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Cand. med. Liv Bente Romundstad

"Assisted fertilization in Norway: safety of the reproductive technology"

PRØVEFORELESNING

Tid: **Fredag 20. november 2009 kl. 10.15**
Sted: **Auditoriet Laboratoriesenteret, St. Olavs Hospital**

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DISPUTAS

Tid: **Fredag 20. november 2009 kl. 12.15**
Sted: **Auditoriet Laboratoriesenteret St. Olavs Hospital**

Ordinære opponenter:
Førsteopponent: Professor Anders Nyboe Andersen, Rigshospitalet København
Andreopponent: Docent Ulla Britt Wennerholm, Sahlgrenska Universitetssjukehus

Bedømmelseskomiteen består av opponentene og post doc Runa Heimstad, NTNU.

Kandidatens veileder har vært professor Lars Vatten, Institutt for samfunnsmedisin.

Professor Sturla Eik-Nes, Institutt for laboratoriemedisin, barne- og kvinnesykdommer, vil lede disputasen.

Liv Bente Romundstad

Assisted fertilization in Norway: safety of the reproductive technology

Thesis for the degree of philosophiae doctor

Trondheim, August 2009

The Norwegian University of Science and Technology

Faculty of Medicine

Department of Public Health and General Practice

NTNU
Faculty of Medicine
Department of Public Health and General Practice

ST. OLAVS HOSPITAL
UNIVERSITY HOSPITAL OF TRONDHEIM

ASSISTERT BEFRUKTNING I NORGE

Prøverørsbehandling, eller assistert befruktning er blitt en vanlig måte å hjelpe ufrivillig barnløse til å bli foreldre. Det første barnet etter assistert befruktning i Norge ble født i 1984 i Trondheim. Det har vært en rivende utvikling innen fagfeltet og skepsisen mot behandlingsteknologien har vært stor. Studier har vist at assistert befruktning er forbundet med økt risiko for svangerskapskomplikasjoner, hyppigere bruk av keisersnitt, for tidlig fødsel, dødelighet og lav fødselsvekt. Om den økte risikoen skyldes forhold hos mor og far eller om den kan knyttes til selve behandlingen er ukjent.

Alle data er hentet fra medisinsk fødselsregister og avhandlingen består av tre delstudier. I alle tre studiene ble svangerskap etter assistert befruktning sammenlignet med svangerskap etter vanlig befruktning.

I de to første studiene ble i tillegg mødre som var registrert med svangerskap etter både assistert og naturlig befruktning identifisert. Hensikten var å studere om den økte risikoen skyldtes forhold hos mødrene eller behandlingsteknologien ved at mødrene ble sine egne «kontroller». Dette ga mulighet til å skille mellom forhold hos mor og forhold ved behandlingsteknologien.

I den første studien sammenliknet vi forekomsten av placenta praevia (forliggende morkake) i 7 568 svangerskap etter prøverørsbehandling med forekomsten i 845 384 svangerskap etter vanlig befruktning. Etter å ha kontrollert for andre risikofaktorer som mors alder, paritet, tidligere keisersnitt og varighet mellom fødsler, var det en seks ganger høyere risiko for placenta praevia i svangerskap etter prøverørsbehandling sammenliknet med svangerskap etter vanlig befruktning.

I sammenligningen hos 1349 mødre som hadde svangerskap etter både assistert og naturlig befruktning var det en tredobling av risikoen for placenta praevia etter assistert befruktning sammenliknet med vanlig befruktning. Resultatet ble det samme uavhengig av om det første eller det andre svangerskapet til disse mødrene var etter assistert eller vanlig befruktning. Studien tyder på at faktorer knyttet til selve prøverørsteknologien kan bidra til den økte risikoen for placenta praevia etter assistert befruktning.

I den andre studien sammenlignet vi forhold ved fødsel blant 8229 enkeltfødte etter assistert befruktning med 1 200 922 enkeltfødte etter vanlig befruktning. I overensstemmelse med tidligere studier ble det funnet en forhøyet risiko for perinatal dødelighet, for tidlig fødsel og lav fødselsvekt blant enkeltfødte etter assistert befruktning. I sammenligningen hos 2546 mødre som hadde svangerskap etter både assistert og vanlig befruktning var det imidlertid ingen forskjeller mellom svangerskap etter assistert og vanlig befrukting. Studien tyder på at behandlingsteknologien er trygg for de utfallene som er studert.

I den tredje studien så vi på forekomsten av seteleie blant enkeltfødte etter assistert befruktning og fant en 50 % høyere forekomst i denne gruppen sammenlignet med forekomst av seteleie blant enkeltfødte etter vanlig befrukting. Etter å ha kontrollert for andre risikofaktorer som mors alder, paritet og svangerskapsvarighet, forsvant imidlertid forskjellen i risiko. De viktigste faktorene som forklarte forskjellen mellom gruppene var kortere svangerskapslengde og flere førstegangsfødende blant mødrene med assistert befruktning. I denne studien fant vi i tillegg at forekomsten av keisersnitt blant mødrene etter assistert befruktning nærmer seg forekomsten av keisersnitt i den generelle befolkningen.

Kandidat: **Liv Bente Romundstad**
Institutt: **Institutt for samfunnsmedisin**
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Finansieringskilde: **Kvinneklinikken, St.Olavs Hospital**

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In my daily work at the Fertility Unit I am blessed with a friendly and cheerful group of colleagues, always embedded in a positive and encouraging atmosphere. Thank you all, and in particular *Hildegunn Stoum, Sigrun Kjøtrød and Knut H. Kierulf,* for allowing space and time to complete this work.

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A heartfelt gratitude to my two daughters, *Regine and Iris*, for your understanding and endless patience throughout this work: you are simply the best!

LIST OF PAPERS

The thesis is based on the following three papers. The papers will be referred to by their Roman numerals.

I. Romundstad LB, Romundstad PR, Sunde A, von Düring V, Skjaerven R, Vatten LJ. **Increased risk of placenta previa in pregnancies following IVF/ICSI; a comparison of ART and non-ART pregnancies in the same mother.** Hum Reprod. 2006 Sep;21(9):2353-8. Epub 2006 May 25.

II. Romundstad LB, Romundstad PR, Sunde A, von Düring V, Skjaerven R, Gunnell D, Vatten LJ. **Effects of technology or maternal factors on perinatal outcome after assisted fertilisation: a population-based cohort study.** Lancet. 2008 Aug 30;372(9640):737-43. Epub 2008 Jul 30.

III. Romundstad LB, Romundstad PR, Sunde A, von Düring V, Skjaerven R, Vatten LJ. **Assisted fertilisation and breech delivery; Risks and obstetric management.** Accepted for publication in Human Reproduction

ABBREVIATIONS

ART	Assisted reproduction technology
CI	Confidence interval
DET	Dual embryo transfer
FER	Frozen embryo replacement
FSH	Follicle stimulation hormone
GnRH-ag	Gonadotrophin releasing hormone agonists
hMG	Human menopausal gonadotrophin
ICSI	Intracytoplasmatic sperm injection
IUI	Intrauterine insemination
IVF	In vitro fertilisation
LH	Luteinizing hormone
LMP	Last menstrual period
MBRN	Medical Birth Registry of Norway
OR	Odds ratio
PGD	Preimplantation genetic diagnosis
PGS	Preimplantation genetic screening
RR	Relative risk/ratio
SD	Standard Deviation
SET	Single embryo transfer
SGA	Small for gestation age
WHO	World Health Organisation

INTRODUCTION

A 37-year-old woman who has never been pregnant and her 40-year-old husband have been attempting to conceive a child for the past 3 years. An infertility evaluation has shown no cause for the difficulty. She is ovulating regularly, and a hysterosalpingogram shows that her reproductive tract is anatomically normal. He has a normal sperm count; he has not fathered any children. They are frustrated and want to proceed with in vitro fertilization. What should you advise?

A review article of assisted fertilisation published in the New England Journal of Medicine opens with this vignette [1]. The scope of fertility treatment has escalated over the last 40 years with an accompanying need for information for the couples affected, general public and all medical personnel involved.

Background

The first successful pregnancy after in-vitro fertilisation (IVF) resulting in the birth of a baby took place in the UK on July 25, 1978 [2]. Since the birth of Louise Brown, more than 4 million babies have been born world wide as a result of assisted reproductive technology (ART) [3]. The scope of fertility treatment is rapidly growing in both western and less developed countries [4]. However, this treatment is still a focus of ethical, medical and social debate [5].

