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Prevalence and Socio-demographic Determinants of Infertility, Success of Infertility Treatments and Health of Treated Women

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To my beloved children Otto and "Papu"

and

to my Mother-in-law Tuula and Grandmother Helena,

I wish so much you were still here

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II Yli-Kuha AN, Gissler M, Luoto R, Hemminki E. Success of infertility treatments in Finland in the period 1992-2005. Eur J Obstet Gynecol Reprod Biol. 2009;144(1):54-8.

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IV Yli-Kuha AN, Gissler M, Klemetti R, Luoto R, Hemminki E. Cancer morbidity among a cohort of 9175 Finnish women treated for infertility. Submitted.

Abbreviations

ART = Assisted reproductive technologies

BESTT = Birth emphasizing a successful singleton at term

CDC = Centers for Disease Control and Prevention

CI = Confidence interval

DMS-III-R = Diagnostic and Statistical Manual of Mental Disorders, revised 3rd edition

EIM = The European IVF Monitoring Program

eSET = Elective single embryo transfer

ESHRE = European Society on Human Reproduction and Embryology

FET = Frozen embryo transfer

FSH = Follicle stimulating hormone

GnRH = Gonadotrophin releasing hormone

HADS = Hospital anxiety and depression scale

hCG = Human chorionic gonadotrophin

HMG = Human menopausal hormone

ICD-10 = International Classification of Diseases, 10th edition

ICSI = Intra cytoplasmic sperm injection

IUI = Intra uterine insemination

IVF = In vitro fertilization

LH = Luteinizing hormone

PCOS = Polycystic ovarian syndrome

POMS = Profile of mood states

SHBH = Sex hormone binding hormone

SIR = Standardized incidence ratio

STAKES = The National Research and Development Centre for Welfare and Health

TFR = Total fertility rate

THL = National Institution for Health and Welfare

TSH = Thyreotrophin, thyroid stimulating hormone

VALVIRA = National Supervisory Authority for Welfare and Health

WHO = World Health Organization

Abstract

Background: Reduced fertility is a common and multifaceted medical and social problem affecting about 10-15% of couples in Western countries. Differences in prevalence of infertility have previously been published by age and socio-demographic factors. Infertility treatments are currently widely used to help couples suffering from infertility. However, the use of infertility treatments also varies by age, education, household income and in some countries ethnicity. For most couples infertility is a serious crisis causing significant negative emotional responses. Among many patients participating in infertility treatments diagnostic criteria of psychiatric disorders, usually anxiety disorder or depression are also fulfilled. For some couples the cause of infertility remains unexplained but many females with reduced fertility have gynaecological disease such as endometriosis or polycystic ovary syndrome causing significant alterations to the body's hormonal or inflammatory balance. During infertility treatments exogenous drugs affecting hormone balance are administered. Thus it is important to know whether these infertility-causing conditions or hormonal infertility treatments predispose women to increased risk for cancer.

Objective: The purpose of this study was to investigate the prevalence of infertility and use of infertility treatments by socio-demographic determinants in Finland. The increase of in vitro ferilizations (IVF), intra cytoplasmic sperm injections (ICSI) and frozen embryo transfers (FET) over time and the changes in causes of infertility behind these treatments were also ascertained. Success of infertility treatments was calculated over time using different indicators and success rates by numbers of embryos transferred and by care site were compared. The health of a cohort of women who received IVF, ICSI or FET was also studied from two perspectives: psychiatric disorders leading to hospitalizations were studied both before and after infertility treatments and incidence of cancer was studied after treatments.

Materials and Methods: In this study two population surveys FINRISK 1997 and 2002, Aggregate IVF Statistics and a cohort of women (N=9175) who received IVF, ICSI or FET 1996-1998 and their age and residence matched controls were used. The cohort was identified through the drug reimbursement records from the Social

Insurance Institution. Hospitalizations due to psychiatric diagnoses were obtained from the Hospital Discharge Register and cancers from the Finnish Cancer Register.

Results: Self-reported life-time prevalence of infertility was 16%. Prevalence of infertility differed significantly by age and education: among the youngest women it was more often reported among the least educated, but in older age groups among the more educated. Infertility treatment seeking was more common among urban, highly educated and affluent women. Number of IVF, ICSI and FET treatments provided more than tripled 1992-2004 and the causes of infertility changed significantly as tubal infertility became less frequent and male infertility more common.

Clinical pregnancy rates and live birth rates after IVF, ICSI and FET treatments remained stable (21-25%) 1994-2005 despite a huge increase in single embryo transfers (from 14% to 51%). The proportions of term singletons and singletons weighting at least 2500 grams increased from 9% to 14%. Especially at the beginning of the follow-up period success rates were better in the private sector than in the public sector among women younger than 35 years of age.

The cohort of IVF, ICSI or FET treated women had fewer hospitalizations for all psychiatric diagnoses before infertility treatments than did the controls but the difference was statistically significant only for psychotic disorders. After treatments during the 8 to 10-year follow-up differences were mainly similar but the women in the cohort had statistically significantly more hospitalizations due to adjustment disorders and statistically significantly fewer hospitalizations due to alcohol and other intoxicant abuse. Those infertile women who gave birth after infertility treatments had fewer hospitalizations for all psychiatric diagnoses than those infertile women who did not have a baby.

The general incidence of cancer was similar among the women treated with IVF, ICSI or FET and controls. In the cohort of treated women statistically fewer cervical cancers and more skin cancers other than melanoma were diagnosed. All lung cancer cases occurred among the controls. Ovarian cancer incidence was greater among infertile women but the difference was not statistically significant.

Conclusions: The prevalence of infertility differed by age and education and there were also socio-demographic differences in the use of infertility treatments. Success

rates of IVF, ICSI and FET treatments have remained stable in spite of a significant increase of single embryo transfers. There have been differences in success rates by care site but this has diminished over time. Women who received IVF, ICSI or FET treatments had in general fewer hospitalizations due to psychiatric diagnoses than did the controls. Hospitalizations after treatments were also significantly fewer among those infertile women who had a baby. General cancer incidence among the cohort of infertile women and controls did not differ significantly. There were, however, differences in the incidence of cervical cancer, lung cancer and skin cancers other than melanoma that suggested a healthy patient effect.

Tiivistelmä

Tutkimuksen taustaa: Heikentynyt hedelmällisyys on yleinen ja moniulotteinen lääketieteellinen ja sosiaalinen ongelma, joka länsimaissa koskettaa noin 10-15 prosenttia pariskunnista. Lapsettomuuden yleisyys vaihtelee aikaisemmin julkaistujen tutkimusten perusteella iän ja sosioekonomisten tekijöiden suhteen. Nykyään lapsettomuushoitoja käytetään laajasti auttamaan lapsettomuudesta kärsiviä pariskuntia. Näiden hoitojen käytön yleisyys kuitenkin vaihtelee iän, koulutustason, tulotason ja joissain maissa etnisyyden suhteen. Valtaosalle pariskunnista lapsettomuus on vakava kriisi, joka aiheuttaa merkittävästi negatiivisia tunteita. Monilla lapsettomuushoitoihin osallistuvilla täyttyvät myös psykiatrisen sairauden, useimmiten ahdistuneisuushäiriön tai masennuksen, diagnostiset kriteerit. Joidenkin parien lapsettomuuden syy jää epäselväksi, mutta monilla naisilla, jotka kärsivät heikentyneestä hedelmällisyydestä, on gynekologinen sairaus - kuten esimerkiksi endometrioosi tai munasarjojen monirakkulaoireyhtymä – joka aiheuttaa merkittäviä muutoksia elimistön hormonaaliseen tai tulehdukselliseen tasapainoon. Lapsettomuushoidoissa myös käytetään lääkkeitä, jotka vaikuttavat hormonitasapainoon. Niinpä on tärkeää tietää, altistavatko lapsettomuutta aiheuttavat sairaudet tai hormonaaliset lapsettomuushoidot syöpäriskin lisääntymiselle.

Tutkimuksen tarkoitus: Tämän tutkimuksen tarkoituksena oli selvittää lapsettomuuden ja lapsettomuushoitojen käytön yleisyyttä Suomessa sosiodemografisten tekijöiden valossa. Lisäksi kuvataan koeputkihedelmöitysten (IVF), siittiön mikroinjektio hoitojen (ICSI) and pakastetun alkion siirtojen (FET) määrän lisäystä ajan myötä ja muutoksia lapsettomuutta aiheuttavien diagnoosien yleisyydessä. Lapsettomuushoitojen onnistumisaste laskettiin useilla indikaattoreilla ja onnistumisastetta suhteessa siirrettyjen alkioiden määrään ja hoitopaikkaan verrattiin. IVF-, ICSI- tai FET- hoidoissa olleen kohortin terveyttä tukittiin kahdesta näkökulmasta: sairaalahoitoon johtaneiden psykiatristen sairauksien yleisyyttä tutkittiin ennen ja jälkeen lapsettomuushoitojen ja syöpätapausten määrää hoitojen jälkeen.

Aineisto ja menetelmät: Tässä tutkimuksessa käytettiin aineistona kahta väestötutkimusta, FINRISKI 1997 ja 2002, IVF Tilastoa, kohorttia naisia (N=9175), jotka saivat IVF-, ICSI-, tai FET-hoitoja vuosina 1996-1998 sekä näiden naisten iän ja paikkakunnan suhteen vakioituja verrokkeja. Kohortti luotiin käyttämällä Kansaneläkelaitoksen lääkekorvausrekisteriä. Sairaalahoitojaksot psykiatrisista syistä saatiin Terveyden ja Hyvinvoinnin Laitoksen Hoitoilmoitusrekisteristä ja syöpätapaukset Syöpärekisteristä.

Tulokset: Itse raportoituna lapsettomuuden elinaikainen esiintyvyys oli 16 %. Se vaihteli merkitsevästi iän ja koulutustason suhteen: nuorimmista naisista vähiten koulutetut olivat yleisemmin kokeneet lapsettomuutta, mutta vanhemmissa ikäryhmissä lapsettomuus oli yleisempää korkeammin koulutetuilla naisilla. Lapsettomuushoitoihin hakeutuminen oli yleisempää kaupunkilaisilla, korkeasti koulutetuilla ja varakkailla naisilla. Annettujen IVF-, ICSI- ja FET-hoitojen määrä yli kolminkertaistui 1992-2004 ja taustalla olevat lapsettomuuden syyt muuttuivat merkittävästi, kun munajohdinperäinen lapsettomuus harvinaistui ja miehestä johtuva lapsettomuus yleistyi.

Kliinisten raskauksien ja elävän lapsen syntymään johtaneiden raskauksien osuus IVF-, ICSI- tai FET-hoitojen tuloksena pysyi vakaana (21-25 %) 1994-2005 vaikka yhden alkion siirtojen osuus lisääntyi suuresti (14 %:sta 51 %:iin). Täysiaikaisten yksisikiöisten raskauksien ja vähintään 2500 grammaa painavien yhden lapsen syntymään johtavien raskauksien osuus hoitojen tuloksena kasvoi 9 %:sta 14 %:iin. Erityisesti seurantajakson alussa hoitojen onnistumisprosentti oli parempi yksityisellä kuin julkisella sektorilla hoidettaessa alle 35-vuotiaita naisia.

IVF-, ICSI- tai FET-hoitoja saaneiden naisten kohortissa oli ennen lapsettomuushoitoja vähemmän sairaalahoitojaksoja kaikkien psykiatristen diagnoosien takia, mutta ero oli tilastollisesti merkitsevä vain psykoottisten häiriöiden suhteen. Hoitojen jälkeen 8-10 vuoden seurantajaksolla erot pysyivät pääsääntöisesti samanlaisina paitsi että lapsettomilla naisilla oli tilastollisesti merkitsevästi enemmän sairaalahoitojaksoja sopeutumishäiriöiden takia ja tilastollisesti merkitsevästi vähemmän hoitojaksoja alkoholin tai muiden päihteiden väärinkäytön takia. Niillä lapsettomilla naisilla, jotka saivat lapsen hoitojen jälkeen,

oli kaikkien psykiatristen diagnoosien takia vähemmän sairaalahoitojaksoja kuin niillä lapsettomilla, jotka eivät hoitojen jälkeen lasta saaneet.

Syöpien kokonaisilmaantuvuus oli samansuuruinen IVF-, ICSI tai FET-hoidoissa olleilla naisilla ja kontrolleilla. Hoidettujen naisten kohortissa oli tilastollisesti merkitsevästi vähemmän kohdunkaulan syöpää ja enemmän muita ihosyöpiä kuin melanoomaa. Kaikki keuhkosyövät diagnosoitiin kontrollinaisilla. Munasarjasyövän ilmaantuvuus oli suurempaa lapsettomilla naisilla, mutta ero ei ollut tilastollisesti merkitsevä.

Johtopäätökset: Lapsettomuuden esiintyvyys vaihtelee iän ja koulutustason suhteen ja myös lapsettomuushoitoihin hakeutumisessa on sosioekonomisia eroja. IVF-, ICSI- ja FET-hoitojen onnistumisprosentti on pysynyt vakaana vaikka yhden alkion siirrot ovat merkittävästi lisääntyneet. Onnistumistuloksissa on ollut hoitopaikan suhteen eroja, jotka ovat ajan myötä pienentyneet. IVF-, ICSI- tai FET-hoitoja saaneilla naisilla oli yleisesti ottaen vähemmän sairaalahoitojaksoja psykiatrisista syistä kuin kontrollinaisilla. Hoitojen jälkeen lapsen saaneilla oli myös merkittävästi vähemmän hoitojaksoja. Syövän kokonaisilmaantuvuudessa ei lapsettomilla naisilla ja kontrolleilla ollut merkitsevää eroa. Kohdunkaulan syövän, keuhkosyövän ja muiden ihosyöpien kuin melanooman ilmaantuvuudessa havaitut erot kuitenkin viittaavat niin sanottuun "terve potilas" –ilmiöön.

1. Introduction

The European Society on Human Reproduction and Embryology (ESHRE) has defined infertility as a serious handicap preventing people from realizing an important life goal. Infertility treatments in turn allow these people to express their autonomy by realizing their reproductive choices thus increasing their well-being (Pennings et al. 2008).

Infertility directly affects about one out of six couples (Evers 2002, Gnoth 2005) and indirectly affects a much larger group of family members, friends and in many cases also colleagues and supervisors at work. To people suffering from infertility the experience is likely to cause a significant amount of stress and grief and even expose to mental problems. Conditions causing infertility and infertility treatments may also, fortunately seldom, cause potentially serious somatic side-effects and later probably expose to some types of cancer.

This study aimed to investigate many different aspects of reduced fertility and the use of infertility treatments. The prevalence of infertility and the use of infertility treatments were studied and the success of infertility treatments was evaluated.

The health of a cohort of women who received IVF, ICSI or FET treatments 1996-1998 was studied from two different perspectives. Firstly, severe psychiatric morbidity of these women was evaluated before and after the need for infertility treatments comparing the number of hospitalizations due to psychiatric diagnoses to that of control women. Secondly it was studied whether this cohort of IVF, ICSI or FET treated women had more cancers than did control women.

2. Review of literature

2.1 Infertility

2.1.1 Definitions and prevalence of infertility

Europe is the continent with the lowest fertility rate. The total fertility rate, TFR, which is calculated as a sum of age-specific fertility rates of a current year, is the lowest (less than 1.54) in the Eastern European countries such as Belarus, Ukraine and Russia and in Southern European countries Greece, Italy and Spain. The highest TFRs exceeding 2.0 needed to approach the population replacement levels are in Northern European countries Norway, Iceland and Denmark and in Ireland, France and Turkey (The ESHRE Capri Workshop Group 2010). In Finland the current TFR is 1.84 (Miettinen & Rotkirch 2008). This decline in total fertility rate is a result of numerous socio-cultural, political, economical, educational, religious and medical factors. The increase in actual incidence of infertility explains this decline less. However, as more and more couples postpone childbearing, the risk of infertility increases as a result of natural decline in fertility (The ESHRE Capri Workshop Group 2010).

According to the most widely used definition, a couple is considered infertile when a pregnancy has not begun after one year of unprotected sexual intercourse (Evers 2002, Gnoth 2005). For each couple the monthly fecundity rate varies. However, it has been estimated that 80% of couples conceive within 6 months and 50% of the remaining couples within the following 6 months (Gnoth 2003, Wang 2003). Even among couples regarded as infertile by definition, the spontaneous pregnancy rate within the following 12 months is up to 50% (Evers 2002).

The prevalence of infertility is most often studied as current prevalence or as life-time prevalence, which is a cumulative prevalence until the time of the study

(Schmidt & Münster 1995). Worldwide the current prevalence of infertility is over 70 million couples (Boivin 2007, Ombelet 2008). Infertility is particularly common in Sub-Saharan Africa, where the prevalence is up to 30% mainly due to sexually transmitted diseases, poor health care and female genital mutilation (Pennings 2009). Infertility can be divided into primary or secondary infertility depending on whether a couple has had a previous pregnancy (Nguyen & Wilcox, 2005)

In a meta-analysis consisting of studies published 1970-1992 Schmidt and Münster concluded that the current prevalence of infertility was 3.6-14.3% and life-time prevalence in turn 12.5-32.6%. A more recent meta-analysis included data from 25 population studies published since 1990 (Boivin 2007). According to this study the current prevalence of infertility was in developed countries 3.5-16.7% and in less developed countries 6.9-9.3%. Life-time prevalence varied in developed countries between 6.6-26.4% and in less developed countries between 1.3-25.7%. According to a Finnish population survey that was not included in the meta-analysis by Boivin et al. (2007) life-time prevalence of infertility was 16% (Malin et al. 2001). This variation can at least partly be explained by differences in the populations studied (entire study population regardless of desire to become pregnant, married women, women, who have given birth etc.)

A woman's age and the duration of childlessness are the most significant factors determining fertility (Evers 2002). A Swedish study estimated factors affecting time to pregnancy. The age of a woman, prior use of oral contraceptives, parity and length of menstrual cycle were significant affective factors and explained 14% of variation in time to pregnancy (Axmon 2006). Woman's age is estimated to start to have a negative effect on fertility from the late 20's onward. A study investigating the day-specific probability of pregnancy found that the probability of pregnancy was twice as high for women aged 19-26 years compared to that of women aged 35-39 years (Dunson 2002).

There have been contradictory reports about changes in the prevalence of infertility over time. According to a study conducted in Scotland, the prevalence of infertility had not increased in 20 years (Bhattacharya et al. 2009). Another study in Iran (Safarinejad et al 2008) in turn found that the prevalence of infertility had risen from

2.6% to 5.5% in the period 1985-2000. Chandra and Stephen (1998) reported that in the United States impaired fecundity rose from 8% to 10% 1982-1995. The same authors, however, found out that among married women prevalence of infertility declined from 8.5% to 7.4% in the period 1982-2002 (Stephen & Chandra 2006). This study has, however, been criticized because of methodological and definitional weaknesses (Thorton & Goldman 2006, Guzick & Swan 2006, Olive & Pritts 2006)

A Swedish population survey suggests that infertile women are less educated than women with no fertility problems (Wulff et al. 1997). Similar data has been reported from the United States (Jain & Hornstein 2005, Bitter et al. 2006) where infertility is significantly more common among women with little education as well as among African Americans and Hispanic women compared with Caucasian women. However, opposite results have been published - according to a Norwegian population study infertility was more common among highly educated women (Rostad et al. 2006)

2.1.2   Causes of reduced fertility

The most common conditions causing impaired fertility among females are ovulation and menstrual cycle disturbances, tubal obstruction, pelvic adhesions and endometriosis. In ovulation and menstrual cycle disturbances the problem may be central: either low follicle stimulating hormone (FSH) secretion which in turn causes low oestrogen secretion or elevated prolactin secretion that down regulates FSH and oestrogen secretion. Decreased ovarian reserve also causes infertility: this state is hypergonadotrophic but hypo-oestrogenic. If a problem in turn is on the hypothalamo-pituitary-ovarian axis, the hormone status may be normogonadotrophic, normo-oestrogenic and normoprolactenemic (Evers 2002).

Poor semen quality and hormonal disturbances are the most important reasons causing reduced fertility among men. The semen analysis gives information on the concentration, motility, morphology and viability of sperm. Other factors such as antisperm antibodies can also be studied (Agarwal et al. 2008). Other reasons for male infertility are anatomical disturbances such as absence of vas deferens and

seminal vesicles, varicocele, obstruction of vas deferens or genetic disorders such as Klinefelter syndrome or chromosome Y microdeletions (Bhasin 2007, Jarow 2007, Sarkar et al. 2007, Sussman et al. 2008). Hormonal states causing male infertility may be gonadotrophin deficiency (characterized by low testosterone concentration and low or normal gonadotrophin concentration), primary testicular failure (low testosterone and elevated gonadotrophin concentration), sertoli cell only syndrome (normal testosterone and LH, but elevated FSH concentration) or partial androgen resistance (high testosterone and LH concentration) (Bhasin 2007).

Among both males and females many chronic diseases and lifestyle factors may impair fertility. Women with diabetes mellitus may suffer from oligomenorrhea or secondary amenorrhea when glycaemic control is bad (Livshits & Seidman 2009). Among diabetic men in turn the risk for sexual disorders such as impotence, retrograde ejaculation, low serum testosterone levels and poor semen quality are increased (Amaral et al. 2008). Hypothyroidism and hyperthyroidism cause alteration in serum sex hormone binding hormone (SHBH) and thus in sex hormone levels in both sexes. Hypothyroidism may cause abnormalities in sperm morphology and among females causes oligomenorrhea. Hyperthyroidism in turn may impair sperm motility and predispose women to hypomenorrhea or polymenorrhea. Autoimmune thyroid disease is more common among females attending infertility clinics (Krassas et la. 2010). A recent meta-analysis suggests that the presence of thyroid antibodies was associated with increased risk for unexplained infertility (Van der Boogard et al. 2011).

Chronic gastroenterological illnesses may cause fertility problems. Population studies indicate that general fertility rates among females with inflammatory bowel disease (Crohn's disease or colitis ulcerosa) is similar to that in general population. However, among those patients who have undergone surgery fertility rates are poorer (Moscandrew & Kane 2009). Untreated coeliac disease may cause impaired fertility (Soni & Badawry 2010, Ozgor & Selimoglu 2010).

Common lifestyle factors impairing fertility are obesity and smoking. Obese women are at risk of developing insulin resistance that causes ovulation problems and other indirect fertility problems probably via metabolic, inflammatory and immunological

changes. Among obese men serum testosterone levels may be lower which may affect sperm production. Underweight women may have FSH and LH deficiency leading to ovulation problems. Smoking has negative effects on fertility. It decreases sperm count and motility and among women accelerates dissipation of eggs and may have negative effects on the zona pellucida around the egg as well as on the endometrium (Anttila 2008, Dondorp et al. 2010).

2.2   Infertility treatments

2.2.1   Definitions and details of the methods

The most common infertility treatments are ovulation induction with or without insemination, in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) and frozen embryo transfer (FET). Fertility can sometimes be improved surgically when for example varicocele, leiomyoma or endometriosis is operated. Weight reduction or cessation of smoking may reduce the need of infertility treatments and improve the outcomes of these treatments (Luke et al. 2011, Waylen et al. 2009, Dondorp et al. 2010).

Ovulation induction with drugs can be used alone to treat women suffering from ovulation problems or it can be combined with insemination. Clomiphene citrate is the most commonly used drug to induce ovulation. Clomiphene citrate is an anti-oestrogenic compound that induces follicle growth by preventing negative feedback caused by oestrogen to production of gonadotrophins. Thus the secretion of FSH, LH and oestrogen increases and the peak of LH secretion induces ovulation.

A more novel class of drugs used to induce ovulation is so called aromatase inhibitors. These drugs prevent the natural conversion of androgens to oestrogens by aromatase enzymes thus decreasing body's oestrogen levels. Clomiphene citrate and aromatase inhibitors are administered orally.

Ovulation can also be induced by drugs that are injected subcutaneously or intramusculary. Exogenous FSH or human menopausal hormone, HMG, can be used

to mature single follicles or to cause hyperstimulation for IVF or ICSI cycles. Human chorionic gonadotrophin, hCG, is usually used in combination with FSH or HMG and it mimics the effects of the endogenous LH (Pharmaca Fennica, 2011).

In intra uterine insemination procedure (IUI) the semen is inserted into the uterus using a catheter. Before the procedure the semen is washed i.e. the un-motile spermatozoa and most other components of the seminal fluid are removed.

In IVF and ICSI protocol woman's menstrual cycle is regulated by drugs and the goal is to achieve regulated ovarian hyperstimulation to produce multiple follicles. The normal, endogenous function of the ovaries is inhibited by administering either gonadotrophin releasing hormone, GnRH, agonists or antagonists. Exogenous FSH is usually used to stimulate the growth of follicles. The maturation of eggs is regularly monitored using ultrasonography and when the desired maturation of the follicles is achieved, hCG is injected to complete the ovulation process. After hCG injection follicles are harvested from the ovaries before spontaneous ovulation occurs.

In IVF procedure the eggs are separated and fertilized in a petri dish by washed semen. In ICSI procedure a single sperm is injected into the egg. Normally the fertilized embryos are cultured until 4-8 cell stage but longer cultivation time until blastocyst phase can also be used. Thereafter the embryo or two embryos are transferred into the uterus with a catheter. Vaginal progesterone is used as support treatment usually until gestational weeks 9-11. (Pharmaca Fennica).

Normally IVF or ICSI cycles produce more good quality embryos that are transferred. These embryos are frozen and used in later treatment cycles (FET). FET can be done on a woman's natural menstrual cycle or after administration of oestrogen and progesterone.

2.2.2　Use of infertility services

In Western countries 44-73% of infertile couples seek medical help (Schmidt et al 1995, Buckett & Bernstick 1997, Chandra & Stephen 1998, Stephen & Chandra 2000, Moreau et al. 2008, Bhattacharya et al. 2009). According to a meta-analysis by Boivin et al. (2007) the proportion of infertile couples seeking medical help in less developed countries varies between 27-74%. The proportion of couples actually receiving infertility treatments, however, is smaller, in Western countries 43-74% of help seeking couples (Buckett & Bernstick 1997, Stephen & Chandra 2000, Moreau et al. 2008). The reasons why infertile couples do not seek medical help can be classified as financial, medical, psychosocial, moral or ethical (Dawson et al. 2005).

Research indicates that the use of infertility treatments is affected by socio-demographic factors. Participation is more common among older, more educated, wealthier and married women (Schmidt et al. 1995, Wulff et al. 1997, Stephen & Chandra 2000, Bitter et al. 2006, Moreau et al. 2008). Studies from the United States indicate that participation is significantly more common among Caucasian women than among African American or Hispanic women (Stephen & Chandra 2000, Jain & Hornstern 2005, Chandra & Stephen 2008) as well as among those who have private health insurance (Chandra & Stephen 2008). A population based survey on the lifetime prevalence of infertility and infertility treatments among women aged 40-55 conducted in the United Kingdom demonstrated that the youngest women had statistically more infertility treatments than the older ones even though the prevalence of infertility itself was similar (Oakley et al. 2008).

In Finland differences in seeking medical help for infertility have been reported. One study found that women who did not seek help were younger, had fewer years of formal education and had tried to become pregnant for a shorter time period than the treatment-seeking women (Malin et al. 2001). In two other studies a higher ratio of seeking of medical help was found among more educated women (Gissler et al. 1995) and among those with a better socio-economic position (Silverio et al. 1996). The utilization of infertility services varies by residence: the age-standardized IVF incidence per thousand women aged 20 to 49 was 7.3 in rural and 8.8 in urban areas (Klemetti et al. 2004).

