within one year (te Velde et al., 2000, Cahill and Wardle, 2002, Taylor, 2003, Habbema et al., 2004, Gnoth et al., 2005) and a half of the rest during the next year (te Velde et al., 2000). Thus, the definition has a great practical impact. About 5% of couples succeed in conceiving spontaneously "only sporadically" (Gnoth et al., 2005) or are "sterile couples" (Habbema et al., 2004). Furthermore, infertility is not only an inability to become pregnant but also a devastating personal experience (Greil, 1997). It can cause anxiety, stress and depression and affect the whole life spectrum: domestic and social lives as well as work.

According to population-based studies, infertility is common. In Finland, for example, 13–17% of women reported difficulties in trying to conceive within 12 months (Rantala and Koskimies, 1986, Notkola, 1995, Malin et al., 2001, Klemetti et al., 2004). Similar proportions have been reported from other industrialized countries (Gunnell and Ewings, 1994, Schmidt and Münster, 1995, Stephen and Chandra, 2000).

The most common causes of infertility are sperm dysfunction, ovulation disorder and fallopian tube damage (Cahill and Wardle, 2002). The suggested or discovered factors that underlie these causes are age, reproductive tract infections, obesity, anorexia, health-related behaviours like cigarette smoking, and too much exercise, as well as occupational exposures (Baird and Strassmann, 2000). About 15% of couples have more than one cause and 10–20% of couples suffer unexplained infertility, i.e. definite causes can not be found (Isaksson, 2002). Infertility can be primary: the failure ever to have achieved a pregnancy or secondary: inability to achieve pregnancy after having had a pregnancy (Nguyen and Wilcox, 2005).

Reproductive behaviour in our society has changed: Childbearing is delayed and births are planned (ESHRE, 2005). The mean age of motherhood has increased; for example in Finland the mean age of maternity was 27.0 years in 1977 and 30.0 in 2003 (Statistics of Finland and Stakes) and in France 26.5 in 1977 and 29.5 in 2000 (ESHRE, 2005). More importantly, postponing the first birth has become common. In Finland the mean age of the first birth increased from 25.4 in 1982 to 27.7 in 1996, but after that the age of first birth has only slightly increased; 28.0 in 2005 (Statistics of Finland and STAKES). Postponing childbearing increases the need for infertility treatments, because fecundity decreases with age.

Female fertility decreases with age due to several factors: the number of oocytes decreases, oocyte quality decreases, intercourse frequency declines (ESHRE, 2005) and unfavourable biological changes occur in the uterus (Baird and Strassmann, 2000). The monthly chance of achieving a pregnancy diminishes gradually after the age of 30 and more rapidly after age 36, being almost zero at the age of 41 (Broekmans and Klinkert, 2004). However, the age of losing fertility can vary according to the individual. How fertility changes by age among men is not well known, but time to pregnancy has been found to increase when the male partner is over 50 years old (ESHRE, 2005).

Strict planning of the timing of childbirth and taking the one-year definition of infertility as a strict rule can lead to impatience with waiting for a natural conception and result in premature use of infertility services (te Velde and Cohlen, 1999). It has been pointed out that appropriate timing for starting treatment is important to avoid over- and under-treatment (Brosens et al., 2004) and it is suggested that the general public has, in many countries, too optimistic a picture of childbearing in later life and of the success of infertility treatments (te Velde and Cohlen, 1999, Heffner, 2004, Cahill and Wardle, 2006). In 2004, the majority of female university students in Sweden would like to have children, but half of Swedish students planned to have children after the age of 35 years and did not know about decreased female fertility in the late 30s (Lampic et al., 2006). In Finland, 90% of university students desired children, but only 8% had a child, although the students were at the optimal childbearing age (Virtala et al., 2006). Leridon

(2004) pointed out that infertility treatments cannot compensate for all births not realised due to postponed childbearing.

2.2 Treatments

Medical treatments for infertility involve a treatment of physiological barriers (e.g. weight reduction or gaining weight), diseases causing infertility (e.g. acute infections) or damaging health habits (e.g. smoking, narcotic use), different surgical techniques (like opening blocked fallopian tubes), hormonal treatment (ovulation induction or ovarian stimulation) and assisted fertilization. In assisted fertilization (AF) the aim is to bring the egg and sperm close to each other to increase the chances of fertilization and achieve a pregnancy (Rowell and Braude, 2003). AF includes intrauterine insemination (IUI) and in vitro fertilization (IVF) with all its subtypes, such as intracytoplasmic sperm injection (ICSI) and frozen embryo transfer (FET), in which both eggs and sperm are handled outside the woman's body (Fig. 1). In IUI, prepared sperm are deposited in the uterus (Rowell and Braude, 2003). The term assisted reproductive technology (ART) has widely been used as a synonym for AF. However, in a recent publication ART has been suggested as including only procedures including in vitro handling of human oocytes and sperm or embryos but not insemination (Zegers-Hochshildt et al., 2006). This study uses the term AF, which here includes IVF with all its modifications including ICSI and FET, and hormonal treatment with or without insemination.

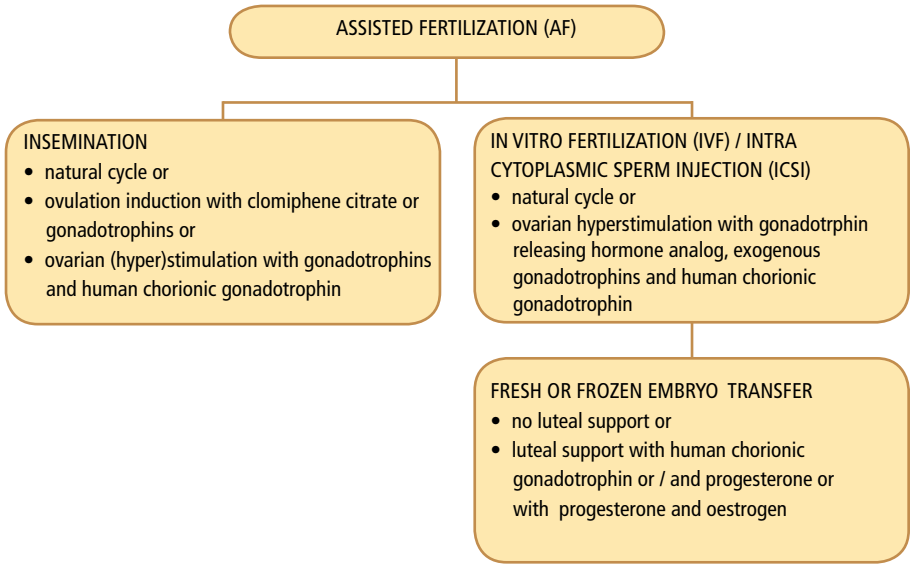

FIGURE 1. Different types of assisted fertilization (AF) and typical hormonal treatment used in AF.

In addition to medical treatments, psychological support is considered important for every couple as a part of infertility treatment (Bagshawe and Taylor, 2003). Counseling is suggested as helping couples in open communication, in clarifying their situation, needs and hopes, in adjusting to their circumstances, being supportive or therapeutic and in helping to understand what kind of effects treatment can have on couple's lives. It has been argued that the situation and experiences of infertile or involuntary childless people are culturally defined and that treatments and prevention of infertility should be seen in a cultural context (Bos et al., 2005).

IVF cannot cure or treat infertility, but it can help couples to conceive a child. This study concentrates on medical treatments, and in particular, hormonal treatment (with or without insemination) and IVF. The terms treatment and treatment cycle are used in spite the fact that AF is not curative.

2.2.1 Ovulation induction (OI)

Ovulation induction and ovarian (hyper)stimulation are two methods of hormonal treatment used in ovarian stimulation (Fauser et al., 2005). In ovulation induction, anovulatory women receive drugs (such as clomiphene citrate or gonadotrophins) to induce mono-ovulatory menstrual cycles. Ovarian (hyper)stimulation is used for women with normal menstrual cycles to induce development of multiple follicles. Both ovulation induction and ovarian (hyper)stimulation can be combined with intrauterine insemination (IUI) (Fig. 1). Particularly in ovarian (hyper)stimulation, the number of oocytes cannot be fully controlled. Multiple pregnancy rates after gonadotrophin ovulation induction have been reported to vary between 5 to 20% and after (hyper)stimulation from 10% to 40% per cycle. Hyperstimulation before IVF has a different aim than stimulation before the IUI. In IVF it is used to obtain a sufficient number of oocytes necessary to the procedure, and typically more drugs and higher dosages are used than in stimulation before the IUI. In this study, the term ovulation induction (OI) is used to describe both ovulation induction and low stimulation (lower dosages of drugs than in hyperstimulation) with or without insemination.

2.2.2 In vitro fertilization (IVF)

In vitro fertilization is the most famous type of AF. The first successful IVF treatment leading to the birth of Louise Brown in 1978 was done as part of a natural cycle without ovarian stimulation (Steptoe and Edwards, 1978). In the thirty years since, IVF has been modified and a current typical strategy includes six phases (Grainger and Tjaden, 2000, Unkila-Kallio, 2001, Fig. 1). However, there is varia-

tion in the drugs used and in their combinations. Firstly the natural function of ovaries is downregulated with various combinations of oral contraceptive pills, gonadotrophin releasing hormone analog, and progestins. Then ovaries are stimulated with exogenous gonadotrophins (follicle stimulating hormone and luteinizing hormone). After that oocytes are collected and fertilized. In this phase different micromanipulation techniques can be used: ICSI, assisted zona hatching or preimplantation genetic diagnosis. In ICSI one sperm is injected into one oocyte. Two to five days after retrieval, the embryo(s) is transferred to the uterus. The uterus is prepared for transfer (luteal support) with human chorionic gonadotrophin or progesterone, or both or with progesterone and oestrogen (Fig. 1).

If the embryo transfer is not possible or more embryos are fertilized than are needed, the embryos can be frozen and used later by thawing, called FET. If the hyperstimulation does not succeed, the procedure does not proceed to oocyte collection or thawed embryos can not be transferred, the treatment cycle is defined as a cancelled cycle (Zegers-Hochshildt et al., 2006). Both donated sperm and eggs can be used in IVF. If the woman has no uterus the embryo can be transferred to another woman's womb, called surrogacy.

3 IVF Success

IVF success can be calculated in many different ways, for example (clinical) pregnancy, delivery, live-birth or take-home baby rates per initiated cycles, per embryo retrievals or per embryo transfers. For most purposes, (one) live-birth or take-home baby rate per initiated cycle or cumulatively, is the best measure of success. The most important factors predicting good success in IVF have been women's young age (declining pregnancy and live-birth rates with increasing age), reasons of infertility (the highest live-birth rates being in male factor infertility and the lowest in respect of uterus-related reasons), the number of embryos transferred, good embryo quality, and previous live birth after IVF (Graigner and Tjaden, 2000).

Among younger women the live-birth rate increased by the number of embryos transferred up to three embryos and for older women up to four embryos, with the live-birth rate declining thereafter (Schieve et al., 1999). However, as the problems of multiplicity gained recognition, it was first recommended that two embryos were transferred and nowadays one embryo transfer is recommended (Tiitinen and Gissler, 2004, Kissin et al., 2005, Koivurova, 2005). According to Finnish experiences, the decreased number of transferred embryos has not led to a marked change in success rates (Tiitinen et al., 2003, Tiitinen and Gissler, 2004). In Finland success rate (live births per number of cycles) improved from 17% in 1994 to 19% in 2002, while the proportion of single embryo transfers has increased from 17% to 39%.

The success rates varied between the clinics and countries; in Europe deliveries per IVF cycle varied from 9.2% in Bulgaria to 25.2% in Norway, being mainly about 20% (Nyboe Andersen et al., 2006). Live-births per cycle and by female age were not reported. Of the register data on success rates found, the success rates and also the multiple birth-rates reported are highest in the United States (Table 1).

Calculations of success, both in terms of clinical pregnancy and live-births per cycle and per women's age showed that success decreased with increasing age (Table 1). It seems that success rates were somewhat improved between 1986 and 2004, but a comparison between earlier studies and currently available register data as well as between different countries have to be interpreted with reservations, due to the different definitions, data collection systems, and sample sizes.

TABLE 1. Success rates of IVF during different time-periods; pregnancy or live-births per initiated cycle, %

Document or Author	Country	Year(s)	Treatment	Multiplicity, %	Pregnancy	Live birth
Piette et al.1990	France	1986	IVF	NA		
<=24					15	
25–29					20	
30–34					19	
35–39					17	
>=40					13	
Devroye et al.1996	Belgium	1991–1993	ICSI	NA		
<40					23	
>=40					7	
Dew et al.1998	Australia	1987–1994	IVF			
<36				16	14	12
36-39				13	13	9
>=40				0	5	3
Meldrum et al.1998 [a]	USA	1994	IVF			
<40				NA	35	28
40–42				NA	21	14
>42				NA	10	5
Lass et al.1998	UK	1988–1995	IVF			
<40				NA	28	
>=40				5	11	
Klipstein et al. 2005	USA	1999–2002	IVF			
>=40				15		10
Waters et al. 2006	Australia and	2003	IVF			
Total	New Zealand			18		19
< 35				NA		25
35–39				NA		15
40+				NA		7
National summary of CDC [b]	USA	2003	IVF			
< 35				38		37
35–37				32		30
38–40				26		20
41–42				17		11
Swedish Statistics [a]	Sweden	2003	IVF+ICSI			
Total				12		23
< 35				NA		29
35–39				NA		20
40+				NA		10
Danish Statistics [a]	Denmark	2004	IVF+ICSI			
< 40				22		22–25
> 40				11		8-11
Statistics of HFEA [c]	UK	2003–2004	IVF			
< 35				28		28
35–37				23		24
38–39				19		18
40–42				12		11
>42				NS		3

[a] Deliveries per cycle started (%)
[b] CDC = Centers for Disease Control and Prevention, 99% is IVF and rest other types of assisted fertilization
[c] HFEA = Human Fertilisation & Embryology Authority, IVF includes fresh embryo transfers
NA = not avalable, NS = non-significant

Reported pregnancy and delivery rates have varied not only by woman's age but also by number of cycles; pregnancy rates have decreased after three or four cycles and delivery rates after four cycles (Meldrum et al., 1998, Lass et al., 1998). Cumulative live births rates per initiated cycles have varied from 3% to 71% by female age and number of cycles (Tan et al., 1994). Olivius et al. (2002) found that an overall cumulative live birth rate after three cycles varied from 56% to 66%. Wang (2006) has pointed out that calculating cumulative pregnancy rates can lead to an overestimation of treatment success. He suggests that the calculation should be limited only to the second or third cycle within one to two years to ensure that most women are included in the calculations.

4 Safety of infertility treatments

4.1 Women's health after IVF and OI

The safety issues related to infertility treatments for women include complications of the treatments and—following successful treatment—complications during pregnancy and delivery. The most common and serious consequence of infertility treatments is multiple pregnancy, which in the case of IVF often occurs with older age. IVF-pregnancies have been reported to be more complicated than natural pregnancies, with for example vaginal bleeding, pregnancy induced hypertension and Caesarean sections being more common (reviewed by Koivurova, 2005). This study concentrates on treatment complications, which have been studied less than pregnancy complications. They can occur during the ovulation induction (or stimulation), the oocyte collection procedure, and also post-operatively. The achieved pregnancy can be ectopic (embryo outside the uterus) or heterotopic (embryo both in and outside the uterus) and it can end up in a miscarriage. The frequency of miscarriages and ectopic pregnancies leading to hospital care is likewise covered in this study.

Ovarian hyperstimulation syndrome (OHSS) is considered the most serious complication of ovulation induction. It can vary from a mild illness to a critical, life-threatening disease requiring hospitalization (Table 2). Due to the various OHSS related symptoms and signs which can vary case by case, OHSS is typically not easy to diagnose. OHSS can occur within a few days of receiving of human chorion gonadotrophin ("early OHSS") or later ("late OHSS"). The multiple pregnancy has been associated with a higher risk of late OHSS (Mathur et al., 2000). The incidence of severe OHSS has been reported to vary from 0.7% to 1.7% per initiated cycle (Bergh and Lundkvist, 1992, Serour et al., 1998, Westergaard et al., 2000, Nyboe Andersen et al., 2006). OHSS has been estimated to lead to hospitalisation in 2.4% of IVF pregnancies (Källén et al., 2005a). Case reports (Cluroe and Synek, 1995, Koo et al., 2002), some studies (Bergh and Lundkvist 1992, Serour et al., 1998, Abramov et al., 1999a, Källén et al. 2005a) and reviews (Beerendonk et al., 1998, Whelan and Vlahos, 2000, Delvigne and Rozenberg, 2003, De Sutter, 2004, Jokimaa 2006) describe some serious aspects of OHSS, such as thromboembolic events, pulmonary manifestations, and death. However, the magnitude of the risk of OHSS is unclear. The frequency of OHSS after OI is unknown (Unkila-Kallio,

TABLE 2. Symptoms and signs related to different degrees of ovarian hyperstimulation syndrome (OHSS)

OHSS
Mild
Abdominal distension and discomfort
Nausea, vomiting and/or diarrhea
Enlarged ovaries
Moderate
Symptoms and signs of mild OHSS
Ascites
Severe
Symptoms and signs of moderate OHSS
Temperature of over 38 degrees
Ascites and / or hydrothorax or breathing difficulties
Weight increase
Hypovolemia
Hemoconcentration
Oligouria
Electrolyte imbalances
Critical
Symptoms and signs of severe OHSS
Impaired renal perfusion
Thromboembolism
Impending multiorgan failure

(Beerendonk et al.1998, Jokimaa 2006)

2001). In one small clinical study, the OHSS hospitalization rate per initiated cycle was 0.07% (Quasim et al., 1997).

The frequencies of IVF complications other than OHSS have been only sporadically reported. For oocyte collection, bleeding has been reported in 0.03 % to 0.5% and infections in 0.02% to 0.3% of embryo transfers (Bergh and Lundkvist, 1992, Nyboe Andersen et al., 2006). From 2% to 5% of IVF pregnancies have been reported to be ectopic and 0.1% to 1.0% heterotopic (Roest et al., 1995, Serour et al., 1998, Waters et al., 2006); both are higher than in naturally conceived pregnancies (Hemminki and Heinonen, 1987, Mäkinen, 1996, Roest et al., 1995). Estimates of IVF pregnancies ending in miscarriage have varied from 15% to 23% (Roest et al., 1995, Serour et al., 1998, Westergaard et al., 2000, Kupka et al., 2003, Schieve et al., 2003, Waters et al., 2006).

4.2 Health of IVF and OI children

Health of newborn

The most common health problems of IVF children are related to multiplicity (Schieve et al., 1999, Tiitinen et al., 2003, Kissin et al., 2005). Although IVF has been associated with an increased number of monozygotic twins (Ericson and Källén, 2001), the main reason for multiplicity is multiple embryo transfer and therefore IVF twins are much more often dizygotic compared to naturally conceived twins (99% vs. 70%, Schachter et al., 2001). Depending on the IVF practice, multiple birth rates have varied from 27% to 40%, being much higher in the United States than in Europe (Fauser et al., 2005): Single embryo transfer has become more common in Europe in recent years. With the preference for single embryo transfers, the multiple birth rate has decreased in Finland from 27% in 1992 to 13% in 2003 (calculated from IVF statistics, http://www.stakes.info/2/1/2,1,4.asp.). During the 1990s, an improved trend in the perinatal health of multiple IVF children was found in Finland, mainly due to a decrease in higher order multiple births (Klemetti et al., 2002).

IVF twins have had poorer perinatal health than IVF singletons but in previous publications no differences were found between the perinatal health of IVF and naturally conceived twins (reviewed by Ludwig et al., 2006). Contrary to these previous publications, recent studies show an increased risk of preterm birth and/or low birth weight for IVF twins (Verstraelen et al., 2005, Wang et al., 2005).

Poorer perinatal health in IVF children is however not only a consequence of multiplicity and a high frequency of twins: the perinatal health of IVF singletons has been found to be worse than that of naturally conceived singletons (Schieve et al., 2002, Helmerhorst et al., 2004, Jackson et al., 2004). Low birth weight and preterm birth were more common among IVF and ICSI singletons compared to naturally conceived singletons of previously infertile women (De Geyter et al., 2006).

Prematurity and low birth weight have been more common also among OI children than among naturally conceived children (Addor et al., 1998, Källén et al., 2002, Gaudoin et al., 2003, Wang et al., 2002, Verstraelen et al., 2006). Two small studies could not find any statistically significant differences between children conceived with intra uterine insemination (IUI) and spontaneously (Nuojua-Huttunen, 1999, De Geyter et al., 2006). In addition to low birth weight and prematurity, OI children have had a higher incidence of very low birth weight, treatment in the neonatal intensive care unit and of most neonatal morbidity parameters (Ombelet et al., 2006).

Some studies have shown an increase in congenital anomalies (CAs) among IVF or ICSI children (Bergh et al., 1999, Dohnt et al., 1999, Wennerholm et al.,

2000, Ericson and Källén, 2001, Anthony et al., 2002, Hansen et al., 2002, Koivurova, 2005, Katalinic et al., 2004), but other studies have not (Loft et al., 1999, Ritzk et al., 1991, Sutcliffe et al., 2001, Westergaard et al., 2000). The higher incidence of CAs among IVF children has involved musculoskeletal, cardiovascular, chromosomal and urogenital defects (Hansen et al., 2002, Koivurova, 2005).

Recently, sufficiently large studies on the CAs of IVF children have been published: two meta-analyses of earlier studies (Rimm et al., 2004, Hansen et al., 2005) and register-based studies from Sweden (Källén et al., 2005b) and Denmark (Zhu et al., 2006). According to the meta-analysis by Rimm et al. (2004), a 1.3-fold risk of major CAs was found among IVF and ICSI children and a 2.1-fold risk was found by Hansen et al. (2005). In the latter review the risk of CAs was increased also separately for singletons (OR 1.35, 1.20–1.51). Risk of specific malformations was not reported.

According to the Swedish study (Källén et al., 2005b) IVF children in total and singletons alone had a 1.3-fold risk of congenital anomalies. The risk was not increased among multiples. The risks for many specific malformations were increased, for example for neural tube defects, different gastrointestinal atresias, major cardiovascular defects, and hypospadias. No differences in the malformation rate by IVF method used were found with the exception of hypospadias after ICSI. In contrast, a meta-analysis comparing IVF children with ICSI children found no significantly increased risk after ICSI (Lie et al., 2005). A recent smaller study from the United States found the same 1.3-fold risk with a borderline significance among all IVF children and, contrary to earlier studies, an increased risk also for congenital anomalies among twins and triplets (Olson et al., 2005).

Olson et al. (2005) studied the risk of congenital anomalies among IUI children and could not find an increased risk. The number of IUI infants was however less than 100. Only one sufficiently large study on anomalies of children born as a result of ovarian stimulation could be found (Källén et al., 2002). There was an increased rate of congenital anomalies, but this could be mainly explained by maternal characteristics.

A Danish study found an increased risk among singletons born as a result of infertility treatments (IVF, ICSI, insemination and hormonal treatment) and interestingly also among naturally conceived children born to previously infertile couples (without treatments) (Zhu et al., 2006). Of the specific CAs, the risk of musculoskeletal and genital anomalies was increased for IVF children, but not the risk of genital anomalies among children born naturally to previously infertile couples. Risk among twins was not increased. The authors suggested that hormonal treatment might cause genital anomalies but otherwise the potential reason for anomalies could be infertility itself or its determinants.

Health in early childhood

According to previous small cohort studies, the morbidity, growth, and development of IVF children have been similar to that of control children (reviewed by Koivurova, 2005). A recent Finnish study found higher childhood morbidity and increased hospitalization (Koivurova et al., unpublished data). Large register-based studies having large sample sizes have been published from the Nordic countries (Ericson and Källén, 2001, Ericson et al., 2002, Strömberg et al., 2002, Pinborg et al., 2004a, Pinborg et al., 2004b, Lidegaard et al., 2005, Källén et al., 2005b, Källén et al., 2005c, Hvintjørn et al., 2006). These studies report an increased use of hospital services, long hospitalizations and an increased risk of infections, epilepsy and tumours (Ericson et al., 2002), asthma (Ericson et al., 2002, Källén et al., 2005c), cerebral palsy (Ericson et al., 2002, Strömberg et al., 2002, Lidegaard et al., 2005, Hvintjørn et al., 2006), sleep disturbances (Lidegaard et al., 2005), convulsions and behavioural problems and accidents (Källén et al., 2005c) among IVF children.

A review including both small cohort studies and some of these large register-based studies concluded that most studies did not find any differences in childhood morbidity, chronic illnesses, surgical interventions, physical development, mental health, and behavioural problems between IVF and naturally conceived singletons, but they found an increase in neurological problems among IVF singletons (Ludwig et al., 2006). Data on chronic illnesses, childhood morbidity, and surgical interventions were so contradictory that the authors could not draw a final conclusion. The data on IVF twins was limited and more data are needed to draw any conclusions on their childhood health. Long-term follow-up studies of OI children are lacking.

5 Use and service costs of infertility treatments

5.1 Human and reproductive rights

The Declaration of Human Rights of the United Nation from the 1948 (available at: www.un.org/Overview/rights.html) sets out the right to marry and establish a family without limitation due to race, nationality or religion. At the 1994 International Conference on Population and Development in Cairo, reproductive rights were defined as follows "…the basic right of all couples and individuals to decide freely and responsibly the number, spacing and timing of their children and to have the information and means to do so, and the right to attain the highest standard of sexual and reproductive health. They also include the right of all to make decisions concerning reproduction free of discrimination, coercion and violence." (available at: http://www.unfpa.org/icpd/summary.htm).

5.2 Right to infertility treatments

The question of whether a right exists for infertility treatments and if so who is eligible to treatments is problematic. Do the human and reproductive rights mean that everyone has the right to receive a child and a right to receive infertility treatments to fulfil these rights? McLean (1993) argued that the right to reproduce does not automatically mean the right to have a child. On the other hand, Blank (1997) pointed out that reproductive rights have different dimensions, for example the right to have a child or the right not to have a child. He continued that infertility treatments belong to the category of rights to have children i.e. positive rights. Positive rights include claims for society to offer services that are needed. If reproductive rights are understood as positive rights, an infertile couple can claim access to infertility services. According to McLean the last conclusion is right, but she argued that the declaration of human rights can be understood as a freedom to reproduce for those who have a capacity for that and not as a right for everyone. But she continued that because infertility technology is already available it is important to somehow control it. Furthermore, she pointed out that it would be necessary to asses how the technology is directed and developed taking into ac-

count related consequences. Daniels and Taylor (1993) argued that it is necessary to formulate selection policies for access to AF to be able to take into account the rights and needs of the child as well as to decide how much public funds are allocated to infertility services.

Daniels and Taylor (1993) pointed out that the criteria for eligibility for AF should be made through a public debate that asks whether access should be restricted, if so on what basis, and who should make the decisions. According to them, exclusion criteria could include for example previous children or females are beyond a certain age. They suggested that decisions should not be left to medical professionals alone but that some kind of expert committee should take into account public opinion.

5.3 Legislation on infertility treatments

Regulations of the eligibility for IVF of European countries, Canada and Israel were studied by a Steering Committee of Bioethics (CDBI), Council of Europe and published in 2005 (CDBI, 2005). They report that nowadays in most European countries, regulation governs who is eligible for IVF treatment, but that eligibility criteria vary between different countries. In 28 of the countries participating in the study, eligibility is regulated by the law. Two countries (Cyprus and Portugal) reported having no law and no regulations for assisted fertilization. The rest of the countries studied (7 including Finland) did not have a law at that time but drafting of legislation was in process or they have some kind of regulations for assisted fertilization. In the United States the criteria for eligibility have been found to vary also between clinics (Stern et al., 2001). AF was available only to heterosexual couples for example in Austria, Denmark, Norway, Germany and Italy, but allowed also for lesbian women in Sweden and for single or lesbian women in the United Kingdom, Israel and Canada.

In most countries, AF is given only for medical reasons but for example in the United Kingdom and Canada, AF could be received also for social reasons (i.e. without a diagnosed fertility problem, CDBI, 2005). Surrogacy was prohibited in most countries, but restrictively permitted for example in the United Kingdom, Canada, Israel, and Estonia. Sperm, oocyte and embryo donations were allowed in most countries but not in Italy, Lithuania and Turkey. In Croatia, Norway, Switzerland and Austria, sperm donation was permitted, but oocyte and embryo donations were not. Donations in studied countries were mostly anonymous, but not in the United Kingdom, Turkey, Sweden, Norway, Netherlands, Georgia and Germany.