During the early days of reproductive technology, implantation rates per treatment cycle were low and just a few treatment cycles were performed per clinic per year. Therefore, the proportion of all children born after ART during the first years was quite modest. Gradually, an increasing proportion is born after assisted fertilisation in developed countries [6], and the procedure of assisted fertilisation is now available in most countries [7, 8]. In some Nordic countries, the proportion of children born after assisted reproductive technology now exceeds 7 percent [6]. Increased accessibility, delaying childbearing until an age where fertility is declining and technological advances are factors that influence the increasing tendency [9]. However, there are still enormous inequalities in the access to assisted fertilisation. This can be due to differences in personal convictions, national economy, insurance coverage or political prioritizing. As an example, a middle income country such as

Turkey now offers treatment from public funding while affluent countries like Switzerland, the US and Japan have little or no public funding of ART [10] (Sunde 2007, http://www.ivf-worldwide.com/Education/policy-of-reimbursement.html)

Key developments in assisted reproduction

The history of fertilizing mammalian eggs *in vitro* dates back to the end of the 19th century. The first successful egg recovery was done from a rabbit by Walter Heap and colleagues in 1890. Three years later Onanoff produced the first successful embryo culture, and the first IVF in mammalian was achieved in 1930 by Pincus [11]. They liberated immature rabbit oocytes from their follicles into culture media and found that 12 hours were needed for maturation. Pincus and co-workers extended their work to human oocytes. In 1946 and 1948, Menkin and Rock claimed that they had fertilized human oocytes. In the early 1950s, M C Chang established the requirements for successful IVF with mammalian spermatozoa and oocytes and could demonstrate successful IVF in the rabbit. In 1955, Shettles and Rock suggested that IVF could be developed into a method for the treatment of infertile couples. However, these advances towards the development of human IVF in the US came to a halt due to a hostile public environment and because some of the key scientists had retired.

In 1965, it was discovered that human eggs require about 37 hours for maturation (Edwards, The Lancet 1965) and in 1968, Patrick Steptoe demonstrated laparoscopic pictures of ovaries and follicles for the first time at a meeting at the Royal Society of Medicine in London. One of the listeners was Robert Edwards, and this meeting turned out to be the start of a historic collaboration between these two researchers. Together they were able to retrieve matured oocytes from the follicles by laparoscopy, fertilize *in vitro* and replace the embryo to the uterus. The early stages of fertilization of human oocytes matured *in vitro* were described and published the following year [12]. The first human blastocyst was seen *in vitro* in 1971. The following year, the first mouse embryo was successfully cryopreserved and thawed. Initially, Steptoe's aim was to bypass blocked Fallopian tubes to enable sterile women to conceive, while Edwards hoped to obtain material from fertilised human eggs to study cell lines with the long term goal of preventing some hereditary diseases and cure others, for instance cancer.

"This is the first time we've solved all the problems at once. We're at the end of the beginning -not the beginning of the end." Patrick Steptoe 1978

The next years to come at the Born Hall Clinic escalated beyond the wildest expectations as more than 1000 children were born in the next 8 years. Births from a number of centers followed world wide and IVF rapidly became an internationally accepted form of treatment for infertile couples.

The first birth after fresh embryo transfer in Norway took place in 1984 [13] and the first birth after frozen embryo transfer in 1987 [14]. There has been a steady increase of children born after assisted fertilisation, with the proportion in Norway reaching close to 2.5% in 2005 (Figure 1).

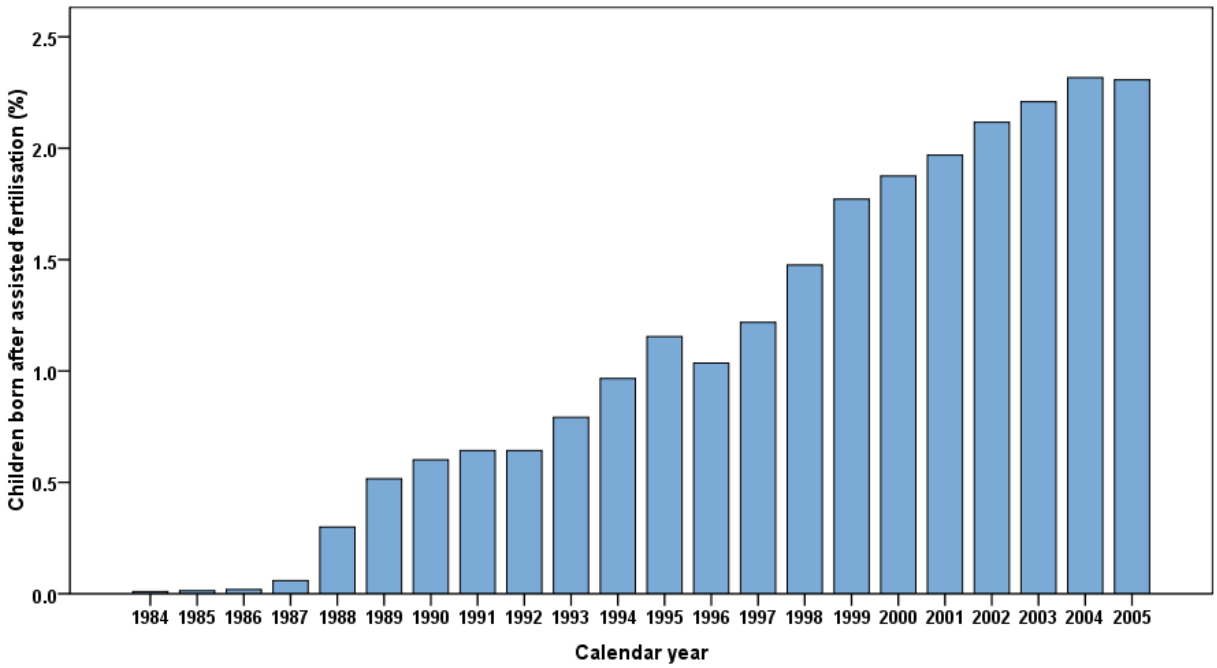


Figure 1. Proportion of children (%) born after assisted fertilisation in Norway 1984-2005.

Infertility

Historically, childlessness is not a newfangled phenomenon. Riddled by myths and legends, different multi-faceted stories of treating and dealing with infertility have survived for centuries. Dating back to the Genesis, in which Rachel said to her husband “give me children or else I will die”. Rachel’s maid was persuaded to be conceived by Rachel’s husband and the maid gave birth to two sons. In Greek, Norse and Roman Mythology several Gods and Goddesses are symbols of fertility and fecundity (Figure 2).

Figure 2: In Norse mythology, Freya is the goddess of fertility and love.

The most common definition of infertility used by clinicians is failure to conceive during 12 months of unprotected intercourse. There has been an ongoing debate regarding nomenclature and definitions of infertility [15].The term infertility covers a wide range of various conditions, from sterility to the possibility of normal fertility if the period of non-conception used to define infertility is of short duration [16]. The duration of 12 months used by clinicians has been described as arbitrary because 50% to 70 % of couples classified as “infertile” under this definition may eventually conceive spontaneously [17, 18]. In epidemiological studies a duration of two years is the standard [19], while in a clinical context, a period of 12 months has become the norm [20]. The World Health Organisation

(WHO) defines infertility as “a failure to conceive after unprotected intercourse for a period of one year”.