2.2.3 Practices of infertility treatments in Finland

It is recommended that a couple suffering from fertility problems first visit a primary care physician or a private gynaecologist who interviews and examines them. Important patient history includes general health, chronic illnesses and medications, surgeries, possible previous pregnancies, history of sexually transmitted diseases, frequency of sexual intercourse, smoking, intoxicant use, weight, physical activity and nutrition. Gynaecological examination should be performed and blood pressure and height, weight and waistline circumference should be measured. The first line medical tests for possible causes of fertility problems include papanicolaou smear, a test to detect Chlamydia trachomatis, blood haemoglobin, prolactin and thyreotrophin (TSH). Sperm analysis and a test for Chlamydia trachomatis are performed on males. HIV and hepatitis B and C antibodies are evaluated in both partners.

Prior possible infertility treatments gynaecological ultrasound and, if semen quality is good, hysterosalpingo-sonography should be performed. With gynaecological ultrasound, for example, uterine leiomyomata, polyps, adhesions or uterine septi may be detected. Ovaries are studied and possible cysts, endometriomas and tumours may be diagnosed. The size of the ovaries and the number of growing follicles (antral follicle count) can be estimated. Possible hydrosalpinx may also be detectable. With hysterosalpingo-sonography in turn the openness of the tubes can be ensured.

There are a few possible ways to estimate the occurrence of ovulation. The peak in LH secretion can be detected from urine 1 or 2 days prior to ovulation. The elevated serum progesterone level is an indicator of ovulation having occurred. Estimates can be made with gynaecological ultrasound. Typical follicle is about two centimetres in diameter before ovulation. The structure of the endometrium changes after ovulation and this can be detected with ultrasound (Nuojua-Huttunen & Anttila 2009).

The World Health Organization (WHO) has published a manual on examining of semen samples. According to this manual, in normal sperm sample the number of sperm should exceed 39 million per ejaculate and total volume of ejaculate should

be at least 1.5 millilitres. At least 40% of sperm should be motile and 32% of sperm should move progressively. The proportion of viable sperm should exceed 58% and at least 4% of sperm should have normal morphology (WHO Manual for the Examination and Processing of Human Semen, 2010). The most important factor predicting male fertility is the number of motile sperm. However, it has been demonstrated that sperm analysis alone has poor power to predict future fertility (Lewis, 2007).

Other indicators are also studied in a semen sample. The agglutination of the sample may be an indication of antisperm antibodies that can impair fertility. The presence of excess white blood cells may explain fertility problems due to chronic infection such as chronic prostatitis (Nuojua-Huttunen & Anttila 2009). After the preliminary examinations and tests the need for infertility treatments can be estimated in a public or private infertility clinic if a couple wants to receive infertility treatments.

In Finland infertility treatments are given in seven public hospitals (in all five university hospitals and in central hospitals in Jyväskylä and Joensuu). In addition there are thirteen private clinics: four in Helsinki, two in Turku and Tampere and one in Kuopio, Oulu, Lappeenranta, Kotka and Jyväskylä.

Infertility treatments were given in Finland without legislation for over twenty years. An act on assisted fertility treatments came into force on 1 September 2007. It stipulates that infertility treatments can be given to married couples, to unmarried cohabitants, to female couples and to single women. All clinics that provide infertility services and store gametes or embryos have to have a permission granted by The National Supervisory Authority for Welfare and Health (Valvira). Another permit from the National Agency for Medicines is also required. A written and signed consent form (hoitosuostumus) must be completed before treatments. It is not allowed to provide infertility treatments if a pregnancy would be a significant risk to the health of either the mother or the child or if it is evident that the parents could not offer a safe childhood.

The law requires that all donors of gametes must give their identification to a register maintained by Valvira. If a child born after the use of these gametes so

wishes, s/he can obtain information on the donor after turning 18 years (22.12.2006/1237, Finlex, http://www.finlex.fi/fi/laki/ajantasa/2006/20061237)

In 2009 Ministry of Social Affairs and Health published guideline on how to provide infertility services. The guideline emphasize that only effective treatments should be provided in public infertility clinics and thus the success rate should be estimated to be at least 10%. In given conditions such as poor ovarian response to gonadotrophins or severe uterine malformation infertility treatments should not be provided in the public sector. A woman's age (39 years or more) or three or more unsuccessful prior IVF or ICSI treatments are exclusion criteria. The guidelines also recommend that if a couple suffering from secondary infertility has already two or more common children or has undergone sterilization infertility treatments should not be offered in the public sector (Uniform criteria for access to non-emergency treatment, http://www.stm.fi/c/document_library/get_file?folderId=2593921&name=DLFE-13802.pdf)

2.2.4 Data collection on infertility treatments

In Finland statistics on the use of infertility treatments have been compiled since 1992. The data was first gathered by Helsinki University Central Hospital and since 1994 by the National Institute for Health and Welfare (THL, formerly the National Research and Development Centre for Welfare and Health, STAKES). The statistics consist of aggregate data on all IVF, ICSI and FET treatments and since 2006 of inseminations and since 2001 about donor gamete cycles (THL, http://www.stakes.fi/FI/tilastot/aiheittain/Lisaantyminen/hoidot/index.htm).

The European Society on Human Reproduction and Embryology (ESHRE) was founded in 1985 to stimulate the research on reproductive medicine. ESHRE currently promotes clinical practices and develops and maintains data registries (ESHRE, http://www.eshre.eu/home/page.aspx/2). The European IVF monitoring program (EIM) was founded in 1997 and since 1999 thirty European countries have reported data about IVF treatments. The number and outcomes of treatment cycles

and side-effects of treatments, availability of services and well-being of children are recorded. Reports on the results of this data collection have been published since 2001 (ESHRE, http://www.eshre.eu/ESHRE/English/Specialty-Groups/Data-collection-Consortia/European-IVF-Monitoring-EIM-/page.aspx/281)

In the United States Centers for Disease Control and Prevention (CDC) has a division concentrating on reproductive health. It has been mandatory since 1992 for all infertility clinics to report all procedures conducted to CDC, which publishes reports annually. Unlike, for example, in Finland in these US reports clinic-specific success rates are published (CDC, http://www.cdc.gov/art/ARTReports.htm).

2.2.5   Infertility treatments worldwide

The uses and practices of infertility treatments vary between different countries. The European Society of Human Reproduction and Embryology has published ten reports on the use and success of infertility treatments in Europe. The most recent study reporting data from 2006 was published in 2010. According to this report the proportion of infants born as a result of infertility treatments was lowest in Montenegro (0.8%), Italy and Latvia (1.0%) and highest in Denmark (4.1%), Slovenia (3.6%) and Iceland (3.4%). In total 850 cycles were performed per 1 million inhabitants (de Mouzon et al. 2010).

The overall clinical pregnancy rate per embryo transfer was 32-33% after IVF and ICSI. After IVF and ICSI the distribution on transfers of one, two, three and four or more embryos was 22.1, 57.3, 19.0 and 1.6% respectively, but there is wide variation between countries. In general in Northern Europe countries and in Belgium single embryo transfers are common (35-69% of all transfers). In Eastern and Southern Europe transfers of three or four embryos are still commonly used (up to 85% of all transfers in Albania). Understandably the proportion of multiple pregnancies varies. The proportion of twin deliveries is between 5.7% (in Sweden) and 38.3% (in Serbia) and the proportion of triplet deliveries between 0% (in Finland and Montenegro) and 14% (in Albania). The general trend was however the small decrease in number of embryos transferred (de Mouzon et al. 2010).

Comparisons between the use of IVF, ICSI and FET between the United States and Europe have been made (Gleicher et al. 2006, Gleicher et al. 2007). The problem with these comparisons is that Europe is analysed as a whole despite the variation between countries. In 2001 the aggregate clinical pregnancy rate for all European countries was 24% and live birth rate 17%. In the United States clinical pregnancy rate in 2001 was 33% and live birth rate 27% (Gleicher et al. 2006). In 2002 the difference was even larger as clinical pregnancy rate was 29% in Europe and 42% in the United States. However, during those years, the treatment protocols were different between the United States and Europe as whole. In Europe in 2002 single embryo transfers were quite rare but conducted anyway in 13.7% of cycles compared to 6.7% in the United States. The proportion of two embryo transfers was 54.8% in Europe and 31.6% in the United States. Three embryos were transferred in 26.8% of cycles in Europe and 33.6% in the United States. The proportion of four embryo transfers in the United States was in 2002 still huge: 28.1% compared to 4.7% in Europe (Gleicher et al. 2007). Also, during those years it was more common in the United States to select embryos, conduct oocyte donation cycles and perform genetic diagnosis prior to implantation (Gleicher et al. 2006). The proportion of multiple pregnancies was significantly higher in the United States (36.2%) than in Europe (24.9%) (Gleicher et al 2007).

One recent study (Baker et al. 2009) aimed to compare success rates between infertility clinics in the United States and Europe that participated in clinical trials with similar protocols and inclusion criteria. One obvious problem with the interpretation of this comparison was the fact that Europe was represented by France and Hungary alone. In any case, the number of embryos transferred was similar and the patients were slightly older in the United States. However, both clinical pregnancy rate (43.4% in the United States and 29.7% in France and Hungary) and live birth rate (38.2% in the United States and 30.4% in France and Hungary) were significantly better in American clinics. The only difference between protocols was larger starting dose of gonadotrophins in the United States and significantly greater number of embryos transferred in blastocyst phase (26% in the United States and 2.2% in Europe).

2.2.6 Costs and funding of infertility treatments

The costs of infertility treatments consists of direct costs including physician's and nurse's services, medications, laboratory tests, ultrasound scans, the ART procedure itself, hospital charges and administrative costs. Immediate indirect costs are losses of working hours and travel costs and are generally regarded as low. However, much more significant possible indirect costs come from hospitalization fees of pregnant women and their premature infants in case of multiple pregnancies as a result of infertility treatments (Ata & Seli 2010).

The direct costs of infertility treatments in different countries have been compared. Chambers et al. (2009) studied the costs of IVF treatments in the United States, Canada, the United Kingdom, Japan, Australia and Scandinavia as whole in 2003. They found that there was a vast variation in both prices of treatment cycles and in expenditure per live birth. The standard IVF cycle was most expensive in the United States, more than 12,500 dollars (in 2006 US dollars), and the cheapest in Japan about 3,950 US dollars. In the United States the costs of a single IVF cycle amounted to 44% of annual income of a single worker earning 100% of average earnings after taking account of average insurance coverage. In Japan this relative cost for a patient was the lowest, 14%. Costs per live birth were also highest in the United States and the United Kingdom, exceeding 40,000 US dollars and lowest in Scandinavia and Japan, exceeding 24,000 US dollars. The writers concluded that the costs of infertility treatments reflect the costliness of the entire healthcare system rather than the regulatory or funding policies and that only in countries with the smallest patient out-of-pocket expense the demand for infertility treatments met the need of these treatments (Chambers et al. 2009).

German researchers studied opinions on fair payment policies for infertility treatments among infertile patients, the general public and professionals working in infertility clinics. According to this study in all groups studied most of respondents were in favour of public coverage of infertility treatments. Opinions about patient's co-payment differed between groups: only around 30% of infertile patients supported this but the proportion was substantially larger among professionals (around 70%) and the general public (around 75%). Generally the respondents

thought that the amount of appropriate patient co-payment should be 15-25% instead of the actual 50% in Germany (Rauprich et al. 2010).

The costs of infertility treatments may be partially or completely funded by a public health care service or private insurer or paid completely by the patient. Comparisons of the use and results of infertility treatments in different funding environments have been published. One study (Navarro et al. 2008) compared funding strategies in the United States and in certain European countries (Belgium, Denmark, Finland, France, Germany, the Netherlands, Norway, Sweden, Switzerland, and the United Kingdom). This paper concluded that the states with either partial or complete public coverage for infertility treatments had statistically significantly more infertility clinics per million inhabitants and significantly more treatment cycles were also performed. The number of ART pregnancies per million inhabitants was almost threefold in the states with complete public funding compared to states with no funding. On the other hand the funding system has the opposite effect on the number of treatment cycles needed to achieve a live birth as in the states with partial or complete public coverage systems significantly more treatment cycles were needed. As expected from this, the number of embryos transferred as well as the proportion of multiple pregnancies, were substantially larger in the states with no public funding. The results from the states with private coverage were in between of those from states with no coverage and those with public coverage (Navarro et al. 2008).

In these comparisons, however, the costs caused by hospitalizations of premature neonates have not been taken into consideration. A study conducted in Belgium compared costs after single and double embryo transfer (DET) and clearly demonstrated that average neonate costs were significantly (p<0.001) higher after DET (Gerris et al. 2004). According to a recent American study 48% of neonates born after infertility treatments were born as a part of multiple infant delivery and 62% of twins and 97% of triplets were delivered preterm. A mean cost of one preterm infant was 51,600 US dollars and the authors estimated total financial burden caused by these preterm neonates is 1 billion US dollars annually (Bromer et al. 2011)

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Studies from different states in the United States indicate that the availability and utilization of infertility treatments are higher in the states with private insurance coverage (Henne & Bundorf 2008, Hammound et al. 2009). A report from Germany studying the effects of a law increasing patient's out-of-pocket payment clearly demonstrates that the utilization of infertility treatments is partly dependent on financial accessibility. The reduction in use of infertility treatments was statistically significantly greater in economically weaker areas (Griesinger et al. 2007).

The European Society on Human Reproduction and Embryology recommends that in affluent societies infertility treatments should be at least partly publicly funded. This funding should be considered in a structural way including efficiency, safety and equality and it is just to fund a fixed number of treatment cycles. They also conclude that the practitioners providing infertility treatments have a moral obligation towards both their patients and the entire health care system to reduce the costs of infertility treatments as far as reasonably possible (Pennings et al. 2008)

2.2.7 Measurement of success of infertility treatments

It is naturally important to have reliable estimates of success with infertility treatments. However, there is still debate about the most accurate indicators. Traditionally used indicators are implantation rate, clinical pregnancies per cycle and live birth delivery rate (Davies et al. 2004, Schieve et al. 2004). The problem with these indicators is that they emphasize the effectiveness of treatments but do not take safety aspects into the consideration.

Two quite similar indicators emphasizing the importance of the durations of pregnancies and preference for singleton pregnancies have been suggested. Min et al. (2004) introduced the concept of BESST (Birth Emphasizing a Successful Singleton at Term) and The European IVF Monitoring Consortium suggested as an indicator "singleton delivery rate per embryo transfer" (Nyboe Andersen et al. 2004).

It has also been recommended that instead of one indicator several endpoints should be considered simultaneously (Davies et al. 2004, Schieve et al. 2004, Pinborg et al. 2004). Pinborg et al. (2004) suggested the use of three parameters to measure the success of infertility treatments: number of oocytes per aspiration is a pre-in vitro parameter, number of ongoing implantations per embryo transfer is an in vitro parameter and number of deliveries per embryo transfer is a post-in vitro parameter.

As the proportion and number of elective single embryo transfers has increased significantly, the importance of indicators concentrating on cumulative probability of pregnancies has also risen. Tiitinen et al. (2004) and Lundin & Bergh (2007) have suggested utilization of cumulative delivery rate per stimulated cycle after all fresh or frozen embryo transfers from the same oocyte retrieval and Veleva et al. (2009) cumulative birth rate per woman.

In recent years relatively large studies investigating elective single embryo transfers (eSET) compared to two embryo transfers have been published. These studies indicate that cumulative pregnancy rate after elective single embryo transfers is comparable to that of two embryo transfer and that the multiple pregnancy rate is largely decreased (Vilska et al. 1999, Thurin et al. 2004, Lundin & Bergh 2007, Bechoua et al. 2009, Fauque et al. 2009, Veleva et al. 2009, Stillman et al. 2009). A Finnish study by Vilska et al. (1999) compared success rates after elective single embryo transfers, single embryo transfers when only one embryo was available and two embryo transfers. Pregnancy rates were similar in the elective single embryo transfer group (29.7%) and the two-embryo transfer group (29.4%) and poorer in single embryo transfer group with only one embryo available (20.2%). Pregnancy rates among younger women (under 35 years) in the elective single embryo transfer group were significantly higher than among women aged over 35 years (32.5% versus 18.8%). The quality of embryos significantly affected on pregnancy rates (Vilska et al. 1999).

Thurin et al. (2004) studied cumulative pregnancy rates among women under 36 years old with at least two good quality embryos. The pregnancy rate after fresh single embryo transfer was 27.6% and after two embryo transfer 42.9%. After possible frozen embryo transfer the cumulative pregnancy rate in the single embryo

group was 38.3% and did not differ significantly from the pregnancy rate after fresh two-embryo transfers. Multiple pregnancy rate was evaluated and it was, as expected, vastly decreased in the single embryo transfer group (0.8% versus 33.1%) (Thurin et al. 2004).

In the study by Lundin and Bergh (2007) cumulative pregnancy rate was similar: 34.8% in the elective single embryo transfer group and 33.5% if two embryos were transferred. A recent French study reports similar findings: among women aged under 35 years with at least three high quality embryos participating in their first treatment cumulative cycle live birth rate after fresh and frozen embryo transfers was 60.8% in the single and 60.5% in the double embryo transfer groups (Bechoua et al. 2009).

In another French study on elective single embryo transfers cumulative pregnancy rate was even higher among women with single embryo transfers (54.7%) than among women with double embryo transfers (49.0%) but this difference was not statistically significant. The participants of this study were under 36 years old, participating in their first or second IVF or ICSI treatments and had adequate ovarian function and at least two top embryos (Fauque et al. 2009).

A recent Finnish study aimed to compare success rates in 1995-1999 when elective single embryo transfers were rarely used (4.2% of all) and in 1999-2004 when their proportion was 42.6% of all transfers. During the period 2000-2004 all indicators studied - the cumulative pregnancy rate per oocytes pickup (38.2 versus 33.1%), cumulative live birth rate per oocytes pickup (28.0 versus 22.5%) and cumulative live birth rate/woman (41.7 versus 36.6%) - were better than in 1995-1999. All differences were statistically significant. Multiple birth rate also decreased significantly (8.9% in 2000-2004 and 19.6% in 1995-1999) (Veleva et al. 2009).

The European Society on Human Reproduction and Embryology has recommended wider used of single embryo transfers since 2001 and The American Society for Reproductive Medicine since 2006. Despite this, elective single embryo transfers are commonly used only in some European countries, on the largest scale in Finland, Sweden and Belgium (Veleva 2008). In Sweden and Belgium preference

for elective single embryo transfers is recommended in law (Nyboe Andersen et al. 2007). In Finland this change in treatment protocols has been made by clinics.

In Finland elective single embryo transfers (eSETs) are particularly common when performing frozen embryo transfers. According to the latest data from 2009, the share of eSETs was 61.7% of all frozen embryo transfers. In fresh IVF and ICSI cycles the share is smaller but significant: 46.5% in 2009. Especially in the case of fresh IVF or ICSI cycles there are, however, some differences in the treatment protocols between the public and the private clinics: in 2009 single embryo was electively transferred in 51.8% of cycles in the public sector and 43.3% of cycles in the private sector. For frozen embryo transfers the difference was significantly smaller: 63.2% and 60.6%, respectively (THL, Statistics on Assisted Fertility Treatments, unpublished statistics, 2011).

Strategies using elective single embryo transfers have been criticized as well. Gleicher and Barad (2006) wrote that elective single embryo transfers are suitable for only a small minority of IVF patients and arguments favouring eSETs appear unrealistic and should be reconsidered.

2.3 Health of women before and after infertility treatments

2.3.1 Psychiatric disorders and fertility

The effects of long-term psychiatric disorders, especially mood and psychotic disorders, on fertility and number of children have been widely studied. Fertility among women with psychotic disorders may be affected by the disorder itself, medications or social factors like the probability of a stable relationship. Epidemiological studies indicate that fertility among women with schizophrenia is lower than in controls or unaffected siblings of patients (Fananas et al. 1995, Howard et al. 2002, Haukka et al. 2003, Howard 2005, MacCabe et al. 2009) and the number of children among parous patients is reduced (Nimgaonkar et al. 1997,

McGrath et 1999). However this difference has diminished over time as a greater proportion of patients is treated on an outpatient basis (Howard 2005).

It is not known whether nulliparous women with schizophrenia do not want to have children or are actually infertile. A person may become ill with a psychotic disorder at any age but, for example, incidence of schizophrenia peaks among women between 25-35 years (Rajji et al. 2009). Thus many patients have to struggle with the fact that they have not yet become parents and the decision to try to become pregnant has to be made knowing that they will be afflicted with a serious illness for the rest of their lives. Fertility may be affected by drugs as many neuroleptics cause hyperprolactinemia and inhibit ovulation (Dickson et al. 2000). Patients with chronic psychotic illness may well face more prejudice than other women and they need to justify more to other people that they "are allowed" to become pregnant or to participate in infertility treatments.

Mood disorders have effects on fertility and number of children. Williams et al. (2007) concluded in their review article that women with mood disorders had fewer observed number of children than the expected number. However, for mood disorders as well this may be due to social factors. A study by Harlow et al. (2003) namely suggests that depressive women have an increased risk for divorce and widowhood.

In addition to social factors, biological and pharmacological factors in individuals with mood disorders may affect fertility (Williams et al. 2007). According to two studies, women suffering from bipolar disorder may have menstrual problems even before taking mood stabilizors (Rasgon et al. 2005, Joffe et al. 2006). For unipolar depression the evidence is inconsistent (Harlow et al. 2004, Rowland et al. 2002, Joffe et al. 2006). However, the use of selective serotonin reuptake inhibitors may potentially influence fertility as the medication can decrease libido and increase the risk of spontaneous abortions (Williams et al. 2007).

2.3.2 Psychiatric disorders among women participating in infertility treatments

Negative emotions are typical and anxiety disorders and depression are common among infertile women participating in infertility treatments. Many couples have found infertility the most distressing experience of their lives (Guerra et al. 1998). Thus grief and emotional distress are understandable and even expected responses to infertility, as infertility can be considered a loss to the couple. The most common reactions are shock, anger, guilt, marital distress, impaired self-esteem, sexual dysfunction, and social isolation (Burns 2007). It may also be difficult to decide whether to start infertility treatments and this may cause anxiety. Typically, when a couple has decided to start infertility treatments, negative emotions and stress fluctuate during the course of treatment procedures (Hammarberg et al. 2001, Verhaak et al. 2007).

The prevalence of depression and anxiety disorders among women participating in infertility treatments is high but estimates have varied widely. This can be explained by variation in diagnostic criteria of the disorders, data collection methods and differences in the backgrounds of infertile couples regarding, for example, duration of childlessness or number of prior treatments. These varied in the studies as well as between the studies.

Domar et al. (1992) used the Beck Depression Inventory and the Center for Epidemiological Studies Depression Scale to compare prevalence of depressive symptoms among 338 women seeking help for infertility and 39 control women who visited physician for routine gynaecological examinations. The prevalence of depression was twofold among the infertile women and highest among those women who had tried to become pregnant for 2-3 years.

Matsubayashi et al. (2001) compared treatment-seeking Japanese infertile women (N=101) to healthy pregnant women (N=81): Emotional distress was estimated by using the hospital anxiety and depression scale (HADS) and the profile of mood states (POMS). They found that the depression/dejection score of infertile women was twice that of pregnant women. Other scores studied with the exception of

fatigue were higher among infertile women suggesting that they had more anxiety, aggression, hostility, lack of vigour, tension, anxiety and confusion.

In a study by Guerra et al. (1998) the prevalence of psychiatric symptoms was evaluated among 110 infertile patients in an infertility clinic. As diagnostic criteria they used DSM-III-R (axis 1). Psychiatric morbidity was found among 61% female and 21% male patients. The most common problem was anxiety disorder. A significant proportion of infertile patients also had significant psychological dysfunction even though they did not fulfill the diagnostic criteria for any specific disorder (Guerra at al. 1998).

Lok et al. (2002) found that 30% of 372 Chinese patients attending for infertility treatments had impaired psychological well-being and 8% were diagnosed with moderate or severe depression. Even more significant psychiatric morbidity was reported among Taiwanese infertile treatment-seeking patients of whom 23% had generalized anxiety disorder, 17% had major depression and 10% dysthymia (Chen et al. 2004).

Sbaragli et al. (2008) compared the prevalence of psychiatric disorders among 81 Italian couples participating in infertility treatment and 70 fertile controls recruited from an obstetrics and gynaecology clinic. Their results demonstrated that the infertile women had significantly more morbidity especially because of adjustment disorders and binge eating disorders (Sbaragli et al. 2008).

Volgsten et al. (2008) evaluated the presence of psychiatric diagnoses among couples being treated for infertility. Their study population consisted of 545 Swedish couples. Of infertile women 26% and of infertile men 9% suffered from mood disorders and 15% of women and 5% of men had anxiety disorder (Volgsten et al. 2008).

2.3.3 Infertility and cancer - possible mechanisms

Among Finnish female population 13,874 cancer cases were diagnosed 2009. The most common cancer was breast cancer (4,474) cases, followed by basalioma (4,007 cases), colon cancer (827 cases) and uterine cancer (806 cases) (Finnish Cancer Registry, 2011).

Although the development of cancer is a complex network of different mutations caused by various endogenous and exogenous factors, it is known that hormonal stimuli promote the development of common cancer types. For breast cancer early age at menarche, low parity, late menopause and late age at first birth increase the risk for cancer development. Risk for ovarian cancer is linked to hormonal factors as high parity and oral contraceptive use are significant protective factors. It is considered that repeated ovulations that disrupt the ovarian epithelium might predispose epithelial cells to malignant transformations. Another explanation is ovarian stimulation of gonadotrophins that directly or via increased oestrogen levels could be carcinogenic. A third hypothesis suggests that inflammatory reactions caused by endometriosis can promote the development of ovarian cancer. The role of androgen secretion has been considered as it has been proposed that excessive androgen secretion may be carcinogenic (Klip et al. 2000)

A risk for uterine cancer is influenced by endogenous and exogenous hormonal factors. Well recognized risk factors for this cancer are nulliparity, polycystic ovarian syndrome (PCOS), late age at menopause, obesity and oestrogen-secreting tumours. The risk is significantly increased in hormone replacement therapy containing only oestrogen. However, when progesterone is combined with the therapy the risk for uterine cancer is no longer increased. Oral contraceptive pills containing both oestrogen and progesterone even decrease the risk for this cancer type. The increased uterine cancer risk in conditions when oestrogen secretion or levels are increased can be explained by high mitogenic activity in the endometrial tissue. The decrease in oestrogen levels and / or increase in progesterone levels in turn decreases mitogenesis and promotes maturation of the endometrium thus lowering the risk for cancer promoting mutations in the tissue (Klip et al. 2000).

The risk for thyroid cancer and melanoma being related to hormonal factors has been studied. Some studies suggest that low parity and late age at delivery are risk factors for the development of melanoma but others have not confirmed this finding. For thyroid cancer the risk is significantly greater among females than among males suggesting that sex hormones have a role in cancer development. It has also been shown that women who have ever been pregnant have increased risk for this cancer compared to nulliparous women. A possible explanation for this risk increase is the higher secretion of thyroid stimulation hormone (TSH) caused by high female sex hormone levels promoting hyperplasia in thyroid tissue exposing the tissue to mutations (Klip at al. 2000).