Two Scandinavian countries have legally defined age-limits for AF: 45 years for women in Denmark and 42–45 for women and 50 for men in Iceland (Legislation

on biotechnology…, 2006). In Sweden women before their "normal age of menopause" and capable of "carrying out parental responsibilities throughout childhood" can receive AF. In the United Kingdom until the end of 2005 the infertile patient's suitability (family and social circumstances) to raise a child had to be examined by consulting the patient's general practitioner (Eaton, 2005). Nowadays, the examination of suitability is left to the fertility clinics.

In Finland, attempts to draw up a law on fertility treatments (insemination and IVF) have continued for twenty years. In October, 2006 a legislative proposal was accepted in the Finnish parliament. During the process, features that were problematic were the eligibility of single and lesbian women, children's right to know their biological origin, and surrogacy (Burrell, 2005). The law will be come into force in 2007. In the coming law, IVF and insemination will not be prohibited for single or lesbian women, children will have the right to know the identity of the donor at the age of 18, and surrogacy will not be allowed. Until now only heterosexual couples have been treated in the public sector, donations have been anonymous both in the public and private sector and about 20 pregnancies have been successful through surrogate mothers (CDBI, 2005). One quarter of parents of the first cases of using surrogacy in Finland has been foreign (Söderström-Anttila et al., 2002).

In the coming Finnish law on AF, no exact age-limit exists and the decision on the eligibility of women is left to medical doctors (Hallituksen esitys…, 2006). The doctor is not allowed to give AF if the achieved pregnancy were to be harmful to the health of the woman seeking AF or to the health of the newborn or if it is evident that the women cannot guarantee a balanced development for the child. Until now, the female age limit for public IVF services has varied between 38 and 42 years, but in the private sector no strict age limit has existed (Malin Silverio and Hemminki, 1996**,** CDBI 2005) and in practice there have been variations in the age of treated women between the clinics.

5.4 Funding of IVF services

It has been much debated whether health insurance should cover IVF. In some countries IVF is offered only in the private sector (for example in Canada and most states in the United States), where its use depends on a couple's ability to pay (Neumann, 1997, Stephen and Chandra, 2000). In the United States it has been found that insurance coverage of IVF increased utilization of IVF but on the other hand decreased the number of transferred embryos, i.e. making IVF more safe (Jain et al., 2002). In some countries IVF is offered both in the public and in the private sector (for example in Finland and Norway) and wealthy couples can shorten their waiting times by using services in both sectors (Svensson and

Stephenson, 1993). In the United Kingdom where 80% of IVF is given in the private sector, authorities have warned that IVF is becoming more commercial and people with insufficient income are in danger of remaining without treatments (Cole, 2006). In some countries IVF services are available mainly in the public sector (for example in France and Germany) (Jones and Cohen, 2004).

Criteria of coverage varied also between countries (Jones and Cohen, 2004, CDBI, 2005). For example in Austria, Switzerland, Turkey, and Poland, IVF is not covered by the social security system mainly because involuntary childlessness is not considered as a disease. Other limiting factors are age and number of cycles. Female age has been used as a criterion to cover IVF: from an age-limit of 35 years in the Ukraine to 45 years in Denmark and Israel (CDBI, 2005). The most common age-limit for coverage is 40 (in Austria, Cyprus, United Kingdom, Luxemburg and Germany). In Finland, the SII, in covering the infertility treatments, follows the limitations given by the Ministry of Social Affairs and Health (STM, 2005). In that document the suggested age-limit is 39 years, but if treatment is based on a specific disease and a medical certificate, treatment is covered regardless of the age of the woman. The advanced age of a male partner is a limitation for coverage in Austria and Germany (50 years) as well as in Norway ("reasonable difference in age" between partners). The coverage according to number of cycles varied: in Cyprus, coverage is for a single cycle, while Israel gives full coverage up until the birth of two children.

In Finland the private sector is an important provider of IVF: some 60% of all IVF cycles are offered by private clinics (IVF Statistics, http://www.stakes.info/2/1/2,1,4.asp.). In 1999, 12 of the 19 clinics were private, and in 2005 that figure was 12 of 18. In general, a woman can seek medical advice for infertility by visiting a general practitioner (GP) at a health care centre or a private gynaecologist at a private clinic. Simple diagnostic tests can be done in both places. After that the GP or gynaecologists can refer the woman to a public hospital for further diagnosis and infertility treatment or the woman can contact a private IVF specialist at a private clinic. About 70% of women who have sought help for infertility had visited private gynaecologists, 30% a gynaecologist at a hospital and 17% a GP in a health care centre (Malin et al., 2001).

In the public sector, women pay a small fee for their clinic visits, and the rest of visits costs are covered by taxes. Nevertheless, to receive IVF they often have to wait. In the private sector, IVF can be received quickly but patients pay more for their visits. However, up to about 60% of the private physician's charges and a part of the laboratory cost (75% of the standard fee) and interventions (60% of the standard fee) are reimbursed by the Social Insurance Institution (SII). Women both in the public and private sector pay for about half of the drug costs and the rest are reimbursed by the SII. If the individual's yearly upper limit of drug costs has been reached, all further costs are paid by the SII.

5.5 Use of IVF by age, socioeconomic position and area of residence

Not all infertile couples seek medical help for infertility in spite of growing number of fertility services and awareness of them. In population-based studies the proportion of infertile couples having sought medical advice (visit to general practitioner, private gynaecologist or hospital) varied from 22% to 95% (Gunnell and Ewings, 1994, Schmidt and Münster, 1995, Stephen and Chandra, 2000). Primarily infertile women sought help more often than secondarily infertile and younger generations more often than older generations. In population-based studies from Finland, 50–67% of infertile women had sought medical advice (examinations or treatments) for infertility (Malin et al., 2001, Klemetti et al., 2004).

There is little reliable data on the use or users of IVF. However, data on IVF treatments given—for example, number of cycles, transferred embryos, pregnancies, short term complications—are registered or collected voluntary in many countries. From these statistics and registers some aspects on the utilization of IVF can be estimated. The European Society for Human Reproduction and Embryology (ESHRE) has collected information on IVF in Europe since 1997 (Nyboe Andersen et al., 2006). Systems to collect the data are different across European countries and some data are lacking, especially from some Southern European countries. In the United States, the Department of Health and Human Services (Centres for Disease Control and Prevention, CDC) reports on the success rates and outcomes of assisted fertilization (http://www.cdc.gov/ART). Treatments given in Australia and New Zealand are registered and reported every year (Waters et al., 2006). In Finland statistical data on IVF treatments have been collected since 1992 as voluntary reporting (http://www.stakes.info/2/1/2,1,4.asp.).

The highest utilization of IVF services among the 25 European countries was reported in Finland and Denmark (Nyboe Andersen et al., 2006). In Finland the use of IVF increased during the 1990s, but has since levelled off (Gissler and Tiitinen, 2001). However, in 2004 the number of IVF cycles grew again (Table 3), with 7.0 cycles per 1000 women of reproductive age (15–49) resulting in increased number of IVF children (IVF Statistics, 2006, http://www.stakes.info/2/1/2,1,4.asp.). In a European context, the use of IVF in Finland is high, but for example in Australia the corresponding rate per 1000 women in 2003 was even higher, at 8.4 (Waters et al., 2006).

Age

According to the statistics of ESHRE (Nyboe Andersen et al., 2006) over 70% of women using IVF in Europe were aged 30 to 39. However, there was variation between the countries from 53% to 88%. About 13% (from 2 % to 25 %) were aged 40 or more. Almost the same proportions are reported from the United States (69% and 20%, http://www.cdc.gov/ART) and from Australia and New Zealand

TABLE 3. Number of IVF, ICSI and FET[a] cycles, pregnancies, life births and cycles per 1000 women aged 15–49 years in 1992–2004 in Finland.

	Year												
	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Cycles	2331	3189	4382	5043	6417	7336	7159	6968	6811	6766	7114	6990	8391
Pregnancies	502	670	840	1040	1496	1611	1663	1636	1536	1523	1662	1807	1848
Live births	392	489	612	763	1092	1205	1229	1191	1179	1147	1259	1353	1395
Cycles per 1000 women aged 15–49 years	1.8	2.5	3.4	4.0	5.1	5.8	5.7	5.6	5.5	5.6	5.9	5.8	7.0

[a] FET: the cycles with the embryo transfer.
Reference: IVF Statistics, 2006, http://www.stakes.info/2/1/2,1,4.asp.

(66% and 20%). In Finland the corresponding rates were 66% and 14% (Nyboe Andersen et al., 2006).

It is well known that complications during pregnancy and childbearing notably increase by female age (Nybo Anderssen et al., 2000, Salihu et al., 2003, Heffner, 2004. Furthermore, success in AF decreases by female age (Graigner and Tjaden, 2000, Table 1). However, the use of donated oocytes has made it possible to achieve occasional pregnancies and live births even among women aged over sixty. Treating older women—even post-menopausal women—raises many ethical questions, such as setting age-limits in the use of AF, the allocation of scarce health care resources, the shortage of donated eggs, and the risks for the child's and the woman's health (de Wert, 1998, Heffner, 2004). Raising children is hard work and it has been asked whether older women are fit enough for it (de Wert, 1998) or if there are too great risks for the child's later psychosocial development with old parents (or as orphan at an early age). On the other hand it has been discussed whether age-limits are violations of human rights (Blank, 1997), and it is assumed that older women have a good capability to raise their children, in that they may have a better education, better economical situation and better emotional preparedness compared to younger women (Eisenberg and Schenker, 1997).

Male partners' age is seldom reported (and limited), and the effect of paternal age on reproductive outcomes has almost been ignored. In Australia the oldest registered male partner in IVF was 87-years-old (Waters et al., 2006). The results of paternal age effects on the outcome of AF are conflicting (ESHRE, 2005). However, a recent study found increased failure to conceive following IVF among fathers over 40 years (De La Rochebrochard et al., 2006).

Socioeconomic position

The over-representation of women from the highest socioeconomic group among IVF users has been found in studies from Canada and Australia (Svensson and Stephenson, 1993), the United States (Wilcox and Mosher, 1993), and the United

Kingdom (Gunnell and Ewings, 1994). In the United States, women with higher levels of education and income were more likely to have received infertility services than women with a lower level of education and income (Stephen and Chandra 2000, CDC: National Survey of Family Growth 2005, Jain and Hornstein, 2005, Bitler and Schimdt, 2006). In France the use of IVF did not differ according to women's socioeconomic position (Tain, 2003).

In Finland, no differences in the education of women were found in those seeking help but those using infertility services more often had a longer education than non-users (Malin et al., 2001, Klemetti et al., 2004). IVF mothers have also been more educated or more often were of a higher socioeconomic position than other mothers (Gissler et al., 1995a, Malin Silverio and Hemminki, 1996, Bergh et al., 1999, Buitendijk, 2000, Klemetti et al., 2002).

Area of residence

It is generally believed that not only women from higher socioeconomic positions but also women in urban areas have easier access to infertility services and also use them more than women from rural areas. Rural women may live considerable distances from cities offering AF and long trips and a possible lack of social support (husbands, friends and relatives far away) needed during the treatment may affect the access and willingness to use AF services (Daniels and Taylor, 1993). So-called satellite clinics have been created at least in the United Kingdom, the United States and the Netherlands to make access easier outside the big cities (Kingsland et al., 1992, Kaplan et al., 1995, Roest et al., 1995).The experiences have been encouraging; success rates did not decline, but stress that was related to the treatment and the costs of treatments did so.

In Finland, IVF clinics have been unevenly distributed; all IVF clinics (19 clinics in 1999 and 18 in 2005) have been situated in eight towns (IVF Statistics, http://www.stakes.info/2/1/2,1,4.asp.). Three out of the 12 of the pre-1995 provinces have had no IVF clinic. Women in some areas have to make long trips (as much as 700 km) to obtain IVF treatments. OI services are available in all parts of Finland. With the exception of one previous study that found that IVF mothers came more often from southern Finland (Malin Silverio and Hemminki, 1996), no data on use by area existed before this study.

5.6 Costs of IVF treatments

The costs of IVF vary from country to country. Costs can be divided into direct and indirect costs. Direct costs include costs of medical consultations, personnel, equipment, drugs, complications, and monitoring, and indirect costs such

as women's travel, time off work, lost wages, long-term complications, multiple pregnancies, and obstetric and neonatal care (Fauser et al., 2002). Many studies on the cost and cost effectiveness of IVF have been published, as have a few studies on cost-effectiveness of IVF versus other AF, and so-called economic benefit studies (reviewed by Garceau et al., 2002). Most published studies have not included indirect costs. Economic-benefit studies have examined IVF couples' or potential child bearers' willingness to pay (WTP) for IVF or have had macroeconomic perspectives comparing costs of IVF to costs of other areas of health care. Problems in comparing these studies include for example different definitions for success in IVF and the high incidence of multiple births and its long-term costs.

Health care costs for IVF treatment by women's age have been previously described in a review by Broekmans and Klinkert (2004) that found that IVF costs EUR 13 000 (without sick-leave, cost of travelling, complications and pregnancy) for women up to the age of 40 and EUR 37 000 for women aged over 40. Based their own small data, the authors suggested that IVF is still cost-effective (cumulative pregnancy rate was 49% and the estimated IVF costs per one child were EUR 18 000) for a selected (tested to have a reasonable probability of ongoing pregnancy) group of women aged 41 to 42 years but not for women aged 43 or older.

Health care costs resulting from IVF have also been previously studied in Finland (Gissler et al., 1995a, Malin Silverio and Hemminki, 1996, Koivurova, 2005, unpublished data by Koivurova et al.). It was found that health care costs for an IVF newborn from pregnancy induction until the age of one week was 5.4-fold compared to that for other newborns (Gissler et al., 1995a), while costs for IVF singletons were higher compared to other singletons and multiple births increased the costs (Koivurova, 2005). Pre-school age health care costs are markedly higher among IVF children compared to other children (Koivurova et al., unpublished data).

The focus in these previous studies has not, however, been in the allocation of scarce health care resources. Empirical data that would quantify the question of equitable use of scarce resources have not been given, nor has the distribution of private and public expenditure been estimated.

6 Equity and infertility treatments

6.1 Equity as a principle in health care

Equity is a key objective of many health care systems and it is present in many policy documents (Mooney, 1994). The same is true also of Finland; many features in the Finnish health care system are intended to support social equity (Keskimäki, 1997). In health care, equity can be defined as equality of access, equality in health, or equality of use for equal need (Mooney, 1994). Equity has been chosen as the first regional target in the World Health Organization European Region and included also in many other targets of the WHO (Whitehead, 1990).

According to the WHO, equity in health care includes equal access to services for equal need, equal use for equal need and equal quality of care (Whitehead, 1990). Equal access does not come about if people are turned away from health care or are unable to use health services due to race, sex, age, religion, poor income or other factors not directly related to the need for care. According to Whitehead (1990) resources and facilities should not be unevenly distributed around the country, resources should not be used for specific services which benefit only a small population, services should not be organized in such a way that only a part of the population are capable of using them, while received care and its quality should be based on need and not on social factors. The different use of services by different social groups is not automatically unequal. But it is unequal if services are organized so that people in different social groups do not have the same possibility to use them.

Mooney (1994) has argued that the WHO's egalitarian view of equal use for equal need is problematic, because it requires people with the same need to use health care services without taking into account people's own preferences for their health and health care. People with the same need may not value their health equally and may not have the same willingness to use services. Mooney pointed out that equal access for equal need is not so problematic; it can be thought to include a desire for equal access. If equal access or use is required for equal need, it is also important to define the need. According to Mooney, a need can be defined as the extent of sickness (defined by a medical practitioner, health care system or some part of it) or the capacity to benefit. Definitions cause many problems, especially

the latter definition, as well as questions such as how different diseases or different grade of diseases will be taken into account, how to measure the benefit, and who will carry out such an assessment. However, the greater the capacity to benefit, the greater the need is, but Mooney reminds that not all diseases or conditions can be treated and that not all sufferers can be made healthier. Mooney commented that need and demand should be differentiated from each other; they are not the same. Need is defined by other people but demand is based on the person's own preferences. According to Mooney, use and consumption are not the same as demand or need. For example, due to factors such as prioritization, higher costs, or lack of services, people who would need services and who demand them have sometimes to wait. In other words, they cannot necessarily use or consume services in spite of a need or demand.

Equity in health care not only means that offering of services is based on need and that services are distributed equally. It has been argued that equity includes also the right to effective and safe treatments (Svensson and Stephensson, 1993). Because the health care system cannot afford to do everything, resources have to be allocated—according to priorities set by society—and in as equitably a way as possible (Svensson and Stephensson, 1993, Mooney, 1994). It has been argued that it would be useful if priorities are set—i.e. choices made—not only by health care professionals and decision makers but also by health care consumers and the public at large (STAKES report 161, 1994).

6.2 Equity in infertility treatments

What does equity mean in infertility treatments? Finding an adequate answer to this question is not easy (Daniels and Taylor, 1993, McLean, 1993, Svensson and Stephenson, 1993, Blank, 1997, Ashcroft, 2005). As in other health care, the first step is to define the need for infertility treatments in the population i.e. infertility prevalence and the wish for a child.

Secondly, it can be asked what priority should be given to infertility treatments compared to other treatments in health care. As in other countries (Daniels and Taylor, 1993, Nisker, 1996, Neumann, 1997), Finland has seen discussion on the following priority-related topics: Should infertility be considered a disease or not, should treatments be given only for medical reasons (infertility is diagnosed) or also for social reasons, and who should have the right to treatments or eligibility? Prioritization has not however been explicitly discussed. IVF is clearly prioritized only by women's age, as already explained in Chapter 5.

Thirdly, it can be discussed whether these treatments are efficacious and safe enough (Peters, 2004). The fourth significant question is how can scarce health care resources be distributed equitably (in terms of geographical variations as well

as variations by socioeconomic position, and age) and with maximum benefit to public health. The allocation of resources is linked to the funding of infertility treatments. If IVF services are available only in the private sector, access will depend on ability to pay.

7 Summary

Infertility is a common problem and IVF and OI are widely used infertility treatments, but not enough is known about their utilization and health effects. Data on the frequency of IVF complications for treated women are sparse and the number of studies reporting complications after OI is even rarer. In spite of the large number of studies on perinatal health of IVF children, some studies on the general health of IVF children are based on early experience of IVF. Some studies concentrate on specific diagnosis or hospital care utilization or singletons or twins only, or do not consider multiplicity. Results on the perinatal health of IVF twins are controversial. Studies on congenital anomalies of IVF children are also controversial and many of them have had methodological problems such as small sample sizes, lack of proper controls, and different definitions of congenital anomalies among IVF and naturally conceived children. Only a few studies have examined congenital anomalies among OI children.

Health care costs for a live-birth among IVF women by age have briefly been described previously but otherwise empirical data that would quantify the question of resource allocation have not been given, nor has the distribution of private and public expenditure been estimated. There are many general assumptions of inequalities in the use of infertility treatments (i.e. urban women and women from higher socioeconomic position use more IVF services than rural women or women from lower socioeconomic positions) but not enough data are available to verify these assumptions. Equity is considered an important principle in health care. To be able to discuss equity in assisted fertilization data on effectiveness or success, safety, costs and resource allocation as well as utilization of assisted fertilization are needed.

8 Aims of the study

8.1 General aims

The general aims of this study were to study the utilization of IVF and OI, the health effects of IVF and OI as well as the equity in the use and resource allocation of IVF by using nationwide Finnish health care registers.

8.2 Specific aims

The specific aims were to study

1. the use of IVF and OI in Finland in 1996–1998 by women's background characteristics.
2. the serious complications and miscarriages leading to women's hospitalization or operations after IVF or OI.
3. the health of IVF children until the age of four years.
4. the prevalence of major congenital anomalies among IVF children.
5. the treatment costs of IVF in Finland.
6. the equity in the resource allocation for IVF in Finland.

9 Methods

Six different nationwide registers were used in the present register-based longitudinal study: Reimbursement records of the Social Insurance Institution (SII), the Central Population Register, the Hospital Discharge Register (HDR), the Medical Birth Register (MBR), the Register of Congenital Malformations (RCM), and the Cause-of-Death Register.

The study plan was approved by the STAKES research ethics committee. For register linkages, the National Data Protection Authority was consulted and permissions from the register keepers were obtained.

9.1 Registers used in the study

9.1.1 Reimbursement records of the Social Insurance Institution

The reimbursements of medical expenses such, as drugs, doctor's fees, and treatment or examination fees, are available by the Finnish national sickness insurance provider, the Social Insurance Institution (SII, http://www.kela.fi/in/internet/English.nsf). Up to 60 % of the doctor's fees and part of the cost of examinations and treatments ordered by a physician in the private sector are covered according to a fixed scale of charges. The part exceeding the fixed charge is not reimbursed.

The reimbursements are filed in electronic registers with personal identification (ID) numbers. The register of reimbursed examinations and treatments also includes the code of the physician, the codes of the examinations or treatments, dates, costs, and the amounts of reimbursements. The register of reimbursed drugs includes the municipality of recipients, the name and class of the drug, the size and numbers of packages, the dose recommended, the dates prescribed and bought, and the code of the physician.

In Finland, patients with certain long-term illnesses are entitled to a higher reimbursement of their costs of medication and clinical nutrients. This so-called Special Refund Category consists of approximately 50 diseases. Among children, the most common special refunded diseases are asthma, epilepsy, diabetes, rheumatoid arthritis, and allergy to cow's milk and/or soya milk. For the present study, information of reimbursements of long-term medication was also available and

the reimbursed medications were taken into account (excluding reimbursements of the clinical nutrients). The data on Special Refunds included the start and end dates of an entitlement period, the types, and the reasons.

The SII also grants child disability allowance for families who have a disabled or a chronically sick child needing continuous help and surveillance at home. The parents applying for benefits are required to supply recent medical documents. The register of the child disability allowance contains information of the start and end dates, the nature of benefit (temporary and permanent), the level of benefit (normal, increased and special), and the diagnoses for the support.

9.1.2 The Central Population Register

The information of marital status and occupation of the women was received from the Central Population Register (http://www.vaestorekisterikeskus.fi). The socioeconomic position was defined by using their occupation and classified into five categories: upper white-collar workers, lower white-collar workers, blue-collar workers, other (entrepreneurs, students, pensioners, unemployed women, and women with an unclassified position), and unknown position (Central Statistical Office, 1989).

9.1.3 The Hospital Discharge Register and the Care Register for Social Welfare

The HDR (http://www.stakes.info/2/9/index.asp) and the Care Register for Social Welfare (http://www.stakes.info/2/10/index.asp) are maintained by STAKES. The HDR collects information of inpatient care as well as of visits to outpatient clinics involving surgical or other procedures. It gathers information of diagnoses (the tenth revision of the International Classification of Diseases, ICD-10 since 1996), operation codes, and dates of admission and discharge. The diagnoses include the main diagnosis (which can consist of separate diagnoses of the reasons and symptoms leading to hospitalization) and two secondary diagnoses (which can also consist of two separate diagnoses of the reasons and symptoms) for each hospital episode. From 1983 to 1995, operations were registered according to a national coding system and, since 1996, according to the Finnish version of the NOMESCO classification system for surgical operations (Toimenpideluokitus, STAKES, 1996). The Care Register for Social Welfare collects information of care episodes in social institutions. Institutional care does not include children taken into children's homes or custody but refers mainly to mentally handicapped children who have stayed in institutions for intellectually disabled persons.

9.1.4 The Medical Birth Register

The MBR (http://www.stakes.info/2/1/2,1,1.asp) includes the unique ID numbers of the mother and the child and contains information of maternal background and on the outcome of all infants born in Finland until the age of seven days. The duration and causes of infertility are not registered. The data are collected by the delivery hospitals and completed by linkage to the Central Population Register and the Cause-of-Death Register. The socioeconomic position of the mothers was defined by using their occupation when delivering, which is collected routinely from maternity hospitals and classified automatically by the MBR into five categories (Central Statistical Office, 1989, Statistics Finland).

9.1.5 The Register of Congenital Malformations

The RCM (http://www.stakes.info/2/1/2,1,5.asp) collects information of all infants with a congenital anomaly (CA) or birth defect through several data sources, including a notification completed by the delivery hospitals, neonatal, pediatric and pathology departments, and cytogenetic laboratories as well as by linkage to several other nationwide registers. In the RCM a CA has been defined as a major congenital structural anomaly, chromosomal defect or congenital hypothyroidism involved in a birth. The CAs reported to the RCM, which do not qualify the criteria of major CA, are not accepted to the register (rejected, not registered cases).The physician responsible for RCM routinely classifies CAs into major, other, and rejected. Other anomalies reported to the register can, for example, be minor anomalies related to major CAs. Rejected anomalies include some minor CAs as defined by the European Surveillance of Congenital Anomalies EUROCAT (http://www.eurocat.ulster.ac.uk) exclusion list (hereditary diseases, dysfunction of organs or tissues, developmental disabilities, congenital infections, isolated minor dysmorphic features, normal variations, and other less significant anomalies).

9.1.6 The Cause-of-Death Register

The Cause-of-Death Register is maintained by Statistics in Finland and it includes personal ID numbers, causes of death (diagnoses according to the ICD-10 since 1996), and dates of death. The data is obtained from the death certificates, which are supplemented with the data from the population information system of the Central Population Register. The data in the Cause-of-Death Register covers the persons who have died in Finland or abroad and who at the time of death were domiciled in Finland.

9.2 Identification of IVF and OI women and their children

The study includes two exposed cohorts: 20–59-year-old women having had IVF treatments (IVF, ICSI and FET, N = 9175) and women having had other infertility treatments including drugs (ovulation inductions or low stimulation with or without artificial insemination, OI, N = 10 254) between 1996 and 1998 in Finland, and their children (Fig. 2). The population controls, matched by age and municipality, were randomly selected for IVF women (N = 9175) from the SII population record (covering the total Finnish population).

The basis for the data collection was that all infertility treatment cycles (not natural cycles and a part of frozen embryo transfers) start with drugs, and some drugs and their combinations are specific to infertility treatments as such. The bought and reimbursement drugs can be found from the reimbursement files of the SII. An algorithm about which drug combination indicates each infertility treatment was created (detailed in Hemminki et al., 2003). The beginning of a treatment cycle was defined by the date of buying the first infertility drug. The cycles were classified as ovulation induction (with or without insemination), IVF without embryo transfer (cancelled cycles and cycles for ovum pick-up), IVF with embryo transfer, and frozen embryo transfer. IVF interventions done in the private sector (over 60%) which are covered and registered by the SII were added to the cycles. The functioning of the algorithm was checked manually 18 times (with the sample sizes between 200 and 2000 women), and the algorithm was improved with the received information. As a whole the algorithm worked well (Hemminki et al., 2003), and a total 24 318 IVF cycles could be identified, which was slightly higher than the number of cycles registered in IVF statistics (21 424). This can be partly explained by the cancelled cycles which were also included in this study and partly by incorrect classification. The number of identified OI cycles was 24 611, which could not be compared to any other number of cycles, since OI cycles are not collected in any statistics. The data on IVF and OI women were created from the women who had received IVF and OI treatment cycles.

To identify the children born after IVF or OI the data were linked to the nationwide MBR by using the personal identification numbers of the women and the dates of birth of the children as the linkage keys. For IVF births the time limit of 44 weeks after the beginning of treatment (the purchase of the first drug) to the date of birth was used as a standard and for OI births it was 48 weeks.

As controls for the children, two groups of children were selected from the MBR. The first control group consisted of all children other than IVF and OI children (N = 190 398) who had been conceived during the same time-period (1996–1998). The second control group (n = 26 877) was a random sample of the first control group and was selected to reduce the workload caused by large register linkages in the SII and the RCM; it was used to study the benefit payments from the SII, CAs from the RCM, and in the combined analysis.

9.3 Register linkages

The data on the identified women who had used IVF and OI were linked to the CPR to receive information of women's background characteristics. The data on the costs and reimbursements were received partly from the SII and partly from the clinics: Helsinki University Central Hospital and the biggest private IVF clinic recommended by other clinics (Paper V). The costs taken into account were direct costs, such as medications, visits, routine examinations, interventions, and costs of equipment and trained staff. Indirect costs, such as costs for travel and sick-leave, were not included. The expenditures were partly based on the average costs in clinics, partly on estimations, and partly on exact paid and reimbursed costs. Private expenditures include costs paid by the patient and public expenditures costs paid by the health care system. All costs and reimbursements have been inflated to correspond to 2005 prices (in euros) using a consumer price index compiled by Statistics Finland.

The data on care episodes at hospital were collected by register linkages to the HDR, and dates and causes of death (during the mean of 3.7-years of follow-up for IVF and control women and 3.8 years for OI women) from the Cause-of-Death Register by using personal ID numbers (Fig. 2).