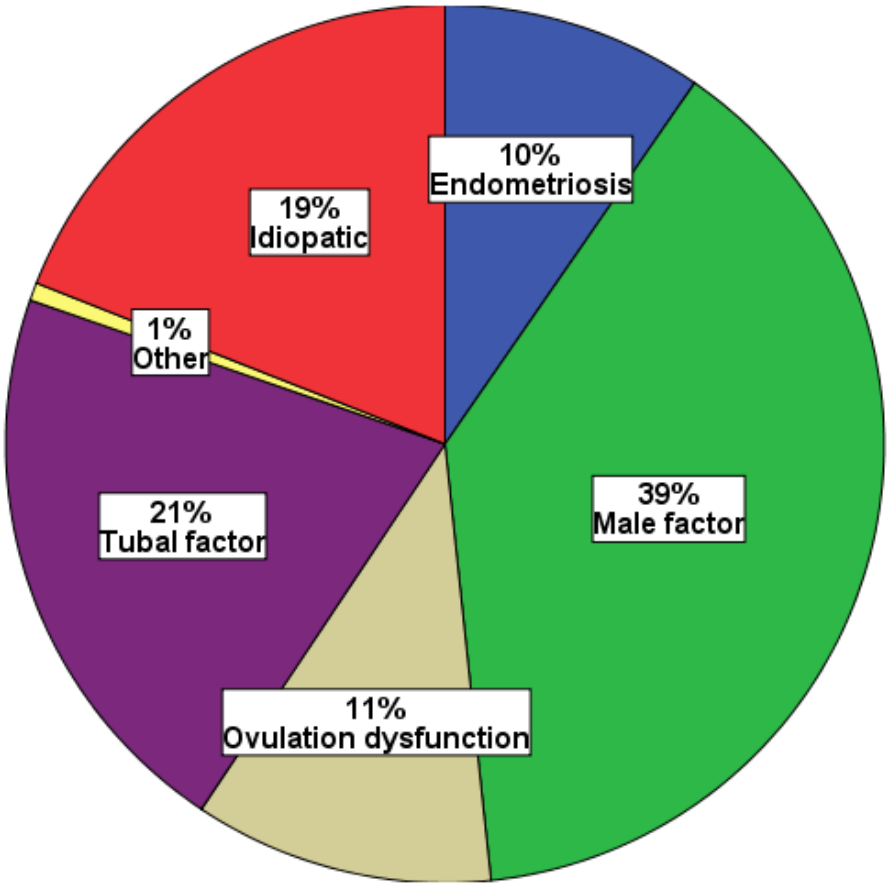
Among demographers, infertility has been characterized as no birth over a defined period of time, irrespective of whether children were wanted or contraception was used. This stems from the fact that their data are mostly collected from birth registers [19]. The time-based definition of infertility introduces a moral dilemma as it relies on the couples’ veracity. Accordingly, an ethical challenge accompanies the time-based definition. The success rates of assisted fertilisation decreases with increasing maternal age. A woman in her late thirties will reduce her chance of achieving a successful treatment cycle while she is waiting to fulfil the criteria of infertility. As a consequence of this dilemma; many clinics have modified the definition, and women > 36 years are therefore offered medical examination and treatment after six months of unprotected intercourse without pregnancy.

Irrespective of definitions, infertility remains a major health problem which has very definite physiological, sociological and psychological implications for affected couples.

Causes of infertility

Couples seeking evaluation and examination for infertility are often desperate in their desire for an explanation. A reminder to both clinicians and the couple is that it is not the intention to pull up the sinner but rather to identify the underlying reason for their inability to conceive spontaneously. There are various reasons for infertility and the prevalence among couples in the western world is approximately 15% [21].

The diagnosis of the couple can roughly be categorised into 3 main groups, consisting of male factor, female factor or as unexplained infertility. Each group accounts for about one third of the cases. For clinical purposes, a more nuanced classification is preferable, while it is important to keep in mind that there are often overlaps between categories. Since 2002, data on indications for fertility treatment are reported to the Medical Birth Registry of Norway. The distribution of indications for IVF/ICSI in Norway is in line with that described by others [22-24] and is illustrated by the pie figure below.



Figur 3: Distribution of main indications for assisted fertilisation in Norway 2002-2006

Assisted reproduction

In the beginning, Steptoe and Edwards obtained oocytes from ovaries that had been hormonally stimulated in order to induce multiple follicular growth. The first pregnancy was an ectopic, and they reverted to natural cycles because they suspected a causal link between hormonal stimulation and tubal pregnancies [2]. In the following years, it soon became obvious that the use of super ovulation was beneficial in assisted fertilisation. The aim was to recruit a large number of follicles, in order to produce a large number of oocytes in each treatment cycle. The first stimulation protocols comprised administration of an oestrogen receptor modulator (clomiphene–citrate) or human menopausal gonadotrophin (hMG) given alone or in combinations. Premature rise of LH was however a problem and many treatment cycles were either cancelled prior to oocyte recovery or the oocytes collected had poor quality due to prematurely luteinised follicles. This problem was eventually solved with the introduction of gonadotrophin releasing hormone agonists (GnRH-ag).

Stimulation protocols then routinely included ovarian down-regulation with a GnRH-ag starting in the midluteal phase. Ovarian hyper stimulation is conducted with recombinant follicle-stimulation hormone (FSH) or urine based human menopausal gonadotrophin (HMG). More recently, gonadotrophin releasing hormone antagonist (GnRH-an) has been introduced allowing ovarian hyperstimulation without prior pituitary down-regulation. The GnRH antagonist is administered in the last phase of gonadotrophin administration to prevent premature LH rise. The recruitment and growth of follicles are monitored during hyperstimulation by ultrasound until an adequate number of larger (>17mm) follicles is observed.

Currently, follicular aspiration is usually performed under transvaginal ultrasound guidance 36 hours after ovulation induction with human chorionic gonadotrophin (HCG). Edwards and Steptoe performed laparoscopic oocyte retrieval and this was the standard method until groups in Copenhagen, Gothenburg [25], and Trondheim simultaneously developed transvesical and subsequently transvaginal ultrasound guided oocyte retrieval in the mid 80-ties.

The follicular fluid containing the oocyte is examined by the embryologist and the oocyte is brought to a suitable medium. The method used for fertilisation (IVF or ICSI) depends on indication for fertility treatment, sperm quality and previously failed IVF cycles. During the next 48-72 hours the developing embryos are carefully stored in an incubator and the development is regularly evaluated by the attending embryologist. Good quality embryos are replaced to the uterus after two to five days. Surplus embryos are cryopreserved for later treatment cycles. After embryo transfer, luteal phase support is normally administered for 14 days. Figure 4 summarizes the procedures and monitoring in assisted fertilisation.

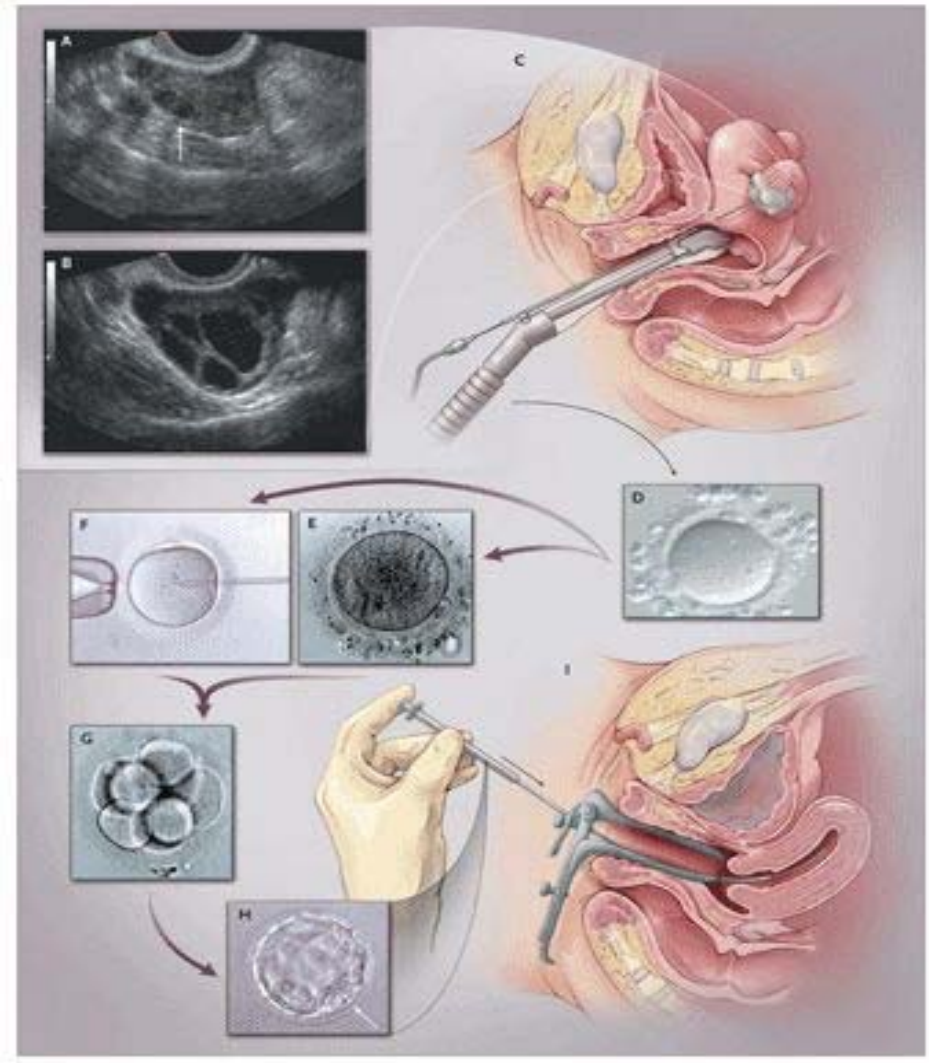


Figure 4. Flow chart of the procedures in assisted fertilisation. (Reprinted from New England Journal of Medicine, Van Voorhis BJ, Vol 356, jan 25, 2007 with permission from NEJM)