Researching whether infertility and hormonal infertility treatments increase cancer risk or not is reasonable as in many infertility-causing conditions the secretion or levels of sex hormones are disturbed and during hormonal infertility treatments exogenous drugs affecting hormone balance are administered. For example women with polycystic ovary syndrome suffer from hyperandrogenism and insulin resistance leading to compensatory hyperinsulinemia. Androgen excess in turn increases gonadotrohpin releasing hormone (GnRH) levels which causes luteinizing hormone (LH) hypersecretion altering normal LH/FSH (follicle stimulating hormone) levels. Women with PCOS have severe ovulation dysfunction marked by high oestrogen secretion that is not followed by normal progesterone secretion. This is a risk for developing uterine cancer (Goodarzi et al. 2011).

Endometriosis is another common disease that typically causes impaired fertility and may increase cancer risk. Although this condition is benign, it is marked by numerous immunological changes suggesting the role of chronic intraperitoneal inflammatory process in endometriosis pathogenesis. This inflammation is in turn characterized by increased macrophage activity and increased secretion of cytokines, other growth factors and angiogenic factors (Brosens & Benagiano, 2011).

A recent review article concludes that present data indicate that women with endometriosis are at increased risk for ovarian cancer. Breast cancer risk may be modestly elevated but the findings are inconsistent. Uterine cancer risk is not

elevated and cervical cancer risk is even reduced. Ovarian cancer diagnosed among endometriosis patients, however, is usually clinically somewhat different from "typical" ovarian cancer as patients are younger, diagnosed in earlier stages and have lower grade tumours and thus better survival rate (Munksgaard & Blaakaer, 2011). The suggested pathogenesis for this type of endometriosis-associated ovarian endometroid cancer is related retrograde menstruation causing increased oxidative stress, activation of anti-apoptotic pathways and aberrant activation of stress signalling pathways (Kobayashi et al. 2011).

2.3.4 Infertility and the risk of uterine, ovarian and breast cancer

The risk of cancer among infertile women with or without undergoing infertility treatments has been studied in various cohort and case-control studies. Reviews of the topic have also been published. Despite significant research activity, the results are still at least partly inconsistent.

Overall cancer risk among infertile women was statistically significantly increased compared to general population according to three relatively large cohort studies. Standardized incidence ratio (SIR) for all cancers was reported to be 1.20 (95% CI 1.0-1.5) among 2,496 Israeli infertile women (Modan et al. 1998). According to an American study among 12 193 infertile women SIR was 1.23 (95% CI 1.1-1.3) (Brinton et al. 2005) and in a large Danish cohort study among 54,362 infertile women parity-specific SIR for all cancers was 1.04 (95% CI 1.00-1.09) (Jensen et al. 2008). However not all cohort studies (population size 1,082-5,556 women) have confirmed these results (Doyle et al. 2002, Dor et al. 2002, Lerner-Geva et al. 2003).

The risk of uterine cancer among infertile women has been estimated in several studies, some of which report significantly elevated risk while others do not. Statistically significantly increased uterine cancer incidences were found in a cohort study by Venn et al. (1995), SIR 2.84 (95% CI 1.18-6.8), Modan et al. (1998), SIR 4.85 (95% Cl 3.0–7.4) and by dos Santos Silva et al. (2009), RR 2.02 (95 % CI 1.37-2.87). According to two studies by Venn et al. (1995, 1999) uterine cancer risk was especially increased among women suffering from unexplained infertility.

However in case control studies by Benshushan et al. (2001) and Brinton et al. (2007) infertility was not observed as a risk factor for uterine cancer, nor was the cancer risk increased in the cohort studies by Venn at al. (1999), Doyle at al. (2002) and Jensen et al. (2008) (Table 1)

Table 1. Uterine cancer incidence among infertile women according to previous studies

STUDY	STUDY TYPE	N	RESULT
Venn et al. 1995	cohort	10,358 infertile women, 5564 exposed to infertility drugs and 4,794 unexposed	SIR 2.84 95% CI 1.18-6.8, for women with unexplained infertility RR 6.64, 95% CI 1.06-38
Modan et al. 1998	cohort	2,496 infertile women	SIR 4.85, 95% CI 3.0–7.4
Venn et al. 1999	cohort	29,700 women infertile women: 20,656 exposed to fertility drugs and 9,044 unexposed	SIR (exposed) 1.09, 95% CI 0.45-2.61 and SIR (unexposed) 2.47, 95 % CI 1.18-5.18. For women with unexplained infertility SIR 4.59, 95% CI 1.91-11.0
Benshushan et al. 2001	case-control	128 women with uterine cancer and 255 controls	OR 1.82, 95% CI 0.99-3.32
Doyle et al. 2002	cohort	5,556 infertile women of whom 75% exposed to infertility drugs	SIR 1.27, 95% CI 0.35–3.25
Brinton et al. 2007	case control	551 endometrial cancer patients and 1,925 controls	OR 1.03, 95 % CI 0.7-1.5
Jensen et al. 2008	cohort	54,362 infertile women	SIR 1.08, 95% CI 0.83-1.38
dos Santos Silva et al. 2009	cohort	7,355 infertile women of whom 43% exposed to ovarian stimulating drugs	RR 2.02, 95 % CI 1.37-2.87

Some previous studies suggest that infertility increases the risk for ovarian cancer. The risk for ovarian cancer was statistically significantly increased according to cohort studies by Rossing et al. (1994), Brinton et al. (2004) and Jensen et al. (2008), in a case control study by Mosgaard et al. (1997) and in a survey by Tworoger et al. (2007). The risk for ovarian cancer was not elevated among infertile women according to the cohort studies by Venn et al (1995, 1999), Doyle et al. (2002) and dos Santos Silva et al. (2009) and case control study by Shushan et al. (1996). However, in the studies by Venn et al. (1995, 1999) ovarian cancer risk was elevated among those infertile women whose infertility remained unexplained (Table 2).

Table 2. Ovarian cancer incidence among infertile women according to previous studies

STUDY	STUDY TYPE	N	RESULT
Rossing et al. 1994	cohort	3,837 infertile women	SIR 2.5 (1.3-4.5)
Venn et al. 1995	cohort	10,358 infertile women, 5,564 exposed to infertility drugs and 4,794 unexposed	SIR (exposed) 1.70, 95% CI 0-55-5.27 SIR (unexposed) 1.62, 95% CI 0.52-5.02, for women with unexplained infertility RR (19.19, 95% CI 2.23-165
Shushan et al. 1996	case-control	200 women with ovarian cancer and 408 controls	SIR 1.31, 95% CI 0.63-2.74
Mosgaard et al. 1997	case-control	684 women with ovarian cancer and 1,721 controls	OR for infertile non-treated nulliparous women compared to noninfertile nulliparous women 2.7, 95% CI 1.3-5.5
Modan et al. 1998	cohort	2,496 infertile women	SIR 1.6, 95% CI 0.8-2.9
Venn et al. 1999	cohort	2,9700 women infertile women: 20,656 exposed to fertility drugs and 9,044 unexposed	SIR (exposed) 0.88, 95% CI 0.42-1.84 and SIR (unexposed) 1.16, 95% CI 0.52-2.59. For women with

			unexplained infertility SIR 2.64, 95% CI 1.10-6.35
Doyle et al. 2002	cohort	5,556 infertile women of whom 75% exposed to infertility drugs	SIR 0.98, 95% CI 0.36-2.14
Brinton et al. 2004	cohort	12,193 infertile women	SIR 1.98, 95% CI 1.4-2.6
Tworoger et al. 2007	survey	107,900 women	SIR 1.36, 95% CI 1.07-1.75
Jensen et al. 2008	cohort	54,362 infertile women	SIR 1.46, 95% CI 1.24-1.71
dos Santos Silva et al. 2009	cohort	7,355 infertile women of whom 43% exposed to ovarian stimulating drugs	SIR 0.97, 95 % CI 0.6-1.48

Two large cohort studies report increased breast cancer incidence among infertile women. In a study by Brinton et al. (2004) SIR was 1.29 (95% CI 1.1-1.4) among 12,193 infertile women. SIR 1.08, 95% CI 1.01-1.16 was found in a study by Jensen et al. (2009) among 54,362 infertile women. However, other cohort and case control studies do not report increased risk for this cancer type among infertile women compared to general population (Venn et al. 1995, Braga et al. 1996, Rossing et al. 1996, Modan et al. 1998, Ricci et al. 1999, Dor et al. 2002, Doyle et al. 2002, Lerner-Geva et al. 2006, Pappo et al. 2008, dos Santos Silva et al. 2009) (Table 3)

Table 3. Breast cancer incidence among infertile women according to previous studies

STUDY	STUDY TYPE	N	RESULT
Venn et al. 1995	cohort	10,358 infertile women, 5,564 exposed to infertility drugs and 4,794 unexposed	SIR (exposed) 0.89, 95% CI 0-55-1.46 SIR (unexposed) 0.98, 95% CI 0.62-1.56
Braga et al. 1996	case-control	2,569 women with breast cancer and 2,588 controls	OR 1.08, 95% CI 0.8-1.5
Rossing et al. 1996	cohort	3,837 infertile women	SIR 0.9, 95% CI 0.6–1.4
Modan et al. 1998	cohort	2,469 infertile women	SIR 1.30, 95% CI 0.96-1.60

Ricci et al. 1999	case-control	3,415 women with breast cancer and 2,916 controls	OR 0.8, 95% CI 0.5-1.1
Dor et al. 2002	cohort	5,026 infertile women	SIR 0.69, 95% CI 0.46-1.66
Doyle et al. 2002	cohort	5,556 infertile women of whom 75% exposed to infertility drugs	SIR 1.15, 95% CI 0.86-1.49
Brinton et al. 2004	cohort	12,193 infertile women	SIR 1.29, 95% CI 1.1-1.4
Lerner-Geva et al. 2006	cohort and nested case–control study	cohort of 5,788 infertile women, 61 cases of women with breast cancer and 120 controls	SIR 1.1, 95% CI 0.9–1.4
Jensen et al. 2008	cohort	54,362 infertile women	SIR 1.08, 95% CI 1.01-1.16
Pappo et al. 2008	cohort	3,375 infertile women	SIR 1.4, 95% CI 0.98-1.96
dos Santos Silva et al. 2009	cohort	7,355 infertile women of whom 43% exposed to ovarian stimulating drugs	SIR 1.13, 95 % CI 0.97-1.30

The risk for other cancers among infertile women has been studied although not as intensively as the risk for breast or gynaecological cancers. Studies indicate that the risk for cervical cancer is statistically significantly lower among infertile women compared to general population (Doyle et al. 2002, Jensen et al. 2008, dos Santos Silva et al. 2009). Thyroid cancer risk according to earlier studies was evaluated in a review by Klip et al. (2000) and no statistically significantly increased risk was found. Similar results have also been reported in two cohort studies published later (Jensen et al. 2008, dos Santos Silva et al. 2009). These studies indicate that the risk for melanoma among infertile women is not elevated (Jensen et al. 2008, dos Santos Silva et al. 2009).

Even though the results are still inconsistent, it seems that in medical conditions causing infertility the risk for some cancers may be slightly increased compared to that in general population. Another important question is whether hormonal

treatments used to help couples suffering from infertility increase cancer risk. Results from large cohort studies on the risk for uterine cancer after infertility drugs are inconsistent. Statistically significantly increased uterine cancer risk among parous women exposed to treatments for ovulation induction compared to other parous women was reported in a recent cohort study (Calderon-Margalit et al. 2009). According to a study by Jensen et al. (2008) the risk after taking any infertility drug was not statistically significantly elevated but after exposure to gonadotrophins and more than six cycles of clomiphene citrate the risk for uterine cancer was statistically significantly increased. However, in the cohort studies by Venn et al. (1999), Doyle et al. (2002) and Althuis et al. (2009), dos Santos Silva et al. (2009) uterine cancer risk after infertility drug treatment was not elevated (Table 4).

Table 4. Uterine cancer risk after infertility drug use according to previous studies

STUDY	STYDY TYPE	N	RESULT
Venn et al. 1999	cohort	29,700 women infertile women: 20,656 exposed to fertility drugs and 9,044 unexposed	SIR (exposed) 1.09, 95% CI 0.45-2.61 and SIR (unexposed) 2.47, 95% CI 1.18-5.18
Doyle et al. 2002	cohort	5,556 infertile women of whom 75% exposed to infertility drugs	RR (exposed/unexposed) 0.72, 95% CI 0.06–8.62
Althuis et al. 2005	cohort	8,431 infertile women	for clomiphene RR 1.79, 95% CI 0.9-3.4
Jensen et al 2009	cohort	54,362 infertile women	For any drug RR1.10, 95% CI 0.69-1.76. for gonadotrophins RR 2.21, 95% CI 1.08-4.50) for clomiphene after 6 or more cycles RR 1.96, 95% CI 1.03-3.72
Calderon-Margalit et al. 2009	cohort	15,030 women who gave birth 1974-1976	HR 3.39, 95% CI 1.28- 8.97
dos Santos Silva et al. 2009	Cohort	7355 infertile women of whom 43%	SIR (exposed) 2.31, 95% CI 1.37-3.64, SIR (unexposed)

| | | exposed to ovarian stimulating drugs | 1.66, 95% CI 0.86-2.94 |

Earlier studies suggest that the overall risk for breast cancer after infertility drug exposure is not statistically significantly increased (Table 5) but in some studies, however, the risk was found to be elevated. According to a study by Lerner-Geva et al. (2006) breast cancer risk after clomiphene citrate use was statistically significantly elevated. Taking progesterone in turn increased the risk statistically significantly but not taking other infertility drugs according to a large cohort study by Jensen et al. (2007). Most studies, however, do not report increased breast cancer risk after infertility drug treatment (Venn at al. 1995, Rossing et al. 1996, Potashnik et al. 1999, Ricci et al. 1999 Venn at al. 1999, Doyle at al. 2002, Burkman et al. 2003, Brinton et al. 2004 Gauthier et al. 2004, Calderon-Margalit et al. 2009, dos Santos Silva et al. 2009).

Table 5. Breast cancer risk after infertility drug use according to previous studies

STUDY	STUDY TYPE	N	RESULT
Venn et al. 1995	cohort	10,358 infertile women, 5,564 exposed to infertility drugs and 4,794 unexposed	Relative risk (exposed/unexposed) 1.11, 95% CI 0.56-2.20
Rossing et al. 1996	Cohort	3,837 infertile women	RR 0.5, 95% CI 0.2–1.2 for clomiphene
Ricci et al. 1999	case-control	3,415 women with breast cancer and 2,916 controls	OR 1.2, 95% CI 0.5-2.6
Venn et al. 1999	Cohort	29,700 women infertile women: 20,656 exposed to fertility drugs and 9,044 unexposed	SIR (exposed) 0.91, 95% CI 0.74-1.13 and SIR (unexposed) 0.95, 95% CI 0.73-1.23
Potashnik et al. 1999	Cohort	1,197 infertile women	SIR 1.65, 95% CI 0.94–2.68
Doyle et al. 2002	cohort	5,556 infertile women of whom 75% exposed to	RR (exposed/unexposed) 0.95, 95% CI 0.47-1.92

		infertility drugs	
Burkman et al. 2003	case–control	4,575 breast cancer patients and 4,682 controls from the same area	OR 1.2, 95% CI, 0.8–1.7 for women diagnosed with infertility
Gauthier et al. 2004	questionnaire	92,555 women of whom 6,602 were treated for infertility	RR 0.95, 95% CI 0.82–1.11
Brinton et al. 2004	Cohort	12,193 infertile women	For clomiphene use SIR (exposed) 1.29, 95% CI 1.1-1.6 and SIR (unexposed) 1.28, 95% CI 1.1-1.5. For gonadotrophin use SIR (exposed) 1.4,0 95% CI 0.9-2.0 and SIR (unexposed) 1.28, 95% CI 1.1-1.4
Lerner-Geva et al. 2006	cohort and nested case–control study	cohort of 5,788 infertile women, 61 cases of women with breast cancer and 120 controls	For clomiphene SIR 1.4, 95% CI 1.0–1.8 (cohort) and OR 2.7, 95% CI 1.3–5.7 (case-control)
Jensen et al. 2007	cohort	54,362 infertile women	For use of gonadotrophins RR 1.20, 95% CI 0.82-1.78, clomiphene RR 1.08, 95% CI 0.85-1.39, hCG RR 0.94, 95% CI 0.73-1.21, GnRH RR 1.28, 95% CI 0.75-2.19, progesterone RR 3.36, 95% CI 1.60-7.07
Calderon-Margalit et al. 2009	cohort	15,030 women who gave birth 1974-1976	HR 1.42, 95% CI 0.99-2.05
dos Santos Silva et al. 2009	cohort	7,355 infertile women of whom 43% exposed to ovarian stimulating drugs	SIR (exposed) 1.26, 95 % CI 1.03-1.33 and SIR (unexposed) 0.99, 95 % CI 0.78-1.25

Studies indicate that overall ovarian cancer risk after infertility drug use is not statistically significantly increased (Venn et al. 1995, Mosgaard et al. 1997,

Parazzini et al. 1997, Modan et al. 1998, Venn et al. 1999, Parazzini et al. 2001, Doyle et al. 2002, Ness et al. 2002, Brinton et al. 2004, Calderon-Margalit et al. 2009, Sanner et al. 2009, Jensen et al. 2009, dos Santos Silva et al. 2009) A recent Swedish study, however, found statistically significantly elevated risk after use of gonadotrophins (Sanner et al. 2009) (Table 6).

Table 6. Ovarian cancer risk after infertility drug use according to previous studies

STUDY	STUDY TYPE	N	RESULT
Venn et al. 1995	cohort	10,358 infertile women, 5,564 exposed to infertility drugs and 4,794 unexposed	Relative risk (exposed/unexposed) 1.45, 95% CI 0.28-7.55
Parazzini et al. 1997	Case-control	971 women with ovarian cancer and 2,758 controls	OR 1.1 (0.4-3.3)
Mosgaard et al. 1997	case-control	684 women with ovarian cancer and 1,721 controls	OR (treated nulliparous/non-treated nulliparous infertile women) 0.8, 95% CI 0.4-2.0 and OR (treated parous/non-treated parous infertile women) 0.6 (0.2-1.3)
Modan et al. 1998	cohort	2,496 infertile women	SIR (exposed) 1.7 and SIR (unexposed) 1.6
Venn at al. 1999	cohort	29,700 women infertile women: 20,656 exposed to fertility drugs and 9,044 unexposed	SIR (exposed) 0.88, 95% CI 0.42-1.84 and SIR (unexposed) 1.16, 95% CI 0.52-2.59
Parazzini et al. 2001	case-control	1,031 women with ovarian cancer and 2,411 controls	OR 1.3 (0.7-2.5)
Doyle et al. 2002	cohort	5,556 infertile women of whom 75% exposed to infertility drugs	RR (exposed/unexposed) 0.59, 95% CI 0.12-3.0)
Ness et al. 2002	pooled analysis of eight case-control studies conducted	5,207 women with ovarian cancer and 7,705 controls	OR for nulliparous subfertile women 1.60, 95% CI 0.90-2.87

		between 1989 and 1999	
Brinton et al. 2004	cohort	12,193 infertile women	For clomiphene RR 0.82, 95% CI 0.4-1.5) and for gonadotrophins RR 1.09, 95% CI 0.4- 2.8)
Calderon-Margalit et al. 2009	cohort	15,030 women who gave birth 1974-1976	HR 0.61, 95% CI 0.08-4.42
Jensen et al. 2009	cohort	54,362 infertile women	For use of gonadotrophins RR 0.83, 95% CI 0.50-1.37, clomifene RR 1.14, 95 % CI 0.79 -1.64), hCG RR 0.89, 95% CI 0.62-1.29, gonadotrophin releasing hormone RR 0.80, 95% CI 0.42-1.51)
Sanner et al. 2009	cohort	2,768 infertile women	SIR 1.19, 95% CI 0.54-2.25, for gonadotrophins RR 5.28, 95% CI 1.70-16.45
dos Santos Silva et al. 2009	cohort	7,355 infertile women of whom 43% exposed to ovarian stimulating drugs	SIR (exposed) 1.10, 95 % CI 0.57-1.93 and SIR (unexposed) 0.78, 95 % CI 0.34-1.53

2.4 Summary

The prevalence of infertility varies depending on definition and population studied. Previous findings suggest that it may differ by time and socio-demographic and ethnic factors. The results of different studies on the subject are, however, somewhat inconsistent. Not all infertile couples seek medical help. It has been estimated that there are also significant differences in treatment seeking depending on the background characteristics of infertile couples.

Infertility is practically always a serious crisis and has negative effects on life. It may also predispose to actual psychiatric disorders that are common among couples treated for infertility. There is, however, significant variation in the prevalence of psychiatric diagnoses among couples receiving infertility treatments. Some of this variation is likely to be explained by different background characteristics of infertile couples, regarding, for example, duration of childlessness and possible previous unsuccessful infertility treatments, or different diagnostic tools to diagnose the conditions.

For many women suffering from infertility the cause of impaired fertility is a gynaecological condition such as endometriosis or polycystic ovaries syndrome that causes significant systemic hormonal or inflammatory effects that could also enhance cancer development. As hormonal infertility treatments affect the body's hormonal balance, it has been questioned whether cancer risk after these treatments is increased. There has been a great deal of research on this subject but the results for some cancer types between studies are still contradictory.

3. Aims of the study

To study the prevalence of infertility and use of infertility treatments over time and socio-demographic factors, success of infertility treatments and health of treated women.

1. Does prevalence of infertility and use of infertility treatments differ over time and socio-demographic determinants in Finland? (I)

2. What is the success rate of infertility treatments with different indicators? What is the influence of the causes of infertility, maternal age or care site on success rates? (II)

3. Did women undergoing IVF, ICSI or FET have more hospitalizations for psychiatric diagnosis than control women before and after treatments? Does the outcome of treatments affect the number of hospitalizations after treatments? Who will provide mental support for infertile women and is this support considered sufficient? (III)

4. Have women undergoing IVF, ICSI or FET more cancers 6-8 years after infertility treatments than control women? (IV)

4. Materials and methods

The materials used in this study included two nationally representative cross-sectional surveys, FINRISK 1997 (I) and FINRISK 2002 (I, II, and adequacy of mental support during infertility and infertility treatments – data not previously published), aggregate IVF Statistics (I, II) and the cohort of 9,175 women receiving IVF, ICSI or FET treatments 1996-1998 and their age and residence matched controls (III, IV). This IVF cohort and the controls were linked to the Hospital Discharge Register to identify hospitalizations for psychiatric diagnoses (III), to Finnish Cancer Registry (IV) and to the Central Population Register to collect background information on marital status and socio-economic position. For Paper III the IVF cohort females were also linked to The Medical Birth Register to obtain information about births after infertility treatments.

4.1 FINRISK 1997 and FINRISK 2002 surveys

FINRISK 1997 and 2002 surveys form part of the large cross-sectional population surveys conducted in Finland every five years since 1972 (THL, http://www.ktl.fi/attachments/finriski/2008b34.pdf). The aim of these studies is to monitor public health and the risk factors of chronic diseases but they include questions on reproductive health. A specific questionnaire for women was included in FINRISK 2002 survey and it contained questions about the menstrual cycle, use of contraception and hormone replacement therapy, pregnancies and births, pregnancy complications and infertility and infertility treatments. In FINRISK 1997 only one question on the use of hormone therapy to treat infertility was included in the questionnaire. FINRISK 2002 included questions about the adequacy and sources of mental support for infertility.

Six areas in Finland were included in the survey in 2002: the cities of Helsinki and Vantaa, South-Western Finland, North Karelia and Kuopio, Oulu and Lapland provinces. Lapland region was not included in FINRISK 1997 survey and therefore was excluded from the present study. FINRISK surveys used a random population sample consisting of subjects aged 25 to 64. The response rate among women (N=3,763) was 76.5% in the FINRISK 1997 survey and 75.8% (N=4,729) in the FINRISK 2002 survey.

Data from FINRISK 2002 survey were used to study the life-time prevalence of infertility by age and education and the participation rate in infertility treatments among females who had suffered from infertility by age, education, residence and household income. Socio-demographic differences in likelyhood to seek treatment were compared in 1997 (FINRISK 1997) and 2002 (FINRISK 2002) in the case of hormone treatments. Life-time birth rates among women who had participated in infertility treatments were studied by age, cause of infertility and type of infertility treatment. Adequacy of mental support during treatments and the source of support were elicited in FINRISK 2002 survey. The following options were given for the adequacy of support 1) enough support, 2) some support but not enough and, 3) no support. The sources of mental support were: 1) spouse, 2) psychiatrist or psychologist, 3) infertility clinic personnel 4) health centre or antenatal clinic, 5) infertility support group, 6) other organizational activity, 7) relatives and 8) friends. Each woman could choose several options.

4.2   Aggregate IVF Statistics

Aggregate IVF statistics are gathered annually from all public and private Finnish infertility clinics using a specific questionnaire originally designed by the International Working Group for Registers on Assisted Reproduction (de Mouzon & Lacaster 1997). The clinics are asked about total number of infertility treatment cycles, pregnancies started, number of embryos transferred, ages of patients, causes of infertility, pregnancy, birth and newborn outcomes, complications and congenital anomalies. The statistics are maintained by National Institute for Health and Welfare (THL).

From this data source number of IVF, ICSI and FET treatments by time, cause of infertility and age of women treated with IVF and ICSI were studied. Success of infertility treatments over time was studied using several different indicators (clinical pregnancies, live births, term singletons and singletons weighing at least 2,500 grams). Pregnancy rates after IVF, ICSI and FET separately, number of embryos transferred and clinical pregnancy rates after single and double embryo transfers were calculated and success of treatments in private and public clinics was compared.

4.3 IVF cohort and controls

The IVF cohort consisted of 9,175 Finnish women who had IVF, ICSI or FET treatment during the period 1996-1998. Each woman was recorded once regardless the number of drug purchases. The control population for these women (N=9175) was selected randomly from the Social Insurance Institution's population record that includes the entirel population of Finland. The controls were matched by age and residence.

The IVF cohort was selected using data on infertility drug prescriptions. In Finland the Social Insurance Institution offers reimbursement for most drugs prescribed by public and private sector's physicians. In most cases reimbursement is deducted from the price already during the drug delivery. When supplying drugs pharmacies collect data on recipient's personal identity number, residence, name and class of drug, the size and number of packages, the dose recommended, the dates prescribed and purchased and the code of the prescribing physician and record this to the Drug Register of the Social Insurance Institution.

In order to generate the IVF cohort information on reimbursements for specific drugs or drug combinations was utilized. This enabled the identification of virtually all IVF, ICSI or FET cycles as they all start with drug therapy (with the exception of FET treatments in the natural cycle). The drugs or drug combinations recorded were clomiphene citrate, gonadotrophins, GnRH agonists and progesterone. These could

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additionally be combined with human chorionic gonadotrophin, estradiol and dydrogesterone (Hemminki et al. 2003).

4.4   Finnish Cancer Registry

The Finnish Cancer Registry was founded in 1952 and collects information about cancer cases diagnosed in Finland since 1953. Since 1961 it has been compulsory for all physicians, hospitals and laboratories to report all diagnosed and suspected cancer cases to the registry using a specific notification. In addition, Statistics Finland sends information on all death certificates where cancer is mentioned, to the registry (Cancer Registry, 2011). The coverage of the registry has been estimated to be very good, 99% for solid tumours (Teppo et al. 1994).