The data on perinatal health of the IVF children and the ID numbers of the children were obtained from the MBR. To receive data on the health of early childhood the identified children were linked to five other nationwide registers by the ID numbers of the children: the Cause-of-Death Register, the HDR, the Care Register for Social Welfare, the RCM (without knowing the mode of conception of the children), and the health-related social benefits from the SII (Fig. 2).

9.4 Data analysis

Use and costs

To calculate the age-specific incidences of the use of IVF and OI, the number of women treated was divided by the number of all women in the same age group in the same area (SOTKA database 2001, STAKES). The age-adjustment was made by using direct age-standardisation. The mean price of different types of IVF cycles by the care sector were calculated as well as the private, public, and total expenditures by women's background characteristics and by live births. The mean population of females aged 20–49 years in Finland by socioeconomic position and area of residence according to census information for 1995 and 2000 available from Statistics Finland was used to count the expenditure by population groups.

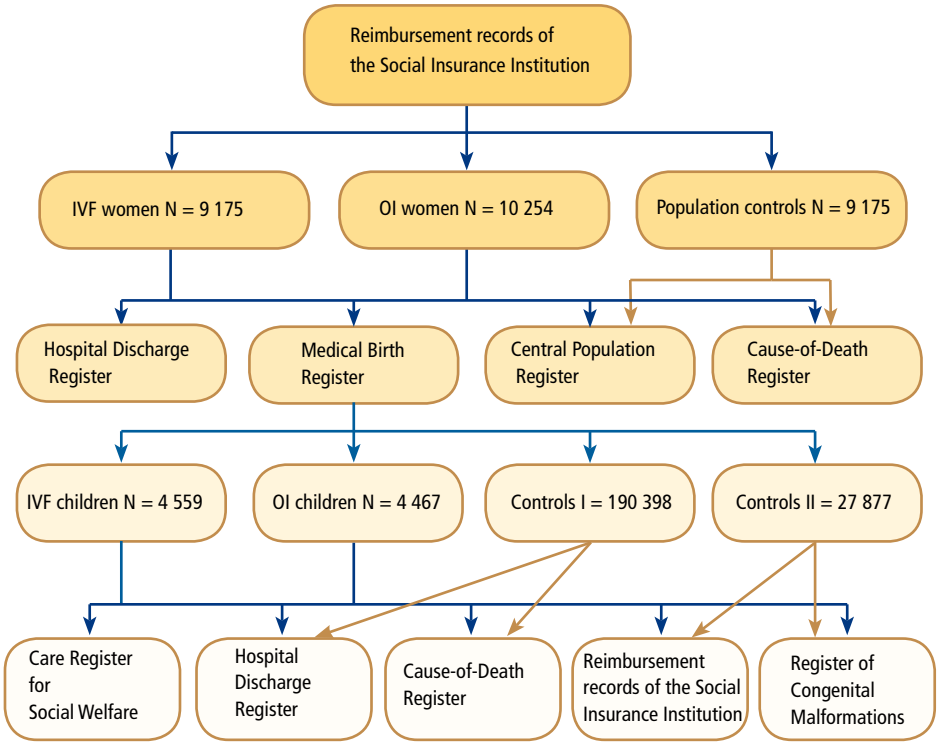

FIGURE 2. Registers, study population, and register-linkages used in the study.

The cycle was defined as having taken place in the private sector in cases where an intervention in the IVF cycle involved reimbursement by the SII. For the other IVF cycles the classification of cycles as private or public was made according to the main work place of the physicians given in a catalogue of physicians (STAKES, 1998). The catalogue is based on the register of health care personnel (TERHIKKI) which receives information of certificate doctors from the Finnish Medical Association. The classification for private and public cycles was crude, since the main work place could not always be defined. The OI cycles could not be classified as private or public.

Complications and miscarriages after IVF and OI and pregnancy and birth treatments

The proportion of the IVF and OI women with a complication (the first occurrence) after the first cycle and after all treatment cycles (in the study window) was calculated separately for each type of complication (risk for a complication after an average of 2.7 treatment cycles). The studied outcomes, follow-up times, and data sources are presented in the Appendix, and the ICD-10 codes of complications are detailed in the Appendix of Paper II. In addition, the diagnoses defined

in the HDR as OHSS (ICD-10 code) as well as symptoms or diseases potentially related to OHSS ("potential OHSS") were searched from the HDR. Some women had both the diagnosed OHSS (with the specific ICD-10 code) and the "potential OHSS".

The causes of death were classified into eight categories: reproductive mortality as defined by Fortney et al. (1986) with the addition of causes related to achieving the pregnancy, diseases of the circulatory system, cancers, suicides, homicides, accidents, other, and unknown causes.

The IVF mothers were compared to the mothers of the control children in their utilization of health care services during the pregnancy and child birth (hospitalization during the pregnancy, Caesarean section, and the hospitalization of seven or more days after the delivery). The same variables were studied also for OI women but were not reported in Paper IV for space reasons as suggested by the referees of the journal.

Health of IVF children

The IVF children were compared to the control children. The studied outcomes, follow-up times, and data sources are presented in the Appendix. The follow-up times varied, because the data were first collected until two years of age and then completed by the data on hospitalizations until the children were four years of age. Information of specific diseases was received by combining the different data sources and by calculating the number of children who had used the services—according to any of the data sources—due to an allergic or chronic disorder or common infection until two years of age. If the child was hospitalized more than once due to the same diagnosis, only the first hospitalization was included. The same variables were studied also for the OI children, but they were not reported in Paper IV for space reasons as suggested by the referees of the journal.

The occurrence of major CAs both among the IVF and OI children was reported (detailed in Paper III). Only major CAs, as defined in the RCM, were included in the analysis. In the analysis of the CAs by the organ system, a child appeared more than once if (s)he had more than one major CA affecting different organ systems. The IVF and OI women were linked to the Register of Induced Abortions to specify induced abortions performed due to a suspected or confirmed CA. The rates were compared to the national rates per 10 000 births.

Statistical analysis

The differences between the IVF and control groups as well as those between the OI and control groups were examined by using tests for relative proportions, t-tests, chi-square tests, and the one-sided analysis of variance. A P-value of less than 0.05 was considered significant.

The IVF mothers were compared to the mothers of the control children and the IVF and OI children were compared to the control children using odds ratios (OR) and 95 % confidence intervals (CI). When the health of the IVF children in the early childhood was studied, two logit models were made: an ordinary logit model where all the children were assumed to be independent and an additional analysis using the iterative generalized least squares method where siblings born in the same delivery were assumed to be dependent.

The singletons and multiples were analysed separately. When the ORs for congenital anomalies were studied, the children were stratified also by sex and multiplicity. For perinatal outcomes adjustment was made by the age of the mother, previous births, smoking, marital status, socioeconomic position, and the residence of region, for congenital anomalies by the age of the mother, parity, socioeconomic position, and the residence of region, and for other childhood outcomes by socioeconomic position using logistic regression.

10 Results and comments

10.1 Use of IVF and OI (Papers I and V)

The background characteristics of IVF, OI, and control women are presented in Table 4. The IVF women were more often married and from the higher socioeconomic position compared to the OI and control women.

TABLE 4. Background characteristics of IVF, OI, and control women[a] in 1996–1998.

	IVF (n=9 175)	OI (n=10 254)		Controls (n=9 175)	
Age group					
20–24	3.5	11.0		3.5	
25–29	20.8	31.4		20.8	
30–34	35.2	31.5		35.2	
35–39	27.7	17.8		27.7	
40–44	10.8	6.9		10.8	
45+	2.0	1.4		2.0	
Total	100.0	100.0	p<0.001[b]	100.0	p=1.000[d]
Marital status					
Non-married [c]	22.3	19.1		36.1	
Married	69.4	72.5		56.7	
Divorced	7.9	7.9		9.4	
Widow	0.4	0.5		0.4	
Unknown	0.0	0.0		1.4	
Total	100.0	100.0	p<0.001[b]	100.0	p<0.001[d]
Socioeconomic position					
Upper white-collar	25.3	20.6		16.3	
Lower white-collar	48.5	48.7		45.7	
Blue-collar	16.2	18.0		19.3	
Others	7.9	10.0		12.3	
Unknown	2.1	2.7		6.4	
Total	100.0	100.0	p<0.001[b]	100.0	p<0.001[d]

[a] Population controls for IVF women, matched by age and muncipality.

[b] P-values for chi square tests (IVF women and OI women).

[c] Includes cohabitation. Divorced and widowed women can also live in cohabitation.

[d] P-values for chi-square tests (IVF women and controls).

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TABLE 5. Number of IVF cycles per treated women by age, socioeconomic position and treatment sector in the study period (mean 1.5 years).

	Age					
	20–29	30–34	35–39	40+	Total	P-value[b]
Socioeconomic position						
Upper white-collar	2.28	2.83	2.91	3.14	2.82	< 0.001
Lower white-collar	2.16	2.69	2.77	2.98	2.62	< 0.001
Blue-collar	2.27	2.56	2.74	2.96	2.56	< 0.001
Others [a]	2.23	2.69	2.59	2.83	2.52	0.003
Sector						
Public	1.93	2.21	2.36	2.18	2.17	< 0.001
Private	2.21	2.65	2.66	2.92	2.61	0.573
Both	3.09	4.43	4.59	5.30	4.19	0.055
Total	2.21	2.71	2.79	3.01	2.65	0.066

[a] Entrepreneurs, students, pensioners, unemployed, and women with an unclassified or unknown position.

[b] P-values for one-sided analysis of variance.

The age-standardised IVF incidence per thousand 20–49-year-old women was 8.8 in the urban and 7.3 in the rural areas. The use of OI was highest in the semi-urban area (10.4) and lowest (8.5) in the capital area. The regional incidence of IVF varied from 6.5 (in eastern Finland) to 9.2 (in the capital area in southern Finland) and of OI from 5.2 (in eastern Finland) to 12.7 (in northern Finland). The northern region had no IVF clinic, and the use of OI was common.

Approximately 53% of IVF women received all IVF treatments from private doctors ('private users'), 35% from public doctors ('public users'), and 12% from both private and public doctors ('both-sector users'). The private users were older (mean age 34.3 years) than the public (32.3 years) and both-sector users (32.8 years, $p<0.001$). In the private sector, the women in the highest socioeconomic position were over-represented (29% private, 18% public, 16% controls). During the mean 1.5-years study period, the IVF women had received a total of 24 318 cycles; the minimum number was one and the maximum 14 cycles. The IVF women

TABLE 6. Rates (per 1000 female population) of women having received IVF by age and socioeconomic position in the study period.

	Age				
	20–29	30–34	35–39	40+	Total
Socioeconomic position					
Upper white-collar	14	30	24	4	13
Lower white-collar	13	25	17	2	9
Blue-collar	8	16	12	1	6
Others [a]	2	5	3	1	2
Total	7	18	14	2	7

[a] Entrepreneurs, students, pensioners, unemployed, and women with an unclassified or unknown position.

received slightly more treatment cycles in the private sector compared to the public sector (p-value for one-sided analysis of variance < 0.001); the frequency was not age-dependent, and the women in the highest socioeconomic position had slightly more cycles than the others (p-value < 0.001, Table 5). In the public sector the number of cycles did not differ by socioeconomic group, and the women aged from 30 to 39 years had more cycles than the others. In the population-based examination it was found that the women from the highest socioeconomic-group used IVF twice as much as the blue-collar women in every age-group.

The over-representation of women in the highest socioeconomic position among the IVF women is in accordance with previous studies (Svensson and Stephenson, 1993, Wilcox and Mosher, 1993, Gunnell and Ewings, 1994, Bachelot and Mouzon, 2002), but in the present study it was found only in the private sector. The higher number of cycles in the private sector cannot be explained solely by age, because the difference was also found in the age-specific analysis. It may indicate effectiveness and an ability to respond to demand, but also a sign of growing commercialism. In the United States, the growing numbers of fertility specialists and clinics have increased competition for clients, and some authors consider the marketing of infertility services aggressive (Mitchell 2002, Spar 2006). The older age of the treated IVF women in the private sector found in the present study can be explained by an informal age limit within the public sector. Some of the women treated were over 50 years of age, but their number was very insignificant.

It is possible that a widespread use of IVF eliminates socioeconomic differences in countries using public resources to provide IVF. In the present study, the public sector made the use of services more equitable for different socioeconomic groups, though it could not compensate for socioeconomic differences created in the private sector. On the other hand, if the private sector did not offer IVF services, the social class differences might be smaller but waiting lists might be longer, and the total number of treatments and women treated would be smaller. Since the regional differences were not great, it seems that long distances are no object; women are prepared to travel to obtain IVF treatments.

10.2 Success of IVF (Papers I and V)

The numbers and rates of women having received IVF was the highest among women aged 30–39 years (Tables 4 and 6), but the treatment was more intense for older women (number of cycles per woman, Table 5). The efficacy of IVF measured by the success rate per cycle and per woman decreased by age (Tables 7 and 8). The higher treatment intensity among the older women did not compensate for the lowered success rate, and approximately 47% of the women aged under 30 years and only 17% of those aged 40 years or older succeeded in achieving a live birth after the treatment period (mean 1.5 years).

TABLE 7. Live-births per number of IVF cycles[a] by age, socioeconomic position, and treatment sector.

	Age				
	20–29	30–34	35–39	40+	Total
Socioeconomic position					
Upper white-collar	0.25	0.18	0.13	0.06	0.15
Lower white-collar	0.23	0.17	0.14	0.05	0.16
Blue-collar	0.19	0.16	0.11	0.07	0.14
Others [b]	0.19	0.16	0.11	0.04	0.14
Sector					
Public	0.20	0.18	0.13	0.04	0.16
Private	0.26	0.20	0.15	0.06	0.17
Both	0.15	0.10	0.08	0.04	0.10
Total	0.22	0.17	0.13	0.06	0.15

[a] All live births and all cycles during the mean 1.5 years treatment period.

[b] Entrepreneurs, students, pensioners, unemployed, and women with an unclassified or unknown position.

The success of the IVF treatment was also dependant on the socioeconomic position: live-births per cycle were more common among the white-collar women than among the blue-collar ones aged less than 30 years (Table 7). Furthermore, the white-collar women in total achieved a live-birth more often than the blue-collar women (Table 8). The success per cycle did not vary much by the treatment sector, being the poorest among the both-sector users (Table 7), but the women treated in the private sector received more often a live-birth than those treated in public sector or in both (Table 8).

TABLE 8. Live-births per IVF women[a] by age, socioeconomic position, and treatment sector.

	Age				
	20–29	30–34	35–39	40+	Total
Socioeconomic position					
Upper white-collar	0.55	0.49	0.38	0.20	0.42
Lower white-collar	0.49	0.46	0.37	0.15	0.40
Blue-collar	0.42	0.40	0.30	0.21	0.36
Others [b]	0.42	0.41	0.29	0.12	0.35
Sector					
Public	0.39	0.40	0.31	0.08	0.35
Private	0.56	0.50	0.39	0.19	0.42
Both	0.44	0.44	0.36	0.23	0.40
Total	0.47	0.45	0.36	0.17	0.40

[a] One live birth per woman during the mean 1.5 years treatment period.

[b] Entrepreneurs, students, pensioners, unemployed, and women with an unclassified or unknown position.

The success rates in this study were age-dependent as also found earlier, but slightly lower than especially in recent publications (Table 1). This can be due to the improved success rates in the course of time or to the different ways to calculate the number of cycles; cancelled cycles were included in this study. The better success of the women from the higher socioeconomic position compared to the other women in the present study can be a consequence of seeking for medical advice after a shorter period of infertility, of more intense treatments or of more serious infertility among women from the lower socioeconomic position. On the other hand, the greater number of cycles received by women in the highest socioeconomic position can be a consequence of seeking for IVF services at an older age as well of a capability to pay for or to request more treatments. The both-sector users were not too old or 'sick' to receive treatment in the public sector and they had evidently enough money to purchase care in the private sector. Since they needed many treatment cycles, it can be assumed that their treatments were less successful. Some of these women may have little or no chance of becoming pregnant, but they did not want to stop trying. However, 40 % of them received a child as a result of the treatments; finally they succeeded as well as the women in this study on average. The number of cycles among the both-sector users was not dependent on the socioeconomic position, which suggests that the care itself was experienced as important and useful.

10.3 Complications after IVF and OI, and pregnancy and childbirth treatments (Papers II and III)

Only a few IVF women were hospitalized due to the OHSS after the first treatment cycle but more after repeated attempts and particularly when the 'potential OHSS' was taken into account (Table 9). After OI the hospitalization due to the OHSS was rare. The risk of having OHSS was highest after the first and the fifth or more IVF treatment cycles (Paper II) and it was more common among twin than among singleton pregnancies ending in birth (3.2% vs. 1.4%, p-value < 0.001 for a test of relative proportions). After IVF treatment, OHSS (ICD-10) was much more common among younger than older women: 3.2% of the women under the age of 35 years were hospitalized due to the OHSS compared to 1% of the older women.

Bleeding and infections necessitating hospital care were rare and even rarer after OI than after IVF (Table 9). Miscarriage was the most common reason for hospital care. The percentage of women that had miscarriage was similar after the first OI and IVF treatment cycle, but after all treatment cycles, miscarriage was 1.6 times more common among the IVF women than among the OI women. The number of miscarriages per 100 births was 23.0 after IVF and 15.0 after OI. Ectopic pregnancies were also more common among the IVF women compared to

TABLE 9. Health problems leading to hospitalization after the first and all IVF or OI treatment cycles in the study period, per 1000 women.

	IVF (N = 9175)		OI (N= 10 254)	
	First	All	First	All
Outcomes				
OHSS, ICD-10 [a]	14.1	22.9	0.3	0.8
Potential OHSS [b]	5.6	13.3	5.6	9.1
OHSS, ICD-10 or potential	19.0	34.7	5.7	9.8
Bleeding	1.0	2.4	0.3	0.3
Infection	5.1	10.9	1.5	3.1
Other [c]	1.1	1.9	0.1	0.5
Ectopic pregnancy	9.3	20.9	8.2	10.7
Miscarriage	41.9	93.1	42.1	61.8

[a] OHSS = Ovarian hyperstimulation syndrome (N98.1, ICD code).

[b] Symptoms potentially related to OHSS (see Paper II).

[c] Other complication than OHSS related to IVF or OI (see Paper II) and thromboembolic events.

the OI women. The ratio per 100 births after IVF was 5.0 and that after OI 0.03. Six IVF women (four registered as pregnant) and four OI women had a thromboembolic event (two registered as pregnant).

After all treatment cycles, 15% IVF and 8% OI women were hospitalized for complications. During the whole follow-up (mean 3.7 years for IVF women and 3.8 years for OI women from the exposure) one death in both the IVF and OI group was related to reproduction (Paper II).

The IVF mothers were older, more often married, and from a higher socioeconomic position than the other mothers (Paper III). They were seldom smokers, the child was more often their first, and they received more hospital care during the pregnancy and Caesarean sections compared to the other mothers. Adjustment to mothers' background characteristics did not change the results. The inspection of singletons and multiples separately showed that this difference was partly, but not totally, explained by IVF children being more often twins.

As reported earlier (Schenker, 1999), women under 35 years of age were at a greater risk of OHSS. The risk was also greater among the women with only one cycle and those with many cycles. In this study it is not known how many cycles the women had received before the year 1996. After many repeated cycles a woman may be in a greater risk due to the repeated doses of drugs (especially gonadotrophin). This should be considered when many attempts are needed. Furthermore, the risk was also higher among twin pregnancies than among singleton pregnancies ending in birth, which has also been found in an earlier study regarding late OHSS (Mathur et al., 2000).

Only a few studies (Quasim et al., 1997, Abramov et al., 1999b) have reported the frequency of OHSS after ovulation induction (OI) alone or compared it to the frequency after IVF. The present study, in accordance with earlier studies from the USA and Israel, shows serious OHSS to be more common after IVF than after OI.

The present study confirmed earlier results that thromboembolic events exist after IVF but are rare complications (Serour et al., 1998), and even rarer after OI. The frequency of bleeding after IVF was the same in the present study as in an Egyptian study with 3500 cycles (Serour et al., 1998), but it was much lower than the frequency found in a recent report from ESHRE (Nyboe Andersen et al., 2006) which covered all bleeding complications, even those not leading to hospitalization. The frequency of infections in the present study was similar to that reported earlier in the Nordic countries (Bergh and Lunkvist, 1992) and Egypt (Serour et al., 1998), but higher than the frequency reported by ESHRE (Nyboe Andersen et al., 2006). The finding of very low rates after OI suggests, that bleeding and infections may be complications of the IVF technique.

It was not possible to identify how many of the treated women had become pregnant, but the miscarriage ratio to 100 IVF births (23.0) suggests similar miscarriage rates as found earlier after IVF (15% to 21%, Serour et al., 1998, Kupka et al., 2003, Schieve et al., 2003, Wang et al., 2004). However, since all miscarriages do not lead to hospital care, the actual rate of miscarriages must have been higher. The miscarriage ratio to 100 OI births was lower than after IVF (15 vs. 23). Whether this was due to women's characteristics or to the procedure itself, could not be judged from this study. Previously, greatly varying rates after clomiphene-induced pregnancies have been reported (9–27%, Venn et al., 1994).

In the present study no pregnant controls were available, but, according to one Finnish study, 8% of women with spontaneous pregnancies needed hospital care due to a miscarriage (Hemminki and Meriläinen, 1996). In one study from the United States the miscarriage rate was similar (15%) among ART women and normal female population (Schieve et al., 2003). However, in another study from the United States, the risk of miscarriages was slightly increased after ART (Wang et al., 2004).

The ectopic pregnancy ratio to 100 IVF births (5.0) in this study was two-fold higher than found earlier in Finland (Hemminki and Heinonen, 1987, Mäkinen, 1996). Information of the reasons for infertility was not available in this study, and the number of women having tubal occlusion, which is considered to be one reason for the high frequency of ectopic pregnancies among IVF women, could not examined. In the case of OI, which requires open tubes in order to be effective, a possible reason for the high rate of ectopic pregnancies could be clomiphene citrate (Venn et al., 1994).

In one study from Australia, the maternal mortality of IVF women was higher than the national rate (Venn et al., 2001). The authors suggested that reasons for that can be advanced maternal age, a high proportion of multiple pregnancies, and a high Caesarean section rate. Due to the lack of a control group of spontaneously pregnant mothers or women aiming at pregnancy, the best control group for IVF women was in this study the group of OI women, though the IVF women were older than the OI women. The present overall mortality was lower than in the general female population (matched by age and municipality), which is in accordance with the Australian study. In particular, the cardiovascular deaths were rarer. It speaks for a "healthy patient effect" among IVF and OI women (Venn et al., 2001): sick women are less likely to be married or to receive infertility treatment than healthy women. The socioeconomic position of the IVF women in this study was slightly higher than that of the control women, which can partly explain the low mortality. Lower mortality among the women having received IVF compared to those who had registered for IVF but never received the treatment has been reported in Australia (Venn et al., 2001).

10.4 Health of IVF children (Papers III and IV)

10.4.1 Health of the newborn

In this study 4 559 children born after IVF and 4 467 after OI could be identified. Of the IVF children 34.7% were twins and 1.1% triplets. The corresponding rates of the OI children were 11% and 1.1%. Among the control children 2.2% were twins and only 13 sets were triplets (0.02%).

The health of the IVF infants was much worse than that of the other infants, which was partly explained by plurality (Table 10). The health of the multiple IVF infants was comparable to that of control multiples; only the risk of a very preterm birth was increased, but not statistically significantly. In the subanalysis of the first births the results were mainly similar to those of all children and no differences in the results of the two logit analyses (see Methods) were found.

Stillbirths were more common among the IVF infants in total compared to the other children in total (7.2/1000 vs. 3.9/1000, p-value < 0.001 in the test for relative proportions) as well as among the IVF singletons compared to the control singletons (6.5/1000 vs. 3.7/1000, p-value $= 0.014$ in the test for relative proportions), but not separately among the multiples.

Among the IVF and OI children 51% of the reported major CAs had been accepted by RCM, whereas the proportion was 46% among control children. The total risk of major CA for IVF singletons was statistically significantly increased (Table 10) and for multiples insignificantly decreased. The prevalence of a major

TABLE 10. Proportions (%) and odds ratios (and 95 % confidence intervals, CI) of infant outcomes as compared to other infants, adjusted to mothers' background variables [a]

	Total			Singletons			Multiples		
	IVF	Controls		IVF	Controls		IVF	Controls	
Number of children	4559	190 398		2930	186 216		1629	4182	
Outcome	%	%	OR (95% CI)	%	%	OR (95% CI)	%	%	OR (95% CI)
Very preterm (< 32 gw)	4.7	0.9	4.45 (3.80-5.21)	2.0	0.8	2.06 (1.56-2.71)	9.6	7.0	1.26 (0.99-1.60)
Preterm (< 37 gw)	23.6	5.5	4.43 (4.10-4.77)	9.5	4.7	1.72 (1.51-1.96)	49.2	42.2	1.06 (0.93-1.21)
Birth weight < 1500 g	4.2	0.8	4.19 (3.55-4.95)	1.9	0.7	2.17 (1.64-2.88)	8.2	7.4	0.95 (0.74-1.22)
Birth weight < 2500 g	19.8	4.0	4.77 (4.40-5.18)	6.5	3.2	1.60 (1.37-1.87)	43.7	39.2	0.92 (0.81-1.06)
Apgar score 0–6	8.8	4.4	1.68 (1.50-1.87)	5.6	4.2	1.07 (0.91-1.26)	14.5	12.5	1.10 (0.90-1.33)
Special care[b]	23.0	8.2	2.71 (2.52-2.92)	12.5	7.6	1.36 (1.21-1.53)	42.1	35.0	1.04 (0.91-1.19)
Respiratory treatment	4.3	1.1	3.61 (3.08-4.24)	2.0	0.9	1.76 (1.34-2.31)	8.4	6.7	1.19 (0.93-1.53)
Hospitalization ≥ 7 days	23.8	6.4	3.42 (3.08-4.24)	10.8	5.8	1.43 (1.26-1.61)	47.4	37.6	1.02 (0.88-1.17)
Perinatal mortality	1.3	0.6	1.85 (1.40-2.44)	0.9	0.5	1.32 (0.88-1.98)	2.0	2.9	0.73 (0.47-1.13)
Congenital anomaly [c]	4.3	2.9	1.31 (1.10-1.57)	4.3	2.9	1.30 (1.05-1.61)	4.3	5.3	0.80 (0.48-1.32)

[a] County, smoking, age, marital status, parity, socioeconomic position.
[b] Treatment in intensive care unit or in newborn surveillance unit.
[c] Total number of controls = 27 078, singleton controls = 26 489, and multiple controls = 589
Reference group (OR=1) = controls.

CA was the same for IVF singletons and IVF multiples but much higher for multiples than for singletons among the OI (Paper IV) and control children. The IVF boys, both singletons and multiples, had major CAs more often than the IVF girls (Paper IV). A significantly increased OR was found among the singleton IVF boys (OR 1.63, CI 1.23–2.15) and a significantly decreased OR among the multiple IVF girls (OR 0.45, CI 0.22–0.93). Furthermore, increased ORs for urogenital and musculoskeletal CAs were found among the singleton IVF boys (Paper IV). Hypospadia was the most common diagnosis of these major urogenital anomalies, and the control boys had more minor hypospadias than the IVF boys. Also the OI singleton boys had a higher risk of urogenital CAs (Paper IV). No risk of specific musculoskeletal CA among the IVF boys was found.

By definition, all IVF mothers were exposed to some infertility drugs, most commonly to progesterone (Paper IV). Most mothers were exposed to several drugs. Only estrogens were used more often by the mothers of malformed than by those of non-malformed IVF children, but the mothers of most malformed children had not received estrogen. Among the OI children no differences in the use of drugs between malformed and non-malformed children were found, neither in the use of a natural nor a synthetic progestin.

During the study period nine out of 9175 IVF women (19.7 per 10 000 IVF birth) and eight out of 10 270 OI women (17.9 per 10 000 OI birth) had an induced abortion due to the suspicion or detected foetal defect. The national rate per 10 000 births in 1996–1998 in Finland was 36.7 (the MBR).

This study confirms the earlier findings of poorer infant health of IVF singletons (Schieve et al., 2002, Helmerhorst et al., 2004, Jackson et al., 2004) compared to naturally conceived singletons. The IVF multiples had a worse health in infancy than the IVF singletons, but the IVF and control multiples were similar in regard to health in infancy, which is largely in accordance with an earlier study (except for the finding of an increased risk of admittance to a neonatal intensive care unit and more common longer hospitalizations after the birth, Pinborg et al., 2004c). In contrast, a recently published Belgian study reported an increased risk of preterm birth also among IVF twins compared to naturally conceived twins, which was, however, largely explainable by the first birth given by IVF women (Verstraelen et al., 2005).