A: Ultrasonography of an unstimulated ovary (natural cycle) shows a small antral follicle

B: The same ovary with multifollicular growth after daily injections with gonodotrophins

C: Transvaginal aspiration of follicular fluid under ultrasound guidance

D: A matured oocyte recovered from the follicular fluid then fertilisation *in vitro* either by:

E: Adding multiple sperm, on the picture attached to the egg's zona pellucida (IVF) or

F: Fertilized by intracytoplasmatic sperm injection (ICSI)

G: A three days eight cell-embryo

H: Cultivation of embryo continued until blastocyst stage, day 5

I : The selected embryo is replaced back to the uterus

Male infertility and intracytoplasmatic sperm injection (ICSI)

IVF became a well established treatment option for endometriosis, tubal disease, ovulation dysfunction and long standing unexplained infertility. It soon became obvious that couples with severe male infertility did not benefit from conventional IVF and the only treatment option for them was insemination of donor sperm to the woman. Several procedures of assisted fertilisation based on micromanipulation of oocytes and spermatozoa were tried. The first techniques involved partial zona dissection (PZD) [26, 27] and subzonal insemination (SUZI) [28]. The first report on a microscope procedure for facilitating fertilisation by injection the spermatozoa directly into the human oocyte (ICSI) was published in 1988 [29]. Four years later, in 1992, the first birth after ICSI was described by a Belgian group [30]. ICSI is an even more invasive technique as not only the zona pellucida is bypassed but also the oolemma is crossed. This technique also involves a non-natural selection of the fertilising sperm and a potential risk that the micropipette with the spermatozoon may interfere with the meiotic spindle within the oocyte.

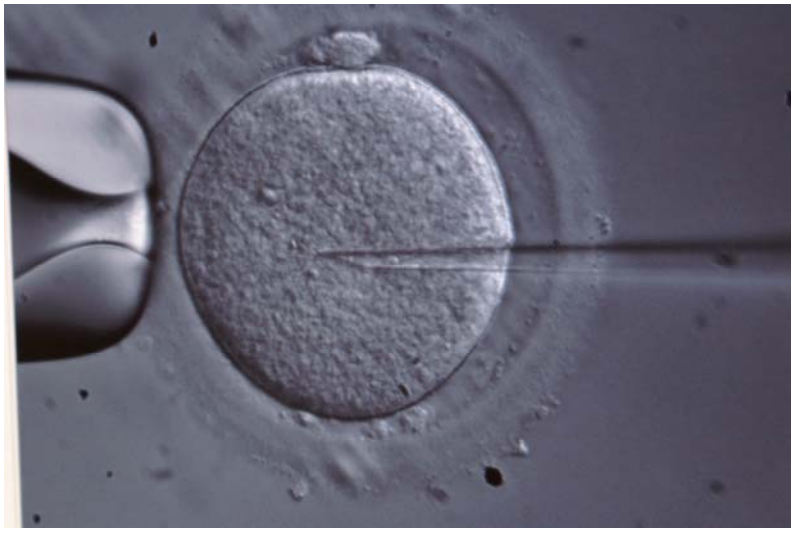


Figure 5: ICSI procedure, a single motile spermatozoon is selected and injected into a fixed mature oocyte. (Source: Ziebe S. Rigshospitalet, Copenhagen, Denmark)

Major concern and scepticism emerged with the introduction of this procedure, as these distinct biological borders were forced through. Safety aspect of the procedure has been

scrutinized by the same Belgian group [31-33] and by others [34-42]. A major concern has been whether ICSI babies are at increased risk of birth defects. However, a meta-analysis of birth defects in ICSI children found no significantly increased risk for cardiovascular defects, musculoskeletal defects, hypospadias, neural tube defects, or oral clefts [43]. The authors do, however, emphasise that data were limited for specific defect categories.

It has been suggested that Y-chromosome deletions, chromosome aberrations and CF-mutations may explain up to 25 % of azoospermia and severe oligozoospermia. If the cause of the infertility is genetic, the use of ICSI may also increase risk of the offspring. Information about genetic testing before treatment has therefore been recommended [44].

There is great diversity between countries regarding the primary choice of method used for fertilisation [45]. Overall, there is an increased use of ICSI that currently seems to exceed 60 % of the cycles [6, 46]. These authors claim that this cannot be explained by a corresponding increase in male infertility, but rather by professional preferences. The number of children born after IVF and ICSI treatment in Norway from 1984 to 2005 is illustrated in Figure 6.

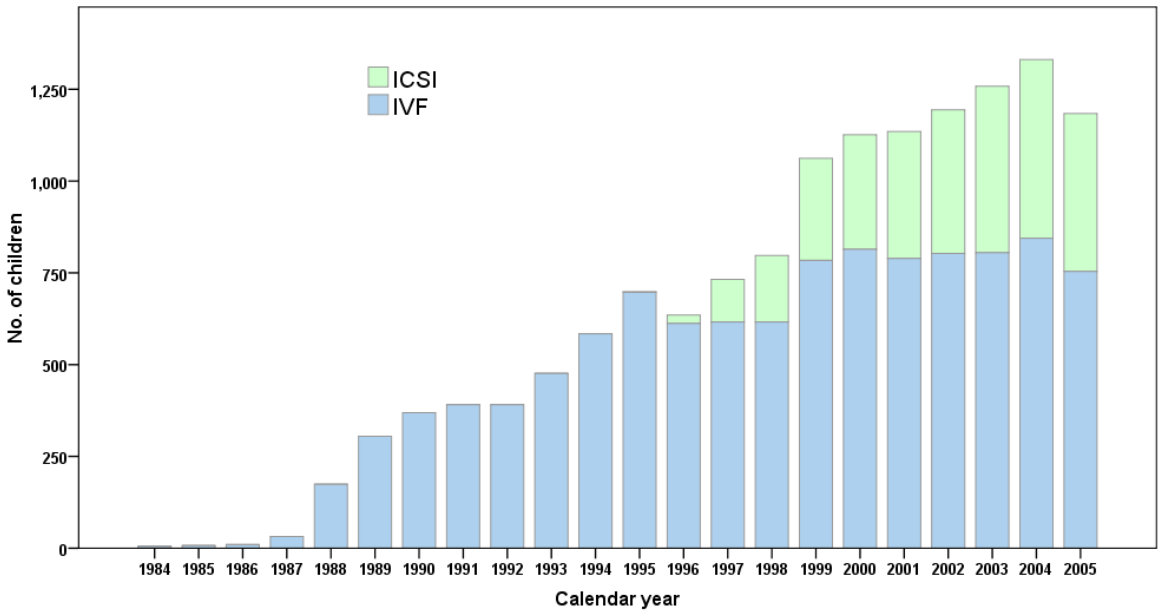


Figure 6. Method used for fertilisation in children born after assisted fertilisation Norway 1984-2005 by calendar year.

Cryopreservation

In 1972, two researchers [47, 48] independent of each other, published data showing that mouse embryos could be successfully cryopreserved and thawed. The first pregnancy after a frozen and thawed embryo was reported in 1983 [49], and the first births were reported in 1984 and 1985 [50, 51]. The first birth was a result of a replacing a cryopreserved/thawed 4-cell embryo while Cohen and co-workers cryopreserved embryos at the blastocyst stage.