For this study all cancer cases among the women in the IVF cohort and controls 1996-2004 were collected. For the IVF cohort cancer cases diagnosed before IVF treatments were excluded from the study. For the controls, the beginning of IVF treatments of the matching treated women was used. The Finnish Cancer registry uses a specific classification for cancer. For the study the cancer cases were classified again according to ICD-10 criteria and divided into 11 categories (ICD-10 code in brackets): breast (C50); ovarian (C56); cervical (C53); thyroid (C73); uterine (C54); pulmonary cancers (C34); melanoma (C43); other skin cancers (C44); tumours of the central nervous system (C70, C71, C72); leukaemia and lymphoma (C81-C96) and gastrointestinal track tumours, including duodenal (C17.0), jejunal (C17.1), ileal (C17.2), colon (C18), splenic (C26), pancreatic (C25) and hepatic cancers (C22), tumours in the gallbladder (C23) and bile ducts (C22.1).

4.5   The Central Population Register

In Finland there is a national register (Population Information System) that contains basic information on all Finnish citizens and foreign nationals who permanently live in Finland. The register is maintained by the Population Register Centre and local registry offices. The data collected in the register contain for example name,

personal identity code, address, municipality of residence, citizenship, family relations, birth (and death) date, first language, occupation, membership of religious community and also possible guardianship, restrictions on legal competence and continuing power of attorney.

The data for the register is obtained from the people themselves and from various public authorities such as local parishes, courts of law, hospitals, health centres, marriage authorities and municipal social services authorities (Population Register Centre, 2011)

The cohort receiving IVF, ICSI and FET and their controls were linked to this register in order to obtain background information on marital status and occupation. The occupation was classified into five categories: upper white-collar worker, lower white-collar worker, blue-collar worker, other (student, entrepreneur, pensioner, housewife, unemployed) and unknown.

4.6 The Hospital Discharge Register

The Hospital Discharge Register contains information on all inpatient care in hospitals and outpatient care in clinics including operations. The register is maintained by National Institute for Health and Welfare. The register contains general information on patients and their illnesses, care site and duration of hospitalization. Possible operations and need for follow-up treatment are registered. If hospitalization is due to a psychiatric diagnosis or severe cardiac disease specific data is also recorded (THL, http://www.stakes.fi/FI/tilastot/tausta/Rekisteriselosteet/ terveydenhuollonhoitoilmoitukset.htm).

The IVF cohort and their controls were linked to the Hospital Discharge Register in order to analyse hospitalizations for psychiatric diagnoses before and after infertility treatments from 1 January 1969 until 31 December 2006. For the newest hospitalizations ICD-10 criteria were used and for the older ones ICD-9 (1987–1995) and ICD-8 (1969–1986) were used. In the present study, the diagnoses were divided into eight categories: psychotic disorders, depression, bipolar disorder or

mania, anxiety disorders, personality disorders, eating disorders, alcohol or other intoxicant abuse and adjustment disorder..

4.7 The Medical Birth Register

For the Medical Birth Register, maintained by the National Institute for Health and Welfare, information on the births of all infants is recorded. The data are obtained from the delivery hospitals and from the Population Information System and Cause-of-Death Register. The health of infants is recorded in the register until the age of seven days. Background information about mother is also included in the register (THL, http://www.stakes.fi/FI/tilastot/tausta/Laatuselosteet/syntymarekisteri.htm).

4.8 Study permissions and ethics

The IVF cohort used also in this study was originally created as a part of large study exploring targeting and health effects of infertility treatments. This study was started by STAKES in the late 1990s (study number 827/402/99). For the original study, permissions were obtained from the Hospital Discharge Register in 2000 (827/402/99), the Social Insurance Institution in 1999 (827/402/99) and the Central Population Register in 2000 (299/40/00). The STAKES research ethics committee and The National Data Protection Authority approved the study plan and register linkages in 2000. For this study further permission for the use of the IVF cohort was applied for to allow register linkages to Finnish Cancer Register and The Hospital Discharge Register in 2006.

During years 1992-2007 it was voluntary for the infertility clinics to report aggregate data to IVF Statistics. However, since an act on assisted fertility treatments came into force, this has been mandatory. As the data is aggregate and patients cannot be identified, additional permissions for data collection are not needed. For this study STAKES granted permission to use this data in 2006.

FINRISK surveys are established cross-sectional population surveys that are conducted every five years. As identification of respondents is not possible from the data obtained for this study, no specific permissions for data use were needed.

4.9   Statistical analysis

In Paper I Chi square test and Odds ratios with 95% confidence intervals were used to measure statistical significance. Odds ratios were age adjusted. In Paper II odds ratios with 95% confidence intervals and a test for relative proportions were used in data calculations.

During the data collection for cohort used as study material in Papers III and IV IVF women and their cohorts were matched for age and residence. Thus in Paper III logistic regression and conditional logistic regression were used for analysis. Odds ratios had 95% confidence intervals. Adjustment for socio-economic position and marital status at the time of infertility treatments was performed due to statistically significant differences with respect to marital status and socio-economic position between IVF cohort and the controls.

In Paper IV odds ratios with 95% confidence intervals for given cancer type between IVF cohort and the controls were calculated with conditional logistic regression analysis after adjustment for socio-economic position and marital status. There were situations when no cancers were observed for some diagnosis among either IVF women or controls and then Fisher's exact test was used. Chi square test was used when comparing possible differences in occurrence time for a cancer after infertility treatments among IVF women and controls.

5. Results

5.1 Prevalence and causes of infertility (I)

Prevalence of infertility

Sixteen percent of women responding to the FINRISK 2002 survey had suffered from infertility. The proportions of infertile women were the smallest among the youngest age group (24-29 years) and among women with least formal education (15% versus 18% among the most educated group). Self-reported infertility differed significantly by education in the different age groups. Among the youngest respondents infertility was more common among the least educated women (12% versus 6% among the most educated ones) However, when older age groups were studied the probability of infertility was the greatest among the most educated group (24% versus 14% among the least educated females) suggesting that women with lower education try to conceive earlier than women with more formal education (Figure 1).
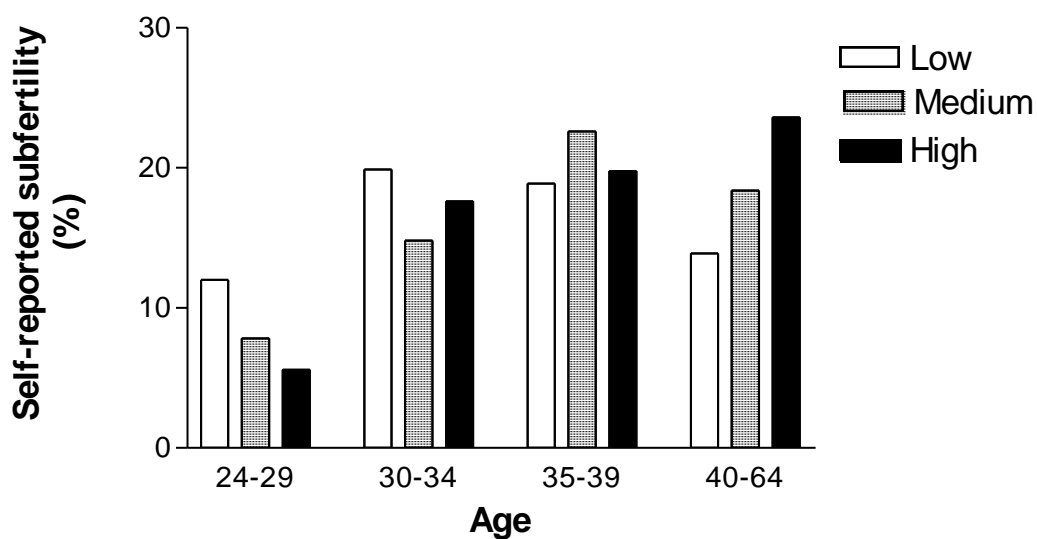

Figure 1. Self-reported infertility in different age classes by low, medium and high education in 2002 (all respondents)

Causes of infertility among couples receiving IVF, ICSI or FET

In the early 1990s tubal infertility was the most common diagnosis among couples receiving IVF or FET (in 35% of all treatments). The next most common was the infertility caused by multiple causes (18%) and male infertility (17%). Over time the role of tubal infertility decreased hugely both in relative and absolute numbers and the proportions of male and unexplained infertility among couples treated increased. In 2004 the most common diagnosis for IVF, ICSI or FET was male infertility (in 28% of all treatments). Tubal infertility as a sole diagnosis was the reason for these treatments for only one of ten couples treated.

5.2   Infertility treatments (I, II)

5.2.1   Use and practices of infertility treatments

Number of IVF, ICSI and FET treatments provided in Finland over time

In 1992, 2,499 IVF and FET cycles were given in Finland. At that time ICSI was not yet available. During the time period 1992-2004, the increase in the number of treatments was over threefold as 8,229 IVF, ICSI and FET cycles were started in 2004. The treatment rate per 1,000 women in fertile age (15-49 years) in turn was 1.8 in 1992 and 7.0 in 2004.

Probability of seeking help for infertility

Of the infertile respondents of FINSRISK 2002 survey 57% had sought medical help. The proportion was smallest among the youngest age group (36%) and largest among oldest women (66%) and among women aged 30-34 (61%). Of the most educated women suffering from infertility 65% sought help whereas the proportion was smallest (55 %) among the least educated women. This difference was not statistically significant (p=0.2). The share of treatment-seeking varied by education in different age groups. Among the youngest respondents treatment-seeking

probability was low in all educational groups. Among women aged 30-34 treatment seeking was most likely among the women with the least formal education but in older age groups the probability was the highest among the most educated ones.
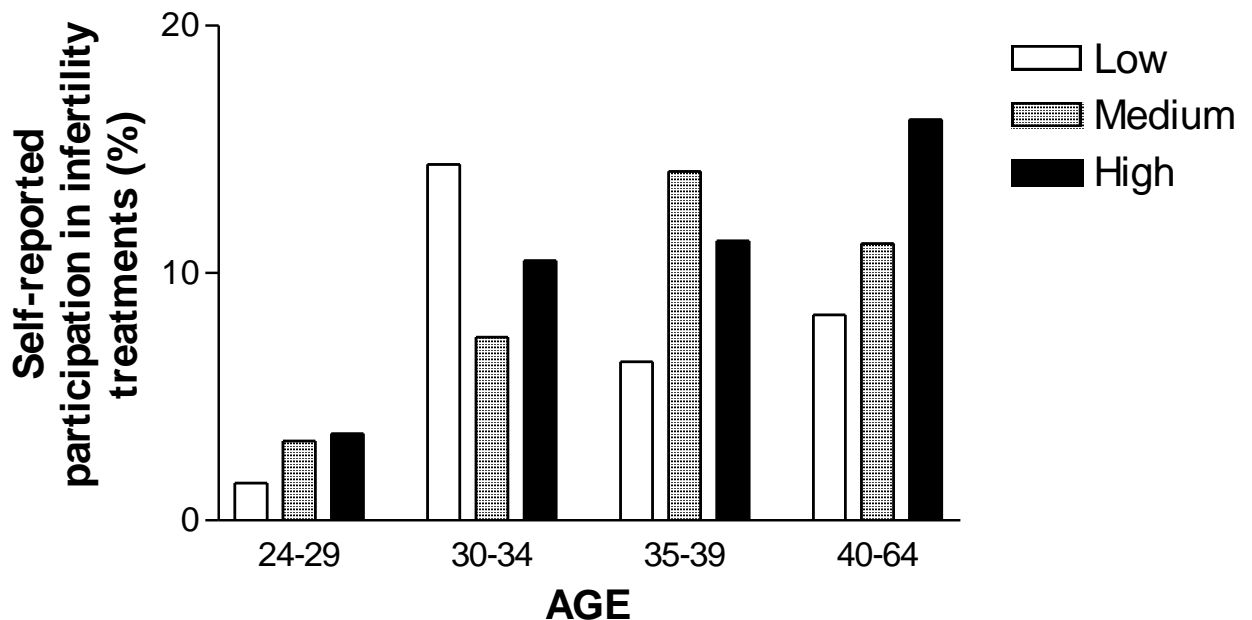

Figure 2. Self-reported participation rate in infertility treatments or medical examinations because of infertility by age in 2002 (all respondents) according to education (low, medium, high).

Use of infertility treatments by age, education, region and household income

In 1997 the oldest respondents to FINRISK survey were statistically significantly less likely to have received hormonal infertility treatments than all other age groups. The difference was greatest when compared with women aged 35-39 (OR 2.8, 95% CI 1.8-4.4). In 1997 the utilization of hormonal infertility treatments was statistically significantly more common among the most educated women and among those with the highest household incomes. The utilization rate was lowest in North Karelia and highest in Helsinki. In all other regions studied the use of hormonal infertility treatments was statistically significantly higher than in North Karelia.

In 2002 when the use of hormone treatments and all infertility treatments were studied the socio-demographic differences persisted but in case of hormone treatments the differences were smaller than in 1997. Changes in the use of all treatments could not be studied over time as they were not elicited in FINRISK 1997 survey. In 2002 the utilization of hormone treatments as well as any infertility treatments was least common among the youngest respondents and statistically significantly more common among all other age groups. In this study the utilization of treatments was also statistically significantly more common among the most educated and the wealthiest ones. Regional differences in use of infertility treatments persisted but were smaller than in 1997 as use of hormonal infertility treatments in 2002 was statistically more common only in Helsinki and Kuopio compared to North Karelia.

Embryo transfers by the number of embryos in 1992-2005 in IVF, ICSI and FET treatments

In 1994 in the majority of the treatment cycles (41%) two embryos were transferred. Three embryo transfers were almost equally common: 37% of all cycles. Single embryo transfers accounted for only 14% of all cycles and in 7% of cycles four embryos were transferred. Over time the proportions of two embryos transferred increased up to 70% in 2000 and started to decrease thereafter being 49% in 2005. The proportion of four and three embryo transfers decreased in the 1990s and after 2000 no four embryo transfers were performed. In 2005 three embryos were transferred in only 0.3% of cycles. The proportion of single embryo transfers in turn increased significantly: in 1999, 21% of transfers were single embryo transfers and in 2005 the share was 51%.

5.2.2 Success of infertility treatments

Success of IVF, ICSI and FET treatments 1994-2005

Success of infertility treatments was measured as clinical pregnancy rate, live birth rate, rate of term singletons and rate of singletons weighing at least 2,500 grams.

The clinical pregnancy rate was 21% in 1994. This rate remained stable between 21-25% in spite of huge increase in elective single embryo transfers. The life birth rate remained quite constant throughout the study period: 15-18%. Instead success rates improved steadily when measuring the rate of term singletons and rate of singletons weighing at least 2,500 grams. Term singleton rate and rate of singletons weighing at least 2,500 grams rose from 9% to 14% per treatment cycle.

Life-time birth rate after infertility treatments

Self-reported life-time birth rate after any infertility treatment was estimated from FINRISK 2002 survey. The rate was highest among women reporting ovulation problems as a cause of infertility: 70%. Among the infertile women with endometriosis the life-time birth rate was 55%. The rate was 42% among the couples suffering from male infertility and 41% among women with tubal failure. The lowest life-time birth rates were reported among women with unexplained infertility (40%) or other causes of infertility (40%). Best self-reported life-time birth rates were achieved with hormone treatments (59%) and with ICSI (58%). For IVF and FET the rate was 47% and for insemination 45%.

Life-time birth rate also differed by age (at time when interviewed), but this difference was not statistically significant (p=0.13). Life-time birth rate for women aged 24-29 years was 67%, for 30-34 years 70%, for 35-39 years 47%, for 40-45 years 56%, for 45-54 years 62% and for women aged 55 years or more 60%.

Clinical pregnancy rates after single and two embryo transfers 1995-2005

In the early 1990s the clinical pregnancy rate after single embryo transfers was notably lower (10%) than after transfer of two embryos (27%). However, over time the clinical pregnancy rate after single embryo transfers increased dramatically being 24% in 2005. In 2005 the clinical pregnancy rate after two-embryo transfers was only slightly better (28%) than after single embryo transfers (24%).

Clinical pregnancy rate by maternal age and cause of infertility and outcome of pregnancies 1995 and 2005 in the public and the private sector

Clinical pregnancy rate in both 1995 and 2005 was statistically significantly better in the private sector than in the public sector among women aged less than 34 years. In 1995 clinical pregnancy rate among women aged less than 30 years was 20.4% in the public sector and 35% in the private sector (p<0.001) and among women aged 30-34 years 20% in the public and 32% in the private sector care. Among older women clinical pregnancy rate was somewhat better in the private sector but this difference was not statistically significant. Among women aged 35-39 years clinical pregnancy rate in the public sector was 20% and in the private sector 24% (p=0.13) and among women aged more than 39 years the rate was 3% in the public sector and 7% in the private sector (p=0.16). In 1995 clinical pregnancy rate among women aged 35-39 was 4.4-fold better (95% CI 2.9-7.4) and among women aged less than 30 years even 6.1-fold better (95% CI 3.8-9.8) than among women aged 40 or more. In 1995 clinical pregnancy rates in the public sector did not differ by age among women aged less than 39 years (20%). In the private sector women aged less than 35 years had significantly better pregnancy rates (32-35%) than women aged 35-39 (24%) or same aged women in the public sector.

In 2005 the clinical pregnancy rate was still better in the private sector among the youngest age groups. Among women aged less than 30 years the rate was 24% in the public sector and 31% in the private sector (p=0.02) and among women aged 30-34 the rate was 24% in the public sector and 31% in the private sector (p<0.01). Among older women the rates did not differ significantly: among women aged 35-39 the rate was 24% in the public sector and 25% in the private sector (p=0.70). Among women aged 40 or more the clinical pregnancy rate was 12% in the public sector and 14% in the private sector (p=0.70). In 2005 the clinical pregnancy rate among women aged 40 or more had improved significantly. The clinical pregnancy rate among women aged 35-39 was 2-fold (95% CI 1.5-2.6) and among women aged less than 35 years 2.3-fold (95 % CI 1.8-3.0) compared to the oldest women.

In 1995 the clinical pregnancy rates were significantly better in the private sector when treating tubal failure (19% in the public sector and 25% in the private sector,

p=0.05) and unexplained infertility (13% in the public sector and 27% in the private sector, p<0.001). For male, other female and multiple causes of infertility the clinical pregnancy rate was slightly better in the private sector than in the public sector but the difference was not statistically significant. In 2005 the differences by care site were not so big: the clinical pregnancy rate was slightly but statistically insignificantly better in the public sector for male and tubal infertility and in the private sector for unexplained fertility and for infertility with multiple causes. Only for other female infertility was the clinical pregnancy rate statistically significantly better in the private sector care sites (22% at the public and 29% at the private care sites, p<0.01).

5.3 Health of women before and after infertility treatments (III, IV)

Background characteristics of IVF cohort and controls

When studying the health of treated women, IVF cohorts and their age and residence matched controls were used as study subjects. Background characteristics of the IVF cohort and controls are presented in Table 7. Statistically significantly more women in the IVF cohort had higher education and were married than among the controls (p<0.001). For the analysis adjustment for marital status and socio-economic position was made.

Table 7: Socioeconomic and marital status of IVF women and their controls
(at the time of infertility treatments)

	IVF women in register study (N=9,175), %	Control women in register (N=9,175), %	P
Socioeconomic position			
Upper white-collar worker	25.3	16.3	
Lower white-collar worker	48.5	45.6	
Blue-collar worker	16.2	19.3	
Student, self-employed, unemployed, housewives	7.9	12.3	
Unknown	2.1	6.4	

			<0.001
Marital status			
Married	69.4	45.3	
Unmarried	22.3	32.7	
Divorced	7.9	8.9	
Widow	0.4	0	
Unknown	0	13	
			<0.001

Psychiatric hospitalizations among the women with the infertility treatments

Hospitalizations for psychiatric diagnoses among the women with infertility treatments were studied before and after infertility treatments. Before infertility treatments the infertile women had fewer hospitalizations than the controls for each category studied (psychotic disorders, depression, bipolar disorder or mania, anxiety disorders, personality disorders, eating disorders, alcohol or other intoxicant abuse and adjustment disorder). Among the infertile women the most common diagnoses for hospitalizations were depression (63 out of 9,175 women), alcohol and other intoxicant use (36 out of 9,175 women), psychotic disorders (33 out of 9,175 women) and personality disorders (30 out of 9,175 women). Depresson was also the most common diagnosis for hospitalizations among the controls (106 out of 9,175 women). Ninety-four control women had hospitalizations for psychotic disorders, 65 for alcohol and other intoxicant abuse and 63 for personality disorders. Even though the number of hospitalizations was smaller among the infertile women than among the controls in each category, the difference was statistically significant only for psychotic disorders (OR 0.38, 95% CI 0.20–0.72).

After infertility treatments depression was the most common reason for hospitalizations among both the women with infertility treatments (101 out of 9,175 women) and the controls (121 out of 9,175 women). The women with infertility treatments had again statistically significantly fewer hospitalizations than controls for psychotic disorders (OR 0.45, 95% CI 0.28–0.73). Hospitalizations because of alcohol and other intoxicant abuse were also statistically more common among the control women after infertility treatments (OR 0.44, 95% CI 0.25–0.75). Interestingly, the women with infertility treatments had after treatments statistically

significantly more hospitalizations for adjustment disorders than did the control women (OR 3.43, 95% CI 1.03–11.4). Hospitalizations because of eating disorders were equally common in the both groups. The women with infertility treatments had fewer hospitalizations for anxiety disorders, bipolar disorder or mania and personality disorders than the controls but these differences were not statistically significant.

The infertile women who had a baby after treatments had fewer hospitalizations for all diagnoses than those infertile women who did not. The difference was significant for anxiety disorders (OR 0.38, 95% CI 0.18-0.81), depression (OR 0.63, 95% CI 0.41-0.96) and alcohol and other intoxicant abuse (OR 0.38, 95% CI 0.18-0.80). When comparing those infertile women who did not give birth to the controls the numbers of hospitalizations did not differ significantly with the exception of more hospitalizations or psychotic disorders (OR 0.38, 95% CI 0.19-0.77) among the control women.

Mental support provided for the infertile women (data not previously published)

In total, 45% of women receiving infertility treatments reported that they had received enough psychological support. About 33% reported that they had received no support, and 22% felt that the support had been insufficient. There was a statistically significant (p<0.001) difference in the reported adequacy of support between women whose infertility treatment had been successful and those whose had not, as significantly more women with unsuccessful treatments found support inadequate.

Most women (85%) had received support from their spouse. Friends (54% of women), relatives (40%), and personnel at the infertility clinic (31%) were also commonly mentioned. Very few women had received help from a psychiatrist or a psychologist (2.1%). Peer groups were also an uncommon source of support (0.6%).

Cancer morbidity after infertility treatments

In the cohort of 9,175 women with previous infertility treatment 178 cancers were diagnosed by the end of year 2004. Cancer incidence among the controls was 193 out of 9,175 women. The incidence of cancers per 1,000 persons per year among the women with infertility treatments was 2.18 and among the controls 2.36. Among the controls cancer cases occurred somewhat earlier than among the women with infertility treatments but this difference was not statistically significant ($p=0.10$)

The number of cancer cases is presented in Table 8. For most cancer types the differences in incidences between the infertile women and the controls were not statistically significant. However, the controls had statistically significantly more cervical cancer (OR 0.51, 95% CI 0.30-0.85) and the women with infertility treatments had statistically significantly more skin cancers other than melanoma (OR 3.11, 95% 1.02-9.6). The women with infertility treatments were also diagnosed with more ovarian cancer (13 cases) than the controls (7 cases) but the difference was not statistically significant (OR 2.99, 95% CI 0.50-17.8). All pulmonary cancer cases occurred among the controls ($p=0.03$).

Table 8. Cancer cases of infertile women and controls (matched for age and residence) after infertility treatments: odds ratios (95% confidence intervals) are adjusted for marital status and socio-economic position.

	IVF women (N=9175)	Control women (N=9175)	OR (95%CI)
Any cancer	178	193	1.01 (0.80-1.27)
Breast cancer	55	60	0.93 (0.62-1.40)
Ovarian cancer	13	7	2.99 (0.50-17.8)
Cervical cancer	34	67	0.51 (0.30-0.85)
Uterine cancer	4	2	2.0 (0.37-10.9)[a]
Pulmonary cancer	0	5	NC[b]
Thyroid cancer	10	8	1.27 (0.31-5.2)
Melanoma	12	9	1.27 (0.34-4.8)
Other skin cancer	24	10	3.11 (1.02-9.6)
Tumours in central nervous system	9	7	9.4 (0.56-159.5)
Gastrointestinal track tumours	12	10	1.88 (0.52-6.8)
Leukaemia or lymphoma	4	5	0.34 (0.04-3.06)

[a]Crude Odds Ratio due to small case number

[b]Non Calculable

6. Discussion

Infertility is a common problem. It directly affects couples desiring a child but in many cases their parents, siblings, friends and work community. According to the sociologist Maili Malin impaired fertility is a medical problem whose social equivalent is involuntary childlessness. Involuntary childlessness can be considered primarily as social problem as the pain caused by the lack of a child is experienced with respect to the other people and the surrounding world. Infertility treatments can be used to artificially overcome the medical problems causing impaired fertility (Lindfors 2011).

According to the most used definition, a couple is regarded as infertile when the woman has not become pregnant after one year of unprotected sexual intercourse (Evers 2002, Gnoth 2005). In Finland around one out of six couples meets these criteria. In addition to these couples there are people who voluntarily choose not to have children and people who would want to have a child but cannot try to conceive due, for example, to sexual orientation or lack of a partnership.

In 2008, 20 % of Finnish females aged 42-43 years old, thus approaching end of their fertile period, did not have biological children. However, only four percent of women and six percent of men think that it is ideal not to have children. The ideal number of children has remained constant among Finnish women 1971-2007 being on average 2.38-2.55 children. According to a population survey 40 % of females and males also thought that the ideal number of children is more than their own actualized number of children (Miettinen & Rotkirch 2008).

This study aimed to explore reduced fertility from various different perspectives without even trying to cover most of them. The extent of the infertility problem and use of infertility treatments were estimated from a population survey FINRISK 2002 on grounds of socio-demographic factors. Absolute numbers in IVF, ICSI and FET

treatments by time and causes of infertility were also explored from aggregate IVF Statistics. The second article aimed to estimate the success of infertility treatments by time, cause of infertility and care site. This subject is naturally very important for couples suffering from infertility but for health care systems as infertility treatments are relatively expensive and time-consuming requiring the help of gynaecologists, nurses, midwives, cell-biologists and laboratory technicians.

Two articles in this study concentrated on important health questions associated with infertility. Reduced fertility and fear of not having children typically cause significant stress and negative emotions and may expose people to mental illness. Our study aimed to compare hospitalizations due to psychiatric diagnoses among women receiving infertility treatments to those of controls before and after infertility treatments. After treatments hospitalizations were also compared between those treated women who gave birth after treatments and those who did not. Due to the severe psychological burden caused by infertility and possible infertility treatments mental support received was also studied.

In various conditions causing infertility hormonal or inflammational balance in the body is disturbed and during hormonal infertility treatments exogenous drugs affecting the hormonal system are administered. Thus it is important to know whether either infertility itself or its treatments can via these hormonal changes predispose to increased risk for cancer. The last article in this study aimed to compare the cancer morbidity of cohort of women treated with IVF, ICSI or FET and cohort women.