The previous finding that twins have more CAs than singletons (Mastroiacovo et al., 1999) was also found among the control children in this study, but not among the IVF children. This is in accordance with Danish studies, in which no differences were found in the malformation rates between IVF/ ICSI and naturally conceived twins (Pinborg et al,. 2004c, Zhu et al., 2006), but contrary to a recent study from the United States (Olson et al., 2005).

The present study verified an earlier result of the overall risk of urogenital and musculoskeletal CAs among IVF children (Hansen et al., 2002, Zhu et al., 2006). The present study was, however, too small to examine the risk of individual diagnoses such as the previously reported hypospadia (Ericson and Källén, 2001, Silver et al., 1999) and could not verify the increased risk of heart anomalies found earlier (Koivurova, 2005).

Potential reasons for the poorer health of IVF infants include infertility itself (Draper et al., 1999, Brink Henriksen et al., 1997, Basso and Baird, 2003, Basso and Olsen, 2005, Zhu et al., 2006), infertility treatments, and varying health behaviour during pregnancy. In IVF treatments one cause for CAs might be the use of hormonal drugs (Silver et al., 1999, Hemminki et al., 1999, Zhu et al., 2006). Although the dangers of hormones in early pregnancy have been discussed for decades (Hemminki et al., 1999, Kruse et al., 2003), they have not been the focus

when the health effects of IVF have been discussed. Other potential causes may be bypassing the fertilization barriers in gametes especially in ICSI, culture media, freezing and thawing of embryos as well as timing of embryo transfer (Shiota and Yamada, 2005). Male genital anomalies have been suggested to have a link to the hereditary paternal subfertility associated with ICSI (Wennerholm et al., 2000). The advanced age of mothers, a lower fertility rate, and an increased reproductive loss rate characterizing women seeking for infertility treatment have all been associated with different foetal and neonatal abnormalities. However, the higher age of mothers did not explain the increased risk of major CAs in this study.

Among IVF singletons the main cause for poorer health has been suggested to be infertility itself due to the higher incidence of preterm birth and a low birth weight also among infertile women without treatment and women with other infertility treatment than IVF (Lambert, 2003). One the other hand, some modifications in the gestational process induced by IVF and ICSI have been suggested (de Geyter et al., 2006) as well as so-called vanishing twins (singletons originating from twin pregnancies, Pinborg et al., 2005, De Sutter et al., 2006).

Zygosity plays a significant role when the health of IVF multiples is compared to the health of other multiples. In general monozygotic twins have had poorer perinatal outcomes and more major CAs than dizygotic twins. Although IVF and OI increase monozygotic twinning (Ericson and Källén, 2001, Källén et al., 2002), transfer of several embryos causes the majority of IVF twins to be dizygotic (30%) compared to naturally conceived pregnancies (1%, Schachter et al., 2001). This can partly explain the results of the similar outcomes of multiples in studies unable to take zygosity into account. In this study 50% of the IVF and 30% the control twins were opposite-sex twins indicating that more IVF children were dizygotic. The fact that the CA rate was not smaller among the IVF twin boys could result from a higher risk of CA among IVF boys.

10.4.2 Health in early childhood

Up to the age of four years a larger proportion of the IVF children were hospitalized and the IVF children had more often long hospital episodes, the average length of their episodes being longer compared to the controls (detailed in Paper III). In all ages the IVF children had slightly more hospital episodes than the control children (the difference being clearest during infancy) and in almost every ICD-10 category the proportion of hospitalized children was higher among the multiples than among the singletons. Perinatal problems were the main single reason for hospitalizations.

When information from different data sources was combined until the age of two years, it was found that IVF children, singletons, and multiples together had a three-fold increased risk of cerebral palsy, and more often disorders in psy-

TABLE 11. Proportion (per 1000) of children and adjusted[a] odds ratios of having an allergic or chronic disorder or a common infection (ICD-10-codes) until the age of two years.

	Controls (n = 26 877) 1 / 1000	IVF (n = 4 527) 1 / 1000	OR (95% CI)
Cerebral Palsy (G80)	1.4	3.8	2.92 (1.63-5.26)
Epilepsy (G40-G41)	2.5	3.3	1.33 (0.76-2.34)
Behavioural disorders (F80-F98)	4.1	6.6	1.68 (1.11-2.53)
Diabetes (E10)	0.5	0.9	1.57 (0.51-4.84)
Asthma (J45-J46)	28.1	30.3	1.08 (0.90-1.30)
Allergy (L20-23, L27, L50)	53.8	59.9	1.07 (0.94-1.23)
Pneumonia (J12-J18)	11.4	9.9	0.85 (0.62-1.17)
Diarrhoea (A08-A09)	38.6	44.2	1.17 (1.00-1.37)

[a] Adjusted to mother's socioeconomic position

chological development or behavioural and emotional disorders than the control children (Table 11). This was not seen when the IVF singletons and multiples were considered separately (Paper III). Of the infants with cerebral palsy, 88% were preterm and 76% from multiple pregnancies. Of the children with developmental or behavioural problems, 60% were multiples.

Until the age of two years a larger proportion of the IVF children and of the IVF singletons had received child disability allowance compared to the controls, but no statistically significant differences in the use of long-term medication were found between the IVF and control children (Paper III).

In the subanalysis of the first births the results were mainly similar to those of all children and no differences in the results of the two logit analyses (see Methods) were found.

According to the Care Registry for Social Welfare Institutions, 2.2 IVF children per 1000 had experienced at least one period of institutional care in a social welfare institutions. For other children born in 1997–1998 the rate was 2.7 per 1000 children.

The total mortality up to the age of two years was two-fold higher among the IVF children compared to the controls (9.0/1000 and 4.1/1000); the main causes being congenital malformations and conditions originating in the perinatal period. Separately, between the mortality rates of the IVF and control singletons and the IVF and control multiples no significant differences were found.

The present study confirms earlier results of higher mortality (Koivurova, 2005), higher number of hospitalizations (Ericson et al., 2002, Källén et al., 2005c), increased risk of behavioural problems (Källén et al., 2005c), CP (Strömberg et al., 2002, Lidegaard et al., 2005, Hvintjørn et al., 2006), and infections (Ericson et al.,

2002) among IVF children. In accordance with an earlier Finnish study based on both outpatient and inpatient visits (Koivurova, 2005) a slightly, but not statistically significant, increased risk of diarrhea was found, but, contrary to that study, no increased risk of pneumonia was seen among the present IVF children.

Unlike previous studies (Strömberg et al., 2002, Lidegaard et al., 2005), no increased risk of CP or sleeping disturbances was found among the IVF singletons; in this study the excess risk of CP was mainly explained by multiplicity. Also in the studies by Strömberg et al. (2002) and Hvintjørn et al. (2006) the main reasons for the increased risk of CP were prematurity and the multiple pregnancy rate. A recent Swedish study could not confirm the increased risk of CP; the risk disappeared after adjustment to confounders (Källén et al., 2005c). Furthermore, contrary to an earlier Swedish study (Ericson et al., 2002), an increased risk for epilepsy, tumours, and asthma among the IVF children in total could not be found in this study. However, no increased risk of epilepsy was found in the recent Swedish study, either (Källén et al., 2005c).

A few previous studies have reported on childhood morbidity of IVF multiples. In two studies no differences in neurological sequelae were found (Strömberg et al., 2002, Pinborg et al., 2004a). In this study no increased risk of any specific disease among IVF multiples was found. However, the IVF multiples showed in general higher childhood morbidity than the IVF singletons.

To the knowledge of the present author, there are no other studies examining the use of long-term medication, child disability allowance, and utilization of institutional care among IVF children. A slightly increased risk of child disability allowance among the present IVF children was explained by multiplicity, while in the utilization of long-term medication and institutional care no statistically significant differences were found between the groups.

10.5 Costs and allocation of resources in IVF (Paper V)

The estimated mean cost of IVF treatment with embryo transfer was EUR 3750 (Paper V). Frozen embryo transfers were much cheaper, EUR 1100. Of the total IVF costs, 36% were due to drugs, 21% to interventions, and 42% to other direct costs.

During the mean 1.5-year follow-up, the total costs per treated woman were EUR 6500, of which EUR 40% was paid from private sources (by women themselves) and 60% from public sources. In the private sector, the share of private expenditure (out-of-pocket payment) was 49% and in the public sector 24% of the total expenditures. The unit costs of IVF did not vary much between the age groups, but the older the women were, the more they paid themselves. The women from the highest socioeconomic position spent more of their own money for IVF

treatment compared to the blue-collar women regardless of the age of the women. This was due to the more frequent use of private services.

The cost of a live birth was on average EUR 16 000 and increased by age (Table 12). Live-births were the most costly among the women using both sectors. The total expenditures of IVF per population were highest among the women aged 30–34 years and then decreased (Table 12) due to the lesser use of IVF among older women (Table 5). Because of the higher use of IVF, in every age group the total expenditure of IVF was approximately two-fold for upper white-collar women compared to blue-collar women (Table 12). No remarkable regional differences were found according to the urbanity of the living area.

In previous studies the cost calculations of the IVF cycles have included different components which vary between countries and therefore make the comparison of the calculations difficult. The cost estimates of a successful IVF cycle in this study are in accordance with an earlier Finnish study (Koivurova, 2005) as well as with earlier international cost calculations by age that have included the same components as used in this study (Broekmans and Klinkert, 2006).

In the present study only some of the actual costs were taken into account. Only routine radiological and laboratory tests were included, and all indirect costs, such as travel costs and sick leaves, were excluded. Furthermore, the costs of complications as well as the pregnancy and birth costs, which are known to be higher among older women, were not included. With the inclusion of all costs, the total costs may have been higher for the older women and possibly also for rural

TABLE 12. Total expenditure per live-birth and per female population in euros by age, socioeconomic position, and treatment sector.

	Total expenditure per live-birth					Total expenditure per population				
	Age					Age				
	20–29	30–34	35–39	40+	Total	20–29	30–34	35–39	40–49	Total
Socioeconomic position										
Upper white-collar	12133	13196	17785	38437	16126	97	200	167	49	113
Lower white-collar	12264	13496	16930	43308	15303	77	158	111	22	75
Blue-collar	14302	14694	20503	31840	16908	49	95	74	16	48
Others [a]	14082	14603	20392	59310	17342	14	33	20	8	16
Sector										
Public	13603	13373	17395	38766	14712	NA	NA	NA	NA	NA
Private	10588	11843	16170	40522	14877	NA	NA	NA	NA	NA
Both	20188	22581	26645	42832	23870	NA	NA	NA	NA	NA
Total	12851	13657	17828	40662	15941	44	116	88	21	55

[a] Entrepreneurs, students, pensioners, unemployed, and women with an unclassified or unknown position.

NA = not available

women due to the longer distances from care facilities. The impact on socioeconomic differences is unclear.

Among infertile women in the IVF care system, older women with poorer success rates (i.e. increased need) received more treatments, and the costs per live birth were much higher among them than among the younger women. The expenditures per population were lower among the older women, since fewer older women were treated. In this study no data of the population-based need for IVF and wish for a child by age were available, and therefore it is not certain whether all older women whishing to have a baby were in the IVF care system. It is also unknown how many of younger women wishing for a child did not receive IVF. In total, more resources were allocated to younger women, which is —due to the higher costs and an increased health risk of older women—a fairer solution than the provision according to the need by age. The women with a higher socioeconomic position had more often used IVF, and the total and societal costs per population were higher than among them compared to the women from lower socioeconomic positions, which indicates inequality.

11 General discussion

The present study was based on registers. In general, the utilization of existing health care registers in health research has several advantages. The total costs and time spent on data collection can be reduced, the collection of longitudinal data is technically easy, a large sample size is possible, no contact with the studied individuals is needed, participating problems can be abolished, and the reporting bias is reduced (Gissler, 1999), which leads to more reliable data than is received by questionnaire surveys. On the other hand, only health problems that are collected or registered can be studied. Furthermore, most of the health care registers are administrative registers, not planned for ad hoc epidemiological studies. Reporting and data collecting systems may vary, and no corrections can be made. Mostly the data of diagnoses are not exact, but crude estimates, and to adjust the register data to scientifically valid information demands a lot of pre-processing (Sund, 2003).

Originally the present study on the health of IVF women and their children was designed to be performed by using data from clinics, but the data could not be successfully collected (Hemminki, 2002). After that it was decided to collect all data of exposed women and children as well as their follow-up, from nationwide registers. This decision allowed a larger sample size, secure processing of high data, and easy follow-up.

The registries used in the present study are of high quality (Keskimäki and Aro, 1991, Teperi 1993, Gissler et al., 1995b). The identification of the cohorts of the IVF and OI women from the reimbursement records and of the IVF children from the MBR, including all infants born in Finland, was successful (Hemminki et al., 2003, Gissler et al., 2004).The existence of a unique personal identification number enables reliable linkages to other health care registers. The cohorts of the IVF and OI women and their children were large enough to study the frequency of even rare health problems after IVF and OI. The data on major congenital anomalies of all children were received from a routine nationwide register, of which information is collected and classified blindly in regard to the IVF status. In addition, reimbursed diseases for long-term medication are clearly defined, and both child disability allowance and support for long-term medication are based on recent medical documents. Therefore it can be assumed that the reimbursement records are relevant in estimating disease occurrence.

In the present study socioeconomic differences were found in the use of IVF services and in the allocation of resources, primarily due to the use of private services. In the identification process as well as in the follow-up several assumptions and estimations had to be made. It is possible that in 1996 some women who had received treatment in the public sector and had used drugs bought and reimbursed before 1996 were missed. Both the grouping of the IVF treatments into private and public sectors and the estimations of the costs were crude. However, the lack of data is estimated to be only about 4% of the IVF and 6% of the OI women (Hemminki et al., 2003), and it is not likely to be biased by age, socioeconomic position or region of residence. The socioeconomic position of the women was defined by using their occupation and classified automatically according to the national classification complied by Statistics Finland (Central Statistical Office of Finland, 1989). Thus, even though the data are not necessarily accurate for each individual, it seems that there was no systematic bias and the differences between the groups are correct.

In the present study the risk of complications for women after each IVF treatment cycle was low, but repeated attempts resulted in serious complications for many women and occurred much more often than after OI alone. Since the method of identification of serious complications and miscarriages was based on a register covering only hospital care, inpatient care, and operations in outpatient clinics, the identification of outcomes was dependent on the care practices and the style of the physicians to record the diagnosis. However, serious complications leading to hospital care could be collected extensively, but less serious cases—also cases needing special care but treated in private clinics or public outpatient clinics —are missing in this data. Thus, the results underestimate the actual complication risks. In addition, the effects on the psychosocial health of IVF and OI women could not be examined in this study.

Although the health of most IVF children in the present study was good, they had more health problems than the other children. The reason for not being able to estimate the occurrence of less serious diseases and cases was the same as among the women: the use of outpatient care is not registered. The results of the health of the children may be biased by different thresholds in hospital admissions between the IVF and control children. The IVF parents, who were more often first-time-parents, may have been more anxious, which can lead to more hospital admissions and longer duration of care. It might also be that IVF children are more carefully examined by physicians or their health problems are more conscientiously reported than those of naturally conceived children. However, several facts speak against this source of bias. Less rejected reports of congenital anomalies were found among the control children than among the IVF children. The rate of hospitalizations was not increased in all categories of diseases among the IVF children. In addition, the results after adjustment to parity and socioeconomic

position and the results in a subanalysis of the first births remained unchanged. Furthermore, informing and advising on the benefits are part of routine clinical practice. The higher frequency of hospitalizations and certain health problems very likely reflect higher morbidity among IVF children. In addition, almost every outcome studied was quite similar between the IVF and control multiples.

As Mooney (1994) pointed out, the first step in discussion on equity is to define the population in need. The need for infertility treatments derives from the wish for a child, the biological capacity to achieve a pregnancy, and the availability of technology, i.e. assisted fertilization. It is known that the biological capacity decreases by increasing age (Baird and Strassmann, 2000, Broekmans and Klinkert, 2004, ESHRE, 2005), and therefore the age-related biological need for IVF is be assumed to be higher among older women compared to younger ones. The need should not be affected by the socioeconomic position in Finland (Notkola, 1995, Klemetti et al., 2004), i.e. the biological need is assumed to be the same in the different socioeconomic positions. In this study no information of the wish for a child, neither by age nor by socioeconomic position, was available.

Despite the existing technology, all infertile couples do not seek medical care (Gunnell and Ewings, 1994, Schmidt and Münster, 1995, Stephen and Chandra, 2000, Malin et al., 2001, Klemetti et al., 2004), and the demand for infertility treatments may vary by age and socioeconomic position. It might be that older women and women from higher socioeconomic positions are more aware of the availability of treatments and more likely to demand them. In addition, recognition of fertility problems, attitudes towards health and medical treatment, social support, health status, and prior contacts and experiences with health care can vary between the groups (Tain, 2003, White et al., 2006). However, as Mooney (1994) pointed out, the need and demand for services should be distinguished in the equity analysis; access should be equal according to the need, not according to the demand, for services. In this study access could not be examined, but, instead, equity in the use of infertility treatments, i.e. among those who already were in the care system, was discussed among the present women.

The next step in the equity analysis is to ask to what extent priority should be given on infertility treatments. Although infertility treatments were not very highly prioritized by a multiprofessional group on the prioritization of medical care in Finland (STAKES report 161, 1994), infertility is considered a disease and defined as such by medical practitioners (CDBI, 2005). Since infertility is defined as a medical problem, a natural consequence—though not the only possibility—is to solve it with medical technology. After the first IVF birth in Finland in 1984, IVF technology was rapidly introduced into all Finnish university clinics (Malin Silverio and Hemminki, 1996). Also private clinics were founded by pioneer physicians. IVF has become a common practice in Finland, but prioritization has not been explicitly discussed. However, the utilization rate of IVF treatments in

Finland, being one of the highest in the Europe (Nyboe-Andersen et al., 2006), may indicate that infertility treatments are considered valuable and important. In addition, the Finnish system, in which infertility treatments are offered both in the private and public sector with some reservations (a couple with two biological children, risk of infections or either female or male partner sterilized) (STM, 2005) and with public funds, speaks on behalf of high prioritization of infertility treatments. However, it can be asked by whom (health care professionals, decision makers, health care consumers or the whole public) the priority of infertility treatments is set in Finland.

According to the present study, inequity in the use of IVF by the socioeconomic position was evident, mainly resulting from the use of the private sector. The services are not organised in an equal way if infertile women of lower socioeconomic position lack opportunity to use private IVF services despite their need (Whitehead, 1990). In Finland it has been traditionally considered unfair that people should have to utilise the private sector to obtain the health care services they need.

Inequality in resource allocation by socioeconomic position was also prevalent: more resources were allocated to the higher socioeconomic groups compared to the lower ones. In this study the personal preferences (Mooney, 1994) could not be studied. However, if fewer resources were allocated to blue-collar women, because they were not willing to use IVF services as often as white-collar women, this differentiated allocation cannot be considered an inequality. On the other hand, women form a higher socioeconomic position used more own money for treatments. It can, however, be argued that those who are able to pay should have the freedom to allocate their own resources as they like. But due to scarcer resources (the same resources i.e. the same physicians work both in the public and private clinics, and, for example, complications leading to hospital care are treated in public clinics regardless of the treatment sector) and the unique Finnish system, in which private treatments are also partly covered, it can be asked whether this argument is applicable—especially considering the treatment of the other women. On the other hand, in spite of the coverage, the private expenditure remains higher, i.e. more own money is needed for treatments in the private sector. According to the review by Dawson et al. (2005), the most common reasons for refusal of IVF treatment have been financial. In this study it was not possible to examine the reasons for the use or non-use of IVF. Neither was it possible to study whether the treatments or the quality of care varied with different socioeconomic positions. In France, despite equal use of IVF, a deeper analysis showed that women from lower positions faced greater risks and lower benefits (Tain, 2003). The author asked whether 'social inequality is being reinforced with the experimentation of new technologies'. Poorer success (benefit) among the blue-collar women in this study may be related to more serious infertility: infertility-related risk factors such

as smoking, obesity (Helakorpi et al., 2001), and probably increased likelihood of genital infections.

In the case of IVF, the differences in age are a more complex and non-traditional equity issue than those between the socioeconomic groups. Is it equitable that in IVF treatment, as in other health care services, the 'sickest' (older women) receive more care—or would it be more equitable to treat women with the best possibility of achieving pregnancy, for example younger women with specified causes of infertility (Mooney, 1994, Neumann, 1997)? In this study the older women of a higher socioeconomic position received more intensive treatment. In the private sector the number of treatments was not age-dependent, but in the public sector the women younger than 40 years of age received more cycles than the older women. This can be a sign of adequate resources and an ability to respond to the need and demand in the private sector, but it might also be a sign of growing commercialism. The success or effectiveness of IVF decreased by increasing age, which speaks against the option of concentrating on treating older women. On the other hand, concentrating on treating younger women can lead to over-treatment (Gnoth et al., 2005). Age-restrictions set in the public sector have reduced waiting lists and conserved public health care resources. It can also be argued that age should not be a reason to turn women away from IVF, because for older women IVF may offer the last chance to become pregnant (Klipstein et al., 2005). However, the costs of live-births among the older women were over three-fold compared to the younger women. Thus, it can be asked whether treating older women is replacing the treatment of younger women and the resources of their treatment, and, if so, whether it is equal.

When discussing access and equity in the use of services, health risks should also be taken into account (Blank, 1997). Pregnancy and birth complications as well as poorer foetal outcome increase by age (Nybo Andersen et al., 2000, Salihu et al., 2003). Furthermore, as shown in the present study, there are IVF-related risks for treated women (serious complications leading to hospitalization) and their children (more health problems), which have to be considered in equity discussion. Also the safety of the new technologies in assisted fertilization is an issue still under debate (Peters, 2004). The use of ovulation induction should be considered carefully. According to the unpublished data by the present author on OI children, ovulation induction contributes to some health problems among children born after OI. From a public health perspective it would be wise to concentrate on treating women in the usual childbearing age, equally in all socioeconomic positions respecting the women's own preferences and to offer IVF treatment for medical reasons only after careful patient selection. Treating sexually transmitted infections at an early stage and encouraging couples to have children at a younger age than nowadays (to avoid potential fertility problems) may, in the future, play a significant role in the prevention of infertility. In addition, treatment costs cannot be ignored in equity discussion.

IVF has offered hope for a number of infertility couples and fulfilled their wish for a child. In this study 40% of the treated IVF women received a child. Other potential benefits of IVF could not be examined in this study. An ideal situation would be the one with healthy singletons without serious health complications neither in child nor mother, or infertile couples satisfied after finding solution for their infertility, either infertility treatment (with or without child), a child via adoption or decision to live contently without children.

The advancement of assisted fertilization has aroused many other questions of the equity and resource allocation than those related to age and socioeconomic position or efficacy and safety of treatments. It has also created a doubtful "baby market" which is characterised by the limits of science, an unmet demand due to the high cost of IVF, and a political system lacking sufficient legalisation (Spar, 2006). Increased marketing can lead to the use of AF earlier than necessary (Mitchell, 2002). In Finland the number of IVF treatment cycles has grown (IVF statistics, http://www.stakes.info/2/1/2,1,4.asp.), there is an increased competition for clients, and IVF has become commercialised as in other countries. So-called reproductive tourism (Blyth and Farrand, 2005) from other countries to Finland has been claimed to be a natural consequence of the permitting situation without legislation. The coming Finnish law is the most permissive one in the Nordic countries, though with some exceptions (for example assisted reproduction allowed for single women in Finland) in line with the Swedish law (Legislation..., 2005). Thus, the reproductive tourism may still continue but will not play a significant role in the use of AF in Finland.

The present study has both clinical and political implications. To avoid overtreatment infertility should be defined in line with the WHO definition: two years without conception, especially among women under 35 years of age. In IVF, transferring only one embryo whenever possible and treating women in the usual childbearing age reduce health problems both in pregnant mothers and their children. Information of the potential health effects and of the chances of having a baby at a certain age are, should be useful for couples seeking medical help for infertility.

Policy implications are to encourage health promotion institutions and experts to give information of the declining fertility by age as well as the complexity of IVF, since IVF is not an equal option to natural conceiving. The policy makers should make resource allocation for high technology transparent and openly discuss the issue of equity.

Additional implications for further studies include examining the short- and long-term health of OI children and the long-term health of IVF children. Studies on puberty and own fertility of IVF and OI children are lacking. Furthermore, it is of importance to examine the long-term health of IVF and OI women (for example cancers and psychosocial health). A deeper analysis of the use and non-use of IVF by different women's background characteristics would be useful for discussing whether equity prevails in infertility services in Finland.

12 Conclusions

1. Although the health of most IVF children was good, they had more health problems than the other children. As this was partly explained by multiplicity, reducing the number of transferred embryos would improve the health of IVF children.
2. Further studies are needed to explain the poorer health of IVF singletons and to examine the long-term health of IVF children as well as the health of children born after ovulation induction alone.
3. The risk of complications for women after each IVF treatment cycle was low, but repeated attempts resulted in serious complications for many women, and the complications occurred much more often than after OI alone.
4. Further studies are needed to examine the long-term health of IVF and OI women.
5. The socioeconomic differences in the use of IVF were due to the use of private services.
6. More resources were used by women from a higher socioeconomic position, adjusting to age.
7. Older women were treated more intensively; the distribution by need could not be studied.
8. The live-births of older women were much more expensive than those of younger women.

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APPENDIX. Health outcomes of IVF and OI women and IVF children; definitions, follow-up times, and data sources.

Outcome	Definiton	Follow-up time	Data source
Women			
OHSS	Diagnoses in ICD-10 [a] and length of hospitalization	120 days [b]	HDR
Potential OHSS			
Bleeding			
Infection			
Other complications			
Misscarriage	Diagnoses in ICD-10 and operation codes	240 days	
Ectopic pregnancy			
Death	Date of death and cause of death (ICD-10)	Mean 3.7 years for IVF and 3.8 years for OI	Cause-of-Death Register
Children			
Preterm	< 37gestation weeks	until 7 days after birth	MBR
Very preterm	< 32 gestation weeks		
Low birth weight	< 2500 g		
Very low birth weight	< 1500 g		
Special care	Treatment in intensive care unit or in newborn surveillance unit.		
Respiratory treatment	Respiratory treatment used		
Apgar scores	One minit scores 0-10		
Hospitalization	7 or more days after birth		
Stillbirth	Death from the completed 22nd gestational week onwards or if birth weight is ≥ 500g.		
Perinatal mortality	Stillbirths and death < 7 days from birth / 1000 live births		
Major congenital anomaly	A major congenital structural anomaly, chromosomal defect, or congenital hypothyroidism	until 1 year	RCM
Use of hospital services	Hospital episodes in the HDR	until 4 years	HDR
Length of hospitalization	Days		
Long-term medication	Support for long-term mecdication received	until 2 years	SII
Child disablity allowance	Child disability allowance received		
Childhood mortality	Deaths after perinatal period and ≤ 2 years / 1000.		Cause-of-Death Register
Cerebral palsy	ICD-10: G80	until 2 years	HDR
Epilepsy	ICD-10: G40-G41		
Behavioural disorders	ICD-10: F80-F98		
Diabetes	ICD-10: E10		
Asthma	ICD-10: J45-J46		
Allergy	ICD-10: L20-L23, L27, L50		
Diarrhoea	ICD-10: A08-A09		
Pneumonia	ICD-10: J12-J18		

[a] ICD-10 codes in Paper II.
[b] Days after the last reimbursement.

Original Articles I–V

Paper I

ORIGINAL ARTICLE

Taylor&Francis healthsciences

Equity in the use of IVF in Finland in the late 1990s

Reija Klemetti, Mika Gissler and Elina Hemminki

STAKES, National Research and Development Centre for Welfare and Health, Health Services Research, Helsinki, Finland

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Aims: The purpose of this study was to describe equity in the use of *in vitro* fertilization (IVF; including micro-injections and frozen-embryo transfers), and compare its use with that of other assisted reproduction technologies (other ARTs; including ovulation inductions with or without inseminations). *Methods*: The women who received IVF ($n=9$, 175) and other ARTs ($n=10{,}254$) between 1996 and 1998 were identified from the reimbursement records of the Social Insurance Institution (SII) covering all Finns. Population controls, matched by age and municipality, were selected for IVF women ($n=9{,}175$). Information concerning background characteristics came from the Central Population Register and the SII's reimbursement files. The sector (public vs. private) was defined using prescribing physicians' codes. IVF use was studied by the proportions of women treated and the frequency of treatment. *Results*: The age-standardized IVF incidence per thousand 20-to-49-year-old women was 8.8 in urban and 7.3 in rural areas, but the use of other ARTs did not vary correspondingly (9.2, 9.3). The regional incidence of IVF and other ARTs varied considerably. In the private sector, women in the highest socioeconomic position were over-represented (29% private, 18% public, 16% controls). During the mean 1.5 years of the study period, the IVF women had somewhat more treatment cycles in the private than in the public sector (mean 3.3, 2.7), and those in the highest socioeconomic position had more cycles than others (3.5, 3.2); the frequency was not age-dependent. In the public sector the number of cycles did not differ by socioeconomic group (mean 2.7–2.8 per woman), and women aged 25 to 39 had more cycles than others. *Conclusion*: There were socioeconomic differences in use of IVF services, but they were small because of the equitable use of public services.