Embryo cryopreservation is now firmly established as a routine adjunct method to IVF and ICSI. Surplus embryos are cryopreserved and replaced in subsequent treatment cycles. This option has been of crucial importance regarding the implementation of elective single embryo transfer by avoiding the need to replace more than one embryo and thereby reducing the incidence of multiple births and hence the increased risk for complications and adverse outcome [52]. The overall risk of ovarian hyper stimulation is also reduced, as the number of stimulated cycles is reduced. A recently published systematic review of outcome data of children born after cryopreservation after slow freezing was reassuring [53]. Accordingly, a recent study from Denmark found a higher adjusted mean birth weight of 200 grams and 2 days longer mean gestational length in singletons born after replacement of thawed embryos compared to singletons born after transfer of fresh embryos [54].

Cryopreservation both maximizes the biological potential of each fertilised oocyte and reduces the strain for the couples by reducing the number of stimulated cycles. There is a steady increase in the proportion of children born after cryopreservation as 24.6% of all ART cycles in Europe in 2005 where after replacement of thawed embryos [6]. A continuous follow-up of short and long term health and safety aspects of children born after cryopreservation is important.

Preimplantation genetic diagnosis and screening

Preimplantation genetic diagnosis (PGD) is a method by which embryos formed through in vitro fertilisation (IVF) can be tested for single-gene disorders or chromosome abnormalities prior to embryo transfer. Successful sexing of rabbit embryos was done as early as 1967 [55]. In the 1980s, PCR-based techniques for the analysis of gene sequences and fluorescent *in situ* hybridisation (FISH) for the analysis of chromosomes were developed. These techniques enable analysis of single blastomeres biopsied from embryos. The first births after genetic

testing of human embryos and selection of human embryos took place in the UK in 1992 [56]. The parents were carriers of delta 508 mutations which will give cystic fibrosis in homozygous individuals, and they experienced the birth of a normal girl after in vitro fertilisation and preimplantation diagnostic testing for cystic fibrosis.

PGD was introduced as an alternative to prenatal diagnosis, to prevent termination of pregnancy in couples with a high risk for offspring affected by a sex-linked genetic disease. In Norway, these couples are evaluated individually and treatment by indication for PDG is, for practical reasons, so far performed abroad.

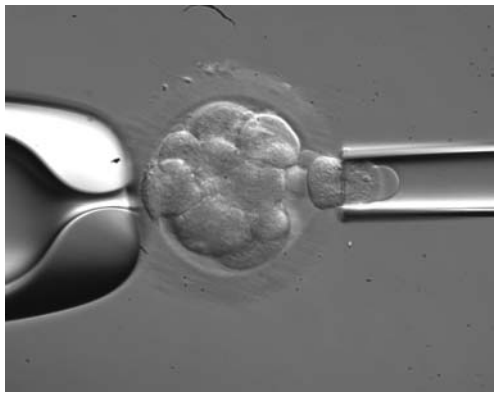


Figure 7. PGD: a single blastomere is removed from the embryo and the genetic composition in this blastomere can be examined. (Source: Ziebe S, Rigshospitalet, Copenhagen, Denmark)

The use of preimplantation genetic screening (PGS) is country specific, and is particularly used in relation to advanced maternal age. PGS is not permitted in Norway, and results from research that may justify the comprehensive use of PGS, is limited. A multicenter, randomized, double-blind, controlled trial comparing ongoing-pregnancy rates after IVF with and without preimplantation genetic screening in women of advanced maternal age, concluded that preimplantation genetic screening did not increase, but instead, significantly reduced the rates of ongoing pregnancies and live births after IVF in women of advanced maternal age [57]. Due to the lack of evidence for the effectiveness of PGS and the accumulating evidence for its harmfulness, it has been claimed that it is unethical to perform additional RCTs for the indication of advanced maternal age to use cleavage stage biopsy [58]. According to a recently published report on ART in Europe, 5846 cycles of PDG/PGS were performed during 2005 and 780 deliveries were reported the same year [6].

Norwegian legislation concerning assisted fertilisation

The legislation regulating the use of assisted fertilisation varies from being absent to being rather conservative between different countries. Norway was one of the first countries to pass a law directly aimed at assisted fertilisation in 1987. The details are stated in the second chapter on "The Laws on Biotechnology" from 2003, and changes of practical use of biotechnology are continuously updated (LAW 2003-12-05 nr 100: "Lov om humanmedisinsk bruk av bioteknologi") by the consultative Norwegian Biotechnology Advisory Board. The latest revision was performed in June, 27th 2008. In §2-2, the law makes demands on cohabitants by requiring that the couple must either be married or living together, thereby excluding single women. Treatment involving donor sperm, both insemination and in vitro fertilisation, has a non-anonymity clause that ensures the offspring's right to demand knowledge of the identity of the sperm donor at the age of 18 (§2-7). The Norwegian law does not permit oocyte donation, embryo donation or surrogacy. The scale of cross border reproductive care is not fully known. The principal reasons for opting to travel abroad for reproductive care are not known, but there are some indications that most patients seek treatment modalities that are not allowed in their home countries. In general, patients travelling to another country for treatment will have to cover all expenses themselves. In the UK, the multiple pregnancy rate in the patients returning from cross border reproductive care seems to be higher that in patients treated in the UK, presenting a challenge for the national maternity care [59].

The Norwegian legislation is considered to be rather conservative, as compared to other Scandinavian countries. Reports from clinics in Denmark, Sweden and Finland indicate some leakage of Norwegian couples for fertility treatment abroad [60], and it cannot be excluded that the conservative Norwegian legislation contributes to this tendency.

Ethical issues

Ethical opposition to culturing human embryos was intense, even before the first successful pregnancy was commenced, and the first paper to discuss ethics related to human IVF was published as early as 1971 [61]. Contemporary medical practice includes ethical uncertainty when innovative or controversial treatments are introduced as pointed out by Sutcliffe and Ludwig [5]. Thus, assisted reproductive technology has made topically important issues into a

source of lively and enthusiastic debate. The ethical debate concerning assisted conception can broadly be divided into three different topics; the moral status of the human embryo, reimbursement of treatment-associated cost for the infertile couples and concerns about the biological safety of the methods used.

The Catholic Church considers that life in a moral sense begins at fertilisation. Pope Benedict has restated that they see IVF and PGD as a "sin of abortion". (Instruction *Dignitas Personae* on Certain Bioethical Questions, Rome, from the Offices of the Congregation for the Doctrine of the Faith, 8 September2008, Feast of the Nativity of the Blessed Virgin Mary). This view appears to be shared by conservative Lutherans.

The majority of Christian churches, Judaism, Islam, Buddhism and Hinduism accept research on human embryos and fertilisation *in vitro,* and differences in religious thinking are reflected in the various laws regulating assisted conception in different countries. Italy and Germany have very restrictive legislation, while Denmark, Sweden, the UK, Israel, Egypt and India have a very permissive legislation. Costa Rica has banned ART due to the clear negative attitude from the Vatican.

In many countries, it has been a heated debate about the right of infertile couples to have access to ART reimbursed by insurance or by the government. Essentially, the key question has been whether involuntary childlessness *per se* is a "disease" or a "condition". In most countries diseases, malformations or genetics are accepted as causes of infertility, but the infertility itself has been a difficult topic. Since there is a strong correlation between religious attitudes and the willingness to reimburse ART, it is tempting to suggest that the debate has focused on moral issues related to ART and not on the underlying medical causes of the infertility. In a statement from 1994, however, WHO recognised the reproductive and sexual needs and the rights of individuals, and called for universal access to sexual and reproductive health services by 2015. (The 4th International Conference on Population and Development (ICPD), Cairo 1994). As a consequence, the European Parliament stated in February 2009 as follows**:** "infertility is a medical condition recognised by World Health Organization that can have severe effects such as depression; points out that infertility is on the increase and now occurs in about 15 % of couples; calls on the Member States, therefore, to ensure the right of couples to universal access to infertility treatment" ("The demographic future of Europe" February 28, 2009 The EU Parliament).

There is a plethora of ethical dilemmas related to ART. For instance, the following questions point to some of the challenges: Is there sufficient evidence on the safety aspects of the reproductive technology to justify treatment? Is the process of decision making about who

receives treatment (age, indications, social setting etc.) fair? Who should receive treatment? The huge inequalities of ART availability (measured as treatment cycles per million population) throughout Europe ranging from 46 per million in Albania to 2209 in Denmark may also rise ethical concerns [6, 62].

Regulation is also a key element. There are some unfortunate examples that this technology in the wrong hands can be characterised as a profit-driven industry without serious ethical considerations.