6.1 Prevalence of infertility and use of infertility treatments

The present study demonstrated that 16% of females responding to FINRISK 2002 survey met the criteria of infertility. True estimates of the prevalence of infertility can, however, be made only among women who have already passed menopause. Among the female respondents to FINRISK 2002 survey aged 50 or more 14 % reported infertility.

In the present study the prevalence of infertility was more common among the most educated women than among the women with less formal education. However, when the prevalence of infertility was studied separately in different age groups by education it was clearly perceived that among females under 34 years infertility was however more often reported among least educated women. This finding strongly supports current view in our society that highly educated women tend to postpone having children and thus they discover their possible infertility later.

Miettinen and Rotkirch studied in a population survey opinions about the timing of having children (Perhebarometri 2008). Their results showed that Finnish women and men think that the ideal age to become a mother is on average 25.6 years and become a farther 27.4 years. This ideal age was smaller elicited from women who themselves had less formal education (on average 24.9 years) than from the most educated ones (26.8 years). However, the ideal age of motherhood among the most educated women was actually on average two years younger than their own age at becoming a mother (Miettinen & Rotkirch 2008).

In 2005, 85% of Finnish women and men aged 25-34 years had completed a higher education degree after compulsory school. (Statistics Finland, 2011) and 31% of women in this age group and 25% of men had a degree from a university (Ministry of Education and Culture, Kehittämissuunnitelma, 2007). The average age to start studies at university in Finland is 21 years (Saarenmaa et al. 2010) and usually it takes at least 5-6 years to graduate. Becoming pregnant during university studies is relative rare as only 13% of university students have children (Saarenmaa et al. 2010). Thus young adults graduating from university or polytechnic have to choose whether trying to start their professional career or to try to become parents.

According to a population survey Perhebarometri 2008, one third of women who did not have children believed that having a child would diminish their work prospects. The prevalence of this view increased as educational level increased. Thirty percent of females aged 25-34 having a permanent employment contract also thought that uncertainty in their career was their reason to postpone having children. The

proportion was even larger, 40%, among childless women on temporary employment contracts (Miettinen & Rotkirch 2008).

The ability to achieve high-quality education and the desired career is naturally a great and desirable goal for most people. Many people also find their spouse later in life and therefore postpone having children for this reason. Natural fertility, however, starts to decline from the late 20´s onwards (Dunson 2002). In order not to increase the prevalence of reduced fertility and need for infertility treatments it would be important to encourage young educated women to dare to become pregnant without significantly compromising their careers. Possible renovations to achieve this would, for example, be to share the employer's cost due to maternity leaves more equally and to create more encouraging atmosphere for fathers to use parental leaves.

The present study also showed that the use of infertility services differed by socio-demographic factors. The use was statistically significantly more common among the most affluent and the most educated women and in the metropolitan area followed by other large cities. In Finland it is possible to be treated for infertility in either public or private infertility clinics. In public clinics patients treated pay only a taken clinic visit fee, in Tampere University Hospital, for example, 27.40 euros per visit (Pirkanmaa Hospital District, 2011). In the private sector patients pay for visits and treatments themselves but the Social Insurance Institute (SII) reimburses part of costs directly for women aged less than 43 years treated for medical reasons (The Social Insurance Institute, http://www.kela.fi/in/internet/suomi.nsf/NET/ 020411112121MH?OpenDocument). However, even after this reimbursement, infertility treatments in private sector typically cost several hundred or thousand Euros. Regardless of the care site patients have to pay for the medications used in infertility treatments themselves after reimbursements from The Social Insurance Institution usually deducted in drug stores. However, the annual costs of reimbursed drugs exceeding 675.39 Euros (in 2011) are reimbursed totally and patients only pay 1.5 Euros per item purchased (Ministry of Social Affairs and Health, http://www.stm.fi/sosiaali_ja_terveyspalvelut/asiakasmaksut/terveydenhuollon_mak sukatto).

The costs of infertility treatments may affect low-income couples' chances to obtain infertility services especially in the private sector. However, fortunately in Finland there are seven qualified public infertility clinics whose treatments provided, even combined with medication expenses, are quite affordable.

According to the present study the use of infertility treatments was clearly least common in North Karelia and most common in the metropolitan area. Oulu was the northern most region covered in the study and thus utilization by people living up to 675 kilometres (Utsjoki) further north cannot be discussed. Even though there are 20 clinics providing infertility services they are located in large cities, typically in Southern Finland. Thus infertile people living far from these clinics may have to travel several hundred kilometres to their nearest care site. This, of course, causes significant loss of time but may be a reason why more rural infertile couples do not participate as often in treatments as urban infertile couples even though equally aware of treatment options. Intensive infertility treatments, such as IVF require 5-7 visits to an infertility clinic during one treatment cycle. Regardless of the distance to the care site, this may be difficult for working infertile women to arrange. When travelling to the infertility clinic takes hours usually a whole working day is needed to arrange one visit. Thus it may be necessary to tell about infertility and the need for these treatments at work and to the relatives and friends wondering about these visits. This may significantly decrease willingness to participate in infertility treatments.

During the follow-up period of Paper I (1992-2004) the absolute number of IVF, ICSI and FET treatments given in Finland more than tripled and the shares of diagnoses for treatments changed significantly. In 1992 over one third of couples treated with IVF or FET had tubal infertility as a reason for need for infertility treatments. However, as the incidence of *Chlamydia trachomatis* infections started to decrease from the late 1980's onwards the number of females with significant tubal infertility decreased. However, from 1995 onwards the incidence of these infections has started to increase again, especially among adolescents under 20 years old. (Hiltunen-Back & Reunala 2005). If these infections are not treated early with antibiotics the role of tubal infertility is likely to increase as these young people try to conceive.

ICSI was introduced in Finland in Mid-1990s revolutionising the treatment options for couples suffering from severe male infertility. Understandably the proportion and absolute numbers of couples treated because of male infertility increased significantly thereafter.

6.2   Success of infertility treatments

During the study period 1994-2005 a significant change in treatment protocols took place in Finland as the number of embryos transferred decreased dramatically and elective single embryo transfers became a common protocol: in 2005 in half of IVF, ICSI or FET treatments only one embryo was transferred. This proportion has remained fairly constant even since: according to the most recent data from 2009, 46.5% of IVF and ICSI treatments were elective single embryo transfers (THL http://www.stakes.fi/tilastot/tilastotiedotteet/2011/Tr15_11.pdf).   These   shares, however, are not totally comparable as in some of the treatment cycles during the follow-up only one embryo may have been transferred because no others were available.

Despite the huge increase in single embryo transfers clinical pregnancy rates and live birth rates remained similar during the study period suggesting that treatment protocols are effective and no "extra" embryos are needed to ensure better success rates. The shares of term singletons and singletons weighing at least 2500 grams in turn increased from 9% to 14%. This improvement was likely largely due to the decreased number of multiple pregnancies as the number of embryos transferred decreased.

The pregnancy rates after elective single embryo transfers combined with frozen embryo transfers from the same treatment cycle are currently similar to those after double embryo transfers (Vilska et al. 1999, Thurin et al. 2004, Lundin & Bergh 2007, Bechoua et al. 2009, Fauque et al. 2009, Veleva et al. 2009, Stillman et al. 2009). Multiple pregnancies are always risk pregnancies requiring more intense monitoring. The risk of pregnancy complications and pre-term birth is also elevated compared to singleton pregnancies. Thus it is understandable that many health care

professionals want to favour single embryo transfers in order to decrease the risk for multiple pregnancies.

However, for couples suffering from infertility a twin pregnancy despite of risks may be an even more desired outcome than a singleton pregnancy. Only one percent of respondents to the Finnish population survey Perhebarometri 2008 considered one child the ideal number of children (Miettinen & Rotkirch 2008). It is understandable that some couples who may have suffered from infertility for several years and already undergone many previous unsuccessful infertility treatment cycles may want to have two children at the same time in order to avoid needing for infertility treatments again.

The data indicated that at the beginning of the study period there were statistically significant differences in pregnancy rates by care site as the rate was better in the private sector especially when young women were treated. However, in 2005 the difference was already much smaller. There may have been differences in treatment protocols in private and public sector care sites for example in numbers of embryos transferred. The results covered IVF, ICSI and FET treatments, so it is possible that in the public sector physicians try even more eagerly cut costs and provide, for example, more inseminations as first line treatments before using more intense IVF or ICSI treatments. Altogether qualified treatments are provided in both public and private clinics in Finland.

From FINRISK 2002 survey it was possible to estimate self-reported lifetime success rates after different infertility treatments. The highest lifetime birth rate, 59%, was obtained after hormone treatments followed by ICSI, 58%, IVF and FET, 47%. However, these success rates cannot be considered actual maximal cumulative live birth rates that can be medically obtained with these treatments. Some of the couples treated for infertility may have become pregnant naturally after unsuccessful infertility treatment cycles and therefore discontinued treatments. Some couples may have decided to try to adopt a child and for some couples infertility treatment may have been too expensive or mentally too hard and they may have abandoned treatments before it was medically suggested.

6.3 Health of women receiving IVF, ICSI or FET treatments

Mental health and support during infertility crisis

Research has demonstrated that depressive symptoms and anxiety are common among infertile women participating in infertility treatments (Newton et al. 1990, Domar et al. 1992, Matsubayashi et al. 2001, Fassino et al. 2002, Lok et al. 2002, Chen et al. 2004, Sbaragli et al. 2008, Volgsten et al. 2008). Therefore it was interesting to study whether women receiving infertility treatments were more vulnerable to psychiatric disorders either before or after treatments than control women.

The present data clearly demonstrated that in both before and after infertility treatments mental health of treated women was better than or similar to that of controls. Only adjustment disorders were slightly but statistically significantly more common among women in the cohort of infertile women after infertility treatments. These results suggest so-called a healthy patient effect as women planning for pregnancy are usually physically and mentally relatively healthy.

This data may not, however, be generalized to all infertile women as it consisted only of those infertile women seeking medical help and receiving relatively intense infertility treatments. It is thus possible that the results would be somewhat different among women suffering from infertility but not participating in infertility treatments. A study by Hammarberg et al. (2001) showed that the decision to start infertility treatments tends to be difficult and thus it is possible that infertile women suffering from mental problems do not have enough strength to make that decision or participate in intense infertility treatments.

Adjustment disorders typically evolve in response to stress or grief and according to the data only this diagnosis after infertility treatments was more common among infertile women than among the controls. This could be explained as a response to unsuccessful treatments or stressful childcare, and that is why the number of hospitalizations among infertile women regarding whether they gave birth after

treatments or not was further studied. The results demonstrated that hospitalizations for all psychiatric diagnoses were statistically significantly less common among those infertility-treated women who gave birth than among those who had unsuccessful treatments suggesting that having children does not predispose infertile women to severe mental problems.

This view is supported in a study by Klemetti et al. (2010) indicating that risk of psychiatric disorders was not increased among formerly infertile women with childen even though risk for dysthymia and anxiety disorders were elevated among infertile women without a child. A Finnish study by Repokari et al. (2007) demonstrated that among 367 couples with IVF or ICSI singletons and control couples with singletons successful infertility treatment was not a risk for marital adjustment of infertile couples. Neither severe fear of childbirth nor pregnancy-related anxiety seemed to be more common among previously infertile women than among spontaneously conceived controls (Poikkeus et al. 2006).

It was found that less than half of infertile women participating in infertility treatments found the mental support received sufficient. Only one third of treated women reported having received mental support from their infertility clinic. In most cases infertility is a severe crisis and emotional distress during infertility and its treatments can be expected. Yet the proportion of women who had consulted a psychiatrist or a psychologist was very small. Earlier studies suggest that the risk for severe emotional distress is greater in the case of pre-existing psychiatric illness (Burns 2007), previous unsuccessful treatment cycles, low socioeconomic status and a lack of support from a spouse (Beutel et al. 1999). Protective factors for distress are conversely good self-esteem, satisfactory job and good relationship (Bringhenti et al. 1997).

In the study women reported that own spouse was the most important supporter. Friends and relatives were more common supporters than health care professionals. Similar findings have been reported from a Dutch infertility clinic where treated women named friends, siblings and their own mothers as the most important support givers (Oddens et al. 1999). According to that study, 46% of women found it hard to

talk about infertility and over half thought that other people were reluctant to discuss the issue with them.

In Finland the Family Federation (Väestöliitto) and infertility clinics of Hospital District of Helsinki and Uusimaa and Oulu University Hospital have conducted a study among 450 patients treated for infertility. Of these couples 15% had not told anyone about their participation in infertility treatments and about half had told only to a few close friends. Women were more likely to tell about the treatments but only a few percent shared their infertility openly. Twenty percent of couples thought that they would have needed more mental support. It was also widely acknowledged that support received from close family members and friends may influence participation in infertility treatments and willingness and strength to continue treatments (Miettinen, 2011)

As mental support received during infertility and infertility treatments is commonly considered insufficient and it is usual that people are only seldom aware of the infertility of their nearest, supporters may also have problems in handling the situation. The Finnish Infertility Association Simpukka has published a guide book for friends and relatives of infertile couples that can be used in order to better support those suffering from infertility (Paasisalo, 2010)

Risk for cancer among infertile women

Up to eight years follow-up overall cancer incidence was similar in both groups studied. Infertile women had statistically significantly fewer cervical cancers and more skin cancers other than melanoma. All pulmonary cancers were diagnosed among control women.

The difference in the incidence of cervical cancer suggest, as the results of Paper III, the so called a healthy patient effect. Women participating in infertility treatments are used to visiting their gynaecologists regularly and thus papanicolaou smears are likely to be taken often, in many cases enabling diagnosis of possible cell atypia before they progress to cancer. It is possible that women suffering from infertility have learned to automatically monitor their health and due to infertility treatments

are used to receiving health care. This may explain the statistically significantly larger incidence of other skin cancers than melanoma among infertile women who might react to their suspicious moles more vigilantly. A part of this difference may also be due to residual socio-economic differences even after adjustment between the groups because skin cancers are more common among highly educated persons (Hemminki & Li 2004).

It is likely that many women desiring children have stopped smoking already when first trying to conceive or at the latest when discovering their difficulties in conceiving because smoking impairs fertility. This may explain differences in the incidence of pulmonary cancer. Socio-economic factors could also explain this difference. More women in the control group had lower socio-economic position and in Finland probability of smoking differs by social class (Rahkonen et al. 2003). However, due to the statistically significant difference in this factor between the cohort and controls, adjustment for socio-economic position was made before data analysis. Thus this difference is unlikely to explain the different pulmonary cancer incidences between the groups.

Existing data on cancer risk among infertile women is still, despite a great deal of research, somewhat inconsistent. One reason is that in most studies infertile women have been analysed as one class regardless cause of infertility. Theoretical knowledge about the pathogenesis of conditions causing infertility, like ovulatory disturbances, endometriosis or PCOS, still suggests different risk potential for different cancer types. For example, it is understandable that among women with long anovulatory menstrual cycles the risk for uterine cancer can be increased as the endometrium is too long exposed to proliferation caused by oestrogen (Goodarzi et al. 2011). Among women suffering from endometriosis the risk for ovarian cancer may be increased (Kobayashi et al. 2011, Munksgaard & Blaakaer, 2011). The numbers of women with these infertility causing conditions is different in different studies. In some studies a larger proportion of infertile couples may suffer from male infertility or tubal infertility caused by untreated *Chlamydia trachomatis* infections. Among women treated for these conditions the gynaecological cancer risk is likely to be similar than that among women without fertility problem with similar other risk factors for these cancers.

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Knowing that certain gynaecological diseases may, in addition to causing infertility, also predispose to cancer could change the treatment protocols of these diseases. For example, for those endometriosis patients who could manage pain caused by the condition with only pain medications, hormonal treatments that also control hormonal and inflammatory changes might be indicated to decrease cancer risk. Overweight women suffering from polycystic ovary syndrome should also know that in addition to increased risk for infertility and cardiovascular disease, their disease may also predispose them to uterine cancer and that loosing weight decreases this risk significantly.

This study did not find increased risk related to IVF, ICSI or FET treatments. Naturally all medical treatments should have a minimal amount of side-effects, especially serious ones. In all cases of infertility effective treatments without exogenous drugs significantly affecting the body's hormonal balance cannot be provided. IVF and ICSI do have well-recognized potentially dangerous side-effects like ovarian hyperstimulation syndrome. The couples participating in these treatments should be well aware of the risks. The desire for children is in many cases so intense that people are ready to take risks potentially affecting their own health in order to have a child. It is unlikely that even in the future, if research data on potential cancer risk after infertility treatments increases, the use of these treatments would significantly decrease.

6.4   Methodological considerations

The materials used in this study were two cross-sectional population surveys, aggregate IVF statistics, a cohort of women (N=9,175) who had received IVF, ICSI or FET treatment 1996-1998 and their age and residence matched controls. The cohort and their controls were linked to several registries. A study setting like this has many advantages but also limitations and disadvantages.

The aggregate IVF statistics utilized in the study are generally regarded as reliable. It was voluntary to the clinics to report data but the rate of report is high, up to 100% in the years studied. Even though a specific questionnaire was used for data

collection it is still possible that the clinics report data differently for example when classifying causes of infertility.

Each year the statistics also collect preliminary data from the previous year which is later compared to actual data from that year. As preliminary and actual data are usually very similar the reliability of the data can be regarded as good. The greatest restriction of the data obtained from IVF Statistics is that it is reported by the clinics in aggregate form and thus no identification of patients treated is received. Thus it is impossible to link these women to different national registries.

The two population surveys used in this study are based on random population sampling and can therefore be considered representative. However, only some regions in Finland are covered in these studies which may naturally cause bias, for example, when studying regional differences in use of infertility treatments. The response rate in these studies was relatively high but it is still possible that the differences in non-responders' by background factors may bias the results. The response rate did not however differ significantly by either age (73-79% in FINRISK 2002) or residence of respondents (71-79% in FINRISK 2002) and therefore the data is probably not significantly biased.

As the survey data is based on self-reported information it is possible that some recall or reporting bias occurred. Generally it is reasonable to try to cover several important health issues is these studies. Therefore it is impossible to include all possible aspects, for example, of reduced fertility to these surveys. In order to enable comparisons over time the questions and answer options on a given issue should remain similar. This was not the case when comparing questions about undergoing infertility treatments in FINRISK 1997 and 2002 surveys and thus no really accurate comparison on possible changes over time could be made.

When studying the health of women treated, a cohort of patients who received IVF, ICSI or FET treatment 1996-1998 and their controls were used as a data source. This cohort was created from the drug reimbursement records. The drug combinations used in IVF, ICSI or FET treatments are not used for other purposes and thus this cohort is very unlikely to include women not having received these

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treatments. Moreover in IVF and ICSI treatments controlled hyperstimulation of the ovaries is required in order to mature several egg cells. This is not possible without drugs and therefore all IVF and ICSI treated women are very likely included in this cohort. Practically the only possible explanation for provided IVF or ICSI treatment not covered in this cohort would be a case when a woman had visited an infertility clinic in December 1995 and then bought drugs for treatments started in January 1996.

Not all frozen embryo transfers were included in the cohort as it is also common to transfer frozen embryos utilizing woman's natural menstrual cycle without exogenous support medications. This, however, unlikely to cause significant bias in the results.

Hospitalizations among the cohort women and their controls were compared both before and after infertility treatments. This comparison does not enable the investigation of actual psychiatric morbidity in these groups as only severe cases requiring hospitalization were recorded. A much larger group of women suffering from milder psychiatric illnesses were probably treated as outpatients. However, there is no reason to believe that the proportions of in-patient care and out-patient care would be different between the cohort and control women. Thus this data source should be reliable for recording severe, psychiatric illnesses requiring hospitalization.

The background characteristics of the women in the cohort and control groups regarding marital status and socio-economic position were statistically significantly different. This could cause significant bias but adjustments for these were made in the data analysis and thus any possible residual confounding caused by these differences is likely to be slight.

When investigating cancer morbidity, the same cohort of 9175 women who had received IVF, ICSI or FET and their controls were used as study material. The follow-up time was relatively short 6-8 years, but as the number of women was large, almost 200 cancer cases were diagnosed in both groups. These numbers are large enough to permit reasonable estimates in most cases of possible differences in

cancer incidences between the groups. For example, during this follow-up time the incidences of cervical cancers, pulmonary cancers and skin cancers other than melanoma were significantly different between the two groups.

In the case of ovarian cancer possible differences in incidence remain unclear: according to the data the incidence seems to be larger (13) among the cohort of infertile women than among the controls (7). Ovarian cancer is a relatively rare cancer and thus larger case numbers are needed to confirm whether this difference of six cancer cases is significant or coincidental. Incidences of uterine cancer were also so small (4 in the cohort and 2 in controls) that it is impossible to estimate accurate differences in incidences. For thyroid cancer, tumours in the central nervous system, gastrointestinal track tumours and leukaemia or lymphoma the differences in incidences were at most a few cases and the number of these diagnoses was large enough to permit the conclusion that clinically significant differences in cancer incidences did not exist.

Most cancers are diagnosed in older age and thus it is to be expected that the number of cancer cases for each diagnoses will be much larger when follow-up time increases. Most women in the cohort (and of course also among the controls) were under 40 years old when receiving infertility treatments and thus were still under 50 years at the end of follow-up.

One significant weakness of the study setting was that the role of infertility itself in affecting cancer incidence cannot be distinguished from that of infertility treatments, as general population was used as controls. The data enabled matching for age and residence and adjustment for marital status and socio-economic position. However, many factors affecting cancer risk such as parity, use of oral contraceptives, genetic predisposition, possible obesity or smoking cannot be controlled for.

The risk of cancer either because of infertility or use of infertility treatments has already been studied in various cohort, case-control and questionnaire studies. For many cancer types the existing data is contradictory between the studies. From the theoretical point of view it is reasonable to expect that any possible increase in cancer risk might differ depending on the cause of infertility. If the infertility drugs

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affect on cancer risk, it is likely to be different depending on which hormonal infertility drug is given.

Thus in future it would be reasonable and important to collect large cohorts enabling estimations of cancer risk depending on the cause of infertility instead of analysing infertile women as one group. Also the follow-up time should be long enough. When estimating cancer risk after taking hormonal infertility treatments, the control group should be un-treated infertile women with the same cause of reduced fertility.

7. Conclusions

1) There were differences in the prevalence of infertility by woman's age and level of education. In general infertility was the most common problem among the most educated women. However, when ascertaining prevalence of infertility among young women, the least educated ones reported problems more often, suggesting that more educated young women tend to postpone childbearing.

2) The number of IVF, ICSI and FET treatments provided in Finland more than tripled in the period 1992-2004. The proportions of causes of infertility changed significantly over time.

3) There were socio-demographic differences in the probability of seeking help for infertility: urban, affluent and the most educated women were most likely to seek help. However, the data from FINRISK 1997 and 2002 suggested that differences in the use of infertility services by these factors may have diminished over time.

4) Clinical pregnancy rate and live birth rate after IVF, ICSI or FET remained similar in the period 1994-2005 despite a substantial increase in single embryo transfers. The term singleton rate and rate of singletons weighing at least 2500 grams rose during the follow-up period, which is at least partly explained by the smaller number of multiple pregnancies as the number of embryos transferred has become smaller.

5) Clinical pregnancy rates after single embryo transfers improved significantly 1994-2005.

6) Success rates were significantly better in the private sector especially when treating young women, but the difference diminished over time.

7) Before participating in infertility treatments infertile women had fewer hospitalizations than controls due to all psychiatric diagnoses. After treatments the number of hospitalizations was still smaller for all other diagnoses but statistically significantly greater due to adjustment disorders.

8) After infertility treatments those infertile women who gave birth had fewer hospitalizations for all psychiatric diagnoses than those who did not give birth.

9) In the cohort of women receiving IVF, ICSI or FET treatments cancer risk was not increased. They had statistically fewer cervical cancers and pulmonary cancers and more skin cancers other than melanoma suggesting a healthy patient effect.

Acknowledgements

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Infertility and the use of infertility treatments in Finland: Prevalence and socio-demographic determinants 1992–2004

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Abstract

Objective: To examine changes in the use of infertility treatments by time, the causes of infertility, lifetime prevalence of subfertility, and the use of infertility treatments by socio-demographic factors.
Study design: Aggregate IVF statistics (1992–2004) and two nationally representative cross-sectional surveys (1997 and 2002).
Results: Total number of IVF, ICSI and FET treatments initiated more than tripled between 1992 and 2004. The proportion of tubal injury as a cause of infertility treatment decreased over time while other female factors, male factor and multiple causes became more common. Self-reported lifetime subfertility was 16.0% in 2002 among women aged 25–64 years. Subfertility differed notably by age and education: young less educated women and older more educated women more frequently reported subfertility. Use of hormone therapy to treat subfertility (1997 and 2002) and participation in infertility treatments or medical examinations (2002) was more common among urban, highly educated and affluent women.
Conclusions: The use of infertility treatments increased and the proportions of causes of infertility have changed over time. Self-reported subfertility differed by age and education. There are socio-demographic differences in the use of infertility treatments.
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Keywords: Subfertility; Infertility treatments; Socio-demographic differences

1. Introduction

Infertility is an important medical and social problem in both magnitude and impact on well-being. According to an often-used definition a couple is regarded as subfertile if the woman has not become pregnant after 1 year of unprotected sexual intercourse [1]. The definition of World Health Organization (WHO) requires as much as 2 years of unprotected intercourse [2]. The prevalence of subfertility is most often studied as current prevalence or as lifetime prevalence, which is a cumulative prevalence until the time of study [3].

It is generally estimated that approximately 10–15% of couples have difficulties in conceiving [1,4]. In their meta-analysis Schmidt and Münster reported that the current prevalence of subfertility in studies published in 1970–1992

varied from 3.6 to 14.3% and lifetime prevalence from 12.5 to 32.6%. In the 1990s the lifetime prevalence of subfertility was reported to be 10% in the United States [5], 16% in Finland [6] and 26% in Denmark [7].

In industrialized countries half of subfertile couples seek medical help [8]. It has been speculated that reasons why subfertile couples may not want to use infertility treatments may be financial, medical, psychosocial, moral or ethical [9]. According to a Finnish study women who did not seek medical help for infertility were younger, had fewer years of formal education and had tried to become pregnant for a shorter time period than the treatment-seeking women [6]. In Finland the per capita use of infertility treatments is approximately the same that in Denmark and Iceland and, for example, five times greater than in the United States [10].

In the United States the utilisation of infertility treatments is significantly higher in those states where the treatments are either partly or completely covered by health insurance

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[11]. The utilisation rate is also higher among educated women and those with high incomes [12]. According to a recent study in a state where insurance coverage of the infertility treatments is mandatory, Caucasian, affluent and more educated women also use notably more infertility treatments [13]. African American women also suffer from subfertility for a longer time period than other ethnic groups before seeking medical help [14].

In Finland, too, there are socio-demographic differences in the use of in vitro fertilization (IVF): the age-standardized IVF incidence per thousand women aged 20–49 was 7.3 in rural and 8.8 in urban areas [15]. Moreover, women who receive infertility treatments are more educated [16] or in a better socio-economic position [17].

The objective of this study was to examine changes in infertility treatments by time, causes of infertility, lifetime prevalence of subfertility and use of infertility treatments by socio-demographic factors.

2. Materials and methods

Two different data sources, aggregate IVF statistics and two cross-sectional surveys (FINRISK 1997 and FINRISK 2002) were utilised.