Key words: equity, infertility treatment, IVF, private sector, public sector.

Reija Klemetti, PO Box 220, 00531 Helsinki, Finland. Tel: 358-9-3967 2265, fax: 358-9-3967 2496. E-mail: reija.klemetti@stakes.fi

INTRODUCTION

Infertility is common (1), and IVF (including micro-injections and frozen-embryo transfers) has become a universal infertility treatment. According to statistics published by the European Society of Human Reproduction and Embryology, the greatest availability of IVF services among 18 European countries was reported in Finland and Denmark (2). In 2001, approximately 2.5% of all Finnish newborns were born as a result of IVF. The number of children born with the help of other assisted reproduction technologies (called here other ARTs) is unknown.

It is generally believed that IVF services are unevenly distributed, and that urban women from upper social classes use these services more than rural women from lower social classes. However, there are few reliable data on the use and users of IVF or other ARTs. In Finland, the 19 IVF clinics were situated in eight towns in 1999 (3). Three out of 12 of the pre-1995 provinces studied had no IVF clinic. Women in some areas had to make long trips (as much as 700 km) to obtain IVF treatment. Other ARTs services were available in all parts of Finland.

Unlike the rest of the health service system in Finland, the private sector is an important provider of IVF; about 60% of all IVF services are supplied by private clinics (3). In 1999, 12 of the 19 clinics were private. In the public sector, patients pay a small fee for their visits, and the rest of visit costs are covered by the tax-financed healthcare system. In the private sector, patients pay significantly more for their visits, but about 60% of the physician's charges are reimbursed by the Social Insurance Institution (SII). About 50% of the drugs used in infertility treatments are reimbursed by the SII in both the public and private sectors. Despite public financial support, IVF treatments are still costly for women, especially in private clinics (4). During 1996–98 on average five IVF cycles were needed to achieve one live birth (Mika Gissler, personal communication). Frozen-embryo transfers are cheaper but more cycles are needed to achieve one live birth.

The aim of this study was to investigate equity in

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the use of IVF in Finland in 1996–98, and to compare it with the use of other ARTs. The use of IVF was studied both by the percentages of women treated and the frequency of treatment (cycles per woman).

MATERIALS AND METHODS

In Finland, IVF, artificial insemination and ovulation inductions are performed in outpatient clinics but in most cases the treatment involves prescribed drugs. Using reimbursements for drugs and infertility interventions in private clinics in the SII files, a cohort of women who had had at least one IVF treatment (*in vitro* fertilization without embryo transfer, *in vitro* fertilization with embryo transfer, or preparations for frozen-embryo transfer, $n=9{,}175$), and women who had had other infertility treatments including drugs (ovulation inductions with or without artificial insemination, $n=10{,}254$) between 1996 and 1998 in Finland were identified, by means of a pre-designed algorithm. The algorithm was based on the fact that some drugs or their combinations, sequence, and dosages are specific to infertility treatments. With the patient advice of IVF clinics, scientific literature, Finnish drug catalogues, and discussions with infertility physicians, we created an algorithm for drugs used in different infertility treatments (unpublished data from Hemminki et al., STAKES, 2003).

If an intervention in the IVF cycle involved reimbursement by the SII, the cycle was defined as having taken place in the private sector. For the other IVF cycles the classification of cycles as private or public was made according to the main work place of physicians given in a catalogue of physicians (STAKES, 1998). The classification was crude because we were not always able to define the main work place. The other ARTs cycles could not be classified as private or public.

Population controls, matched by age and municipality, were randomly selected for IVF women ($n=9{,}175$) from the SII population record (covering the total Finnish population).

Information on the women's background characteristics was obtained from the Central Population Register (CPR) and from the reimbursement files of the SII. According to the municipality of residence, the women were divided into urban, semi-urban, and rural groups. To calculate the age-specific incidences, the number of women treated was divided by the number of all women in the same age group in the same area (SOTKA database 2001, STAKES). The age adjustment was made by using direct age-standardization.

The socioeconomic position of the women was defined by using their own occupation (5): unknown, upper white-collar workers, lower white-collar workers, blue-collar workers, entrepreneurs, students, pensioners, and others, including unemployed women and women with an unclassified position. In the analysis, the four last categories were combined. Marital status (from CPR) at the beginning of the treatment was defined by the starting and ending dates of marriages, and there were five categories: non-married, married, divorced, widowed, and unknown. There was no information on cohabitation.

To study the frequency per woman of IVF treatment, data on women with at least one IVF treatment in 1997 ("1997 IVF data", $n=4{,}909$) were analysed. All cycles of these women in the years 1996–98 were included, and the number of treatment cycles per woman during the study period (range 0.5–3.0 years, mean 1.5 years, assuming an even distribution of first cycles in 1996–98), was calculated.

Tests for relative proportions, *t*-tests, chi-square tests, and one-sided analysis of variance were used to measure statistical significance. A *p*-value of less than 0.05 was considered significant. The statistical analyses were mainly performed using SPSS, version 10.

RESULTS

Characteristics of IVF women, other ARTs women, and population control women are presented in Table I. The IVF women were older than the other ARTs women (mean age 33.4 vs. 31.1 years). Women who had received any infertility therapy were more often married than the population controls were. A fifth of the women treated were never married.

There were more women in the highest socioeconomic category among IVF women than among control women (Table I). The upper white-collar women underwent IVF treatments at older ages than the other women (34.5 years for upper white-collar vs. 33.3 for lower white collar vs. 32.3 for blue-collar), measured either by age distribution (data not shown) or by mean age.

The age-standardized incidence of IVF, calculated per thousand 20-to-49-year-old women varied by region from 6.5 (in eastern Finland) to 9.2 (in the capital area in southern Finland). The age-standardized incidence of other ARTs varied by region from 5.2 (in eastern Finland) to 12.7 (in northern Finland). Women from the capital area underwent IVF and other ARTs treatment at older ages than women in other parts of Finland. When the use rates of IVF and other ARTs were combined, infertility treatments were significantly more common in one region of northern Finland and in the capital area than in the

Table I. *Background characteristics of IVF women, Other ARTs women and population controls* in 1996–98 in Finland, (%)*

	IVF (n=9,175)	Other ARTs (n=10,254)		Controls (n=9,175)	
Age group					
20–24	3.5	11.0		3.5	
25–29	20.8	31.4		20.8	
30–34	35.2	31.5		35.2	
35–39	27.7	17.8		27.7	
40–44	10.8	6.9		10.8	
45+	2.0	1.4		2.0	
Unknown	0.0	0.0		0.0	
Total	100.0	100.0	*p<0.001*†	100.0	*p=1.000*§
Marital status					
Non-married‡	22.3	19.1		36.1	
Married	69.4	72.5		56.7	
Divorced	7.9	7.9		9.4	
Widowed	0.4	0.5		0.4	
Unknown	0.0	0.0		1.4	
Total	100.0	100.0	p<0.001†	100.0	p<0.001§
Socioeconomic position					
Upper white-collar	25.3	20.6		16.3	
Lower white-collar	48.5	48.7		45.7	
Blue-collar	16.2	18.0		19.3	
Others	7.9	10.0		12.3	
Unknown	2.1	2.7		6.4	
Total	100.0	100.0	p<0.001†	100.0	p<0.001§

*Population controls for IVF women, matched by age and muncipality.
†P-values for χ^2-tests (IVF women and Other ARTs women).
‡Includes cohabitation. Divorced and widowed women can also live in cohabitation.
§P-values for χ^2-tests (IVF women and controls).

country as a whole. The northern region had no IVF clinic, and the use of other ARTs was common.

There was a small but statistically significant difference in the total use of IVF between urban and rural women (test for relative propositions $p<0.001$, Table II). Adjustment by age did not change the result. When the data were examined by age group, the difference remained only among women over 35 years old ($p<0.001$). The total use of other ARTs was also more common among urban than rural women, but after age adjustment, the difference disappeared; the use was most common among semi-urban women. When the use of IVF and other ARTs was combined, infertility treatments were more common among urban ($p<0.001$) and semi-urban ($p<0.001$) women than among rural women.

Some 53% of IVF women received all their IVF treatments from private doctors (“private users”), 35% from public doctors (“public users”), and 12% from both private and public doctors (“both-sector users”, Table III). The private users were older (mean age 34.3 years) than public users (32.3 years) and both-sector users (32.8 years, $p<0.001$). Most women in both the private and the public sector category were

Table II. *Raw and age-standardized incidences per 1000 20-to-49-year-old women for IVF and Other ARTs women†, by urbanity*

	Raw rates		Age-standarised rates	
	IVF (n=9,136)	Other ARTs (n=10,207)	IVF (n=9,136)	Other ARTs (n=10,207)
Urban	8.7	9.4	8.8	9.2
Capital	9.7	8.8	8.9	8.5
Other	8.5	9.7	8.5	9.5
Semi-urban	7.9	9.9	8.2	10.4
Rural	7.0	8.7	7.3	9.3
Total	8.3	9.3	8.3	9.3

†Women over 49 years, women living abroad and women whose place of recidence is unknown are excluded.

Table III. *The distribution of IVF women by socioeconomic position and by care site (%)*

	Only private (n = 4,809)	Both sectors (n = 1,118)	Only public (n = 3,225)
Socioeconomic position			
Upper white-collar	29	29	18
Lower white-collar	48	48	50
Blue-collar	14	15	20
Others	7	6	9
Unknown	2	2	3
Total	100	100	100

For χ^2-test (socioeconomic position and sector) $p < 0.001$.

between 30 and 39 years old, but younger age groups were larger and older age groups smaller in the public than in the private sector; 19% of private sector users and 5% of public sector users were aged 40 years or more.

The private and both-sector users were more often women in the highest socioeconomic groups than were the public users (Table III). In the public sector, women in the highest socioeconomic position were not over-represented when compared with population controls (Table I).

The background characteristics of women in the "1997 IVF data" did not differ from that of IVF-treated women in total. During the examination period (estimated average 1.5 years), the mean number of IVF cycles was 3.3 (Table IV). The mode was two, and the maximum number was 14 cycles. A quarter of the women underwent five or more IVF cycles. In the private sector, the number of IVF cycles was higher than in the public sector, and in the private sector the number did not depend on a woman's age. In the public sector, the youngest and the oldest women did not undergo as many IVF cycles as other women. In all age groups, more women underwent five or more IVF cycles in the private than in the public sector. Both the number of IVF cycles and the number of women undergoing five or more cycles were highest among both-sector users.

Women in the highest socioeconomic group underwent more cycles than women in the other socioeconomic groups (mean 3.5 for upper white-collar vs. 3.3 for lower white-collar vs. 3.2 for blue-collar group). The number of cycles was age dependent only among the women from the highest socioeconomic position; 40-to-44-year-old women underwent more cycles than the other women (data not shown). In the private sector, women from every socioeconomic group had more IVF cycles than in the public sector but the users of both sectors had most IVF cycles. Socioeconomic position had no impact on whether women underwent five or more cycles in the public sector but it had some impact in the private sector.

Overall, the frequency per woman of IVF treatments was the same for urban, semi-urban, and rural women as well as in different regions (data not shown).

DISCUSSION

There are two main questions that are asked when one discusses equity in infertility: first, what priority

Table IV. *Mean number (standard deviation) of treatment cycles in 1996–98 of IVF-women† who had at least one treatment cycle in 1997 by care site, and the proportion of women with 5 or more cycles*

	Age in years						
	20–24 (n = 163)	25–29 (n = 1,048)	30–34 (n = 1,765)	35–39 (n = 1,308)	40–44 (n = 540)	45–49 (n = 77)	Total‡ (n = 4,901)
Care site							
Only private (n = 2,457)	2.8(1.9)	3.3(2.1)	3.3(2.1)	3.3(2.0)	3.4(2.2)	3.0(2.1)	3.3(2.1)
Only public (n = 1,620)	2.6(1.5)	2.8(1.6)	2.7(1.5)	2.7(1.6)	2.5(2.3)	1.4(0.6)	2.7(1.6)***
Both sectors (n = 824)	3.6(1.6)	4.6(1.9)	4.6(1.8)	4.5(2.0)	4.6(1.8)	3.3(1.0)	4.6(1.9)*
Total	2.7(2.0)	3.5(2.2)	3.3(2.0)	3.3(2.0)	3.3(2.0)	2.9(1.7)	3.3(2.0)**
≥5 cycles, %§							
Only private	19	26	24	25	26	18	24
Only public	0	9	15	13	12	15	13
Both sectors	0	46	44	48	48	19	46
Total	17	25	24	24	26	14	24

†Women living abroad and women whose place of recidence is unknown are excluded.
‡For one-sided analysis of variance *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
§For χ^2-test (age and care site of women undergone 5 or more cycles) $p < 0.001$.

should be given to infertility services; and second, how scarce healthcare resources can be distributed equitably and with maximum benefit to public health (6). In addition, issues of reproductive rights, safety, efficacy, and access to infertility services have been discussed (7). Access to services is linked to the funding of services. Economic status, information on available programs and morality (8), and geographical variations, age, marital status, and sexual orientation of women (7) have also been issues. Our study provides answers to some of these questions as they apply to equity in the use of IVF in Finland.

The first main finding of our study was that the differences between socioeconomic groups were relatively small. Additionally, the observed differences were mainly a consequence of the use of the private sector. The third finding was that although the IVF clinics were unevenly distributed geographically in Finland, the distribution of women receiving IVF treatment was less skewed. The finding that differences were due to use of the private sector suggests that the supply and cost of IVF treatments are likely to create inequalities.

Can these results be trusted? A potential weakness of our study lies in the accuracy of exposure, constructed from reimbursement files. Despite the complexity of the process, the identification went well, the high quality of register data and the existence of a unique personal identification number suggest that the identification of women was not biased by their social class or region of residence (unpublished data from Hemminki et al., STAKES, 2003, unpublished data from Gissler et al., STAKES, 2003).

Our findings concerning the over-representation of women from the highest socioeconomic group are in line with those of some earlier studies from Canada and Australia (6), the United States (9), the United Kingdom (10) and France (11). In the United States in 1995, college graduate women were more likely to have received infertility services – but not assisted reproductive technology – than other women; but the total number of women being treated by means of assisted reproductive technology was very small (12). A recent Swedish study found no clear trend with regard to the level of education of IVF mothers (13). However, the Swedish study included only successful treatments, whereas our study included all treatments, a fact which may explain the difference between the two studies. It is possible that treatments of women in the highest socioeconomic position are less successful, because these women resort to IVF services at an older age than others. However, it is also possible that widespread use of IVF eliminates socioeconomic differences in countries using public resources to provide IVF.

There are few reliable data concerning the need for infertility services in different socioeconomic groups or geographical areas. One Finnish study indicates no significant socioeconomic or regional differences in infertility rates but it suggests that secondary infertility could be more common among women from the highest socioeconomic group, and primary infertility in southern Finland (1). On the other hand, because smoking and obesity, which have been linked to infertility, are more common among women from lower socioeconomic groups (14), the need for infertility treatment may be greater among them.

Easy availability may increase the use of services, and the uneven geographic distribution of IVF clinics can create inequalities. Because the regional differences were not great, it seems that long distances are no object; women are prepared to travel to obtain IVF treatments. The use of all infertility services was common in the capital area, where many clinics are situated and distances to clinics are short. On the other hand, use was even more common in one region of northern Finland where long distances are involved. Reimbursement of travel expenses by the SII may somewhat decrease regional inequalities.

In our study, over-representation of women in the highest socioeconomic position was found only in the private sector. Furthermore, in the private sector, the IVF-treated women underwent more cycles than women in the public sector. The larger number of cycles cannot be explained solely by age, because the difference was also found in the age-specific analysis. Nor can it be explained by the type of cycle: equal proportions of frozen-embryo transfers and IVF cycles are performed in private clinics. A higher number of cycles in the private sector can be a sign of effectiveness and an ability to respond to demand but also a sign of growing commercialism. In the United States, the growing numbers of fertility specialists and clinics have increased competition for clients, and some consider the marketing of infertility services aggressive (15). Increased marketing can lead to the use of ARTs earlier than used to be the case – perhaps unnecessarily. Although in Finland the number of IVF clinics and the number of treatment cycles stabilized in the late 1990s after a growth period during that decade (3), there *is* competition for clients, and IVF has become commercialized in Finland as well as in other countries.

The public sector made the use of services more equitable for different socioeconomic groups, even though it could not compensate for socioeconomic differences created in the private sector. On the other hand, if the private sector did not offer IVF services, the social class differences might be smaller but

waiting lists might be longer, and the total number of treatments and women treated would be smaller.

"Both-sector users" were an interesting group in our study. They were not too old or "sick" to receive treatment in the public sector, and they evidently had enough money to purchase care in the private sector. We did not study the order of IVF treatments (private or public first), and we do not know the reasons for infertility among these women. It is possible that treatments were less successful, because these women underwent so many cycles. Some of these women may have little or no chance of becoming pregnant, but they do not stop trying to have a baby. The number of cycles did not depend on the socioeconomic position of women, which suggests that care was experienced as important and useful.

Differences in rates of utilization of healthcare services do not automatically mean that they are inequitable (16). However, if the over-representation of higher socioeconomic groups in our study is due to the fact that infertile women in the lower socioeconomic position do not have the opportunity to use IVF services, then services are not organized in an equitable way. In Finland it has also traditionally been considered unfair that people should have to use the private sector to obtain the healthcare services that they need.

It is a common ethical principle that access to care should not be affected by socioeconomic position or region of residence. In the case of IVF, differences involving marital status and age are a more complex and non-traditional equity issue. In many countries, infertility services are limited to married or heterosexual couples (17). In Finland, IVF is not legally restricted, and in our study a fifth of the women treated were not married. However, we do not know how many of the single, divorced, and widowed women in our study were cohabiting and how many were really single. If IVF services are offered to single or lesbian women who are not infertile, i.e. have no medical reasons to undergo IVF, and if equal access is understood to cover all persons who ask for treatment, we are no longer dealing with a health issue but a social issue.

Our study found that in the private sector older women were treated more than in the public sector. Some of the women treated were aged over 50 years but their number was very insignificant. The differences can be explained by an informal age limit that the public sector has introduced. Many other countries have legal age limits for IVF (7). Supporters of age limits base their arguments on the lower success rates and increased maternal and fetal morbidity and mortality among older women (17). However, it has also been argued that age limits are a violation of human rights (7), and that late motherhood means a higher level of financial and professional security and greater motivation in fulfilling the role of a parent (17). From the health perspective, it would be better to concentrate on treating women in their normal fertile age in order to minimize the adverse health effects for mothers and children due to advanced maternal age. Age restrictions also reduce waiting lists and conserve public health care resources.

With regard to equity in IVF use, many important questions remain open. Is it equitable that in IVF treatment, as in other health care services, the "sickest" (i.e. those for whom becoming pregnant is the most difficult) receive more care, as do the 40- to 44-year-old women in the highest socioeconomic position in our study? Or would it be more equitable to treat women with the best possibility of achieving success, for example younger women with specified causes of infertility (18)? How can the scarce health care resources be equitably distributed between IVF and other health care services? Currently it is difficult to estimate what is best and most equitable, since the health effects of IVF on women and children are largely unknown. As Svensson and Stephenson (6) have pointed out, it is important to study the safety and efficiency of IVF in order to help decide what constitutes equity in the use of IVF.

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Paper II

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Complications of IVF and ovulation induction

Reija Klemetti[1,3], Tiina Sevón[1], Mika Gissler[2] and Elina Hemminki[1]

[1]Research on Practices and [2]Information Unit, STAKES, National Research and Development Centre for Welfare and Health, Helsinki, Finland

[3]To whom correspondence should be addressed: STAKES, P.O.Box 220, 00531 Helsinki, Finland. E-mail: reija.klemetti@stakes.fi

BACKGROUND: The frequency and importance of complications of IVF and other ovulation induction (OI) are poorly known. We examined the occurrence of serious complications and miscarriages leading to hospitalization or operation after IVF (including microinjections and frozen embryo transfers) and OI treatment (with or without insemination). METHODS: Women who received IVF (*n* = 9175) or OI treatment (*n* = 10 254) 1996–1998 in Finland were followed by a register linkage study until 2000. RESULTS: After the first IVF treatment cycle, 14 per 1000 women had a serious case of OHSS (ovarian hyperstimulation syndrome), with 23 per 1000 throughout the study period (mean of 3.3 treatments). The corresponding values after OI were very low. The rates of registered ectopic pregnancies and miscarriages after IVF were nine and 42 respectively per 1000 women, with corresponding rates after OI of eight and 42. Infections and bleeding were not common after IVF and even rarer after OI. Overall, 15% of IVF and 8% of OI women had at least one hospital episode during the study period. CONCLUSIONS: Though there was a low risk of complications after each IVF treatment cycle, repeated attempts resulted in serious complications for many women, and these occurred much more often than after ovulation induction alone.

Key words: complications/IVF/OHSS/ovulation induction/register-based study

Introduction

Impaired fertility has increasingly become a health service issue because of the availability of new treatments, especially IVF and its related procedures, such as ICSI and frozen embryo transfer (FET) (called here IVF). Older treatments, including ovulation induction with or without insemination (OI), are still in wide use. In Finland, currently ~5% of infants are born as a result of IVF or ovulation induction (Gissler, 2003). According to our unpublished data, the estimated yearly number of treatment cycles between 1996 and 1998 was 8200 for IVF and 6550 for OI, compared to 1320 and 1360 resultant births per year.

The novelty of IVF has attracted a large number of studies on the health of the newborn (Helmerhorst *et al*., 2004), but less is known about the long-term health effects of IVF on children (Hampton, 2004) or about the health effects on the women. Complications can occur during the ovulation induction, the oocyte collection procedure, and post-operatively. The pregnancy achieved can be ectopic (embryo outside the uterus) or heterotopic (embryo both in and outside the uterus), and it can end in a miscarriage.

Ovarian hyperstimulation syndrome (OHSS) is considered the most serious complication of ovulation induction. It can vary from being a mild illness to a severe, life-threatening disease requiring hospitalization. OHSS can occur as soon as a few days after receiving HCG ('early OHSS') or later ('late OHSS'). Multiple pregnancy has been shown to be associated with a higher risk of late OHSS (Mathur *et al.*, 2000). The incidence of severe OHSS has been reported to vary from 0.7 to 1.7% per initiated cycle (Bergh and Lundkvist, 1992; Serour *et al.*, 1998; Westergaard *et al*., 2000; Nyboe Andersen *et al*., 2005). Some case reports (Cluroe and Synek, 1995; Koo *et al.*, 2002), studies (Bergh and Lundkvist, 1992; Serour *et al*., 1998; Abramov *et al.*, 1999a), and reviews (Whelan and Vlahos, 2000; Delvigne and Rozenberg, 2003; De Sutter, 2004) describe some serious aspects of OHSS, such as thromboembolic events, pulmonary manifestations, and death, but the magnitude of the risk is unclear.

The frequency of IVF complications other than OHSS has been only sporadically reported. For oocyte collection, bleeding has been reported in 0.03–0.5% and infections in 0.02–0.3% of embryo transfers (Bergh and Lundkvist, 1992; Nyboe Andersen *et al.*, 2005). Two to 5% of IVF pregnancies have been reported to be ectopic and 0.1–0.3% heterotopic, and estimates of IVF pregnancies ending in miscarriage have varied from 15 to 23% (Roest *et al.*, 1996; Serour *et al.*, 1998; Westergaard *et al.*, 2000; Kupka *et al.*, 2003; Schieve *et al.*, 2003; Bryant *et al*., 2004).

Most studies reporting complications after ovulation induction with or without insemination are based on old data (St Clair Stephenson, 1991; Venn *et al.*, 1994), and the frequency of OHSS after OI is unknown (Unkila-Kallio, 2001). In one small clinical study, the OHSS hospitalization rate per initiated cycle was 0.07% (Quasim *et al*., 1997).

Even though various adverse effects of IVF and OI on treated women have been identified, many of the published

studies and reports are deficient. They are based on old data, voluntary reporting, or a small number of cases or treatment cycles and concentrate on only one complication, or they lack information on the severity of the complications. The purpose of this study is to estimate the frequency of serious complications and miscarriages following IVF and OI. The criterion of seriousness is the need for hospital care, either in the form of hospitalization or an operation at a hospital outpatient clinic. This study is the first extensive study examining the different serious complications of both IVF and OI.

Materials and methods

The study is a historic cohort study based on prospectively collected register data on the following two exposed cohorts: 20–59 year old women having had IVF treatments (IVF, ICSI and FET, n = 9175) and women having had other infertility treatments including drug-based treatments (ovulation inductions with or without artificial insemination, OI, n = 10 254) between 1996 and 1998 in Finland. The women were identified with a pre-designed algorithm using the reimbursement files of the Finnish Social Insurance Institution (SII) (Hemminki *et al.*, 2003). Population controls, matched by age and municipality, were randomly selected for IVF women (n = 9175) from the SII population record (which covers the entire Finnish population).

The data included detailed information on the use of infertility drugs, including dates of prescription and purchase. The beginning of a cycle was defined by the date of the first purchase of the drug. All drugs bought within 35 days of the first purchase were considered part of the same treatment cycle with the exception of clomiphene citrate; a new prescription of clomiphene was considered the beginning of a new cycle regardless of the time interval. Consecutive cycles without a new prescription could not be separated.

The women's background characteristics were obtained from the Central Population Register, information about care episodes in hospitals from the Hospital Discharge Register (HDR), and dates and causes of death from the Cause-of-Death Register. The HDR collects information on inpatient care as well as on those visits to outpatient clinics that included an operation. It gathers information on diagnoses (10th revision of the International Classification of Diseases, ICD-10), operation codes, and dates of admission and discharge. The diagnoses include the main diagnosis (which can consist of separate diagnoses of the reasons and the symptoms leading to hospitalization) and two secondary diagnoses (which can also also consist of two separate diagnoses of the reasons and the symptoms) for each hospital episode. Miscarriages and ectopic pregnancies can be identified if they lead to inpatient care or an operation (such as laparoscopic surgery or curettage). From 1983 to 1995, operations were registered according to a national coding system; since 1996, according to the Finnish version of the NOMESCO classification system for surgical operations (Toimenpideluokitus, STAKES, 1996).

All hospital episodes due to OHSS, pelvic infections and abscesses, bleeding, other complications, miscarriages, and ectopic pregnancies were identified using the HDR (codes in Appendix); the dates for the start and end of the hospital stays were recorded. In cases of miscarriage and ectopic pregnancy, the hospitalization can be registered with an ICD-10 code and/or an operation code. A hospital outpatient visit is registered only when an operation has been carried out. By using ICD-10 codes, 71% of miscarriages after IVF and 74% after OI could be identified, and the rest were identified by using only operation codes. Almost all ectopic pregnancies were identified by using ICD-10 codes (98% of IVF and 97% of OI cases).

In addition to the diagnoses defined in the HDR to be OHSS-related, we searched for women having had symptoms or diseases potentially related to OHSS ('potential OHSS'). Our definition was based on one unpublished Finnish clinical study of women with diagnosed OHSS, on consultations with experienced clinicians, on symptoms and diseases described in the literature, and on diagnoses given to women in our data just before OHSS diagnosis (ICD-10 code N98.1). Five of the 48 women listed in the Finnish clinical OHSS data could be found in the HDR with the ICD-10 code N98.1. Two other women were hospitalized after IVF treatment with a diagnosis of pain localized in other parts of the lower abdomen (R10.3), and one due to other and unspecified ovarian cysts (N832). The diagnoses women received just before they were hospitalized due to OHSS were E15 (non-diabetic hypoglycaemic coma), R10.3, and J90 (pleural effusion, not elsewhere classified).Combining these diagnoses with those found in the literature, we made a list of diagnoses probably related to OHSS by consulting experienced clinicians (see Appendix).