Competing moral claims may induce tensions. With ART, this issue includes balancing the desires, rights, and interests of potential parents with those of subsequently born children and the society that might have to provide financial support for them [5]. A particular concern is the extent to which the interests of potential children might be subsumed by the rights of putative parents and the growing technological imperatives of assisted reproduction. There are concerns that children in our society do not receive the consideration they ought to [63, 64].

Ideally, the ethical issues that arise in ART should be considered from the child's perspective instead of being driven by moral claims of the parents or by society, or by the moral basis of the medical community [5].

Safety aspects related to assisted reproduction technology

From two to one

In order to compensate for low implantation rates, replacement of more than one embryo in the same cycle has been carried out. This practise has led to high incidence of multiple births in pregnancies after ART as compared to spontaneously conceived pregnancies. Since the inception, the most frequent measure of a successful fertility treatment has been the number of live births, irrespective of outcomes. There are huge variations in the frequency of multiple births after ART between countries [65]. Several papers have been published on perinatal outcome after assisted fertilisation, and there is a general agreement that the higher prevalence of twins explains the lion's share of the amplified risk in ART pregnancies [66-70]. This has turned the ongoing debate on measures of successful fertility treatment towards "births emphasizing a successful singleton at term"; abbreviated the BESST measure [71]. As a consequence, there has been a shift in focus, to risk of prematurity [72].

This has led to an extensive debate on embryo transfer limits in assisted fertilisation. Should elective single embryo transfer (eSET) be required for all first-time in vitro fertilisation patients younger than 38 years of age? In settings where costs are covered by insurance or by public reimbursement, patients more easily accept judicious eSET. Information on the reduced risk of complications for mother and neonate, reassurance of an acceptable cumulative pregnancy rate and focus on the pros of a singleton pregnancy, all appear to be plausible arguments for the prospective parents. However, one study in the USA found that infertile couples wanted multiple births [73], and a more recent publication from Sweden indicated that many patients want two embryos transferred despite detailed information about the complications associated with multiple pregnancies [74]. Over the last decade there has been a growing awareness of this issue and there are huge differences in how these concerns are handled, both between and within countries.

The awareness of the strong association between twins and adverse perinatal outcomes led to a shift towards elective single embryo transfers (eSET) in combination with a tighter focus on the cryopreservation programme for handling of the surplus embryo. The Nordic countries, and in particular Finland, were pioneers in this paradigm shift [75-79]. The cumulative pregnancy rates per oocyte retrieval have been shown to be satisfactory provided a good cryopreservation programme [78]. Furthermore, with the immediate effect on twin rates, it has been shown that the distribution of singletons versus twins approaches the rates of spontaneously conceived pregnancies [24, 77, 80, 81]

Transferring one embryo mainly results in singletons, but there are still concerns about reduced birth rates, and the introduction of elective single embryo transfer (eSET) has been opposed by similar concerns. However, a large randomized controlled trial demonstrated that the cumulative live birth rates for eSET among women less than 36 years of age were comparable to that of double embryo transfer (DET), with an almost elimination of multiple births [81]. A recently published Cochrane review concludes that there is no notable difference in the cumulative birth rate following eSET including one additional thawed embryo replacement and the live birth rate following a single cycle of DET [82]. Different approaches in order to implement eSET have been initiated. In Sweden, state regulation says that in principle only one embryo should be replaced, apart from in exceptional circumstances[83]. Data from Sweden, since eSET regulations were adopted, show that 70% of all ART cycles are eSET and accordingly, there has been a dramatic decrease in multiple births after ART (from 25% to 5%). In Belgium, the government agreed to reimburse the costs of six ART cycles in exchange for the number of embryos replaced [84]. Data from

Belgium, after the implementation of reimbursement, are in accordance with the trends from Sweden [85]. Although legislation is effective, it has been claimed that changing attitudes have been more important [86, 87]. In June of 2008, the American Society for Reproductive Medicine (ASRM) issued updated guidelines on the number of embryos that should be transferred to the women in order to reduce the proportion of high order multiplets. According to these guidelines, no more than two embryos should be transferred in women younger than 35 years, down from the maximum of three recommended in 1998, and women over 40 should attempt no more than five. As this indicates, there are enormous gaps between countries in regulations, medical practise and funding of assisted fertilisation, and there are hot-tempered debates going on between the extreme perspectives. These gaps can partly be explained by cultural, political and religious differences.

Outcome of ART singletons

Several studies have focused on safety aspects of the reproductive technology. Most studies have investigated differences in pregnancy complications, perinatal outcomes, maternal risks, long term morbidity and development comparing pregnancies following assisted fertilisation with pregnancies after spontaneous conception in the general population. The first indication that ART singleton pregnancies may have poorer perinatal outcomes as those spontaneously conceived appeared already in 1985 [88]. However, for several years attention to safety regarding outcome was been towards the multiplets. Recently, along with the implementation of the single embryo transfer, focus on safety aspects and possible draw backs of the reproductive technology have turned towards the outcome of singletons born after assisted fertilisation. In 2004, three systematic reviews on perinatal outcome in singleton pregnancies after ART were published [89-91]. In 2005, two reviews on the same issue were published [92, 93]. These reviews came out with comparable odds ratios (OR) for several important outcome variables such as a two-fold higher risk of preterm birth < 37 weeks of gestation and perinatal mortality, and low birth weight. The overall results from these studies confirm that there is an increased risk of adverse perinatal outcome in singletons born after ART as compared to those spontaneously conceived in the general population.

There are, however, major methodological problems in many of the studies that have evaluated effects of ART. In particular, comparisons of outcomes in pregnancies achieved by

assisted fertilisation in subfertile women and outcomes following spontaneous conception in fertile women may be problematic [94, 95]. Several studies have demonstrated an association between subfertility, as indicated by a long time to pregnancy, and adverse perinatal outcome [96-101]. Therefore, most studies have been faced with criticism due to problems of comparability between subfertile women with groups of healthy, fertile women in the general population, and it is unclear whether the increased risk of adverse perinatal outcome after ART can be attributed to the reproductive technology or to factors related to the inherent infertility.

A variety of different approaches have been carried out in order to explain the gap between the outcomes of spontaneously conceived singletons and ART singletons. One approach has been to study potential differences in outcome related to indications for fertility treatment (female, male, unexplained etc) [23, 102].

Differences in outcome for IVF and ICSI have also been studied, in order to separate the potential adverse effect of the microinjection per se [103]. [104]. It is, however, unclear how many mothers in the ICSI group who are classified as fertile with no additional infertility causes.

Subgroups of treated women have been studied by comparing “low technology treatment” (insemination), ART and spontaneous conception [105]. A 50 % increased risk of preterm birth in the insemination group and a two-fold higher risk in the ART group were found. The study concluded that both infertility itself and the reproductive technology may be associated with an increased risk of preterm birth. Another study found comparable pregnancy outcomes after IVF and insemination, and concludes that the adverse outcome in IVF pregnancies compared to spontaneously conceived pregnancies may be related to specific patient characteristics [106].

It has been suggested that subfertile women who eventually conceive spontaneously would provide a more valid comparison group [107]. However, the definition used for subfertility comprise a heterogeneous group that may differ substantially from ART treated couples. Thus, most of the suggested approaches have methodological weaknesses in separating the influence of the reproductive technology from inherent factors related to infertility.

Placenta previa and assisted fertilisation

Placenta previa is a pregnancy complication in which the placenta partly or totally covers the internal cervical os. The aetiology of placenta previa is unclear, but advanced maternal age, multiparity, previous caesarean section and previous abortions have been associated with increased risk of placenta previa [108]. In several studies assisted fertilisation has been associated with increased risk of placenta previa [22, 109-114]. Six of these were included in a meta-analysis [89], including a total of 39 cases of placenta previa in 1610 ART pregnancies. In this meta-analysis there was a three-fold higher risk of placenta previa related to ART. It is, however, uncertain whether the increased risk of placenta previa is due to the reproductive technology or factors related to the infertility.

Breech presentation and assisted fertilisation

Previous studies have suggested that ART may be associated with higher risk of breech presentation and that obstetric management may differ compared to spontaneously conceived pregnancies [115-118]. In particular, there has been a tendency for more caesarean sections in deliveries of ART neonates. Breech presentation is strongly associated with caesarean section, but it is not known if the obstetric management of breech deliveries differs between ART and spontaneously conceived pregnancies.