2.1. Aggregate IVF statistics

IVF statistics are gathered annually by STAKES (the National Research and Development Centre for Welfare and Health). For the years 1992, 1995, 2000 and 2004 the data consist of aggregated data from IVF, ICSI and FET treatments in the public and private sectors.

For this data source all clinics in Finland were asked about the number of treatment cycles and pregnancies started, the cause of infertility, the number of embryos transferred, pregnancy, birth and newborn outcomes, complications and congenital anomalies using a specific questionnaire [18,19]. The clinics report the data themselves and participation is voluntary. In years 1995 and 2004 all clinics participated. In 1992 and 2000 one clinic did not participate as it had already discontinued its operations at the time of data collection. Infertility treatments were given in 13 locations in 1992 and 18 in 2004.

For this study we used data from IVF statistics concerning the number of IVF, ICSI and FET cycles, the age distribution of the women starting IVF or ICSI treatment and the causes of infertility. The age of women receiving FET treatment was not elicited from the clinics, due to different ways of recording the age (age at ovum harvesting or age at frozen embryo transfer).

2.2. Survey data: FINRISK 1997 and FINRISK 2002

As another data source we used two cross-sectional surveys (FINRISK 1997 and FINRISK 2002) that were coordinated and conducted by National Public Health Institute. These surveys monitor public health and risk factors of chronic diseases and included questions on reproductive health. Six regions in Finland were included in the survey: the cities of Helsinki and Vantaa in the metropolitan area of Finland, South-Western Finland, North Karelia and Kuopio, Oulu and Lapland provinces [20]. Lapland region was not included in the FINRISK 1997 survey and was therefore excluded from this study. FINRISK surveys used a random population sample consisting of subjects aged 25–64. The response rate among women ($N = 3763$) was 76.5% in the FINRISK 1997 survey and 75.8% ($N = 4729$) in the FINRISK 2002 survey [20].

In the FINRISK 1997 survey the women were asked whether they had ever used hormone therapy to treat infertility either in outpatient or inpatient care. The FINRISK 2002 survey included a separate questionnaire on women's reproductive health including menstruation, contraception, pregnancies and pregnancy complications, use of hormone replacement therapy and infertility. Participants were asked if they had experienced a time period when they had tried to become pregnant, but had not conceived or conception took more than 12 months. Medical examinations because of infertility or use of infertility treatments were elicited as a combined question: Have you ever been in medical examinations or been treated for infertility? Infertility treatments were elicited with the following alternatives: insemination, in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), frozen embryo transfer (FET) and other treatment. The number of pregnancies and births resulting from treatments was elicited.

The lifetime prevalence of subfertility and the participation rate in infertility treatments and medical examinations due to subfertility were available from the FINRISK 2002 survey. Subfertility was analysed among all respondents by age and education. Use of infertility treatments was studied among subfertile women by age and education and among all respondents by residental region, education and household income. The education of participants was classified into three classes. In FINRISK 1997 "low" consisted basic compulsory education, "medium" vocational training, college and upper secondary school and "high" university. In the FINRISK 2002 the classes "low" and "medium" were corresponding but the class "high" also included polytechnic which was not an option in the FINRISK 1997 survey. Household income per year was pre-divided into nine classes. The highest was in FINRISK 1997 more than 53,800 euros and in FINRISK 2002 more than 67,280 euros. For this study we further classified income into three categories "low", "medium" and "high" so that each category included about one third of the respondents.

Chi-square test and odds ratios with 95% confidence intervals were used to measure statistical significance. Odds ratios were age adjusted. SPPS 14.0 for Windows (Chicago, Illinois, USA) was used to analyse results.
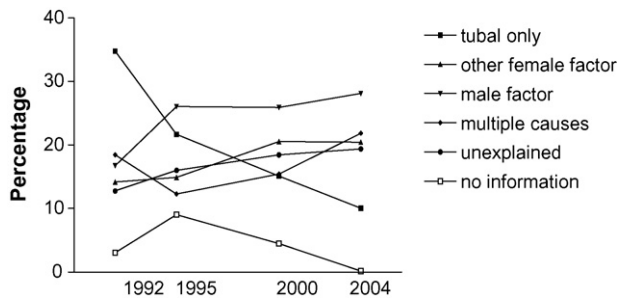
Fig. 1. Causes of infertility in initiated IVF and ICSI cycles in 1992, 1995, 2000 and 2004 (IVF statistics).

3. Results

3.1. Aggregate IVF statistics

The use of IVF services increased significantly: in 1992, 2499 IVF and FET cycles were started in Finland: ICSI was not yet used. In 1995 the total number of IVF, ICSI and FET cycles initiated was 5193 but the number increased to 7388 in 2000 and to 8229 in 2004. The increase was over threefold from 1992 to 2004. Treatment rate per 1000 women in fertile age (15–49 years) increased from 1.8 in 1992 to 7.0 in 2004 (numbers not shown in a table). The number of IVF or ICSI cycles increased notably over time in every age group except in the oldest (40 years or more) from 1992 to 2004. The age of women receiving FET treatment was not available.

The proportions of the causes of infertility changed notably from 1992 to 2004. The relative incidence of tubal injuries as the reported cause of infertility treatment has decreased significantly (Fig. 1), likewise the absolute numbers (not shown). Another important trend was the rise of the proportion of male factor in 1992–1995.

3.2. Survey data

Of the women participating in the FINRISK 2002 survey 16.0% reported a history of subfertility at least once in their
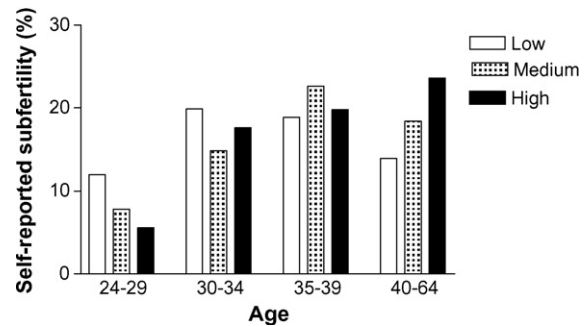

Fig. 2. Self-reported subfertility in different age classes by education in 2002 (all respondents).

lifetime (Table 1). The proportion of subfertile women was smallest in the youngest age group and in the least educated group. Subfertility was proportionally most common women aged 40–44 years. Of all subfertile women 57% had sought medical help. The proportion was smallest in the youngest age group and largest among the age groups 50–64 and 30–34 ($p = 0.004$). More educated women were also more prone to seek medical help than subfertile women with less formal education. This difference was, however, not statistically significant ($p = 0.2$).

In the youngest age group the least educated women were more likely to report subfertility than more educated ones, but among women in the oldest age group the opposite was found (Fig. 2). The use of infertility treatments or attendance at medical examinations because of infertility varied by education in a similar manner (Fig. 3).

The proportion of women reporting using of hormone therapy for infertility (5%) remained the same in 1997 and 2002. However, in 2002 nine percent of women reported infertility treatments or medical examination for subfertility (Table 2). In 1997, women aged 35–39 had significantly ($p < 0.001$) most often received hormone treatments while women aged over 50 were proportionally most seldom treated. By comparison, in 2002 women aged 40–44 years were most often and women aged less than 30 most seldom

Table 1

Proportions of subfertile women by age and education and use of infertility treatments or medical examinations because of infertility in 2002 in Finland

Age	N	Subfertile respondents (%)	Subfertile respondents been treated (%)[a]	OR (95% CI)[b]
24–29	554	44 (8)	16 (36)	1.0
30–34	528	90 (17)	54 (61)	2.6 (1.2–5.5)
35–39	531	110 (21)	57 (52)	1.9 (0.9–3.9)
40–44	551	125 (23)	66 (53)	2.0 (1.0–4.0)
45–49	540	97 (18)	54 (56)	2.2 (1.1–4.6)
50–64	1667	235 (14)	151 (66)	3.1 (1.6–6.1)
Total	4371	701 (16)	398 (57)	
Education				
Low	2049	300 (15)	162 (55)	1.0
Medium	1473	251 (17)	142 (57)	1.2 (0.9–1.8)
High	825	146 (18)	93 (65)	1.7 (1.1–2.6)
Total	4347	697 (16)	397 (58)	

[a] Calculated from subfertile women.
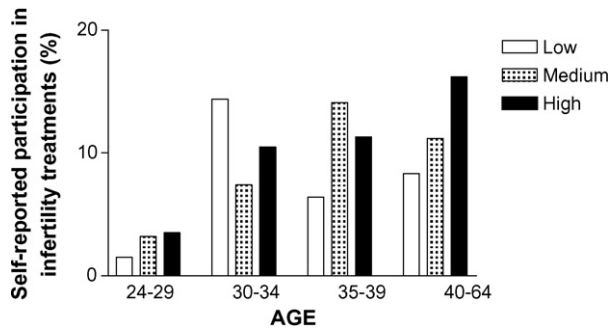[b] Odds ratios are age adjusted.

Fig. 3. Self-reported participation rate in infertility treatments or medical examinations because of infertility by age in 2002 (all respondents).

treated ($p < 0.001$). The age of women at the time of treatments was, however, not elicited.

Age-adjusted self-reported use of hormone therapy to treat subfertility (1997 and 2002) and participation rate in infertility treatments or medical examinations (2002) varied among the study population by place of residence, education and income (Table 2). The most highly educated women had about twofold use of infertility treatments compared to women in the lowest education group ($p < 0.01$). A similar trend was found by household income. In 1997 the difference between the highest and the lowest income groups was almost threefold and in 2002 almost twofold (any treatment) or threefold (hormone therapy). These results were all statistically significant ($p < 0.001$).

The use of infertility treatments was most common in large cities and least common in the most eastern county of North Karelia. However, regional differences in the use of hormone therapy become smaller over time. The regional difference in the use of hormone treatments was statistically significant both in FINRISK 1997 and FINRISK 2002 ($p < 0.001$). However, difference in use of any treatment in FINRISK 2002 was not significant ($p = 0.11$).

4. Discussion

The total number of IVF, ICSI and FET treatments initiated in Finland more than tripled between 1992 and 2004. In addition to an increased need for infertility treatments, this may have been caused by an increased supply of infertility services and improved technology. The number of clinics offering infertility services rose from 13 in 1992 to 18 in 2004. ICSI was introduced into Finland in 1994, enabling better treatments options for couples suffering from male infertility.

The use of IVF services is more common in Finland than in many other industrialized countries. Less than half of treatments are given in the public sector and mainly covered by national health insurance. Private services are also partly reimbursed regardless of the woman's age if the couple is treated for medical reasons. However, for women aged 45 or more (2001–2005) or 40 or more (2005 onwards) this reimbursement requires a statement from a treating

Table 2
Self-reported use of hormone therapy to treat infertility (1997 and 2002) and participation in infertility treatments or medical examinations because of infertility by age, education, region and household income (all respondents)

Age	1997			2002				
	Users (hormone therapy, %)	Number of respondents in class	OR (95% CI)	Users (hormone therapy, %)	Number of respondents in class	OR (95% CI)	Users (any treatment, %)	OR (95% CI)
24–29	5.0	402	1.7 (1.0–3.0)	2.0	557	1.0	2.9	1.0
30–34	7.6	459	2.8 (1.7–4.4)	5.2	522	2.7 (1.3–5.5)	10.3	3.9 (2.2–6.9)
35–39	7.7	456	2.8 (1.8–4.4)	7.2	528	3.8 (1.9–7.6)	11.0	4.2 (2.4–7.4)
40–44	6.9	481	2.5 (1.5–3.9)	8.2	547	4.4 (2.3–8.7)	12.8	5.0 (2.8–8.7)
45–49	5.5	489	2.0 (1.2–3.2)	5.2	541	2.7 (1.3–5.5)	10.2	3.8 (2.2–6.8)
50–64	2.9	1443	1	4.3	1664	2.2 (1.2–4.2)	9.3	3.5 (2.1–5.9)
Education								
Low	3.1	1273	1.0	3.8	2049	1.0	8.2	1.0
Medium	5.8	1992	1.5 (1.0–2.3)	5.4	1466	1.5 (1.1–2.1)	10.0	1.4 (1.1–1.7)
High	8.1	445	2.2 (1.3–3.5)	7.3	822	2.3 (1.6–3.2)	11.4	1.6 (1.2–2.2)
Region								
North Karelia	2.2	742	1.0	3.0	737	1.0	7.2	1.0
Kuopio	5.4	794	2.6 (1.5–4.7)	5.8	765	2.0 (1.2–3.3)	9.9	1.4 (1.0–2.0)
Turku/Loimaa	5.1	746	2.5 (1.4–4.5)	3.9	724	1.3 (0.7–2.3)	8.3	1.2 (0.8–1.7)
Helsinki	7.4	715	3.7 (2.1–6.5)	7.0	698	2.5 (1.5–4.1)	11.5	1.7 (1.2–2.4)
Oulu	5.7	733	2.8 (1.5–5.0)	5.6	726	1.9 (1.1–3.3)	9.6	1.4 (1.0–2,0)
Income								
Low	2.7	1367	1.0	3.0	1586	1.0	6.8	1.0
Medium	5.5	1121	2.1 (1.4–3.2)	5.0	1379	1.7 (1.2–2.5)	9.5	1.4 (1.1–1.9)
High	7.8	1143	3.0 (2.0–4.5)	7.3	1279	2.5 (1.7–3.6)	12.0	1.9 (1.5–2.4)

Odds ratios are age adjusted.

physician. This changed reimbursement policy may have affected the treatment rate among older women but not the rate among all women in fertile age.

The proportion of tubal injuries has decreased notably and the proportion of other reasons (other female, male, multiple, unexplained) has increased. Decrease in tubal injuries may be due to decreased incidence of *Chlamydia trachomatis* infections in the late 1980s and early 1990s in Finland [21] as *C. trachomatis* causes the majority of pelvic inflammatory diseases [22]. Over one third of women infected with *C. trachomatis* in Finland are less than 20 years old and they are likely to try become pregnant about 10 years later. The number of couples treated because of male infertility increased remarkably in the period 1992–1995 as ICSI treatments were started in Finland and male infertility could be treated better.

An American study reported that the ratio of 15–44 years old women reporting impaired fecundity rose from 8% in 1982 to 10% in 1995. This increase occurred regardless of age, parity, education, marital status and ethnicity and according to the writers was probably due to delayed childbearing [5]. We could not estimate changes in subfertility as subfertility was not enquired in FINRISK 1997 study.

The overall lifetime prevalence of subfertility observed in FINRISK 2002 was 16.0%, which is parallel with previously reported cumulative prevalences [3,5–7]. However, the prevalence of ever subfertility can only be measured among postmenopausal women [3]. Women aged 50 years or more (12.6%) participating in the FINRISK 2002 survey had suffered from subfertility at some point their lives. Interestingly, this prevalence is smaller than among younger women.

Lifetime prevalence of subfertility differs by age and education: more educated women were more often subfertile. The opposite was found in an American study, where more educated women were less likely to be subfertile compared to less educated women [13]. In the United States this may be due to a higher prevalence of sexually transmitted diseases among less educated women [14]. In Finland, by contrast, this educational difference is largely due to a trend among more educated women to postpone childbearing.

Both regional (urban/rural) [15] and educational differences in the use of IVF treatments have been previously reported for Finland [16,17]. Our results for 2002 are parallel with earlier studies: self-reported use of infertility treatments or medical examinations because of infertility is also more common in urban areas and among women with high education and high household income. Regional differences in the use of hormone therapy in Finland, however, were greater in 1997 than in 2002. The diminished difference may be due to better awareness of treatments in rural areas. However, differences in use of hormone therapy by education or incomes did not change notably.

Ethnicity is another factor producing social differences in infertility services. In the United States there are significant differences in the proportions of subfertility and in the use of infertility services by ethnicity [13,14]. Lower prevalences of subfertility have been reported among Caucasian women than among non-Caucasian [13], and African American and Hispanic women had significantly more often tubal infertility [14]. Our data sources did not include information on ethnicity or race due to a national confidentiality regulation. The impact of ethnic minorities, however, is small in Finland since the proportion of first generation migrant parturients is low, less than 4% in 1999–2001 [23].

The aggregated IVF statistics used in this study cover IVF, ICSI and FET treatments given in public and private clinics in Finland. Participation in statistics is voluntary, but the participation rate was high, up to 100% in the years studied. The clinics report the data themselves which may cause bias. The cause of infertility especially may be reported differentially by different clinics. However, the statistics are generally regarded as reliable. The statistics also contain preliminary data from the previous year and in the next report this data is compared to actual data. Preliminary data and actual data are very similar and possible inaccuracies are corrected yearly.

The FINRISK 1997 and 2002 surveys are good in external validity since they are based on random population sampling [24]. In addition to this, the response rate was high. However, data is self-reported which may cause some recall or reporting bias. The differences in non-participation by background factors may also potentially bias our results. However, response rate did not differ significantly by respondent's age (73–79% in FINRISK 2002) or place of residence (71–79% in FINRISK 2002) and therefore it is very likely that the data is not significantly biased.

It is impossible to know the exact prevalence of infertility as the respondents to the FINRISK 2002 survey were not asked if they had tried to become pregnant. Therefore the prevalence of infertility from this study can be regarded as the need for infertility treatments at population level. Moreover, the FINRISK 1997 survey included only one question concerning the utilisation of hormone treatments to treat infertility. Therefore only this utilisation rate can be used when comparing the FINRISK 1997 and FINRISK 2002 surveys.

Monitoring the prevalence of subfertility and the use of infertility treatments is important, since there are no signs that the need for treatments will decrease, rather the opposite. As suggested by the EU-funded REPROSTAT project on reproductive health indicators, measuring change over time is a key element in health monitoring [25]. If countries would use the same indicators, national trend studies and international comparisons would become more reliable.

5. Conclusions

The use of infertility treatments has more than tripled in Finland 1992–2004 and the causes for treatments have

changed. There are socio-demographical differences in the use of infertility treatments as their use is more common among urban, affluent and more educated women.

Acknowledgement

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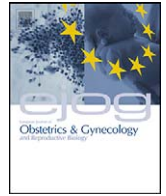
Success of infertility treatments in Finland in the period 1992–2005

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ABSTRACT

Objectives: The objective was to study the success rates of infertility treatments in the period 1992–2005 in public and private clinics.
Study design: Aggregate IVF statistics (1992–2005) and nationally representative cross-sectional survey (2002).
Results: The success rates of infertility treatments remained stable, despite a substantial increase in single-embryo transfers. In 2005, the clinical pregnancy rate was 23/100 initiated cycles and a live birth rate of 17/100 cycles. The proportions of term singletons and singletons weighing at least 2500 g improved over time and both rates were 14/100 in 2005. Pregnancy rates improved most among older women during the study period. The success rate in the private sector was significantly better than that in the public sector among women younger than 35 years.
Conclusion: The single-embryo policy has not decreased pregnancy and birth rates. The proportions of term singletons per initiated cycle and singletons weighing at least 2500 g per initiated cycle have improved over time. The higher success rate in the private sector may be because of different clientele.

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1. Introduction

Implantation rate, clinical pregnancies per cycle, and live birth delivery rate are traditional indicators for measuring the success of infertility treatments [1,2]. However, an optimal indicator should take into account not only the effectiveness of the treatments, but also their risks [3–5].

While the clinical pregnancy rate measures the quality of care in clinics, the efficiency of care can be measured by the live birth rate. Other indicators have also been developed. Min et al. introduced the concept of BESST (Birth Emphasizing a Successful Singleton at Term) to measure the success of infertility treatments [5]. The European IVF Monitoring consortium has also introduced a similar outline of "singleton delivery rate per embryo transfer" [6]. Tiitinen et al. suggested utilization of the cumulative delivery rate per stimulated cycle after all fresh or frozen embryo transfers. This indicator would take into account the role of elective one-embryo transfers and the later utilization of frozen embryos from same oocyte retrieval [4]. It has also been suggested that instead of one indicator, several endpoints should be considered simultaneously [1,2]. Pinborg et al. suggested the use of three parameters to measure the success of infertility treatments: the number of oocytes per aspiration as a pre-in vitro parameter, the number of ongoing implantations per embryo transfer as an in vitro parameter, and the number of deliveries per embryo transfer as a post-in vitro parameter [3].

Women's age and the duration of childlessness are the most important single factors to determine the outcome of infertility treatments [7,8]. According to registry data from the United States, women under 27 years of age have a live birth rate of over 40%, whereas the rate is only 6% for women over 43 years of age. Reduced pregnancy rates in older women are mainly because of the diminished ovarian function and poor egg quality [9]. Older women also have poorer implantation rates and are at an increased risk of miscarriages [10].

In general, the cause of infertility has only a limited effect on pregnancy rates. Low-ovarian response to gonadotropins independently decreases pregnancy rates. Women with polycystic ovaries (PCOS), hydrosalpinges, leiomyomata or endometriosis have even poorer success rates [8,10], likewise overweight women or smokers [11].

In Finland, the use of elective single-embryo transfers has increased notably and the twin delivery rate is now 10% [4]. In general, the implantation rate is 10–12% per embryo [12]. Elective one-embryo transfers still have good success rates. In a Finnish study based on data from a large university clinic in 1998–1999, the pregnancy rate was 40.0% after double-embryo transfer. After elective single-embryo transfer, the rate was 39% and the

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cumulative pregnancy rate after frozen embryo transfers per oocyte retrieval was 53% [13]. According to CDC data from the United States, women under the age of 35 years had a pregnancy rate of 47/100 after single-embryo transfer and 52/100 after double-embryo transfer [9].

In this study, we report the outcomes and trends of infertility treatments in Finland over the period 1992–2005. We also study the success of infertility treatments by using pregnancy rates in relation to women's age, the number of embryos transferred, and the cause of infertility, and calculated alternative success rates taking into account infant outcome.

2. Materials and methods

In this study we utilized two different data sources: national aggregate IVF statistics and a cross-sectional population study, FINRISK 2002.

2.1. Aggregate IVF statistics

Aggregate IVF statistics have been collected annually since 1992. The data were first gathered by Helsinki Central University Hospital and since 1994 by STAKES (the National Research and Development Centre for Welfare and Health). The IVF statistics used in this study consist of data on IVF, ICSI, and FET treatments (excluding donor cycles) in both the public and private sectors. Infertility treatments were given in 13 locations in 1992 and 18 in 2004. Six clinics are public.

For IVF statistics all Finnish clinics report the number of treatment cycles and pregnancies, causes of infertility, the number of embryos transferred, pregnancy, birth and newborn outcomes, complications, and congenital anomalies [14,15]. For data collection a specific questionnaire, originally designed by the International Working Group for Registers on Assisted Reproduction [16], has been in use since 1994, with minor changes in 2001 and 2005. The clinics report the aggregated data themselves. Identification numbers of the patients are not required. Two thousand five hundred treatment cycles were started in 1992 and 8200 cycles in 2005. Participation in IVF statistics was voluntary during the study period. In 1995 and 2004 all clinics participated in data collection. In 1992 and 2000, data from one clinic each year is missing as they discontinued operation during the study year.

2.2. Survey data: FINRISK 2002

FINRISK 2002 is a cross-sectional population survey gathered by the National Public Health Institute. The self-report questionnaire included questions on subfertility and the use of infertility treatments. Alternative causes of infertility given in the questionnaire were tubal injury, ovulation problems, endometriosis, male infertility, unexplained, and other. The infertility treatments elicited were hormone treatments, insemination, IVF, ICSI, FET, and other. Pregnancies and births were elicited as a treatment outcome. This data source was used to estimate lifetime success rates, which cannot be achieved using aggregate IVF statistics.

The participants of the FINRISK 2002 survey are from six areas in Finland: (1) the cities of Helsinki and Vantaa in the metropolitan area, (2) southwest Finland, (3) North Karelia, (4) Kuopio, (5) Oulu, and (6) Lapland. The population sample is random and consists of subjects aged 25–64. The response rate among women was 75.8% ($N = 4729$).

The statistical comparisons were made using a test for relative proportions and odds ratios with 95% confidence intervals.

3. Results

3.1. Aggregate IVF statistics

Fig. 1 gives the success rates calculated by different endpoints. The proportions were calculated per initiated IVF, ICSI, and FET cycle. The clinical pregnancy rate and live birth rate increased slightly. The more significant increase is in the proportion of term singletons and singletons weighing at least 2500 g. In 1992 the rates of term singletons and singletons weighing at least 2500 g were both 9 per 100 initiated cycles. In 2004 these success rates were both 14/100.

We calculated the live birth rate after IVF, ICSI, and FET separately over the time period 1994–2005 (ICSI was introduced in Finland in 1994). The live birth rate after IVF and ICSI increased slightly in the mid-1990s and remained stable thereafter. The live birth rate after FET in turn increased evenly over the period 1995–2005 and was 11% in 1995 and 17% in 2006.

The number of embryos transferred decreased notably over time. In 1992, in 14% of treatment cycles one embryo, in 41% two embryos, in 37% three embryos, and in 7% four embryos were transferred. The number of cycles with four embryos transferred decreased rapidly and after 2000 no such cycles were carried out. The ratio of single-embryo transfers also increased drastically: 51% of treatments were single-embryo transfers in 2005 (Fig. 2).

The pregnancy rates after a single-embryo transfer also increased notably in 1995–2005 ($p < 0.001$) from 10% to 24%. The pregnancy rate after two-embryo transfers remained stable (26%) over the study period. Pregnancy rates after two-embryo transfers are in 2005 even better than after single-embryo
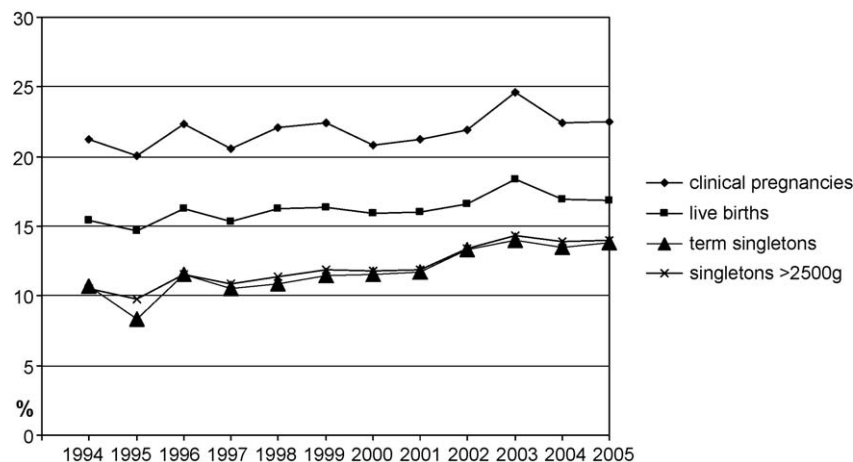

Fig. 1. Success rates after IVF, ICSI, and FET treatments over the period 1994–2005.
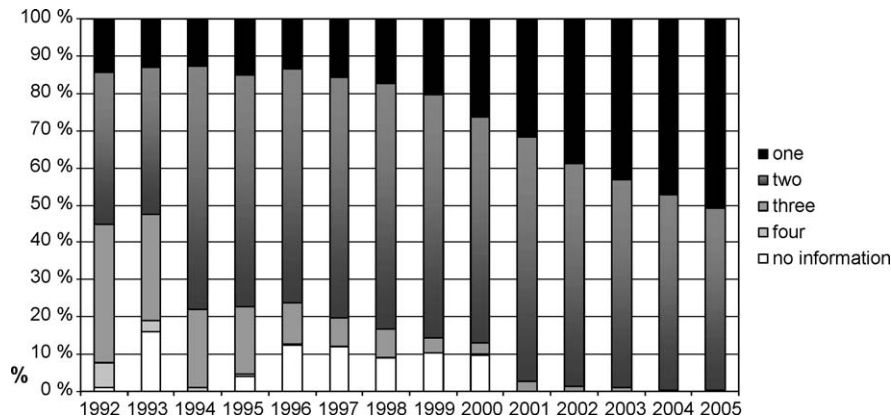
Fig. 2. Embryo transfers according to the number of embryos over the period 1992–2005.

transfers, but this difference has diminished over time (Table 1). Overall pregnancy rates remained stable during the study period (1992–2005) despite the substantial increase in single-embryo transfers (Fig. 1).