Using all diagnoses and operation codes for all hospital episodes, we searched for those due to an IVF/OI complication (hereafter called a complication episode). To be eligible, the episode had to have occurred within 120 days from the beginning of the IVF/OI treatment in the case of OHSS, infections, abscesses, bleeding, and other complications. A time lag of 240 days was chosen in the case of miscarriages and ectopic pregnancies. These time lags were defined after studying the shapes of distribution curves of each complication to find a point when incidences clearly decreased. In addition, we consulted experienced clinicians in calculating the probable time lag from the start of treatment (first purchase date of the drug) to the occurrence of potential complications. If a woman had several treatments within this time frame, the latest was defined to be the treatment that led to the complication. If the same episode included different complications (e.g. OHSS and bleeding), they were all counted.

The complication risk was calculated in two ways. First, the proportion of women whose first complication occurred after the first treatment cycle (in our study window) was calculated separately for each type of complication (risk after the first treatment). Secondly, all treatment cycles were considered, but still only the first occurrence of each complication was taken into account, and the proportion of women having at least one complication (of each type) was calculated (risk of a complication after an average of 3.3 IVF and 2.7 OI treatment cycles). Furthermore, the risk of OHSS in each treatment cycle was calculated. In this calculation, individual women can appear more than once. The proportion of women having had any complication episode during the study period was calculated as well as the proportion of women whose hospital visit had lasted >5 days.

To calculate whether OHSS is more common in multiple than singleton pregnancies (among pregnancies ending in birth) and the rate of miscarriages and ectopic pregnancies per 100 births, we linked the data to the nationwide Medical Birth Register by using the women's personal identification numbers. For IVF and OI births, time limits of 44 and 48 weeks respectively were used to define whether births were the result of IVF or OI or spontaneous pregnancies; times were calculated from the beginning of treatment (the first purchase date of the drug) to the date of birth. In addition, to be able to estimate the risk of each complication per initiated cycle and to find comparable rates for earlier studies, the number of women having had each type of complication was divided by the total number of treatment cycles. This calculation produced only raw estimates because only the first occurrence of each complication was counted.

The numbers of deaths during and after the exposure to IVF and OI until the end of 2000 (after an average of 3.7 and 3.8 years for IVF and OI women respectively) were obtained from the Cause-of-Death Register. The follow-up time of the control group was as long as that of

the IVF women (from the first date of IVF exposure to the end of 2000). The causes of death were classified according to the following eight categories: reproductive mortality (Fortney *et al.*, 1986) including methods related to achieving pregnancy, diseases of the circulatory system, cancers, suicides, homicides, accidents, other, and unknown causes.

The differences were tested by using a χ^2-test or a test of relative proportions. The statistical analyses were performed in SAS, version 9.

Results

The background characteristics of the women are presented in Table I.

Depending on the definition of OHSS, the number of women having OHSS after the first treatment cycle varied from 14 to 19 per 1000 women and after all treatment cycles from 23 to 35 (Table II). As a specified (N98.1 in ICD-10) and potential diagnosis, OHSS was most common 1–2 and 2–3 months respectively after the beginning of IVF treatment. Depending on the definition of OHSS, the total rate of hospitalization due to OHSS per initiated IVF treatment cycle varied from 0.9% (210 cases/24 318 cycles) to 1.4% (330 cases/24 318 cycles). The mean length of hospitalization due to OHSS and potential OHSS was 4.1 and 3.3 bed days respectively.

After OI (94% of women treated with clomiphene citrate) hospitalization due to OHSS was rare (Table II). Depending on the definition of OHSS, the total rate of hospitalization per OI treatment cycle varied from 0.04% (eight patients/18 000 cycles) to 0.5% (100 patients/18 000 cycles). Most cases of OHSS occurred in the first month after the treatment cycle. Potential OHSS typically appeared 2–3 months after the treatment cycle.The mean length of hospitalization due to ICD-10 OHSS and potential OHSS was 2.4 and 1.9 bed days respectively.

The risk of OHSS was highest after the first and after the fifth or more IVF treatment cycles (Table III).

In our data, 21.2% of IVF pregnancies ending in birth (total of 3737 births) were twin births and 0.4% were triplets. The risk of OHSS (ICD-10 code) was more common among twin than among singleton pregnancies ending in birth (3.2 versus 1.4%, $P < 0.001$ for a test of relative proportions). In triplet pregnancies, no OHSS was registered.

After IVF treatment, OHSS (ICD-10) was much more common among younger than older women; 3.2% of women <35 years of age were hospitalized due to OHSS, but only 1% of older women. This was also the case when potential OHSS was taken into account.

Bleeding that necessitated hospital care was a rare complication (Table II). Most instances of bleeding occurred within 2 months of starting the treatment cycle. The total rate per initiated treatment cycle was 0.09%. Ten per 1000 IVF women were hospitalized due to infections; infections were diagnosed somewhat later than bleeding. The total rate per treatment cycle was 0.4%. The mean length of hospitalization after all treatment cycles was 2.1 bed days for bleeding and 3.7 for infections. After OI, hospitalizations due to bleeding and infections were even rarer than after IVF (Table II).

Only 17 IVF women were hospitalized due to complications other than OHSS, bleeding, and infections, and these mainly occurred 1–2 months after starting the treatment (Table II). Six women (four registered as pregnant) had a thromboembolic event. Three of these six cases were serious: one cerebral infarction and two pulmonary embolisms. None of the six women was registered as having OHSS in their thromboembolic episodes, but the cerebral infarction occurred just after hospitalization due to OHSS. One pulmonary embolism was registered as a complication of assisted reproduction (ICD-10 N98.8) that had included excision of the ovary and Fallopian tube.

After all OI treatment cycles, a total of five women had another complication. Four women (two registered as pregnant) had a thromboembolic event, but there was no information in the register about any of them possibly having OHSS. One was a serious case with a pulmonary embolism.

After the first IVF treatment cycle, 42 per 1000 women had received hospital care due to miscarriage; after all treatment cycles, the value was 93 per 1000 women (Table IV). The need for hospital care increased steadily until 4 months after IVF treatment, but the hospitalizations were short; the mean length of hospitalization was 1.2 bed days. The number of miscarriages per 100 births after all IVF treatment cycles was 23 (854/3737).

After the first IVF treatment cycle, nine per 1000 women, and after all IVF treatment cycles, 21 per 1000 women had needed hospital care due to an ectopic pregnancy (Table IV). Ectopic pregnancies had led to hospitalization most commonly during the first 3 months after the beginning of the IVF cycle, and the mean length of hospitalization was 2.1 bed days. The rate of ectopic pregnancies per 100 births after all IVF treatment cycles was 5.0 (187/3737).

Table I. Background characteristics of women in the IVF, ovulation induction (OI) and control[a] groups at the beginning of the 1996–98 follow-up in Finland

	IVF (n = 9175)	OI (n = 10 254)	Controls (n = 9175)
Age (years) (mean ± SD)	33.4 ± 5	31.1 ± 6	33.4 ± 5
Age group (years) (%)			
20–24	3.5	11.0	3.5
25–29	20.8	31.4	20.8
30–34	35.2	31.5	35.2
35–39	27.7	17.8	27.7
40–44	10.8	6.9	10.8
≥45	2.0	1.4	2.0
Total	100	100[c]	100
Marital status (%)			
Single[b]	22.3	19.1	36.1
Married	69.4	72.5	56.7
Divorced	7.9	7.9	9.4
Widow	0.4	0.5	0.4
Unknown	0.0	0.0	1.4
Total	100	100[c]	100[d]
Socioeconomic position (%)			
Upper white-collar	25.3	20.6	16.3
Lower white-collar	48.5	48.7	45.7
Blue-collar	16.2	18.0	19.3
Others	7.9	10.0	12.3
Unknown	2.1	2.7	6.4
Total	100	100[c]	100[d]

[a]Population controls for IVF women, matched by age and muncipality.
[b]Includes cohabitation.
[c]$P < 0.001$ for χ^2-tests (distributions of IVF women and OI women).
[d]$P < 0.001$ for χ^2-tests (distributions of IVF women and controls).

Table II. Serious complications in the first[a] IVF or ovulation induction (OI) treatment cycle, and including all[b] treatment cycles in the study period, according to the time lag from the start of the cycle to hospitalization, per 1000 women

	Time lag (days)[c]									
	First treatment cycle					All treatment cycles				
	≤30	31–60	61–90	91–120	Total	≤30	31–60	61–90	91–120	Total
IVF (*n* = 9175)										
OHSS, ICD-10[d]	2.4	10.7	0.3	0.7	14.1	6.3	14.4	1.0	1.2	22.9
Potential OHSS[e]	1.0	1.9	1.3	1.4	5.6	3.3	3.9	3.6	2.5	13.3
OHSS, ICD-10 or potential	3.4	12.2	1.4	2.0	19.0	9.4	17.6	4.1	3.6	34.7
Bleeding	0.3	0.5	0.0	0.1	1.0	0.9	1.0	0.3	0.2	2.4
Infection	0.9	1.4	1.9	1.0	5.1	2.1	3.3	3.4	2.2	10.9
Other[f]	0.0	0.9	0.1	0.1	1.1	0.2	1.4	0.1	0.1	1.9
OI (*n* = 10 254)										
OHSS, ICD-10[d]	0.1	0.1	0.0	0.1	0.3	0.4	0.1	0.1	0.2	0.8
Potential OHSS[e]	0.9	1.0	1.5	1.7	5.6	1.6	1.8	2.8	2.9	9.1
OHSS, ICD-10 or potential	1.0	1.1	1.5	1.6	5.7	2.0	1.9	2.9	3.0	9.8
Bleeding	0.1	0.1	0.1	0.0	0.3	0.1	0.1	0.1	0.0	0.3
Infection	0.4	0.2	0.4	0.4	1.5	0.6	0.7	0.9	1.0	3.1
Other[f]	0.1	0.0	0.0	0.0	0.1	0.2	0.0	0.2	0.1	0.5

[a]First treatment cycle in our study.
[b]With an average of 3.3 IVF and 2.7 OI treatment cycles. For each problem, the follow-up is truncated after the first problem.
[c]Number of days between first purchase of the drug in the cycle and the first day of hospitalization due to the complication.
[d]OHSS = ovarian hyperstimulation syndrome (N98.1, ICD-10 code).
[e]Symptoms potentially related to OHSS but not registered as OHSS (see Appendix).
[f]Other complication than OHSS related to IVF or OI (see Appendix) and thromboembolic events.
ICD-10 = International Classification of Diseases, 10th edition.

Table III. Proportion (%) of IVF women[a] having ovarian hyperstimulation syndrome (OHSS) leading to hospitalization and the proportion with long hospitalization in each treatment cycle

	n	OHSS		In hospital ≥5 days[b]			
		ICD-10[c]	Including potential	ICD-10	(*n*)	Including potential	(*n*)
Treatment cycle							
1st	9175	1.4	1.9	27.1	(129)	20.6	(175)
2nd	6066	0.6***	1.1	28.6	(35)	18.5	(65)
3rd	3844	0.7***	1.2	12.0	(25)	8.9	(45)
4th	2320	0.6**	0.9	7.7	(13)	4.8	(21)
≥5th	1318	1.2	2.1	25.0	(16)	14.3	(28)
Total	9175	2.4	3.6	24.3	(218)	17.1	(334)

[a]Includes the first OHSS episode in each treatment cycle, so individual woman can appear more than once.
[b]% of cases.
[c]For test of relative proportions: ***$P < 0.001$, **$P < 0.01$ compared to the first cycle.
ICD-10 = International Classification of Diseases, 10th edition.

The percentage of women having a miscarriage was similar after the first OI and IVF treatment cycle, but after all treatment cycles, miscarriage was 1.6 times more common among IVF women than among OI women (Table IV). The number of miscarriages per 100 births (15.0) after all OI treatment cycles (634/4188) was lower than the corresponding rate after IVF (23.0). Ectopic pregnancies were almost equally common after the first treatment cycle in both groups, but they were more common among IVF women than OI women after all cycles. The number of ectopic pregnancies per 100 births after all OI treatment cycles was 2.6 (107/4188).

Overall, after all treatment cycles, 1354 IVF (15%) and 824 OI (8%) women were hospitalized for complications. Of these hospital episodes, 10.5% of IVF and 1.6% of OI women's episodes lasted >5 days.

A total of 12, 15 and 37 women died in the IVF, OI and control groups respectively during the follow-up as a whole (after an average of 3.7 years (IVF) and 3.8 years (OI) from the time of exposure). The causes of deaths are presented in Table V. One death in both the IVF and the OI group was related to reproduction.

Discussion

The risk of complications after each IVF treatment cycle was low, but cumulatively repeated attempts led to hospital care in the case of many women. After ovulation induction (OI) treatment, there were far fewer complications. OHSS and miscarriages were the most common reasons for hospital care. OHSS occurred after IVF much more often than after OI alone, but

Table IV. Miscarriage or ectopic pregnancy leading to hospitalization or an operation after the first[a] IVF or ovulation induction (OI) treatment cycle, and including all[b] treatment cycles in the study period, according to the time lag from the start of the cycle to hospitalization, per 1000 women

	Time lag (days)[c]									
	First treatment cycles					All treatment cycles				
	≤60	61–120	121–180	181–240	Total	≤60	61–120	121–180	181–240	Total
IVF (n = 9175)										
Miscarriage	14.0	19.3	5.8	2.8	41.9	31.3	41.9	13.3	6.6	93.1
Ectopic pregnancy	3.0	4.1	0.9	1.3	9.3	9.1	7.9	2.3	1.6	20.9
OI (n = 10 254)										
Miscarriage	7.0	15.7	9.6	5.3	42.1	12.3	24.8	15.5	9.2	61.8
Ectopic pregnancy	2.1	2.7	1.4	1.3	8.2	3.4	3.6	1.9	1.8	10.7

[a]First treatment cycle in our study.
[b]An average of 3.3 IVF treatment cycles and 2.7 OI treatment cycles. For each problem, the follow-up is truncated after the first problem.
[c]Number of days between first purchase of the drug in the treatment cycle and the first day of hospitalization due to the complication.

Table V. Deaths by cause from 1996 to 2000 [after an average 3.7 years for women in IVF and control groups, and 3.8 for ovulation induction (OI) women after the first exposure]

	IVF (n = 9175)	OI (n = 10 254)	Controls (n = 9175)
Cause of death			
Reproductive-related[a]	1	1	0
Diseases of the circulatory system	1	2	10
All cancers	4	2	13
Breast cancer	1	0	3
Ovarian cancer	0	1	0
Suicide	4	5	4
Homicide	0	3	0
Accident	2	0	3
Other	0	0	6
Unknown (died abroad)	0	2	1
Total	12	15	37

[a]Includes causes attributable to IVF and OI treatment, pregnancy, and childbirth.

miscarriages and ectopic pregnancies were equally common after OI and IVF after the first treatment cycle. Other serious complications, infections, and instances of bleeding were quite rare, especially among OI women.

Are our estimates of complication risks reliable? The identification of IVF and OI cohorts from the reimbursement records went well (Hemminki *et al.*, 2003). We also believe that the data covered most Finnish women treated from 1996 to 1998. The cohorts are large enough to study the frequency of even rare complications caused by IVF and OI. However, our method of identification of serious complications and miscarriages was based on a register covering only hospital care, inpatient care, and operations in outpatient clinics; therefore our identification of outcomes depended on care practices and the diagnosis recording style of physicians.

Even though the validity of the HDR has been high (Keskimäki and Aro, 1991), it is a routine care register that does not have the accuracy of *ad hoc* epidemiological studies. For example, OHSS is not always easy to diagnose. Symptoms may be atypical, and there may be no questions about a history of IVF or OI treatments; or a physician may not enter the code for a specific form of OHSS and instead list its symptoms, such as abdominal pain, enlarged ovaries, or dyspnoea. Likewise, the identification of miscarriages using the register is difficult (Hemminki, 1998). The time lags (between the start of a cycle and hospitalization due to a complication) were defined on the basis of drug purchases, and the chosen thresholds were relative. We only had data on the purchase day, not the actual start of the cycle. There may have been intervals between drug purchases and use. On the other hand, due to the character of IVF treatment and the costs of the drugs, it is unlikely that women would have bought the drugs a long time before their use.

Overall, we think that our results underestimate the real complication risks. Mild (less serious) cases are missing in our data. To calculate how reliable our definition of OHSS is, we correlated our data with unpublished Finnish clinical data from the same time period. This showed that only 16% of OHSS cases are in the HDR (10% with the OHSS code and 6% with codes related to OHSS symptoms). Most likely the rest of the cases are missing because the women had had a less serious OHSS that did not lead to hospitalization or to an operation. Some cases may be missing because OHSS was not correctly diagnosed or registered. The overall frequency of OHSS, including mild forms, is no doubt much higher than our results show. On the other hand, some symptoms of OHSS such as abdominal pain are common and can relate to many other diseases. Thus some of our OHSS cases (‘potential OHSS’) may have actually been other diseases.

Our results cannot be extrapolated to countries with a less advanced health care system or less developed practices, in which treated women are less strictly screened or more risks are taken. For example, multiple pregnancies are suspected to entail a higher risk of late OHSS (Mathur *et al.*, 2000). In our population, plural births were lower than in many other countries (Bryant *et al.*, 2004; Nyboe Andersen *et al.*, 2005).

In our study, the hospitalization rates of OHSS per initiated IVF treatment cycle are somewhat higher and the length of hospital stays shorter than reported earlier (Quasim *et al.*, 1997; Serour *et al.*, 1999). Earlier studies are, however, based on less extensive or older data than ours (from 1980s to mid 1990s). It is possible that serious OHSS became more common from the 1980s to the late 1990s, when more potent treatments were used. At least in Israel, the incidence of severe OHSS

after IVF increased from 1987 to 1996 (Abramov *et al.*, 1999b). On the other hand, it might be that OHSS has become better known and more readily diagnosed. Shorter stays at hospital for OHSS may relate to the general trend towards shorter hospital stays.

As earlier reported (Schenker, 1999), women aged <35 years are at greater risk of developing OHSS. According to that study, the risk is also greater among women who receive only one treatment cycle or many cycles. It is generally assumed that a woman with a previous OHSS is at greater risk of OHSS in a following cycle (Whelan and Vlahos, 2000). For that reason, it may be assumed that women with previous OHSS are more carefully monitored during the next cycle to prevent OHSS. However, the women's first cycle was the first in our study window. We do not know how many cycles the women had received before 1996. After many repeated cycles, a woman may be at greater risk due to the repeated doses of drugs (especially gonadotrophin). This should be considered when many attempts are needed. Furthermore, the risk was also higher among twin pregnancies than among singleton pregnancies ending in birth. This was also found in an earlier study on late OHSS (Mathur *et al*., 2000). We were not able to classify the OHSS cases as late or early.

Only a few studies (Quasim *et al.*, 1997; Abramov *et al.*, 1999b) have reported the frequency of OHSS after ovulation induction (OI) alone or compared it to the frequency after IVF. Our study, as well as the older ones from the USA and Israel, shows serious OHSS to be more common after IVF than after OI. In addition, according to our study, the length of hospital stay was longer after IVF than after OI. This suggests that OHSS after IVF is more serious than after OI.

Our study confirmed earlier results that thromboembolic events exist after IVF but are rare complications, and even rarer after OI. In our study, the proportion of women reported as having a thromboembolic event leading to hospitalization (0.07%) was much lower than in an earlier Egyptian study (0.2%) (Serour *et al.*, 1998). The difference between the studies might be explained by different data collection methods (register/clinical study) and different time periods. In the Egyptian study, all cases were related to severe OHSS. In contrast, none of the women in our study were registered as having OHSS at the same time as thromboembolic complications. We do not know whether this is because thromboembolic events related to OHSS were not specifically recorded (but considered a part of OHSS), or whether OHSS was not diagnosed or not present. In one case report (Ulug *et al.*, 2003), a woman had venous thrombosis without OHSS after ovulation induction and ICSI. According to an extensive review, many studies have reported thromboembolic phenomena related to IVF or ovulation induction without any signs of OHSS (Delvigne and Rozenberg, 2003). However, severe OHSS was diagnosed in >76% of thromboembolic cases. Some case reports have described a cerebral infarction complicating OHSS (Koo *et al.*, 2002).

The frequency of bleeding per initiated IVF cycle was the same in our study as in an Egyptian study with 3500 cycles (Serour *et al.*, 1998). But it was much lower than in a recent report from the ESHRE (Nyboe Andersen *et al.*, 2005), covering all bleeding complications, even those not leading to hospitalization. The frequency of infections in our study was similar to that reported earlier in the Nordic countries (Bergh and Lunkvist, 1992) and Egypt (Serour *et al.*, 1998), but higher than reported by ESHRE (Nyboe Andersen *et al.*, 2005). The very low bleeding and infection rates after OI suggest that bleeding and infections were complications of IVF technique.

We found that >9% of IVF and >6% of OI women received hospital care due to miscarriages. We could not identify how many of the treated women had become pregnant, but the number of miscarriages per 100 IVF births (23.0) suggests similar miscarriage rates found earlier (15–23%; Serour *et al.*, 1998; Kupka *et al*., 2003; Schieve *et al.*, 2003; Wang *et al.*, 2004). However, the real miscarriage rate must have been higher, for not all miscarriages lead to hospital care. The miscarriage rate per 100 OI births was lower than the rate per 100 IVF births (15 versus 23). Whether this was due to characteristics of the individual women or the procedure itself could not be judged on the basis of this study. Previously, greatly varying miscarriage rates have been reported after clomiphene-induced pregnancies (9–27%; Venn *et al*., 1994).

Were the miscarriage rates after IVF higher than in natural pregnancies? We did not have a pregnant control group, but 8% of women with spontaneous pregnancies needed hospital care due to a miscarriage according to one Finnish study (Hemminki and Meriläinen, 1996). In one study from the USA, the miscarriage rate was similar (15%) among assisted reproduction treatment women and the rest of the female population (Schieve *et al*., 2003). However, in another study from the USA, the risk of miscarriage slightly increased after assisted reproductive treatment (Wang *et al*., 2004).

The rate of ectopic pregnancies per 100 IVF births (5.0) in our study is twice that of earlier studies in Finland (Hemminki and Heinonen, 1987; Mäkinen, 1996). The frequency per initiated IVF cycle (0.8%) is also somewhat higher than in earlier studies of IVF treatments (Bergh and Lundkvist, 1992; Serour *et al.*, 1998; Bryant *et al*., 2004). We do not have information on the reasons for infertility among the women in our study. We also could not examine how many of the women studied had tubal occlusion, which is considered to be one reason for the high frequency of ectopic pregnancies among IVF women. In the case of OI, which requires open tubes in order to be effective, clomiphene citrate could be a possible reason for the observed high rate of ectopic pregnancies (Venn *et al*., 1994).

Hardly any data have been published about maternal mortality or other deaths occurring as IVF complications. In one study from Australia, the maternal mortality of IVF women was higher than the national rate (Venn *et al.*, 2001). We did not have a control group consisting of spontaneously pregnant mothers or women trying to become pregnant. The best control group for IVF women that we had was OI women, although IVF women were older than OI women. Total mortality within an average of 3.7 years (IVF) and 3.8 years (OI) of follow-up was nearly equal among IVF and OI, and one death in both groups was connected with reproduction. The overall mortality in our study was lower than in the general female population (matched by age and municipality). In particular, the cardiovascular deaths were rarer. This indicates a 'healthy patient

effect' among IVF and OI women, i.e. sick women are less likely to be married or to receive infertility treatment than healthy women. The socioeconomic position of IVF women in our study was somewhat higher than that of the women in the control group, which can explain some of the lower mortality. Lower mortality has been reported in Australia among women who received IVF compared to women who had registered for IVF but never received the treatment (Venn *et al*., 2001).

Register-based studies with sufficiently large populations enable the examination of rare events. However, such studies have their limitations. Registers provide only limited information, and the coding of diagnoses are very likely to vary. Estimates of the frequencies of complications are needed to help clinicians in choosing safer methods, in applying new methods, and in informing women who contemplate IVF or OI treatment. It would be important to establish a routine follow-up system for IVF and OI treatments and their complications. This should also provide information on the duration and causes of infertility, the exact nature and duration of maternal drug exposure, and maternity background data. In countries with computerized health care and IVF registers, it would be easy to implement such a system. However, even before the possible establishment of such a new follow-up system, current estimates of the complication risk should be available both to women and physicians.

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Appendix. ICD-10 and operation codes and their explanations used in identifying the complications of IVF and ovulation induction (OI)

Ovarian hyperstimulation syndrome (OHSS)	
ICD-10	
N98.1	Hyperstimulation of ovaries
Potential OHSS	
ICD-10	
E15	Non-diabetic hypoglycaemic coma
J80	Adult respiratory distress syndrome
J90	Pleural effusion, not elsewhere classified
J94.8	Other specified pleural conditions (hydrothorax)
K65.0	Acute peritonitis
N17	Acute renal failure
N83.0	Follicular cyst of ovary
N83.1	Corpus luteum cyst
N83.2	Other and unspecified ovarian cysts
N99.0	Post-procedural renal failure
R06.0	Dyspnoea
R10.2	Pelvic and perineal pain
R10.3	Pain localized in other parts of lower abdomen
R10.4	Other and unspecified abdominal pain
R18	Ascites
R34	Anuria and oliguria
R60	Oedema, not elsewhere classified
Infections	
ICD-10	
N70	Salpingitis and oophoritis
N71	Inflammatory disease of uterus, except cervix
N73	Other female pelvic inflammatory diseases
N74.8	Female pelvic inflammatory disorders in other diseases classified elsewhere
N98.0	Infection associated with artificial insemination
Bleedings	
ICD-10	
N83.6	Haematosalpinx
N85.7	Haematometra
N93.8	Other specified abnormal uterine and vaginal bleeding
N93.9	Abnormal uterine and vaginal bleeding, unspecified
K66.1	Haemoperitoneum
T81.0	Haemorrhage and haematoma complicating a procedure, not elsewhere classified
Other	
ICD-10	
N98.2	Complications of attempted introduction of fertilized ovum following IVF
N98.3	Complications of attempted introduction of embryo in embryo transfer
N98.8	Other complications associated with artificial fertilization
N98.9	Complication associated with artificial fertilization, unspecified
I26	Pulmonary embolism
I63	Cerebral infarction
I74	Arterial embolism and thrombosis
I80	Phlebitis and thrombophlebitis
I82	Other venous embolism and thrombosis
Miscarriages	
ICD-10	
O02.1	Missed abortion
O03	Spontaneous abortion
O05	Other abortion
O06	Unspecified abortion
O08	Complications following abortion and ectopic and molar pregnancy
Operation codes	
1350	Other operation in uterus
8113	Curettage of body of uterus
8319	Destruction of endometrium
8501	Evacuation of uterus by aspiration
8502	Evacuation and abrasion
8509	Other operation related to miscarriage
LCA10	Curettage of body of uterus
LCA13	Curettage of cervix and body of uterus
LCA16	Destruction of endometrium
LCA96	Other intrauterine operation
LCA98	Other transluminal endoscopic operation on uterus
Ectopic pregnancies	
ICD-10	
O00	Ectopic pregnancy
O08	Complications following abortion and ectopic and molar pregnancy
Operation codes	
8231-8239	Operations related to ectopic pregnancy
LBC00-LBC98	Tube conserving operations for tubal pregnancy

Paper III

Health of Children Born as a Result of In Vitro Fertilization

Reija Klemetti, Tiina Sevón, Mika Gissler and Elina Hemminki

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ARTICLE

Health of Children Born as a Result of In Vitro Fertilization

Reija Klemetti, MHSc[a], Tiina Sevón[a], Mika Gissler, DrPhil, MSocSc[b], Elina Hemminki, MD[a]

[a]Health Services Research and [b]STAKES Information, STAKES, National Research and Development Centre for Welfare and Health, Helsinki, Finland

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ABSTRACT

OBJECTIVE. The purpose of this study was to use nationwide registries to examine the health of children up to 4 years of age who were born as a result of in vitro fertilization.

METHODS. Children born after in vitro fertilization (N = 4559) from 1996 to 1999 were monitored until 2003. Two control groups were selected from the Finnish Medical Birth Register as follows: all other children (excluding children born after ovulation induction) from the same period (N = 190 398, for study of perinatal health and hospitalizations) and a random sample of those children (n = 26 877, for study of health-related benefits). Mortality rates and odds ratios for perinatal outcomes, hospitalizations, health-related benefits, and long-term medication use were calculated.

RESULTS. Although the health of most in vitro fertilization children was good, such children had more health problems than other children. A total of 35.7% of in vitro fertilization children and 2.2% of control children were multiple births, and the health of multiple births was worse than that of singletons. Perinatal outcomes of in vitro fertilization children were worse and hospital episodes were more common than among control children. Risks for cerebral palsy and psychological and developmental disorders were increased. Among in vitro fertilization singletons, worse results for perinatal outcomes and hospitalizations, but no increased risk for specific diseases, were found. The health of in vitro fertilization multiple births was comparable to the health of control multiple births.