AIMS OF THE STUDY

General aim of the thesis

To study the effect of the reproductive technology on specific pregnancy complications and perinatal outcomes, and to disentangle the effect of factors related to the technology from the effect of factors related to the underlying infertility.

Specific aims of the papers

1) To estimate the risk of placenta previa in pregnancies after assisted fertilisation and in pregnancies after spontaneous conception, and to evaluate to the role of the reproductive technology.

2) To compare perinatal outcomes in singleton pregnancies following assisted fertilisation with perinatal outcomes in spontaneously conceived singleton pregnancies, and to evaluate to the role of the reproductive technology versus the underlying infertility.

3) To study the association of assisted fertilisation with breech presentation and to identify factors that influence this association.

4) To describe obstetric handling/management in a time trend perspective of singleton pregnancies after both assisted fertilisation and spontaneous conception for both breech and cephalic presentations.

MATERIALS AND METHODS

The Medical Birth Registry of Norway

The Medical Birth Registry of Norway (MBRN) was established in 1967 and contains information on more than 2.2 million births [119]. The notification is compulsory and filled inn by the attending midwife/physician. The form gives demographic information on the mother and father, mother's health before and during pregnancy, complications during pregnancy, and delivery. The form also has information on the infant obtained within one week after birth. Data on maternal disease and conditions of the infant are coded at the registry according to the definitions in the International Classification of Diseases, from 1967 to 1998, the 8th version was used, and from 1999 onwards the 10th revision. Since 1998, details on transmission to neonatal intensive care unit are also reported.

All live births are also notified to the Central Bureau of Statistics in a parallel civil system for registration of births. The unique national identification number of the newborn is generated and a new record is established in the Central Person Registry. To ensure medical notification of every newborn in the country, all MBRN records are matched with those of the Central Person Registry, resulting in a mutual updating of files.

Data on all stillbirths notified to MBRN are forwarded to the Central Bureau of Statistics, and MBRN data are routinely linked to the Statistics Norway database, to obtain information on infant mortality until 2 years of age through the unique identification number.

For Study I we used data from 1988-2002. For study II and III we used data from 1984 to July 2006.

IVF Register/Pregnancies after assisted fertilisation

All fertility clinics in Norway report detailed information about pregnancies conceived by assisted fertilisation to the MBRN. Assisted fertilisation is defined as fertilisation *in vitro,* notably IVF and ICSI. In these methods fertilisation occurs outside the body and the resulting embryos are transferred to the uterus. The registry does not include information on pregnancies after ovulation inductions or inseminations. The notification from the fertility

clinics is mandatory, and the database is considered to be virtually complete from 1988 and onwards. The record gives information on method used for fertilisation (*in vitro* fertilisation or intracytoplasmatic sperm injection) and whether the transferred embryos were fresh or thawed after cryopreservation. Date of embryo transfer, number of embryos replaced and the number of foetuses confirmed by ultrasound during the first trimester, are also reported. Specific indications for fertility treatment have been recorded since 2002.

Study Design

The three studies of this thesis are population based cohort studies, using prospectively recorded data reported to the MBRN. The birth record of one child can be connected to other births from the same woman by the use of unique project specific anonymous numbers assigned to all mothers in the MBRN. The mothers can be divided into three different groups:

1) Spontaneous conception only
2) ART only
3) Both spontaneous and ART

For the sib-ship analyses in paper I and II, eligible mothers from category 3 were selected. The criteria were subsequent singleton pregnancies, where one singleton was conceived by assisted fertilisation and one after spontaneous conception. In paper I, 1349 mothers fulfilled these criteria and were the basis for the sib-ship file. In paper II, 2546 mothers were eligible for the sib-ship comparison with consecutive singletons with different modes of conceptions. By using these sib-ship data files, we were able to study risks and complications within the pair of siblings with different mode of conception. In paper II, we studied the effect of parity on offspring birth weight within these three categories of mothers. The following flow charts (Figures 8 and 9) show the number of participants who contribute to the respective analyses.

Figure 8. Flow chart of pregnancies in the study population in paper I (MBRN, 1988 - 2002)

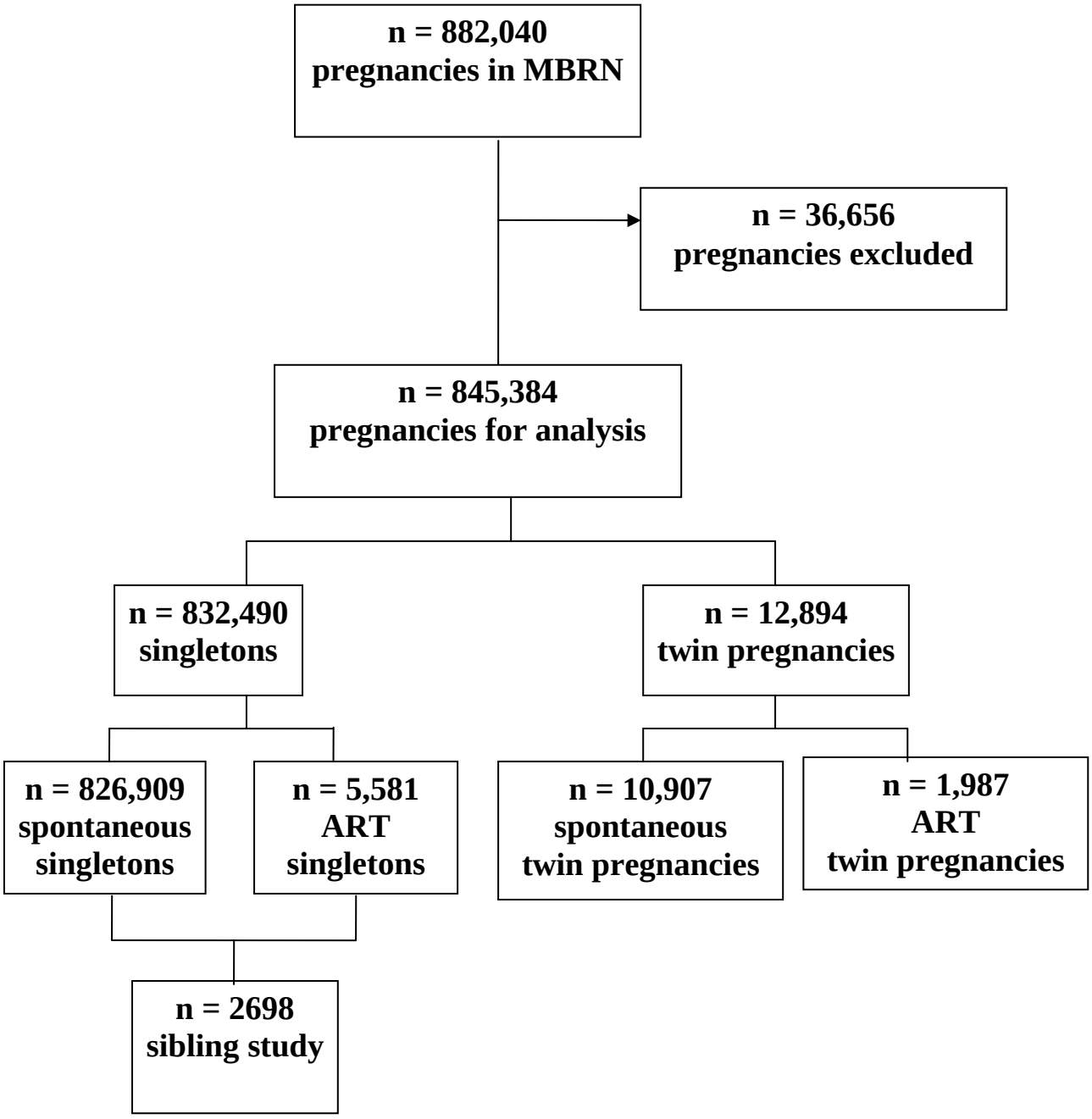
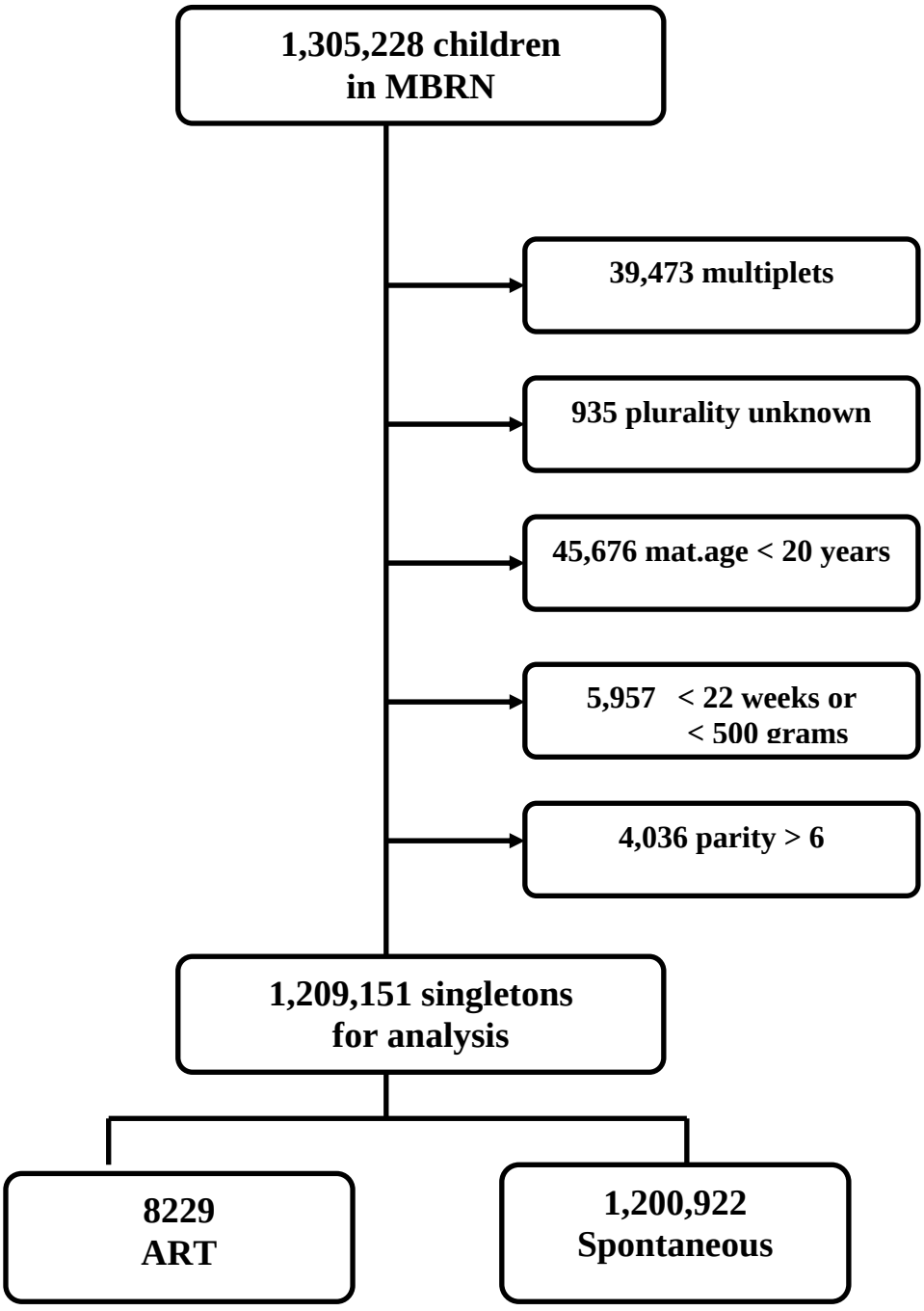