We compared success rates between the public and private sectors by calculating the clinical pregnancy rate in 1995 and 2005. There were some differences according to the cause of infertility. In 1995, the clinical pregnancy rate after all treatments was 18% in the public sector and 22% in the private sector. In 2005, the rate was 21% in the public sector and 23% in the private sector. Among women less than 35 years of age, the clinical pregnancy rate was statistically significantly better in the private sector. Also, life-birth rates in the private sector were slightly, but statistically significantly better in 2005. In Finland overall, however, care site does not have a big influence on success rates (Table 2).

When comparing success rates between the public and private sectors according to maternal age, it can be perceived that in 1995 clinical pregnancy rates were significantly better for younger women in the private sector, and 10 years later these rates in private clinics were still somewhat better. A more important finding, however, is that the difference in success rates according to age has diminished. In 1995, the clinical pregnancy rate was 6-fold for women aged under 30 years of age compared with the rate for women aged 40 or more; in 2005, this difference was only 2.3-fold (Table 2).

3.2. Survey data

Self-reported lifetime success rates were obtained from the FINRISK 2002 survey. The highest lifetime birth rate was for

women reporting ovulation problems (70%). For endometriosis the rate was 55%, for male infertility it was 42%, for tubal failure it was 41%, and for unexplained infertility it was 40%.

When different treatment options were compared, the best self-reported lifetime birth rates were achieved with hormone treatments (59%) and with ICSI (58%). For IVF and FET, the rate was 47% and for insemination 45% (Fig. 3).

The lifetime birth rate also differed according to age (at interview), but this difference was not statistically significant ($p = 0.128$). The lifetime birth rate for women aged 24–29 years was 67%, that for 30–34 years was 70%, that for 35–39 years was 47%, that for 40–45 years 56% was, that for 45–54 years was 62%, and for women aged 55 years or more it was 60%.

4. Discussion

In this study we demonstrated that, despite a remarkable decrease in embryos transferred per cycle, pregnancy rates remained stable. We also found increased pregnancy rates, especially for women aged 40 years or more. Differences in success rates between the private and public sectors were small but statistically significant among women less than 35 years of age. The difference is clinically significant, but may be because of the different clientele. According to our study, the self-reported lifetime birth rate was, depending on the cause of infertility, 40–70%.

In Finland, the overall clinical pregnancy rate (IVF, ICSI, and FET) was 23% and the live birth rate 17% in 2005. These success rates are comparable with European success rates, but poorer than success rates reported from the United States. The aggregate clinical pregnancy rate for all European countries in 2001 was 24% and the live birth rate 17%. In the United States, the clinical pregnancy rate in 2001 was 33% and the live birth rate 27% [17]. However, it is noteworthy that in Finland the proportion of frozen embryo transfers is almost three times greater than that in Europe or in the United States and the success rates after FET are significantly lower than those after IVF or ICSI. Also, it is common in the United States to select embryos, conduct oocyte donation cycles, and perform genetic diagnosis prior to implantation [17]. These procedures may improve the quality of embryos transferred and thus also success rates.

These days in Finland, the general method of conducting infertility treatments is to provide IVF or ICSI treatment and freeze extra embryos. Subsequent cycles can thus be conducted as FET cycles as a part of a seamless chain of care. This manner is cost effective and also easier for the couple treated.

Thus, the role of elective single-embryo transfers has been strongly emphasized in recent years in Finland. According to this procedure only a single embryo is transferred and other embryos are frozen and used in later cycles. Our data show that in 2005, in

Table 1
Clinical pregnancy rates after single, two, three and four embryo transfers.

	Number of cycles	Clinical pregnancies	%	p
1995				
One	656	67	10.2	
Two	2707	730	27.0	0.02
Three	779	214	27.5	0.02
Four	42	11	26.2	0.05
2000				
One	1803	379	21.0	
Two	4099	1067	26.1	0.01
Three	327	84	25.7	0.02
Four	6	1	16.7	
2005				
One	3632	874	24.1	
Two	3476	956	27.5	0.001
Three	19	6	31.6	0.09
Four	1	0	0	

Table 2
Clinical pregnancy rate per 100 cycles by maternal age and the cause of infertility and the outcome of pregnancies.

	1995				2005			
	PUBLIC (%)	PRIVATE (%)	p^a	OR^b (95% CI)	PUBLIC (%)	PRIVATE (%)	p^a	OR^b (95% CI)
Maternal age								
<30	20.4	34.7	<0.001	6.1 (3.8–9.8)	24.0	30.6	0.02	2.3 (1.8–3.0)
30–34	20.3	32.3	<0.001	5.5 (3.4–8.7)	23.6	31.1	<0.01	2.3 (1.8–3.0)
34–39	20.0	24.3	0.13	4.4 (2.9–7.4)	24.1	25.1	0.70	2.0 (1.5–2.6)
≥40	3.3	6.9	0.16	1	12.0	14.3	0.70	1
Cause of infertility								
Tubal	19.2	25.3	0.05		25.1	21.6	0.38	
Other female	19.0	23.4	0.29		21.5	29.1	<0.01	
Male	23.5	25.8	0.46		26.6	26.4	0.80	
Multiple	17.3	22.5	0.30		23.9	25.4	0.55	
Unexplained	13.3	26.7	<0.001		23.9	26.0	0.46	
Outcome of pregnancy								
Live birth	74.5	72.7	0.52		75.4	76.1	0.02	
Spontaneous abortion (<22 gw)	19.9	23.9	0.13		20.3	20.1	<0.01	
Ectopic pregnancy	4.0	2.9	0.34		3.3	2.8	<0.01	
Induced abortion	0.3	0.5	0.63		0.7	1.0	<0.01	
Stillbirth (22–27 gw)	1.3	0	<0.001		0.1	0	<0.01	
Stillbirth (≥28 gw)	0	0			0	0.1	<0.01	
TOTAL	17.5	21.8	<0.001		21.1	23.3	0.02	

[a] When comparing success rates in public and private clinics.
[b] When comparing overall success rates (both public and private) by maternal age.

almost half of embryo transfers only a single embryo was transferred. Hence, it is remarkable that despite a significant decrease in embryos transferred per cycle, pregnancy rates have remained the same for years. In fact, according to recent studies, similar pregnancy rates can be achieved after single-embryo transfer compared with double-embryo transfers [8,13]. In Finland, 1587 elective single-embryo transfers were conducted in 2006 (the most recent data at the time of writing) with high-clinical pregnancy rates (34%) and live birth rates (26%) [18] It has also been demonstrated that pregnancy rates peak when two embryos are transferred and only multiple gestations are increased when more than two embryos are transferred [19]. However, twin pregnancies are also a medical problem. Despite the Finnish method of strongly emphasizing the role of single-embryo transfers, 10% of pregnancies after infertility treatments are twin pregnancies, as the proportion in naturally conceived pregnancies is only 1.2%.

Therefore, it is paradoxical that despite similar success rates, in as many as 32% of American and 6% of European cycles four or more embryos are still transferred [17]. In Finland, only sporadic three-embryo transfers are made and four or more embryos are never transferred. In the United States, the transfer of multiple embryos is at least partly caused by the lack of insurance coverage for infertility treatments: Jain et al. showed that in the United States there was an association between state-mandated insurance
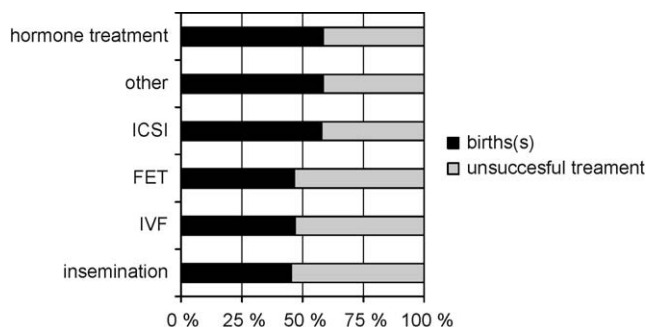
coverage and the number of embryos transferred [20]. Thus, despite higher pregnancy and live birth rates in the countries conducting three- or four-embryo transfers, the modern success rates measuring the proportion of term singletons in those countries are quite poor.

Our data demonstrated that proportions of term singletons per cycle and singletons weighing at least 2500 g per cycle have increased. This increase in term singletons is noteworthy, as 57% of IVF twins are preterm and 55% have low-birth weight [21]. The infant mortality rate is also 5.3-fold for multiple gestations [21]. Multiple gestations also increase babies' risk of respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular bleeding, cerebral palsy, and pneumonia [22]. For women, multiple gestations in turn increase the risk of hypertension, postpartum bleeding, cesarean sections, and maternal mortality [8].

It is also remarkable that subfertility itself seems to have a deleterious effect on pregnancy outcomes. It has been demonstrated that previously subfertile women delivering singletons are at increased risk of pre-eclampsia and antepartum bleeding compared with controls when age and parity are assessed [23]. Moreover, singletons born after infertility treatments are at increased risk of low-birth rate and prematurity compared with naturally conceived babies [24].

From the IVF statistics used in this study it is not possible to calculate cumulative success rates, as data are aggregated and no single treatment cycle or subfertile woman can be identified. Thus, we used the cross-sectional population survey FINRISK 2002 to estimate the self-reported lifetime birth rate. In our study, the lifetime birth rate was the lowest, 40%, for women suffering from unexplained infertility and the highest, 70%, for women with ovulation problems. Our birth rates were in line with earlier studies, which have reported cumulative pregnancy rates ranging from 48% to 87% [25–29].

The aggregated IVF statistics used in this study cover IVF, ICSI, and FET treatments given in public and private clinics in Finland 1992–2005. Participation in the IVF statistics was high, up to 100%, despite voluntary reporting. Some bias may, however, occur as the clinics report data themselves, and, for example, there are no generally accepted guidelines on how to define the cause of infertility, for example. In addition, the live birth rates per maternal

Fig. 3. Self-reported lifetime birth rates according to treatments.

age, cause of infertility, and number of embryos transferred were collected in 2005 for the first time, and we were not able to use this in our trend comparisons. In general, however, IVF statistics are regarded as reliable [30]. The response rate to FINRISK 2002 was high, but it is still possible that the differences in non-participation according to background factors may cause bias. Moreover, the data are self-reported, which may have caused some recall or reporting bias.

5. Conclusion

The single-embryo policy has not decreased pregnancy and birth rates. Proportions of term singletons per initiated cycles and singletons weighing at least 2500 g per initiated cycle have improved over time. The higher success rate in the private sector may be because of the different clientele.

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human reproduction

ORIGINAL ARTICLE *Psychology and counselling*

Psychiatric disorders leading to hospitalization before and after infertility treatments

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BACKGROUND: This study aimed at determining the psychiatric morbidity of women undergoing infertility treatments, before and after treatment as compared with control women.

METHODS: The number of women hospitalized because of psychiatric disorders was obtained from the Hospital Discharge Register (1969–2006) in a cohort of women who purchased drugs for *in vitro* fertilization, intra-cytoplasmic sperm injection or frozen embryo transfer treatments ($n = 9175$) in 1996–1998 in Finland and their controls ($n = 9175$). The age- and residence-matched controls were further adjusted in the analysis for socio-economic position and marital status.

RESULTS: Women with infertility treatments had fewer hospitalizations due to depression, psychotic disorders, personality disorders, anxiety disorders, bipolar disorder or mania, eating disorders, adjustment disorders and alcohol or other intoxicant abuse before their treatments than did controls. However, the difference was statistically significant only for psychotic disorders [Odds ratios (OR) 0.38, 95% confidence intervals (CI) 0.20–0.72]. Differences in hospitalization remained similar also during the 10-year post-treatment follow-up. The exceptions were increased risk of hospitalizations due to adjustment disorders (OR 3.43, 95% CI 1.03–11.4) and decreased risk of alcohol or other intoxicant abuse (OR 0.44, 95% CI 0.25–0.75) among the women with infertility treatments. The infertile women who gave birth had fewer hospitalizations for all psychiatric diagnoses than did infertile women who did not have a baby. The difference was statistically significant for anxiety disorders (OR 0.38, 95% CI 0.18–0.81), depression (OR 0.63, 95% CI 0.41–0.96) and alcohol or other intoxicant abuse (OR 0.38, 95% CI 0.18–0.80). Hospitalizations among infertile women who did not have a baby and controls were similar, with the exception of significantly more hospitalizations for psychotic disorders among controls (OR 0.38, 95% CI 0.19–0.77).

CONCLUSIONS: Women treated for infertility had less serious psychiatric morbidity leading to hospitalization than did the controls, both before and after treatments, suggesting a healthy patient effect. After treatments, the risk of hospitalization due to adjustment disorders was increased among the infertile women. Having a baby after infertility treatments was associated with fewer hospitalizations following psychiatric diagnosis.

Key words: assisted reproduction / epidemiology / infertility

Introduction

Infertility is a common medical and social problem that affects 10–15% of couples in the course of their lifetime (Evers, 2002; Gnoth *et al.*, 2005). Grief and emotional distress are understandable and expected responses to infertility, as it can be regarded as a loss by the couple (Burns, 2007). Many couples have found infertility the most upsetting experience of their lives (Guerra *et al.*, 1998).

Even if a person with decreased fertility or infertility does not suffer from a psychiatric disorder, some emotional distress related to

infertility itself and infertility treatments can be expected. The most common reactions are shock, anger, guilt, marital distress, lowered self-esteem, sexual dysfunction and social isolation (Burns, 2007). The decision whether to start infertility treatments is also a difficult one, and it may provoke anxiety. Negative emotions and stress also vary during the course of treatment procedures (Hammarberg *et al.*, 2001; Verhaak *et al.*, 2007).

Previous studies have reported a high prevalence of depression and anxiety disorders among women receiving infertility treatments, but

Table I Socio-economic and marital status of IVF women and their controls (at the time of infertility treatments).

	IVF women in register study (n = 9175), %	Control women in register (n = 9175), %	P-value
Socio-economic position			<0.001
Upper white-collar worker	25.3	16.3	
Lower white-collar worker	48.5	45.6	
Blue-collar worker	16.2	19.3	
Student, self-employed, unemployed	7.9	12.3	
Unknown	2.1	6.4	
Marital status			<0.001
Married	69.4	45.3	
Unmarried	22.3	32.7	
Divorced	7.9	8.9	
Widow	0.4	0	
Unknown	0	13	

the estimates vary widely. This can, at least partly, be explained by variation in diagnostic criteria for the disorders, data collection methods and differences in the backgrounds of the infertile couples in regard of matters such as duration of childlessness or number of prior treatments. These varied within the studies as well as between them. At least mild depression has been reported in 12–54% of women during infertility treatments (Newton *et al.*, 1990; Domar *et al.*, 1992; Matsubayashi *et al.*, 2001; Fassino *et al.*, 2002; Lok *et al.*, 2002; Chen *et al.*, 2004; Volgsten *et al.*, 2008). Also, 12–23% of women have been reported to have anxiety disorders (Newton *et al.*, 1990; Sbaragli *et al.*, 2008; Volgsten *et al.*, 2008).

Previous studies suggest that the prevalence of symptoms of depression and anxiety disorders among women participating in infertility treatments is relatively high. We wanted to study whether the psychiatric morbidity of infertility-treatment-seeking women differs from that of controls both before and after infertility treatments. The impact of successful infertility treatment was also evaluated; hospitalizations were compared between the infertile women who gave birth and those who did not.

Materials and Methods

We utilized a cohort of women who had received *in vitro* fertilization (IVF), intra-cytoplasmic sperm injection (ICSI) or frozen embryo transfer (FET) treatments in 1996–1998 (n = 9175) in Finland (Klemetti *et al.*, 2005). This IVF cohort was identified from reimbursement files for women who had bought drugs or combinations of drugs that are specific to infertility treatments and typically used at the beginning of treatments. The cohort covers practically all women who received IVF treatments during the chosen time period in Finland. The creation of the algorithm has been previously described (Hemminki *et al.*, 2003).

For the IVF cohort population, controls (n = 9175) matched by age and municipality were randomly taken from the Social Insurance Institution's population register including all Finnish citizens and permanent residents. The controls were further adjusted for marital status and socio-economic position for the analysis. The background characteristics of the women with and without infertility treatments are presented in Table I. The sample of women having had infertility treatments had a larger proportion of upper-level white-collar workers and married women than the control group did.

The hospitalization episodes of the IVF cohort and their controls were searched for in the Hospital Discharge Register, using the personal identification code as the linkage key. This register is currently maintained by THL (the National Institute for Health and Welfare), previously by STAKES (the National Development and Research Centre for Welfare and Health). It contains data on all in-patient care given (since 1969) and all out-patient visits that involve procedures (since 1994). The search included all hospitalizations before and after infertility treatments from 1 January 1969 to 31 December 2006. Since 1996, diagnoses were reported according to the ICD-10 classification (International Classification of Diseases, 10th revision). For earlier hospitalizations, ICD-9 (1987–1995) and ICD-8 (1969–1986) were used.

For this study, all psychiatric diagnoses were identified and the main diagnosis for each hospitalization was used. Each patient was considered one case regardless of the number of hospitalizations recorded for the same diagnosis. If a woman had many hospitalizations for different main diagnoses, she was counted several times and categorized according to each main diagnosis. The time of infertility treatments was a cut-off point for each patient, and if she had post-treatment hospitalizations for the same diagnoses as before treatments she was counted again for the same diagnosis. There were 150 hospitalizations among 81 persons whose main diagnosis was reported according to both ICD-9 and ICD-10 for the same hospitalization where those diagnoses differed significantly. These hospitalizations were excluded from the study.

The diagnoses were divided into eight categories: psychotic disorders, depression, bipolar disorder or mania, anxiety disorder (including also obsessive-compulsive disorder, dissociative disorders, somatization disorder and other neurotic disorders), personality disorder, eating disorder, alcohol or other intoxicant abuse and adjustment disorder. The classifications are presented in Table II. The diagnoses of organic mental disorders (F00–F09), mental retardation (F70–F79), disorders of psychological development (F80–89) and behavioural or emotional disorders of childhood or adolescence (F90–99) occasionally diagnosed among controls were excluded from the study.

Among infertile women, data about births after infertility treatments until the end of 1999 were obtained from the nationwide Medical Birth Register covering all births in Finland, and by recording women's ID numbers.

Table II Classification of the diagnoses in different categories (ICD-8, ICD-9, ICD-10).

Category	ICD-8	ICD-9	ICD-10
Alcohol or intoxicant abuse	291.00, 291.10, 291.20, 291.30, 291.98, 291.99, 294.30, 303.00, 303.10, 303.20, 303.98, 303.99, 304.00, 304.10, 304.20, 304.30, 304.40, 304.50, 304.60, 304.70, 304.88, 304.99	2913, 2914, 2918, 2928, 303, 3039, 3040, 3041, 3042, 3043, 3044, 3045, 3046, 3049, 3050, 3051, 3052, 3053, 3054, 3055, 3056, 3057, 3059	F10−19
Psychotic disorders	295.00−295.99, 297.00, 297.10, 297.98, 299.99,	2951−2959, 297, 298	F20−29
Bipolar disorder and mania	296.10, 296.20, 296.30, 296.88, 296.99	2962, 2960, 2964, 2967,	F30−F31
Depression	296.00, 300.40, 300.41	2961, 2963, 3004, 2968	F32−F39
Anxiety disorders	300.10, 300.20, 300.30, 300.50, 300.60, 300.70, 300.88, 300, 99	3002, 3003, 3007, 3008, 3009	F40−42, F44, F45, F48
Adjustment disorders	307.99	309	F43
Eating disorders		3071, 3075	F50
Personality disorders	301.00, 301.10, 301.20, 301.30, 301.40, 301.50, 301.60, 301.70, 301.80, 301.88, 301.99	3010, 3011, 3012, 3014, 3015, 3016, 3017, 3018,	F60−62

Table III Number of hospitalizations for psychiatric diagnoses before and after treatments among 9175 women receiving infertility treatments and 9175 age- and residence-matched controls, with OR (95% CI) adjusted for marital status and socio-economic position.

	Before treatments (1969−1996/8)				After treatments (1996/8−2006)			
	IVF	Controls	OR	CI (95%)	IVF	Controls	OR	CI (95%)
Anxiety disorders	26	37	0.70	0.33−1.48	39	55	0.68	0.40−1.55
Depression	63	106	0.73	0.49−1.10	101	121	0.84	0.64−1.16
Bipolar disorder or mania	11	17	1.02	0.26−4.0	20	29	0.75	0.34−1.63
Psychotic disorders	33	94	0.38	0.20−0.72	33	106	0.45	0.28−0.73
Personality disorders	30	63	0.57	0.30−1.04	15	36	0.73	0.31−1.71
Alcohol and other intoxicants	36	65	0.81	0.47−1.41	41	86	0.44	0.25−0.75
Eating disorders	8	10	3.28	0.23−46	4	4	1.0	
Adjustment disorders	27	29	1.04	0.52−2.10	20	16	3.43	1.03−11.4

The statistical comparisons were made by using logistic regressions and conditional logistic regressions. Odds ratios (OR) were calculated with 95% confidence intervals (CI). We adjusted the number of hospitalizations for psychiatric diagnoses for the women's marital status and socio-economic position at the time of the infertility treatments.

Results

Before infertility treatments, the most common psychiatric disorders among infertile women were depression and alcohol and other intoxicant abuse (Table III). Among the controls, the most common diagnoses were depression and psychotic disorders. The women in the control group had significantly more hospitalizations for psychiatric disorders than the women with infertility treatments. The greatest difference was found for the prevalence of psychotic disorders (OR 0.38, 95% CI 0.20−0.72). The control population also had more depression, personality disorders, bipolar disorder or mania, anxiety

disorders and alcohol and other intoxicant abuse, but these differences were statistically insignificant after adjustment for socio-economic position and marital status. The prevalence of adjustment and eating disorders was similar.

The main finding was also similar after the treatments (Table III), but the difference with regard to alcohol and intoxicant abuse was now statistically significant (OR 0.44, 95% CI 0.25−0.75). Adjustment disorders, in turn, were statistically significantly more common among infertile women (OR 3.43, 95% CI 1.03−11.4).

The infertile women who gave birth after infertility treatments had fewer hospitalizations for all diagnoses than did those infertile women who did not have a baby (Table IV). The number of hospitalizations among infertile women without a baby after the treatment and non-treated controls did not differ significantly for any diagnosis with the exception of psychotic disorders. Infertile women had fewer hospitalizations due to psychotic disorders when compared with control women.

Table IV Number and proportion of women with hospitalization for psychiatric diagnoses after treatments among women with infertility treatments with and without births during the study period and non-treated controls (matched for age and residence), with OR (95% CI), adjusted for age, marital status and socio-economic position.

	Infertile women with births n (%)	Infertile women without births n (%)	Controls n (%)	Infertile women with and without births: OR (95% CI)	Infertile women without births and controls: OR (95% CI)
Anxiety disorders	9 (0.2)	30 (0.6)	29 (0.6)	0.38 (0.18–0.81)	0.87 (0.45–1.69)
Depression	33 (0.8)	68 (1.4)	57 (1.3)	0.63 (0.41–0.96)	1.22 (0.79–1.89)
Bipolar disorder or mania	8 (0.2)	12 (0.2)	13 (0.3)	0.90 (0.36–2.25)	0.85 (0.29–2.54)
Psychotic disorders	13 (0.3)	20 (0.4)	57 (1.2)	0.88 (0.42–1.80)	0.38 (0.19–0.77)
Personality disorders	5 (0.1)	10 (0.2)	14 (0.4)	0.56 (0.19–1.68)	1.80 (0.35–9.20)
Alcohol and other intoxicants	9 (0.2)	32 (0.6)	43 (0.9)	0.38 (0.18–0.80)	0.80 (0.40–1.60)
Eating disorders	1 (0)	3 (0.1)	3 (0)	0.30 (0.03–2.92)	1.00
Adjustment disorders	8 (0.2)	12 (0.2)	9 (0.2)	0.82 (0.33–2.05)	1.01 (0.20–5.09)

The number of hospitalizations for adjustment disorders did not differ in comparison of the formerly infertile women who delivered multiples to other infertile women (OR 1.12, 95% CI 0.26–4.88).

Discussion

In this study, we found that women receiving infertility treatments had less psychiatric morbidity leading to hospitalizations than their control group after matching and adjustment for age, municipality, socio-economic position and marital status. The results were similar before and after they entered infertility treatments with the exception of significantly more adjustment disorders arising among the women with infertility treatments after their treatments. The infertile women who gave birth after treatments had fewer hospitalizations for all psychiatric diagnoses than those infertile women who did not. Furthermore, infertile women not having a baby after the treatment had fewer hospitalizations than control women did.

We used a cohort of women who had purchased infertility drugs that are not used for other purposes in these combinations. Therefore, this cohort very probably includes all Finnish women who entered IVF, ICSI or FET treatment in 1996–1998. The number of cases in 1996–1998 was as high as 9175, and, therefore, the number of women with psychiatric diagnoses was also significant.

A limitation of our study was that only severe psychiatric morbidity was captured, because hospitalization due to the disorder was required. Many milder cases that are treated in out-patient care with, for example, medication and/or psychotherapy are therefore not included in this study. Even though our study underestimates the incidence of psychiatric disorders, there is no reason to presume that different proportions of disorders among infertile women and the controls would be treated differently in terms of in-patient and out-patient care. This is, therefore, unlikely to cause any bias due to a difference between the groups.

Probably our results of fewer psychiatric hospitalizations among the women with infertility treatments can at least partly be explained by the healthy patient effect. Women planning pregnancy tend to be physically and mentally quite healthy. The desired number of children among women with severe psychiatric disorders may be smaller, or they may be more reluctant to start infertility treatments. The background information for our subjects supports this, as women participating in infertility treatments were more often married and upper-level white-collar workers. In the analysis, we adjusted for marital status and socio-economic position, but some residual confounding may have remained. The healthy patient effect has also been reported for mortality of IVF patients (Venn et al., 2001).

Our study population consists of those infertile women who sought medical help. It is possible that these women differ from those infertile women who do not participate in infertility treatments. A study by Hammarberg et al. (2001) showed that it may be difficult to make the decision to start infertility treatments and it is possible that some infertile women suffering from psychiatric disorders do not have sufficient strength to make that decision.

In our study, the largest difference in prevalence between the infertile women and the controls was observed for psychotic disorders, which were three times more prevalent among the control group. The women with the psychotic disorders have lower fertility than controls do (McGrath et al., 1999; Howard et al., 2002; Howard, 2005; MacCabe et al., 2009), but this difference has diminished over the years (Howard, 2005) as a greater proportion of schizophrenia patients are treated on an out-patient basis. It is not known whether nulliparous women with schizophrenia do not want to have children or are actually infertile. Furthermore, it is possible that women with psychotic disorders willing to get pregnant have to face more prejudice than other women and they need justify more to other people that they 'are allowed' to get pregnant or to participate in infertility treatments. Infertility among patients with psychotic disorders may also be elevated, as many neuroleptics cause hyperprolactinaemia and impair ovulation (Dickson et al., 2005).