CONCLUSIONS. Reducing the number of transferred embryos would improve the health of in vitro fertilization children. Additional studies are needed to explain the poorer health of in vitro fertilization singletons, as well as follow-up studies to examine the health of in vitro fertilization children from 4 years onward.

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Key Words
in vitro fertilization, perinatal health, morbidity, multiplicity, registry-based study

Abbreviations
CP— cerebral palsy
IVF—in vitro fertilization
HDR—Hospital Discharge Register
MBR—Medical Birth Register
SII—Social Insurance Institution
OR— odds ratio
CI— confidence interval
ICD-10 —*International Classification of Diseases, 10th Revision*

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Address correspondence to Reija Klemetti, MHSc, PO Box 220, 00531, Helsinki, Finland.

In vitro fertilization (IVF) (including intracytoplasmic sperm injections and frozen embryo transfers) is a common infertility treatment. In Finland, currently ~2.5% of infants are born as a result of IVF,[1] with women <40 years of age being able to receive 2 to 5 IVF treatment cycles within the public sector[2] while paying a small fee for visits. Approximately 60% of all IVF services are supplied by private clinics, with no strict age limit. Private physicians' charges and drug costs are partly reimbursed by the Social Insurance Institution (SII). Usually, the pharmacies and IVF clinics take care of billing for the reimbursements. Approximately 76% of total IVF costs (visits, examinations, treatments, and drugs) are covered in the public sector and 50% in the private sector, with the rest being paid by women (R.K., T.S., M.G., and E.H., unpublished data, 2006).

The perinatal health of IVF singletons has been reported as being worse than that of naturally conceived singletons,[3–5] with more-recent studies also showing an increased risk for preterm birth and/or low birth weight for twins.[6,7] However, studies of the long-term health of IVF children are few, and their results are conflicting.

According to previous small cohort studies, the morbidity rates, growth, and development of IVF children are similar to those of control children (as reviewed by Koivurova[8]). Although the health of children is mainly good, large studies are needed to clarify potential health problems. Registry-based studies allow for large sample sizes and are published regularly from the Nordic countries.[9–17] In the case of IVF children, research has found an excess use of hospital services, long hospitalizations, and increased risk for infections, epilepsy, and tumors,[10] asthma,[10,17] cerebral palsy (CP),[10,11,14] sleep disturbances,[14] convulsions, behavioral problems, and accidents,[17] and congenital malformations.[9,10,15–17] However, some of those studies were based on early IVF experience and concentrated on specific diagnoses, hospital care utilization, or singletons/twins only or did not consider multiplicity.

Results on the perinatal health of IVF twins are controversial, whereas data on the long-term health of IVF children are sparse. For this reason, our aim was to perform a large, thorough, up-to-date, registry-based study of the health of IVF children up to 4 years of age, separately for singletons and multiple births, by using several population-based registries.

METHODS

Identification of IVF Children

The study is based on children born to women who received IVF between 1996 and 1998 in Finland. The women were identified, with a predesigned algorithm, from the reimbursement files of the SII.[18] Data on children born as a result of IVF treatment (N = 4559) and their perinatal health were obtained from the Finnish Medical Birth Register (MBR)[15,19] by using women's personal identification numbers and the children's dates of birth as the linkage keys. The MBR also includes the children's unique identification numbers. It contains information on maternal backgrounds and on infant outcomes until the age of 7 days for all infants born in Finland. The data are collected by delivery hospitals and are completed by linkage to the Central Population Register and cause-of-death statistics (compiled by Statistics Finland). The identified children were linked to 4 other nationwide registries through the children's identification numbers, namely, cause-of-death statistics, the Hospital Discharge Register (HDR) (hospital episodes, diagnoses, ie, *International Classification of Diseases, 10th Revision* [ICD-10] codes, and dates of admissions and discharges), the Care Register for Social Welfare (episodes in institutional care), and health-related social benefits from the SII (reimbursements for long-term medication use and child disability allowance).

Control Groups

As control groups, 2 groups of children were selected from the MBR. The first control group consisted of all children other than IVF children or those born as a result of ovulation induction (N = 190 398) who had been conceived during the same period (1996–1998). The second control group (n = 26 877) was a random sample of the first control group, selected to reduce the workload caused by large registry linkages in the SII, and was used to study the benefit payments from the SII and for the combined analysis.

Data Collection

The number of deaths of all children from 1996 to 2001 until the age of 2 years was obtained from cause-of-death statistics. We grouped the causes of deaths (given as ICD-10 codes) into 4 categories, namely, conditions originating from the perinatal period, congenital malformations, other medical causes, and deaths from external causes.

The HDR collects information on inpatient care and visits to outpatient clinics involving surgical or other procedures. The HDR gathers information on diagnoses (ICD-10 codes) and dates of admissions and discharges. The diagnoses include the main diagnosis and 2 secondary diagnoses for each episode. All hospitalizations until the children were 4 years of age were studied (1996–2003).

The Care Register for Social Welfare collects information on care episodes in social institutions, such as institutions for people with intellectual disabilities. For this study, we received information on the numbers of IVF children having ≥1 period of institutional care up until the end of 2004. We compared the rates of institutionalized children with the national rates for children born

in 1997 or 1998, excluding the numbers of children from IVF or ovulation induction.

The SII grants child disability allowances for families who have a disabled or chronically sick child needing continuous help and surveillance at home. A child's parents applying for benefits are required to supply recent medical documents. The register of child disability allowances contains information on start and end dates, type (temporary or permanent), level (normal, increased, or special), and diagnoses. The special refund category covers ~50 chronic diseases, entitling patients to receive higher reimbursements of long-term medication costs. Among children, the most common diseases in the special refund category are asthma, epilepsy, diabetes mellitus, and rheumatoid arthritis. The data on special refunds included the start and end dates of entitlement periods and the reasons. Information on both child disability allowance and long-term medication use was gathered from 1996 to 2001 (ie, until the children were 2 years of age).

Data Analyses

A comparison was made between control and IVF mothers in their utilization of health care services during the pregnancy and child birth (hospitalization during the pregnancy, cesarean section, and hospitalization of ≥7 days after delivery) and in infant outcomes, first including all children and then including first births only. As health outcomes, we used very low birth weight (<1500 g), low birth weight (<2500 g), very preterm birth (<32 weeks), preterm birth (<37 weeks), low 1-minute Apgar scores (scores of 0–6), treatment in an ICU or neonatal surveillance unit, need for respiratory treatment, hospitalization of the child for ≥7 days after birth, and perinatal death.

All inpatient hospital episodes until 2 years and 4 years of age were collected separately from the HDR. The total number of hospital episodes, the length of the episodes, and the number of hospitalized children were determined. We grouped diagnoses (ICD-10 codes) into 16 categories. The 2 categories of "symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified" (codes R00–R99) and "factors influencing health status and contact with health services" (codes Z00–Z99) were combined and renamed as "other." Both main and secondary diagnoses were taken into account. If the child was hospitalized more than once because of the same diagnosis, then only the first hospitalization was included.

We calculated the numbers of IVF and control children who had received ≥1 child disability allowance period or reimbursement for long-term medication. The most common reasons for child disability allowance and reimbursement were counted and IVF children were compared with naturally conceived children. Finally, we combined information from the different data sources and calculated the number of children who had used services, according to any of the data sources, because of an allergic and chronic disorder and common infection-like allergy (ICD-10 codes L20–L23, L27, and L50), asthma bronchial (ICD-10 codes J45 and J46), CP (ICD-10 code G80), epilepsy (ICD-10 codes G40 and G41), diabetes mellitus (ICD-10 code E10), diarrhea (ICD-10 codes A08–A09), pneumonia (ICD-10 codes J12–J18), or disorders of psychological development and behavioral and emotional disorders usually occurring in childhood and adolescence (ICD-10 codes F80–F98).

Statistical Analyses

The differences between the IVF and control groups were first tested with a χ^2 test and t test for relative proportions and with logistic regression analysis, adjusting for available background characteristics. For perinatal outcomes, these characteristics were county, smoking, maternal age, socioeconomic position, and previous births. The socioeconomic position of the women was defined by using their own occupation when delivering, which is collected routinely from maternity hospitals and classified automatically by the MBR into 5 categories according to the national classification compiled by Statistics Finland, that is, upper white-collar workers, lower white-collar workers, blue-collar workers, others (entrepreneurs, students, pensioners, unemployed women, and women with an unclassified position), and unknown position.[20] All analyses were made separately for singletons and multiple births. Two logit models were used, namely, an ordinary logit model in which all children were assumed to be independent and an additional model created by using the iterative, generalized, least-squares method, in which siblings born in the same delivery were assumed to be dependent.

Research Ethics and Data Protection

The study plan was approved by the National Research and Development Centre for Welfare and Health research ethics committee (September 18, 1998). For register linkages, the National Data Protection Authority was consulted, and permissions were obtained from the registry keepers.

RESULTS

Of the 4559 IVF children, 34.7% were twins and 1.1% were triplets. Among the 190 398 control children, 2.2% were twins and only 13 sets were triplets (<0.01%). IVF mothers were older, more often married, and from a higher socioeconomic position than other mothers (Table 1).

Compared with other mothers, IVF mothers received more hospital care during pregnancy and more cesarean sections (Table 2). Adjustment for mothers' background characteristics did not change the results. Inspection of singletons and multiple births separately showed that

TABLE 1 Mothers' Background Characteristics According to Group and Plurality for IVF and Control Mothers

	Total Births			Singleton Births			Multiple Births		
	IVF (n = 3737)	Control (n = 188 298)	P	IVF (n = 2930)	Control (n = 186 216)	P	IVF (n = 807)	Control (n = 2084)	P
Maternal age at delivery									
Mean ± SD, y[a]	33.9 ± 4.5	29.7 ± 5.3	<.001	34.1 ± 4.6	29.7 ± 5.3	<.001	33.1 ± 4.3	30.5 ± 5.2	<.001
Age group, %									
<25 y	2.9	22.4		2.6	22.4		4.1	17.4	
25–29 y	20.1	33.6		18.8	33.7		24.5	31.7	
30–34 y	41.2	29.4		41.2	29.4		41.5	33.2	
35–39 y	41.2	12.2		28.3	12.2		25.3	15.4	
≥40 y[b]	8.1	2.3	<.001	9.1	2.3	<.001	4.6	2.3	<.001
Marital status									
Married or cohabiting	95.3	87.5		95.4	87.5		94.9	86.4	
Single	3.9	10.6		3.9	10.6		4.0	11.3	
Missing information[b]	0.8	1.9	<.001	0.8	1.9	<.001	1.1	2.4	<.001
Socioeconomic position, %									
Upper white-collar	25.1	15.1		25.5	15.1		23.7	17.0	
Lower white-collar	48.5	40.6		48.2	40.6		49.9	40.3	
Blue-collar	13.0	17.0		13.0	17.0		12.6	16.1	
Others	8.0	18.5		8.0	18.5		8.1	18.2	
Unknown[b]	5.4	8.9	<.001	5.3	8.9	<.001	5.7	8.4	<.001
Smoked during pregnancy[c]	6.6	14.8	<.001	6.6	14.8	<.001	6.6	16.6	<.001
First birth[c]	72.2	39.5	<.001	72.0	39.5	<.001	72.9	35.6	<.001

The control group consisted of all other mothers whose children were fertilized in the same time period as IVF children.

[a] For t tests in comparisons between IVF and control subjects.

[b] For χ^2 tests in comparisons between IVF and control subjects.

[c] For tests for relative proportions in comparisons between IVF and control subjects.

TABLE 2 Raw Proportions and Adjusted ORs of Pregnancy and Birth Treatments and Infant Outcomes Among IVF Mothers and Infants, Compared With Other Mothers and Infants

	Total Births			Singleton Births			Multiple Births		
	No. or Proportion		OR (95% CI)	No. or Proportion		OR (95% CI)	No. or Proportion		OR (95% CI)
	IVF	Control		IVF	Control		IVF	Control	
Deliveries, n	3737	188 298		2930	186 216		807	2084	
Infants, n	4559	190 398		2930	186 216		1629	4182	
Mother, %									
Hospital treatment[a]	43.0	20.6	2.61 (2.43–2.79)	36.4	20.2	1.99 (1.84–2.16)	66.9	54.2	1.51 (1.24–1.85)
Hospitalization of ≥7 d[b]	16.8	4.5	2.33 (2.11–2.57)	9.6	4.2	1.23 (1.07–1.41)	46.8	31.7	1.04 (0.83–1.30)
Cesarean section	35.8	15.3	1.95 (1.81–2.10)	30.4	15.0	1.51 (1.39–1.65)	55.5	41.8	1.24 (1.03–1.50)
Infant, %									
Very preterm (<32 wk)	4.7	0.9	4.45 (3.80–5.21)	2.0	0.8	2.06 (1.56–2.71)	9.6	7.0	1.26 (0.99–1.60)
Preterm (<37 wk)	23.6	5.5	4.43 (4.10–4.77)	9.5	4.7	1.72 (1.51–1.96)	49.2	42.2	1.06 (0.93–1.21)
Birth weight of <1500 g	4.2	0.8	4.19 (3.55–4.95)	1.9	0.7	2.17 (1.64–2.88)	8.2	7.4	0.95 (0.74–1.22)
Birth weight of <2500 g	19.8	4.0	4.77 (4.40–5.18)	6.5	3.2	1.60 (1.37–1.87)	43.7	39.2	0.92 (0.81–1.06)
Apgar score of 0–6	8.8	4.4	1.68 (1.50–1.87)	5.6	4.2	1.07 (0.91–1.26)	14.5	12.5	1.10 (0.90–1.33)
Special care[c]	23.0	8.2	2.71 (2.52–2.92)	12.5	7.6	1.36 (1.21–1.53)	42.1	35.0	1.04 (0.91–1.19)
Respiratory treatment	4.3	1.1	3.61 (3.08–4.24)	2.0	0.9	1.76 (1.34–2.31)	8.4	6.7	1.19 (0.93–1.53)
Hospitalization of ≥7 d	23.8	6.4	3.42 (3.08–4.24)	10.8	5.8	1.43 (1.26–1.61)	47.4	37.6	1.02 (0.88–1.17)
Perinatal death	1.3	0.6	1.85 (1.40–2.44)	0.9	0.5	1.32 (0.88–1.98)	2.0	2.9	0.73 (0.47–1.13)

ORs were adjusted for mother's county, smoking, age, marital status, parity, and socioeconomic position. The reference group (OR = 1) was the control group.

[a] During pregnancy.

[b] After delivery.

[c] Treatment in ICU or in newborn surveillance unit.

this difference was partly, but not totally, explained by IVF children more often being twins.

Similarly, the indicators of perinatal health showed much worse health of IVF children, which was explained partly by plurality. The perinatal health of IVF multiple births was comparable to that of control multiple births; the risk for very preterm birth was increased but not statistically significantly.

Stillbirths were more common among IVF children in total, compared with other children in total (7.2 cases

per 1000 vs 3.9 cases per 1000; $P < .001$), and among IVF singletons, compared with control singletons (6.5 cases per 1000 vs 3.7 cases per 1000; $P = .014$ in a test for relative proportions), but not separately for multiple births. The main causes of stillbirths were conditions originating in the perinatal period (for example, placental infarction, extreme immaturity, and abruptio placentae).

The total mortality rate up to the age of 2 years was twofold higher among IVF children, compared with control children (9.0 deaths per 1000 and 4.1 deaths per 1000, respectively). Among singletons, rates of deaths after birth until the age of 2 years were similar in all groups of children; the main causes were congenital malformations (2.4 cases per 1000 among IVF children and 1.4 cases per 1000 among control children) and conditions originating in the perinatal period (for example, extremely low birth weight and respiratory distress syndrome; 1.4 cases per 1000 and 1.3 cases per 1000, respectively). The main causes among multiple births were the same as those among singletons (malformations: 11.2 cases per 1000 and 4.6 cases per 1000; perinatal causes: 11.2 cases per 1000 and 14.8 cases per 1000, respectively), and no significant differences between the groups were found.

According to the Care Registry for Social Welfare Institutions, 2.2 IVF children per 1000 had had ≥1 period of institutional care at a social welfare institution. For other children born in 1997 to 1998, the rate was 2.7 per 1000 children. Institutional care does not include children taken into children's homes or custody but refers mainly to mentally handicapped children who stayed in an institution for people with intellectual disabilities.

Until the age of 2 years, larger proportions of IVF children and IVF singletons received child disability allowances, compared with control children (Table 3). The most common reasons (according to ICD-10 classification) for receiving child disability allowances were the same for IVF and control singletons, namely, diseases of the skin and subcutaneous tissue, diseases of the respiratory system, and conditions involving the eyes and ears. For multiple births, the most common reasons included, in addition, certain conditions originating in the perinatal period. No statistically significant differences in long-term medication use were found between IVF and control children.

When information from different data sources until the age of 2 years was combined, it was found that IVF children, singletons and multiple births taken together, had a threefold increased risk of CP and more often had disorders of psychological development or behavioral and emotional disorders, compared with control children (Table 4). This was not the case when IVF singletons and multiple births were considered separately. Of the infants with CP, 88% were preterm.

Up to the age of 4 years, a larger proportion of IVF children were hospitalized, IVF children more often had long hospital episodes, and the average length of their episodes was greater, compared with control children (Table 5). IVF children had somewhat more hospital episodes than control children at all ages, but the difference was clearest during infancy.

Compared with control children, the risk of being hospitalized was increased among IVF children for many categories of diseases (according to ICD-10 grouping), even after adjustment for the mother's socioeconomic position (data not shown). The risk among IVF singletons was increased statistically significantly for perinatal problems (ICD-10 codes P00–P96; odds ratio [OR]: 1.76; 95% confidence interval [CI]: 1.54–2.01), congenital malformations (codes Q00–Q99; OR: 1.45; 95% CI: 1.20–1.75), and problems of the genitourinary system (codes N00–N99; OR: 1.40; 95% CI: 1.11–1.77) and decreased for diseases of the respiratory system (codes J00–J99; OR: 0.86; 95% CI: 0.76–0.97). IVF multiple births had increased risk for hospitalization because of diseases originating from the perinatal period (OR: 1.34; 95% CI: 1.18–1.53) and "other" diagnoses (codes R00–R99 and Z00-Z99; OR: 1.27; 95% CI: 1.09–1.48) and decreased risk for hospitalization because of diagnoses in the categories of eye and ear (codes H00–H95; OR: 0.77;

TABLE 3 Raw Proportions of Children and Crude and Adjusted ORs (and 95% CI) of Having Any Child Disability Allowance Period or Any Long-Term Medication Use Until the Age of 2 Years

	Total		Singleton		Multiple	
	IVF ($n = 4527$)	Control ($n = 26\,877$)	IVF ($n = 2911$)	Control ($n = 26\,296$)	IVF ($n = 1616$)	Control ($n = 581$)
Any child disability allowance						
Proportion, %	10.6	9.5	10.5	9.5	10.8	13.1
Crude OR (95% CI)	1.13 (1.02–1.25)	1.00	1.13 (0.99–1.28)	1.00	0.81 (0.61–1.08)	1.00
Adjusted OR (95% CI)	1.11 (1.00–1.23)	1.00	1.10 (0.97–1.25)	1.00	0.81 (0.62–1.10)	1.00
Any long-term medication use[a]						
Proportion, %	3.3	2.8	2.9	2.8	4.1	4.5
Crude OR (95% CI)	1.18 (0.98–1.41)	1.00	1.03 (0.82–1.29)	1.00	0.91 (0.57–1.45)	1.00
Adjusted OR (95% CI)	1.18 (0.98–1.41)	1.00	1.03 (0.82–1.30)	1.00	0.95 (0.59–1.52)	1.00

The ORs were adjusted for mother's socioeconomic position. The reference group (OR = 1) was the control group.

[a] Reimbursements for cow's milk or soy milk intolerance were excluded.

TABLE 4 **Raw Proportions of Children and Adjusted ORs of Having an Allergic or Chronic Disorder or a Common Infection (ICD-10 Codes) Until the Age of 2 Years, From Any Available Data Source**

	Total		Singleton		Multiple	
	IVF ($n = 4527$)	Control ($n = 26\,877$)	IVF ($n = 2911$)	Control ($n = 26\,296$)	IVF ($n = 1616$)	Control ($n = 581$)
CP (code G80)[a]						
Proportion, cases per 1000	3.8	1.4	1.4	1.3	8.0	5.2
OR (95% CI)	2.92 (1.63–5.26)	1.00	1.15 (0.40–3.27)	1.00	1.52 (0.43–5.40)	1.00
Epilepsy (code G40–G41)[b]						
Proportion, cases per 1000	3.3	2.5	3.4	2.5	3.1	3.4
OR (95% CI)	1.33 (0.76–2.34)	1.00	1.39 (0.71–2.71)	1.00	0.95 (0.18–5.01)	1.00
Behavioral disorders (code F80–F98)[a,c]						
Proportion, cases per 1000	6.6	4.1	4.1	4.1	11.1	3.4
OR (95% CI)	1.68 (1.11–2.53)	1.00	1.05 (0.57–1.91)	1.00	3.05 (0.70–13.29)	1.00
Diabetes mellitus (code E10)[b]						
Proportion, cases per 1000	0.9	0.5	1.0	0.5	0.6	1.7
OR (95% CI)	1.57 (0.51–4.84)	1.00	1.98 (0.56–7.07)	1.00	0.28 (0.02–4.50)	1.00
Asthma (code J45–J46)[b]						
Proportion, cases per 1000	30.3	28.1	26.5	27.8	37.1	43.0
OR (95% CI)	1.08 (0.90–1.30)	1.00	0.95 (0.74–1.20)	1.00	0.93 (0.57–1.51)	1.00
Allergy (code L20–L23, L27, L50)[b]						
Proportion, cases per 1000	59.9	53.8	61.8	54.0	56.3	46.5
OR (95% CI)	1.07 (0.94–1.23)	1.00	1.10 (0.94–1.30)	1.00	1.25 (0.80–1.96)	1.00
Pneumonia (code J12–J18)[a]						
Proportion, cases per 1000	9.9	11.4	9.6	11.4	10.5	8.6
OR (95% CI)	0.85 (0.62–1.17)	1.00	0.81 (0.55–1.20)	1.00	1.26 (0.46–3.49)	1.00
Diarrhea (code A08–A09)[a]						
Proportion, cases per 1000	44.2	38.6	35.4	38.1	60.0	60.2
OR (95% CI)	1.17 (1.00–1.37)	1.00	0.94 (0.76–1.15)	1.00	1.04 (0.69–1.56)	1.00

ORs were adjusted for mother's socioeconomic position.

[a] Data sources: the HDR and child-care support.

[b] Data sources: the HDR, long-term medication use, and child-disability allowance.

[c] Disorders of psychological development and behavioral and emotional disorders.

TABLE 5 **Use of Hospital Services Until the Age of 4 Years Among IVF and Control Children, According to Multiplicity**

Use of Hospital Services	Total		Singleton		Multiple	
	IVF ($n = 4527$)	Control ($n = 189\,656$)	IVF ($n = 2911$)	Control ($n = 185\,530$)	IVF ($n = 1616$)	Control ($n = 4126$)
Total no. of hospital episodes	4397	136 782	2281	131 459	2116	5323
Hospitalized children, %	40	33	34	32	50	49
OR (95% CI)	1.40 (1.31–1.48)	1.00	1.12 (1.04–1.21)	1.00	1.07 (0.95–1.20)	1.00
Time in hospital per child, d	6.3	2.7	3.8	2.6	10.8	9.8
Proportion of long hospital episodes (≥7 d), %	20	11	14	10	28	24

ORs were adjusted for mother's socioeconomic position. The reference group (OR = 1) was the control group.

95% CI: 0.63–0.95) and the respiratory system (OR: 0.74; 95% CI: 0.63–0.87). Otherwise, their outcomes were comparable to those of control multiple births. However, in almost every category the proportion of hospitalized children was higher among multiple births than among singletons.

In the subanalysis for first births, the results were mainly similar to the results for all children; although IVF children in total had increased risk for asthma (adjusted OR: 1.39; 95% CI: 1.08–1.79), the risk for mothers' long hospital stay for IVF singletons (OR: 1.17; 95% CI: 0.89–1.58) and the risk for cesarean sections for multiple births (OR: 1.19; 95% CI: 0.92–1.53) were not statistically significantly increased. In addition, IVF multiple births had statistically significantly decreased risk for low birth weight (adjusted OR: 0.78; 95% CI: 0.65–0.93).

There were no differences in the results of the 2 logit analyses (an ordinary logit model and an additional analysis using the iterative generalized least-squares method; see Methods). For some rare outcomes, adjustment for mother's socioeconomic position was not possible in the additional analysis because of small numbers.

DISCUSSION

We found an increased burden of disease associated with IVF, with poorer perinatal health, higher mortality rates, increased risk for hospitalization and CP, and longer

hospital episodes. This burden depended in part on higher twin rates among IVF children. However, the burden of disease resulted not only from the greater number of twins but also from the poorer health of singletons, compared with naturally conceived singletons. Increased morbidity was attributable not to any specific disease but rather to small increases in many groups of diseases. In general, the health of IVF multiple births was comparable to that of other multiple births.

Are the results reliable? IVF children were identified on the basis of drugs used, laboratory and radiologic examinations, and infertility treatment procedures. We might have missed some IVF children, who would therefore be included in the control group. However, the number of missing children cannot be large[18,19] and would not affect the results. The data on deaths and perinatal health received from the MBR[21,22] are reliable. However, other outcome measures depend on service utilization (seeking care or applying for benefits); technically, the registers are considered to be of good quality.[23]

The occurrence of less-serious diseases and cases cannot be estimated from these registries, because the use of outpatient care is not registered. Our results might be biased by different thresholds for hospital admissions between IVF and control children. IVF parents, who were more often first-time parents, might have been more worried, which might have led more easily to hospital care and also longer hospital stays. It might also be that IVF children were examined more carefully by physicians, compared with naturally conceived children, if the mode of conception was known to the physicians. However, because IVF children did not have an increased rate of hospitalizations in all categories of diseases and because adjustment for parity and socioeconomic position and a subanalysis of first births did not change our results, it is unlikely that the anxiousness of parents, more-careful examinations, or lower thresholds for hospitalization alone could explain the greater frequency of visits. Rather, the greater frequency likely reflects higher morbidity rates among singleton IVF children. Furthermore, rates of almost every outcome studied were quite similar between IVF multiple births and control multiple births.

In Finland, most health care is public, financed by taxes. Private health care is covered by the national social security system, but some children are covered by additional voluntary private insurance. No private hospitals for children exist but, in 2005, ~28% of children up to 4 years of age used private (outpatient) physicians (Social Insurance Institution of Finland, unpublished data, 2005). It is possible that, in the case of small surgical procedures, private specialist outpatient care competes with hospital outpatient clinics. If IVF children were treated more or less frequently in such private care, then a bias would result.

In Finland, health-related social benefits (child care allowance and reimbursement for long-term medication use) must be applied for. It might be that some parents are more capable of applying for the benefits. Because the adjustment for socioeconomic position did not change the results, however, there is no reason to assume that parents of IVF children with a higher socioeconomic position would receive benefits more easily than parents of control children. Informing and advising parents on these benefits is part of routine clinical practice. In addition, reimbursed diseases for long-term medication use are defined clearly, and recent medical documents are needed for receipt of both child disability allowance and support for long-term medication use. Child disability allowance is based on ICD-10 classifications and long-term medication support on defined diagnoses; therefore, it can be assumed that these are relevant in estimating disease occurrence.

Our study confirms earlier findings of poorer perinatal health,[3–5,8] greater numbers of hospitalizations,[9] and increased risk for congenital anomalies[15,16,24] for IVF singletons, compared with naturally conceived singletons. Perinatal problems had a significant role also in hospitalizations; diseases originating from the perinatal period represented one of the most common diagnoses leading to hospitalization, among both singletons and multiple births. IVF multiple births had worse perinatal health than did IVF singletons, but IVF and control multiple births were similar with respect to perinatal health, which is largely in accordance with an earlier study (except for the finding in that study of an increased risk of admittance to a NICU and more-common longer hospitalizations after the birth).[25] In contrast, a recently published Belgian study found an increased risk for preterm birth also among IVF twins, compared with naturally conceived twins, which was largely explainable by the first birth of IVF women.[7] In accordance with the study by Pinborg et al,[13] we did not find any excess use of hospital services among IVF multiple births.

In addition, our study confirms earlier results of higher mortality rates,[8] greater numbers of hospitalizations,[10,17] and increased risks for behavioral problems,[17] CP,[11,14] and infections[10] among IVF children overall. In accordance with an earlier Finnish study based on both outpatient and inpatient visits,[8] we found a slightly but not statistically significantly increased risk for diarrhea; contrary to that study, however, we did not find an increased risk for pneumonia.