Mood disorders and fertility are linked to each other in many ways. A review article by Williams et al. (2007) concludes that women with

mood disorders had a lower observed number of children as compared with the expected number. However, it cannot be distinguished whether this is due to infertility, voluntary childlessness or social factors such as lack of a sexual relationship. With respect to the last of these, study by Harlow et al. (2003) suggests that depressive women have an increased risk of divorce and widowhood.

Biological and pharmacological interactions between mood disorders and fertility have also been studied (Williams et al., 2007). According to two studies, women suffering from bipolar disorder may have menstrual problems even before use of mood stabilizers (Rasgon et al., 2005; Joffe et al., 2006). For unipolar depression, the evidence is inconsistent (Rowland et al., 2002; Harlow et al., 2004; Joffe et al., 2006). However, the use of selective serotonin re-uptake inhibitors may potentially influence fertility, as the medication can decrease libido and increase the risk of spontaneous miscarriages (Williams et al., 2007).

Due to this complex interaction, infertility could be more actively taken into consideration when treating patients with psychiatric problems. Infertility clinics in turn should pay more attention to previous history of psychiatric disorders among their patients and provide more intense support during infertility treatments.

According to our study, adjustment disorders were equally common among infertile women and controls before treatments but more common among infertile women after treatments. This disorder evolves typically in response to stress and grief and is therefore understandable among infertile females. The larger numbers of hospitalizations due to adjustment disorders after infertility treatments could be explained as a result of unsuccessful treatment, or more stressful child-care, as the number of multiple births after infertility treatments is elevated. Our results support the impact of unsuccessful treatments but not that of twins causing extra stress.

As infertility and participation in infertility treatments often cause stress and negative emotions, it would be expected that the outcome of treatments affects the mental health of infertile women. In a study by Hammarberg et al. (2001), psychological symptoms among infertile women did not differ by outcome of treatments. However, in a study by Klemetti et al. (2010), risk of psychiatric disorders was not increased among *formerly* infertile women with a child, even though infertile women without a child had an increased risk of anxiety disorders and dysthymia. Also Verhaak et al. (2007) reported in their study that infertile women who gave birth had significantly less anxiety and depression. In our study, risk of hospitalizations for psychiatric disorders was higher among those infertile women who did not give birth than among those who did. Thus, our data suggest that unsuccessful treatments seem to expose women to psychiatric disorders whereas formerly infertile women with a child had fewer hospitalizations.

Conclusions

Women receiving IVF treatments had lower psychiatric morbidity leading to hospitalization than did women in a control group of similar age and municipality after socio-economic and marital status are taken into account. Having a baby after infertility treatments was associated with fewer hospitalizations for psychiatric diagnosis.

Authors' roles

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Cancer morbidity in a cohort of 9,175 Finnish women treated for infertility

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Abstract

Background: Results of earlier studies on cancer risk in infertile women are inconsistent for many cancer types. Our goal was to study cancer incidence among a cohort of women treated with in vitro fertilization (IVF), including intra cytoplasmic sperm injection (ICSI) and frozen embryo transfer (FET), compared to that of a control population.

Methods: A cohort of women who purchased drugs for IVF (including ICSI and FET treatments, N=9,175) in the period 1996-1998 in Finland (later called IVF women) and their age and residence matched controls, further adjusted for socio-economic position and marital status, were linked to the Finnish Cancer Registry 1996-2004.

Results: The overall cancer incidence and combined incidence of hormonal related breast, uterine and invasive ovarian cancers were similar among IVF women and controls. IVF women had statistically significantly less cervical cancer (OR 0.51, 95% CI 0.30-0.85), but more skin cancers other than melanoma (OR 3.11, 95% 1.02-9.6). IVF women had three times more invasive ovarian cancers than controls, but this difference was not statistically significant, possibly due to the small number of cases. IVF women had slightly fewer breast cancers but difference was likewise not statistically significant. All cases of pulmonary cancer were diagnosed among controls (p=0.03).

Conclusions: General cancer risk or risk of hormonal related cancers in IVF women was not increased. The differences in certain cancers suggest a healthy patient effect or may be partly caused by residual socio-economic differences. More large studies and re-analysis of existing studies are needed to evaluate cancer risk among infertile women by sub-groups regarding the cause of infertility. When evaluating risk of cancer after drug exposure dosage and the use of different medicaments should be taken into consideration.

Key words: infertility, infertility treatments, cancer incidence

Introduction

Many gynaecological diseases such as polycystic ovaries syndrome or endometriosis cause significant changes in the body's hormonal or inflammatory balance. These imbalances may predispose to fertility problems but could potentially also promote cancer development (Klip et al. 2000). During hormonal infertility treatments exogenous drugs affecting the hormonal system are administered. The risk of cancer among infertile women has been explored in many studies but for many cancer types the results are inconsistent and partly contradictory. Much of this is caused by methodological weaknesses including too small number of cases weakening the statistical power.

According to three cohort studies the overall cancer incidence among infertile women compared to general population was slightly increased. Modan et al. (1998) studied a cohort of 2,496 infertile women and reported a standardized incidence ratio (SIR) of 1.20 (95% CI 1.0-1.5) for all cancers. In a large Danish cohort study among 54,362 infertile women parity-specific SIR for all cancers was 1.04 (95% CI 1.00-1.09) (Jensen et al. 2008) and in an American study among 12,193 infertile women SIR was 1.23 (95% CI 1.1-1.3) (Brinton et al. 2005). However, in other cohort studies (population size 1,082-5,556 women) the cancer incidence did not differ significantly (Doyle et al. 2002) (Dor et al. 2002) (Lerner-Geva et al. 2003).

Most studies exploring the risk of cancer in infertile women have focused in hormonal related gynaecological and breast cancers. Twenty years ago American researchers combined data from several case-control studies and reported that a risk for the borderline tumours of the ovary was increased among infertile women and that invasive ovarian cancers were more common among women who had taken fertility drugs (Harris et al. 1992, Whittemore et al. 1992). Increased risk for borderline tumours of the ovary among infertile women has also been reported in two other studies: a cohort study by Rossing et al. (1994), SIR 3.3 (95% CI 1.1-7.8), and a case-control study by Shushan et al. (1996) adjusted OR 9,38 (95% CI 1.66-52.08). The results for invasive ovarian cancer are inconsistent. Seven earlier cohort studies (population sizes 2,496-29,700) did not report elevated risk among infertile women compared to general population (Rossing et al. 1994, Venn et al. 1995, Shushan et al. 1996, Parazzini et al. 1997, Modan et al. 1998, Venn et al. 1999, Doyle et al. 2002) but two cohort studies (population sizes 12,193 and 54,362) reported statistically significantly elevated SIR: Brinton et al. (2004) SIR 1.98 (95% CI 1.4-2.6) and Jensen et al. (2008)

SIR 1.46 (95% CI 1.24- 1.71). In a case-control study by Mosgaard et al. (1997) SIR 2.7 (95% CI 1.3-5.5) and in a survey by Tworoger et al. (2007) SIR 1.36 (95% CI 1.07-1.75) was reported.

According to eight studies the risk of breast cancer among infertile women compared to that of general population was not significantly increased (Venn et al. 1995, Braga et al. 1996, Modan et al. 1998, Venn et al. 1999, Ricci et al. 1999, Dor et al. 2002, Doyle et al. 2002, Pappo et al. 2008). The population size of the cohort studies varied between 2,469 and 10,358 women and in the case-control studies 2,569-3,415 cases. However, in a cohort study by Brinton et al. (2004) exploring the risk among 12,193 infertile women SIR was 1.29 (95% CI 1.1-1.4) and in a study among 54,362 infertile women SIR 1.08 (95% CI 1.01-1.16) was reported (Jensen et al. 2008).

The risk for uterine cancer among infertile women also varies according to different studies. Three cohort studies reported statistically significantly increased risk (Venn et al. 1995, Modan et al. 1998, dos Santos Silva et al. 2009). In addition, according to two studies the risk was increased among females with unexplained infertility (Venn et al. 1995, Venn et al. 1999). However not all studies have reported elevated risk. According to two case-control studies (Benshushan et al. 2001, Brinton et al. 2007) and three cohort studies (Venn et al. 1999, Doyle et al. 2002, Jensen et al. 2008) the risk for uterine cancer did not differ statistically significantly from that of general population.

Cancer risk related to use of infertility drugs has also been studied. According to a study by Doyle et al. (2002) the use of infertility drugs did not increase the overall cancer risk compared to the non-exposed infertile women. However, in a cohort study by Calderon-Margalit et al. (2009) among 15,030 women the hazard ratio of all cancers among parous women treated with infertility drugs compared to other parous women was significantly increased (HR 1.36, 95% CI 1.06-1.74).

According to a cohort study by Calderon-Margalit et al. (2009) the risk for uterine cancer after infertility drug use compared to other parous women was increased. A study by Jensen et al. (2008) reported elevated risk after exposure for gonadotrophins and more than six cycles of clomiphene citrate even though the risk after any infertility drug use was not elevated. In cohort studies by Venn et al. (1999), Doyle et al. (2002), Althuis et al. (2009) and dos Santos Silva et al. (2009), however, uterine cancer risk after infertility drug use was not increased.

Previous studies exploring the risk of cancer after infertility drug use have suggested that the general risk for breast cancer compared to either general population or other un-treated infertile

women is not statistically significantly increased (Venn et al. 1995, Rossing et al. 1996, Potashnik et al. 1999, Ricci et al. 1999 Venn et al. 1999, Doyle et al. 2002, Burkman et al. 2003, Brinton et al. 2004 Gauthier et al. 2004, Calderon-Margalit et al. 2009, dos Santos Silva et al. 2009). The general risk of invasive ovarian cancer after infertility drug exposure is likewise not increased (Venn et al. 1995, Mosgaard et al. 1997, Parazzini et al. 1997, Modan et al. 1998, Venn et al. 1999, Parazzini et al. 2001, Doyle et al. 2002, Ness et al. 2002, Brinton et al. 2004, Calderon-Margalit et al. 2009, Sanner et al. 2009, Jensen et al. 2009, dos Santos Silva et al. 2009). Studies by Ness et al. (2002) and Sanner et al. (2009), however, reported statistically significantly elevated risk for borderline tumours of the ovary, SIR 2.43 (95% CI 1.01-5.80) and SIR 3.61 (95% CI 1.45-7.44), respectively. A few studies also suggests, that the risk for breast or invasive ovarian cancers may be elevated after certain drug exposure (Lerner-Geva et al. 2006, Jensen et al. 2007, Sanner et al. 2009).

In this study we compared cancer risk among women receiving IVF treatments to that of control women drawn from the general population. We studied cancer risk in general and separately for different cancer types.

Materials and methods

As the exposed population we used a cohort of women who received in vitro fertilization (IVF, also including intra cytoplasmic sperm injection ICSI and frozen embryo transfer FET) treatments 1996-1998 in Finland (N=9175). In this study these women are called IVF women. The creation of this cohort has been described earlier (Hemminki et al. 2003). In brief, the women were identified from the reimbursements for drugs or drug combinations that are specific to these infertility treatments. Each woman having received one of these treatments was recorded once in the cohort regardless the number of drug purchases 1996-1998. It has previously been estimated that the cohort covers practically all Finnish women who received IVF, ICSI or FET treatments 1996-1998 (Klemetti et al. 2005).

The control women were randomly picked from the Population Register maintained by the Social Insurance Institution and matched by age and municipality. The information on marital status and socio-economic position at the beginning of the study period was collected from the Central Population Register. In this national register socio-economic position is self-reported and based on occupation. It was further classified into four categories in the National Research and Development Centre for Welfare Health (currently National Institution for Health and Welfare): upper white-

collar worker, lower white-collar worker, blue-collar worker and other. For women temporarily at home, e.g. on maternity leave, socio-economic position is based on their occupation before the leave. Housewives who are permanently at home are included to the class "Other". The socio-economic position and marital status varied between the groups (Table 1) and thus for the analysis we further adjusted women for these determinants.

In order to identify cancer cases, IVF women and their controls were linked to the Finnish Cancer Registry. This is a nationwide registry that collects information on all cancers and cancer deaths. The coverage of the registry is considered very good: according to an earlier study, it records 99% of solid tumours (Teppo et al. 1994). We collected all cancer cases reported among the IVF women and controls from 1996 to 2004. Cancers diagnosed before IVF treatments were excluded, for the controls, the beginning of IVF treatments of the matched IVF woman was used.

The cancer cases were divided into 12 categories (ICD-10 code in brackets): breast cancer (C50); invasive ovarian cancer (C56); borderline tumours of the ovary (C56) cervical (C53); uterine (C54); thyroid (C73); pulmonary cancer (C34); melanoma (C43); other skin cancers (C44); tumours of central nervous system (C70, C71, C72); leukaemia and lymphoma (C81-C96) and gastrointestinal track tumours, including duodenal (C17.0), jejunal (C17.1), ileal (C17.2), colon (C18), splenic (C26), pancreatic (C25) and hepatic cancers (C22), tumours in the gallbladder (C23) or bile ducts (C22.1). Invasive ovarian cancers and borderline tumours of the ovary were grouped depending on the malignancy rate also recorded in the Cancer Registry. Rare cases of other tumours (less than three cases per cancer type) were included in the total number of cases, but not reported separately. The cancer incidences were calculated first starting from the last IVF treatment (covering the whole follow-up time) and secondly starting from twelve months after the last recorded IVF treatment (Table 2). There were 11 women who had two cancers registered. Three of them had the same cancer type twice and these cases were calculated in the analysis only once. Eight women had two independent cancers and these 16 cancers were included twice in the analysis by cancer type, but only once in the total number of women with cancer. The follow-up time was until 31 December 2004, on average seven years and nine months.

During the data collection IVF women and their controls were matched for age and residence. In the present study odds ratios with 95% confidence intervals for given cancer type between the two groups were calculated with conditional logistic regression analysis after adjustment for socio-economic position and marital status. If no cancers were observed for some diagnosis among either

IVF women or controls, Fisher's exact test was used. X^2 test (in the case of breast cancers) and Fisher's exact test (in the case of invasive ovarian cancers and uterine cancers) were used to compare possible differences in occurrence time for a cancer after infertility treatments among IVF women and controls.

Results

Background characteristics of IVF women and controls are given in Table 1. A larger proportion of IVF women were married and upper white-collar workers. Differences with respect to both marital status and socio-economic position between the groups were statistically significant and adjustment for these factors was done for the analysis.

The total cancer incidence was slightly but statistically insignificantly greater among the control women: among IVF women 178 and among the controls 193 cancer cases were reported after infertility treatments by the end of 2004. The combined incidences of hormonal related cancers (breast cancer, invasive ovarian cancer and uterine cancer) did not differ between the groups.

Cumulative incidences for hormonal related cancers among IVF women and controls are presented in Figure 1. Among IVF women five breast cancers were diagnosed within the first year after receiving infertility treatments compared to two cases among the controls. Thereafter breast cancer incidence between the groups did not differ significantly (p=0.09). For uterine cancer and invasive ovarian cancer, too, the differences in time of occurrence were not statistically significant (p=0.467 and p=0.705 respectively).

As expected, most cancer cases in both groups were diagnosed among women aged 35 years or more. Among the IVF women this share was 80.9% and among the controls 76.7%. The difference was not statistically significant (p=0.322).

Among IVF women the most common cancers reported after infertility treatments were breast cancers (55 cases), cervical cancers (34 cases) and skin cancers other than melanoma (24 cases). The most common cancer types among controls were in turn cervical cancers (67 cases), breast cancers (60 cases) and skin cancers other than melanoma and gastrointestinal track tumours (10 cases).

After adjusting for socio-economic position and marital status the differences between IVF and the control women with respect to the incidences of most cancer types were statistically insignificant (Table 2). However, IVF women had statistically significantly less cervical cancer (OR 0.51, 95% CI 0.30-0.85), but more skin cancers other than melanoma (OR 3.11, 95% 1.02-9.6). IVF women also had three times more invasive ovarian cancers (9 cases) than the controls (3 cases), but the difference was not statistically significant. The incidence of borderline tumours of the ovary was similar in the groups. All pulmonary cancers (n= 5) occurred among the control women. This difference was statistically significant, p=0.03 (calculated with Fisher's exact test), but this comparison was unadjusted and unmatched due to the small number of cases.

In order to reduce the risk of recording cancers that were already developing when infertility treatments were provided, we also studied the number of cancers diagnosed 12 months or more after infertility treatments. The differences in cancer incidences between the groups remained unchanged. (Table 2).

Discussion

According to our study the general cancer incidence or combined incidence of hormonal related cancers among the Finnish women treated with IVF (including ICSI and FET) in the period 1996-1998 did not differ significantly from that among the control population which was matched for age and municipality and further adjusted for marital status and socio-economic position. The incidence of invasive ovarian cancer was three times greater among IVF women than controls but the case number was low which may explain why the difference was statistically insignificant.

IVF women in our study had statistically significantly fewer cervical and pulmonary cancers, but more skin cancers other than melanoma. The difference in cervical, skin and pulmonary cancer is likely to be explained by the healthy patient effect as women desiring pregnancy tend to be relatively healthy. The same effect was also found in another study reporting lower mortality among infertile patients (Venn et al. 2001) and in our earlier study according to which IVF women had a smaller number of hospitalizations for psychiatric disorders than controls (Yli-Kuha et al. 2010).

A lower insidence of cervical cancer among infertile women attending to infertility clinics has also been reported in other studies (Doyle et al. 2002) (Jensen et al. 2008) (dos Santos Silva et al. 2009).

The incidence of cervical cancer depends on sexual behaviour, and it is possible that infertile women or their partners engaged in different sexual behaviour from the control women. Furthermore, this difference could be explained by surveillance bias, as it is likely that IVF women are used to visiting their gynaecologists regularly and thus more papanicolaou smears are taken, which enables earlier treatment of suspicious cell atypia.

It is possible that the greater number of skin cancers diagnosed among IVF women is partly explained by the differences in socioeconomic position between the groups even though adjustment for this was made. The composition of the class "Other" is likely to be different between IVF women and controls which may cause some bias. Also, the share of women in class "unknown" is different. Skin cancers are more common among highly educated people (Hemminki & Li 2004) at least partly because of more intense exposure to solarium and more frequent holidays. It is also possible that IVF women may react to their suspicious moles more vigilantly as they are used to monitoring their health.

The probability of smoking is likely to be different between the two groups explaining differences in pulmonary cancer incidence. Smoking is significantly more common among people from lower than from higher socioeconomic position in Finland (Katainen, 2010). However, for the analysis we adjusted for social class. It is also likely that many smokers stop smoking when trying to get pregnant or at least when discovering their infertility as smoking may impair fertility.

A strength of our study was the large cohort of 9,175 IVF women and their controls. Because of the size of the study population, a significant number of cancer cases occured even during this relatively short follow-up time of on average seven years and nine months. The cohort is also representative as it is estimated that virtually all Finnish women treated by IVF 1996-1998 are included in this cohort (Klemetti et al. 2005). A weakness of this study is that the control group consisted of women from general population.

There are also important risk factors that could not be adjusted for in the analysis. Parity between groups is likely to be different as the control women probably had more children than IVF women. Low parity is a risk factor, for example, for ovarian cancer (Risch 1998) (Riman et al. 2002) (Sueblinvong & Carney 2009), breast cancer (Butt et al. 2009) (Kawai et al. 2009) and uterine cancer (Parazzini et al. 1998) (Salazar-Martinez et al. 1999) (Reis et al. 2009). On the other hand the group of control women may include infertile women not having received these treatments

1996-1998. Other risk factors not adjusted for are use of oral contraceptives or other hormonal treatments, smoking, obesity, and possible genetic predisposition, for which no register-based information is available in Finland.

The possibly increased cancer risk among infertile women or after infertility drug exposure has been evaluated in several studies with partly inconsistent results. Some of this difference may be explained through methodological weaknesses such as too small study material or too short follow-up time. It is, however, possible that study settings analysing infertile women as a one group cannot reliably determine this risk. From a theoretical point of view it is likely that different conditions causing impaired fertility have different risk potential for given cancers. For example, earlier studies suggest that women with polycystic ovaries syndrome may have increased risk for uterine cancer (Goodarzi et al. 2011) and women with endometriosis for ovarian cancer (Kobayashi et al. 2011). The proportion of women treated for male infertility or suffering from tubal infertility caused by untreated *Chlamydia trachomatis* infection, thus probably not having increased cancer risk caused by infertility, may also vary significantly between different studies.

In future it would be reasonable to reanalyse existing data and in future studies collect a large number of study subjects enabling analysis in sub-groups depending on the cause of infertility. When evaluating if infertility drugs affect cancer risk infertile non-treated women with the same cause of impaired fertility should be used as controls. It would also be important to analyse drug exposure separately for each drug used, also taking into consideration dosage and number of treatment cycles with the given drug. Because cancer development also typically takes several years, follow-up time should be long enough. This would also take into consideration the possibility that infertility drugs could enhance the growth of already existing tumours as during long follow-up the possible differences in time of occurrence of cancers between the groups would be levelled off.

Conclusions: According to this study the risk of cancer among women undergoing IVF, ICSI or FET was not increased. Earlier studies report partly contradictory results in the evaluation of cancer risk. In future it will be important to reanalyse existing data and collect large study populations thereby also enabling analysis among sub-groups with different causes of infertility. The exposure and dosage of different drugs should also be taken in to consideration in the analysis when assessing if infertility drugs affect cancer risk.

Authors' roles

The study was originally designed by E.H., M.G., R.L., R.K. and A.-N.Y. The classification and interpretation of the data were done by A.-N.Y. The manuscript was drafted by A.-N.Y. and revised by E.H., M.G., R.L., R.K. All authors approved the final version of the manuscript.

Table 1. Age, marital status and socio-economic position of IVF women (N=9175) and controls (N=9175) at the time of infertility treatments (1996-1998)

	IVF women %	Control women %
Age		
20-24	3.5	3.5
25-29	20.8	20.8
30-34	35.2	35.2
35-39	27.2	27.2
40-44	10.8	10.8
45 or more	2.0	2.0
Marital status [1]		
Married	69.4	45.3
Unmarried	22.3	32.7
Divorced	7.9	8.9
Widow	0.4	0.0
Unknown	0.0	13.0
Socio-economic position [1]		
Upper white-collar worker	25.3	16.3
Lower white-collar worker	48.5	45.6
Blue-collar worker	16.2	19.3
Other [2]	7.9	12.3
Unknown	2.1	6.4

[1] $p < 0.001$

[2] (Student, entrepreneur, housewife, unemployed)
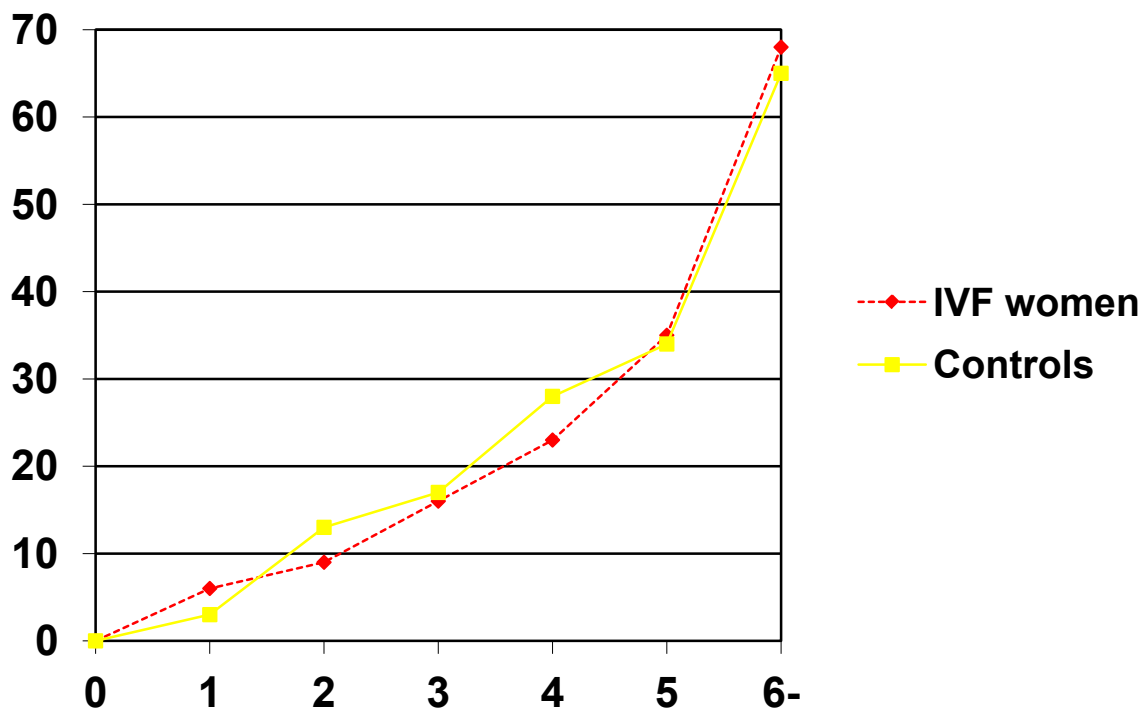
Figure 1. Cumulative number of breast cancers, uterine cancers and invasive ovarian cancers among IVF women and controls by the time (years) after infertility treatments.

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Table 2. Cancer cases of IVF women and controls (matched for age and residence) after infertility treatments and one or more years after treatments: odds ratios (95% confidence intervals) are adjusted for marital status and socio-economic position.

	After infertility treatments			One or more years after infertility treatments		
	IVF women (N=9175)	Control women (N=9175)	OR CI)	IVF women (N=9175)	Control women (N=9175)	OR (95% CI)
Any cancer	178	193	1.01 (0.80-1.27)	166	174	1.01 (0.80-1.29)
Breast cancer	55	60	0.93 (0.62-1.40)	50	58	0.86 (0.57-1.30)
Invasive ovarian cancer	9	3	2.57 (0.69-9.63)	8	3	2.25 (0.59-8.68)
Borderline tumours of the ovary	4	4	1.68 (0.31-9.27)	4	3	2.25 (0.59-8.68)
Cervical cancer	34	67	0.51 (0.30-0.85)	32	59	0.54 (0.32-0.91)
Uterine cancer	4	2	2.0 (0.37-10.9)[1]	4	1	NC[2]
Pulmonary cancer	0	5	NC[2]	0	5	NC[2]
Thyroid cancer	10	8	1.27 (0.31-5.2)	10	7	1.79 (0.38-8.48)
Melanoma	12	9	1.27 (0.34-4.8)	11	6	0.67 (0.11-3.99)
Other skin cancer	24	10	3.11 (1.02-9.6)	23	10	3.20 (1.04-9.87)
Tumours in central nervous system	9	7	9.4 (0.56-159.5)	8	7	7.14 (0.69-74.3)
Gastrointestinal track tumours	12	10	1.88 (0.52-6.8)	11	9	3.9 (0.38-39.8)
Leukaemia or lymphoma	4	5	0.34 (0.04-3.06)	4	4	0.38 (0.04-3.56)[1]

[1]Crude Odds Ratio due to small case number
[2]Non Calculable