Unlike previous studies,[11,14] we did not find an increased risk for CP or sleeping disturbances among IVF singletons. In our study, the excess risk for CP was mainly explainable by multiplicity. In the study by Strömberg et al,[11] the main reasons for the increased risk for CP were prematurity and the multiple pregnancy rate. A recent Swedish study could not confirm the increased risk for CP; the risk disappeared after adjust-

ment for confounders.[17] Furthermore, we could not find increased risk for epilepsy, tumors, or asthma among IVF children in total, as found earlier in Sweden.[10] However, increased risk for epilepsy was not found in the recent Swedish study.[17]

A few previous studies reported about childhood morbidity for IVF multiple births. In 2 studies, no differences in neurologic sequelae were found.[11,12] In our study, no increased risk for any disease among IVF multiple births was found. In general, however, IVF multiple births had higher childhood morbidity rates than did IVF singletons.

We could not find any other study examining long-term medication use, child disability allowance, and utilization of institutional care among IVF children. A slightly increased risk for child disability allowance among IVF children in our study was explainable by multiplicity, whereas no statistically significant differences in the utilization of long-term medication therapy and institutional care between the groups were found.

Potential reasons for the poorer perinatal health of IVF children include infertility itself,[26–29] infertility treatments, and varying health behavior during pregnancy. Among IVF singletons, the main cause of poorer perinatal health has been suggested to be infertility itself, because of the higher incidence of preterm birth and low birth weight also among infertile women without treatment and women with infertility treatments other than IVF.[30] Some modification in the gestational process induced by IVF and intracytoplasmic sperm injection has been suggested,[31] as well as so-called vanishing twins (singletons originating from twin pregnancies).[32] It has also been found that the risk for preterm birth increases with low-technology treatments, compared with natural pregnancy, and increases further with high-technology treatments.[33]

Zygosity plays a significant role when the health of IVF multiple births are compared with the health of other multiple births. In general, monozygotic twins have poorer perinatal outcomes than dizygotic twins. A larger proportion of twins are dizygotic among medically assisted pregnancies (30%), compared with naturally conceived pregnancies (1%).[34] This can partly explain the results of the similar outcomes of multiple births in studies unable to take zygosity into account. In our study, 50% of IVF twins and 30% of control twins were opposite-gender twins, which suggested that more IVF children were dizygotic.

During the 1990s, the perinatal health of IVF children improved in Finland, mainly because of a decrease in higher-order multiple births.[35,36] Because so many IVF pregnancies in the late 1990s were still multiple births, the health of IVF children in total was worse than that of naturally conceived children, with increased risks for CP and developmental and psychological problems. The best way to improve the health of IVF children is to favor single-embryo transfers. The way to improve the health of singletons is more problematic, because we do not know the reasons for the findings. Sufficiently large follow-up studies that consider the health of IVF children from 4 years onward are needed.

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Paper IV

Children born after assisted fertilization have an increased rate of major congenital anomalies

Reija Klemetti, M.H.Sc.,[a] *Mika Gissler, D.Phil.,*[b] *Tiina Sevón,*[a] *Sari Koivurova, M.D.,*[c] *Annukka Ritvanen, M.D.,*[b] *and Elina Hemminki, M.D. Dr. P.H.*[a]

[a] Health Services Research and [b] Information Unit, National Research and Development Centre for Welfare and Health (STAKES), Helsinki; and [c] Department of Obstetrics and Gynecology, University Hospital of Oulu, Oulu, Finland

Objective: To study the occurrence of major congenital anomalies (CAs) among children born after IVF (IVF, microinjections, and frozen embryo transfers) and after ovulation inductions with or without insemination (other assisted reproductive technologies [ART]).
Design: Register-based study.
Setting: Data regarding CAs were obtained from the Register of Congenital Malformations.
Patient(s): Children from IVF (n = 4,559), children from other ART (n = 4,467), and controls (n = 27,078, a random sample of naturally conceived children) from the Medical Birth Register.
Intervention(s): In vitro fertilization and other ART treatment in ordinary practice.
Main Outcome Measure(s): Rate of major CAs. Children from IVF and other ART were compared with control children, both overall and by plurality, controlling for confounding factors by logistic regression.
Result(s): For IVF children, the adjusted odds ratio (OR) was 1.3 (95% confidence interval [CI], 1.1–1.6). Stratifying by gender and plurality showed that the risk was only increased for boys, and the risk was decreased for multiple IVF girls (OR = 0.5, 95% CI 0.2–0.9). The crude OR of major CA for other ART children was 1.3 (95% CI 1.1–1.5), but adjusted differences by gender and plurality were statistically insignificant.
Conclusion(s): In vitro fertilization was associated with an increased risk for major CAs among singleton boys and a decreased risk among multiple girls. The risk after other ART was only slightly increased. (Fertil Steril® 2005;84:1300–7. ©2005 by American Society for Reproductive Medicine.)

Key Words: Major congenital anomaly, ART, register-based study

In vitro fertilization and its related procedures—intracytoplasmic sperm injection (ICSI)and frozen embryo transfer (FET)—have become common infertility treatments. For example, in Finland approximately 2.5% of all infants are born as a result of these therapies (1). The exact number of children born after other assisted reproduction technologies (ART), such as ovulation inductions and inseminations, is unknown, but according to our estimation during 1996–1999 2.4% of all infants were born after other ART in Finland.

Some studies (2–9) but not others (10–13) have shown an increase in some congenital anomalies (CAs) among IVF or ICSI children. Most published studies have had methodological problems, such as small sample sizes, lack of proper controls, and different definitions of CA among IVF and naturally conceived children. In a recent Australian study, the rate of musculoskeletal, cardiovascular, chromosomal, and urogenital defects was increased among IVF children (7). In a small Finnish study, the prevalence of heart malformations was fourfold among IVF infants compared with control infants (8). We found only one study on malformations of children born as a result of other ART (14). There were increased rates of congenital malformations, but these could be mainly explained by maternal characteristics.

In this study, we compared the prevalence of major CAs among IVF and other ART children with that among naturally conceived children, controlling for confounding factors. The data source of CAs was the same for all children—the Finnish Register of Congenital Malformations (RCM)—and we have information regarding the drugs used in the infertility therapy.

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Reprint requests: Reija Klemetti, M.H.Sc., STAKES, Health Services Research, P.O. Box 220, Helsinki 00531, Finland (FAX: 358-9-3967-2496; E-mail: reija.klemetti@stakes.fi).

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MATERIALS AND METHODS

The study is based on children born to women having received IVF (IVF, ICSI, and FET) and other ART between 1996 and 1998 in Finland. The women were identified with a predesigned algorithm from the reimbursement files of the Social Insurance Institution (15) and linked to the Finnish Medical Birth Register (MBR); the time difference between the beginning of the last treatment cycle and the birth of the child was used to estimate which infants resulted from IVF or other ART (16).

The MBR includes the mother's and child's unique personal identification numbers and contains information on maternal background and on the infant's outcome until the age of 7 days for all infants born in Finland. The duration and causes of infertility are not registered. The data are collected by delivery hospitals and completed by linkage to the Central Population Register and the Cause-of-Death Register. The quality of the MBR has been found to be high for the variables used in this study (17, 18).

We identified 4,559 IVF and 4,467 other ART children born between October 1996 and September 1999. As controls, 27,078 naturally conceived children (three times the number of cases) were selected randomly from the MBR, excluding children having a note of IVF or other ART in MBR. Children from ICSI (n = 861) could be distinguished from IVF children only if the treatment had been given in private clinics because a specific code for ICSI exists only there.

The identified children were linked to the RCM according to the mothers' identification numbers and the childrens' dates of birth. The RCM collects information on all infants with a CA or birth defect through several data sources, including a form completed by delivery hospitals, neonatal, pediatric, and pathology departments, and cytogenetic laboratories and by linkage to several other nationwide registers. More than 99% of the major CAs are registered before the age of 1 year.

In the RCM a CA has been defined as a major congenital structural anomaly, chromosomal defect, or congenital hypothyroidism involved in a birth. The register records all notified cases, but the physician responsible for RCM routinely classifies congenital anomalies into major, other, and rejected. Rejected anomalies include some minor congenital anomalies, as defined by the European Surveillance of Congenital Anomalies (European Concerted Action on Congenital Anomalies and Twins [EUROCAT]; http://www.eurocat.ulster.ac.uk) exclusion list (hereditary diseases, dysfunction of organs or tissues, developmental disabilities, congenital infections, isolated minor dysmorphic features, normal variations, and other less significant anomalies). For this study, the physician reviewed all diagnosis and inclusion criteria without knowing the mode of conception of the children.

The study plan was approved by the National Research and Development Centre for Welfare and Health (STAKES) research ethics committee. For register linkages, the National Data Protection Authority was consulted and permissions from the register keepers were obtained.

The differences were tested by *t*-test, a test for relative proportions, and a χ^2 test. The statistical analyses were performed in SAS, version 8 (SAS Institute, Cary, NC). The IVF and other ART children were compared with the control children according to odds ratios (OR) and 95% confidence intervals (CI), stratifying by gender and multiplicity. Twins and triplets were analyzed separately. Differences in age of the mother, parity, socioeconomic position (measured from maternal occupation), and the region of residence were controlled by logistic regression.

In the analysis by organ system, a child appeared more than once if (s)he had more than one major CA affecting different organ systems. Different CAs in the same organ system were calculated as one, but if the child had a major CA both in the urinary and genital system, only one was taken into account by combining these two groups as the "urogenital system." Only major CAs, as defined in the RCM, were included in the analysis, but minor urinary and genital CAs were separately compared between studied groups.

To investigate which of the infertility drugs used in the treatment were related to CAs, a nested case–control design in the IVF and other ART cohorts was used: mothers of children with CAs were compared with mothers of nonmalformed children. Drugs used during the last IVF cycle preceding the birth were classified into five groups: GnRH, FSH, hCG, progesterones (Ps) (among IVF women 99% and among other ART women 50% were natural Ps), and estrogens (Es), and the age-adjusted ORs for using at least one of the drugs from the category were calculated.

To estimate the total prevalence of major CAs, we linked the IVF and other ART women to the Register of Induced Abortions, specifying induced abortions performed because of a suspected or confirmed CA. The rates were compared with the national rates per 10,000 births.

RESULTS

In vitro fertilization and other ART mothers differed from control mothers, and IVF mothers from other ART mothers in regard to most characteristics (Table 1). Multiplicity was much higher in the IVF than in the other ART group, but the number of triplets was the same (16 vs. 17).

Among IVF and other ART children, 51% of reported major CAs had been accepted by the RCM, whereas among control children the proportion was 46%. In total, 195 IVF children (4.3%), 166 other ART children (3.7%), and 787 control children (2.9%) had at least one major CA. The prevalence of a major CA was the same for IVF singletons and IVF multiples but much higher for multiples than for singletons among other ART and control children (Table 2).

TABLE 1

Characteristics of IVF, other ART, and control mothers and children by multiplicity and gender.

	IVF	Other ART	Controls
Mothers	n = 3,737	n = 4,188	n = 27,022
Age (y) (mean ± SD)[a]	33.9 ± 4.5	31.2 ± 4.6	29.8 ± 5.3
Age (y)[b]			
<25	2.2	8.3	19.7
25–29	17.3	34.1	32.2
30–34	40.6	37.2	31.4
35–39	30.1	16.4	13.5
40+	9.8	4.0	3.1
Married[c]	76.1	74.8	60.5
Parity[b]			
0	71.7	54.3	38.7
1	21.1	32.4	33.4
2	4.2	9.3	16.4
3+	2.4	3.3	10.1
Missing	0.6	0.7	1.4
Socioeconomic position[b]			
Upper white-collar	26.1	21.2	15.7
Lower white-collar	48.8	47.8	41.3
Blue-collar	12.8	13.9	16.6
Other	12.3	17.2	26.4
Place of residence[b]			
Southern Finland	44.8	38.6	40.6
Western Finland	33.4	38.3	34.4
Eastern Finland	9.9	9.5	10.4
Northern Finland	11.6	13.3	13.9
Missing	0.3	0.3	0.7
Children	n = 4,459	n = 4,467	n = 27,078
Singletons	64.3	87.9	97.8
Girls	32.7	42.8	48.6
Boys	31.6	45.1	49.3
Multiples	35.7	12.1	2.2
Girls	17.6	6.0	1.2
Boys	18.1	6.0	1.0

Note: Values are percentages, unless otherwise noted.

[a] $P<.001$, *t*-test.

[b] $P<.001$ for all comparisons (IVF vs. other ART, IVF vs. controls, and other ART vs. controls), χ^2 test.

[c] $P<.001$ (IVF vs. controls and other ART vs. controls), test for relative proportions.

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Boys from IVF, both singletons and multiples, had major CAs more often than IVF girls (Table 3). The same was seen among multiples from other ART.

An increased OR for having any major CA was found in the crude analysis both for IVF and other ART children (Table 3). The adjustment for maternal age or other confounding factors somewhat decreased the ratio for IVF children but not for other ART children. The total risk for singletons was statistically significantly increased and for multiples insignificantly decreased. A significantly increased OR was found among singleton IVF boys, and a significantly decreased OR for multiple IVF girls. The result did not change after taking into account the confounding factors. In the separate analysis for twins, excluding triplets, the results for IVF girls remained similar (the adjusted OR was 0.31, 95% CI 0.11–0.88).

In the analysis by different organ system, compared with controls, IVF children had a higher risk for CA for most categories. Compared with other ART children, IVF children had more CAs in the categories of "eye, ear, face, and neck,"

TABLE 2

Prevalence of major congenital anomalies per 10,000 infant by the organ system affected.[a]

	Singletons								Multiples							
	IVF (n = 2,930)			Other ART (n = 3,926)			Controls (n = 26,489)		IVF (n = 1,629)			Other ART (n = 541)			Controls (n = 589)	
	n	/10,000	*P*[b]	n	/10,000	*P*[b]	n	/10,000	n	/10,000	*P*[b]	n	/10,000	*P*[b]	n	/10,000
Any	125	427	<.001	138	352	.022	756	285	70	430	.335	27	499	.836	31	526
Central nervous system	9	31	.008	12	31	.003	31	12	9	55	.071	7	129	.006	0	0
Eye, ear, face and neck	12	41	.009	6	15	.693	48	18	5	31	.583	1	18	.952	1	17
Heart	44	150	.042	59	150	.021	287	108	33	203	.791	11	203	.840	13	221
Other circulatory system	6	20	.740	12	31	.088	47	18	2	12	.790	0	0	.338	1	17
Respiratory system	5	17	.284	5	13	.647	27	10	3	18	.496	0	0	.175	2	34
Cleft palate and cleft lip	12	41	.034	14	36	.076	56	21	5	31	.904	0	0	.175	2	34
Digestive system	14	48	.028	16	41	.083	67	25	5	31	.093	4	74	.836	5	85
Urogenital system	35	119	<.001	26	66	.150	129	49	12	74	.789	4	74	.836	5	85
Musculoskeletal system	34	116	.004	30	76	.588	182	69	20	123	.270	6	111	.441	4	68
Skin, hair and nails	1	3	.533	2	5	.757	17	6	2	12	.395	0	0	NA	0	0
Chromosomal anomalies	8	27	.304	7	18	.927	49	18	3	18	.496	2	37	.932	2	34
Other congenital anomalies and the defects	12	41	.171	19	48	.020	71	27	9	55	.237	3	55	.381	6	102

Note: NA = not applicable.

[a] n = number of children. If a child had a major malformation in more than one organ system, the child appears several times in the table. If the malformations affect the same organ system, the child appears only once in the table.

[b] Test for relative proportions, control group as a reference group.

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TABLE 3

Total risk of major congenital anomalies and risk according to organ system affected[a] by gender and multiplicity.

		Risk								
		Girls			Boys			Total		
Multiplicity	Group	n[b]	OR (95% CI)	OR[c] (95% CI)	n[b]	OR (95% CI)	OR[c] (95% CI)	n[b]	OR (95% CI)	OR[c] (95% CI)
Singletons										
Total	Control	348	1.00	1.00	408	1.00	1.00	756	1.00	1.00
	IVF	48	1.23 (0.90–1.66)	0.97 (0.69–1.36)	77	1.79 (1.40–2.30)	1.63 (1.23–2.15)	125	1.52 (1.25–1.84)	1.30 (1.05–1.61)
	Other ART[d]	67	1.34 (1.02–1.74)	1.21 (0.98–1.67)	71	1.16 (0.90–1.50)	1.12 (0.86–1.46)	138	1.24 (1.03–1.49)	1.17 (0.97–1.41)
Heart	Control	128	1.00	1.00	136	1.00	1.00	264	1.00	1.00
	IVF	17	1.17 (0.71–1.95)	1.05 (0.62–1.78)	19	1.30 (0.80–2.11)	1.21 (0.73–2.00)	36	1.24 (0.87–1.75)	1.13 (0.79–1.62)
	Other ART	29	1.57 (1.04–2.35)	1.52 (1.01–2.28)	24	1.17 (0.76–1.81)	1.17 (0.75–1.81)	53	1.36 (1.01–1.83)	1.33 (0.99–1.80)
Urogenital	Control	52	1.00	1.00	80	1.00	1.00	26	1.00	1.00
	IVF	9	1.53 (0.75–3.11)	1.47 (0.70–3.07)	22	2.57 (1.60–4.14)	2.46 (1.49–4.07)	31	2.14 (1.44–3.17)	2.05 (1.36–3.10)
	Other ART	4	0.53 (0.19–1.46)	0.52 (0.19–1.45)	20	1.66 (1.02–2.72)	1.62 (0.99–2.65)	24	1.23 (0.79–1.90)	1.20 (0.78–1.87)
Musculosceletal	Control	72	1.00	1.00	110	1.00	1.00	182	1.00	1.00
	IVF	11	1.35 (0.72–2.55)	1.26 (0.65–2.44)	23	1.95 (1.24–3.07)	1.75 (1.09–2.81)	34	1.70 (1.17–2.45)	1.55 (1.05–2.27)
	Other ART	12	1.15 (0.62–2.12)	1.11 (0.60–2.05)	18	1.09 (0.66–1.79)	1.04 (0.63–1.72)	30	1.11 (0.76–1.64)	1.07 (0.73–1.58)
Multiples										
Total	Control	18	1.00	1.00	13	1.00	1.00	31	1.00	1.00
	IVF	26	0.55 (0.30–1.02)	0.45 (0.22–0.93)	44	1.13 (0.60–2.14)	1.31 (0.64–2.71)	70	0.81 (0.52–1.25)	0.80 (0.48–1.32)
	Other ART	7	0.44 (0.18–1.08)	0.41 (0.16–1.05)	20	1.59 (0.77–3.26)	1.56 (0.71–3.42)	27	0.95 (0.56–1.61)	0.91 (0.52–1.61)
Total	Control	366	1.00	1.00	421	1.00	1.00	787	1.00	1.00
	IVF	74	1.19 (0.93–1.54)	0.97 (0.73–1.28)	121	1.77 (1.44–2.17)	1.66 (1.31–2.10)	195	1.49 (1.27–1.75)	1.31 (1.10–1.57)
	Other ART	75	1.26 (0.98–1.62)	1.15 (0.89–1.50)	91	1.30 (1.03–1.64)	1.26 (0.99–1.59)	166	1.28 (1.08–1.52)	1.21 (1.02–1.44)

[a] Reference group (OR = 1) = control children. If a child had a major CA in more than one organ system, the child appears several times in the table. If the CAs affect the same organ system, the child appears only once in the table.

[b] n = number of malformed children.

[c] For all major CAs adjusted by age, parity, socioeconomic position, and region, and for some specific anomalies according to organ system adjusted only by age owing to the small number of cases.

[d] One other ART child excluded owing to missing gender status.

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TABLE 4

Major genital anomalies (and all hypospadias) among singleton boys: number and rate per 10,000.

	IVF (n = 1,440)	Other ART (n = 2,014)	Controls (n = 13,339)
Total			
No.	11	6	15
Rate	76	30	11
P[a]	<.001	.036	
Hypospadias			
No.	7	3	10
Rate	15	7	4
P[a]	<.001	.287	
All hypospadias[b]			
No.	11	8	38
Rate	76	40	29
P[a]	.003	.390	

[a] Test for relative proportions, compared with controls.
[b] Also includes glandular hypospadias.

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"respiratory system," "urogenital system," and "musculoskeletal system." When stratifying the analysis to singletons and multiples (Table 2), IVF singletons had statistically significantly more major CAs than control singletons in many categories. Among multiples the rates were the opposite: in most categories, IVF multiples had fewer major CAs than control multiples, and none of the differences were statistically significant. Among other ART children, singletons had more and multiples had fewer CAs in most organ systems than control singletons, but the differences were not as clear as that between IVF and control children.

When inspecting the risk according to the organ system affected, by gender and multiplicity, we found a slightly increased OR for major heart anomalies among singleton other ART girls and increased ORs for urogenital and musculoskeletal CAs among singleton IVF boys (Table 3). The results remained the same after adjustment for age. Among IVF singleton boys, major urogenital CAs were more severe than among controls. When we checked for minor urogenital CAs of singleton boys, no reported minor urinary CA was observed. In the separate analysis of urinary and genital CAs, it was found that the increased risk was mainly due to the genital CAs. Hypospadia was the most common diagnosis of these major genital anomalies, and control boys had more minor hypospadias than IVF boys (Table 4). In addition, other ART singleton boys had a higher risk for urogenital CAs. No specific musculoskeletal CA among IVF boys was found.

Out of 861 ICSI children, 40 (4.6%) had one or more CA. The frequency of major CAs was in general as among all IVF children. Because of the small number of cases, a more specific analysis of the ICSI group was not done.

By definition, all IVF mothers were exposed to some infertility drugs, most commonly to P (Table 5). Most mothers were exposed to several drugs. Only Es were used more often by the mothers of malformed than by the mothers of

TABLE 5

Drugs used by mothers of malformed and nonmalformed children.

Group	Malformed[a]	Non-malformed	*P*[b]
IVF[c]	n = 179	n = 4,088	
P	87	88	.736
FSH or hMG	59	63	.241
GnRH	55	62	.050
hCG	17	20	.286
E_2	20	12	.003
Other ART	n = 166	n = 4,301	
Clomiphene citrate	81	86	.056
P	30	30	.896
FSH or hMG	14	11	.250
hCG	5	4	.598

Note: Values are percentages.
[a] At least one major congenital anomaly.
[b] Comparisons of malformed and nonmalformed groups, test for relative proportions.
[c] Two hundred ninety-two IVF children are excluded owing to the lack of information on drugs used.

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nonmalformed IVF children, but mothers of most malformed children had not received it. Some 27% of the mothers of singleton boys with a genital CA had used Es (vs. 13% of mothers of nonmalformed singleton boys) and 82% P (vs. 82% of mothers of nonmalformed singleton boys). Among other ART children, no differences in the drugs used between malformed and nonmalformed children were found, neither in the use of a natural nor a synthetic progestin.

During the study period, 9 of the 9,175 IVF women (19.7 per 10,000 IVF births) and 8 of the 10,270 other ART women (17.9 per 10,000 other ART births) had an induced abortion owing to the suspected or detected fetal defect. The national rate per 10,000 births in 1996–1998 in Finland was 36.7 (The Finnish Medical Birth Register).

DISCUSSION

We found increased total rates of major CAs for IVF and other ART singletons. Singleton boys from IVF in particular had more major urogenital and musculoskeletal CAs, and other ART singleton girls had more major heart anomalies. Among multiples, the total risk for a major CA was not increased, and for multiple IVF girls the risk had even decreased.

Can our results be trusted? Our data include most infants born as a result of IVF and other ART in Finland during the study period. The identification was based on drugs used in infertility therapy and reimbursed treatments (only private clinics) (15, 16). It is possible that we missed some women who had received their treatment in the public sector and had used drugs bought and reimbursed before 1996. We have estimated that our data lack approximately 4% of IVF women and 6% of other ART women (15), but the identification of the women was made before pregnancy and is unlikely to relate to the occurrence of major CAs.

Data on major CAs in all three groups came from a routine nationwide register, the RCM, to which information is collected and classified blindly with regard to IVF or ART status. However, we do not know whether physicians who reported CA to the register knew the mode of conception. It could be that IVF children were more carefully examined and/or that CAs for them were more conscientiously reported than those for naturally conceived children. However, the fact that more reports that were rejected by the RCM occurred for control children than for IVF children speaks against this source of bias. Likewise, the checking of minor genital anomalies showed that the number of reported minor CAs of IVF children was smaller than that of controls. One could have expected it to be greater if the IVF and other ART children had been more carefully examined and reported. The types of genital anomalies suggest that classification into major CAs has been clear-cut.

We do not have information regarding induced abortions of the naturally conceived children's mothers or of major CAs among them. However, the rates of induced abortions due to CAs were so low that they are unlikely to bias the results.

According to previously published studies, twins have more CAs than singletons (19). That was also true among control children in our study but not among IVF children, which is in accordance with the results from a recent Danish study of IVF and ICSI twins, in which no differences in malformation rates between IVF/ICSI and naturally conceived twins were found (20). What, therefore, could explain this discrepancy between multiples and singletons? One explanation could be the fact that many singletons originated from multiple ET and from multiple pregnancy with a higher risk (during the study period 15% of ETs [IVF, ICSI, and FET] were single-embryo transfers, but 88% of live births were singleton births [21]). If two embryos succeed during implantation and develop in assisted reproduction, it can be assumed that conditions have to have been especially favorable.

Another possible explanation is zygocity: monozygotic twins have more malformations than dizygotic, and monozygosity is rarer among twins of assisted reproduction than among naturally conceived twins (1% vs. 30%) (22). Although IVF and other ART increase monozygotic twinning (6, 14), transfer of several embryos causes the majority of IVF twins to be dizygotic. The fact that the CA rate was not smaller among IVF twin boys could result from a higher risk of CA among IVF boys.

Most hormones in IVF treatment are used before pregnancy, and the half-life of most of these drugs is short. However, the duration of active drugs and metabolites in the body and their individual variations are not clear. Some drugs are also used as luteal-phase support during pregnancy. In addition to direct toxic effect, the drugs might have their effect through the mother's hormonal secretion balance. Although the dangers of hormones in early pregnancy have been discussed for decades (23, 24), this has not been the focus when the health effects of IVF have been discussed. We had information regarding fertility drugs (dosages and number of packages) bought, but the exact date and duration of their use was not known. Because the treated women received many and varied medicines during the last cycle, it was not possible to identify any specifically harmful drug.

Our study verified an earlier result of the overall risk for urogenital CAs (7), but ours was too small to study the risk of individual diagnoses, such as the hypospadia previously reported (6, 25). The use of P during IVF treatment has been offered as one explanation for the increased risk of one genital CA, hypospadia (25). Children exposed in utero to E and P or only P were found to have more male genital malformations than nonexposed children (23). However, in our study no difference in P use was found among boys with major genital anomalies and other IVF boys. Instead, E use was more frequent, but most boys with genital CAs were not exposed to it.

Another explanation for the higher rate of male genital anomalies might be the hereditary paternal subfertility associated with ICSI (5). Unfortunately, we could identify ICSI children only when the treatment was given in a private clinic. Because of the possible bias and the small number of children, we did not study specific CAs of ICSI children. Because the genital CAs were more severe among IVF than among control children, the risk for major urogenital CAs could be greater than our results show. The risk was also somewhat increased among other ART boys.

In another Finnish study, IVF children had more heart anomalies than control children (8). This was also true in our study, but the risk was not statistically significant. Rather, it was found among other ART children. This might relate to the use of clomiphene citrate (14). The increased risk for musculoskeletal CAs among IVF children is in accordance with a previous study from Australia (7).

Other than drugs, potential causes for congenital anomalies could include infertility itself, the advanced age of mothers, and factors related to the IVF procedure, such as the freezing and thawing of embryos. We did not have any information about the duration and causes of infertility and could not adjust data for them. The higher age of mothers did not explain the increased risk for major CAs.

In conclusion, our study verifies an increased risk for major CAs among IVF singleton boys and suggests that the risk after other ART is also slightly increased and not explained by those maternal characteristics available in the Finnish MBR. The actual risk is, however, quite small. Because our findings regarding different organ systems are based on small numbers of children, further studies are needed to explain them. It would be important to perform a large follow-up study of IVF and other ART births which includes information on the duration and causes of infertility, exact information regarding maternal drug exposure, and other maternal background characteristics. Meanwhile, the techniques used in IVF and other ART should be considered potentially teratogenic, thus requiring that information be given to the physicians and the public.

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