Figure 9. Flow chart of the study population in paper II and III (MBR, 1984 - 2006).



Variables

Placenta previa: The persistence of placenta previa had to be confirmed at birth in order to be reported to the Medical Birth Registry. The reporting did not separate between "previa totalis" and "previa marginalis".

Breech presentation: The fetal presentation at birth was notified by the attending midwife. Until 1998 breech delivery was recorded as a specific complication of delivery (specified in the instructions in the form), but thereafter, breech presentation was ticked off in a specific checkbox.

Birth weight: Measurements of birth weight are regarded objective and reliable measures. The neonate is weighed by the attending midwife or nurse-maid. The completeness of this variable is satisfactory as only 2 % of the births did not have data on birth weight.

Gestational length: Before 1999, data on gestational length was based on reporting of last menstrual period (LMP). There are some uncertainties related to self reporting of menstrual dates, due to irregular cycles, forgotten dates, and continued use of hormonal contraceptives etc. For ART pregnancies, date mimicking last menstrual period is calculated from embryo transfer. After 1998, gestational length is based on data from ultrasound dating. If data from ultrasound examination were not available, we used LMP. For ART pregnancies, ultrasound has been found to be a reliable predictor of day of delivery [120] and it ensures measurement comparability between ART and spontaneous pregnancies. In total, data on duration of gestation were missing in 6 % of the pregnancies.

Small for gestational age (SGA): Low birth weight was defined as 2 standard deviation (SD) below mean birth weight adjusted for gestational age and offspring sex. In a sensitivity analysis we also used the less conservative 10 percentile definition.

Perinatal mortality: Defined as stillbirth after 22 weeks of gestation or as death within the first week of life after 22 completed weeks of pregnancy. The Medical Birth registry is continuously updated by a linkage to Statistics Norway to update data on infant mortality.

Statistical analyses

In general, all analyses were first conducted without adjustments (crude analyses) and then with adjustment for potential confounding factors. Stratified analyses were done for combinations of year of birth, maternal age, and parity.

In paper I, logistic regression analyses were used to estimate the odds ratio of placenta previa according to mode of conception. In the adjusted analyses we controlled for maternal age (20-29, 30-34, 35-39, and 40+ years), parity(0, 1, and 2+), time between births (<3 years and >= 3 years), calendar period (1988-92, 1993-97, 1998-2002) and previous c-section (yes, no) . We used the "cluster" option in Stata and a robust standard error to account for potential correlation in outcome within the same mother. In additional analyses we also used generalized estimating equations (GEE) which produced similar results.

In paper II, odds ratios for premature birth before 37 weeks of gestation, small for gestational age and perinatal mortality were estimated using a random effects logistic regression model. We performed both unadjusted and adjusted analyses for maternal age, parity, offspring sex, time between pregnancies and year of birth. Mean birth weight and mean gestational age were estimated using random-effects linear regression. In the sib-ship comparison we assessed whether order of mode of conception (ART first vs. spontaneous first) modified the results by testing for interaction between the type and order of conception.

In paper III, the risk of breech presentation in pregnancies conceived after assisted fertilisation and spontaneously conceived pregnancies was calculated by using a binomial regression model, and the differences in risk were presented as risk ratios (RR) with the corresponding 95% confidence intervals (95% CI). To account for correlated outcomes within the same mother, we used the robust standard error. In the analyses we controlled for potential confounding by maternal age, parity and year of delivery. We also evaluated gestational age in six categories (22-27 weeks, 28-32 weeks, 33-36 weeks, 40-41 weeks, and 42+ weeks) as a potential mediating factor.

We used STATA for Windows (version 9 and 10, College Station, Texas, USA) and SPSS for Windows (Version 13, Chicago, USA) for the statistical analyses.

MAIN RESULTS

Paper I.

Increased risk of placenta previa in pregnancies following IVF/ICSI; a comparison of ART and non-ART pregnancies in the same mother.

In comparisons with the total population, the risk of placenta previa was 6-fold higher in ART pregnancies (adjusted OR 5.6, 95%CI 4.4-7.0) compared to spontaneously conceived pregnancies.

In the sib-ship analysis, we identified 1349 mothers who had conceived at least one singleton after assisted fertilisation and one after spontaneous conception, and compared the risk of placenta previa in these pregnancies within the same mother. The results of this analyse showed a 3-fold higher risk of placenta previa in ART pregnancies (adjusted OR 2.9, 95%CI 1.4-6.1). The association was similar regardless of order of mode of conception. We concluded that the increased risk of placenta previa in ART pregnancies could be directly related to the reproductive technology.

Paper II.

Effect of technology or maternal factors on perinatal outcome after assisted fertilisation: a population based cohort study.

Compared to outcomes of spontaneously conceived pregnancies in the general population, we found that assisted fertilisation was associated with 25 gram lower mean birth weight (95% CI 14 to 35g) and 2 days shorter duration of gestation (CI 1.6 to 2.3 days). We also found 30% higher risk of small for gestational age offspring (OR 1.26, 1.10 to 1.44), and 30% higher risk of perinatal death (1.31, 1.05 to 1.65) for ART singletons.

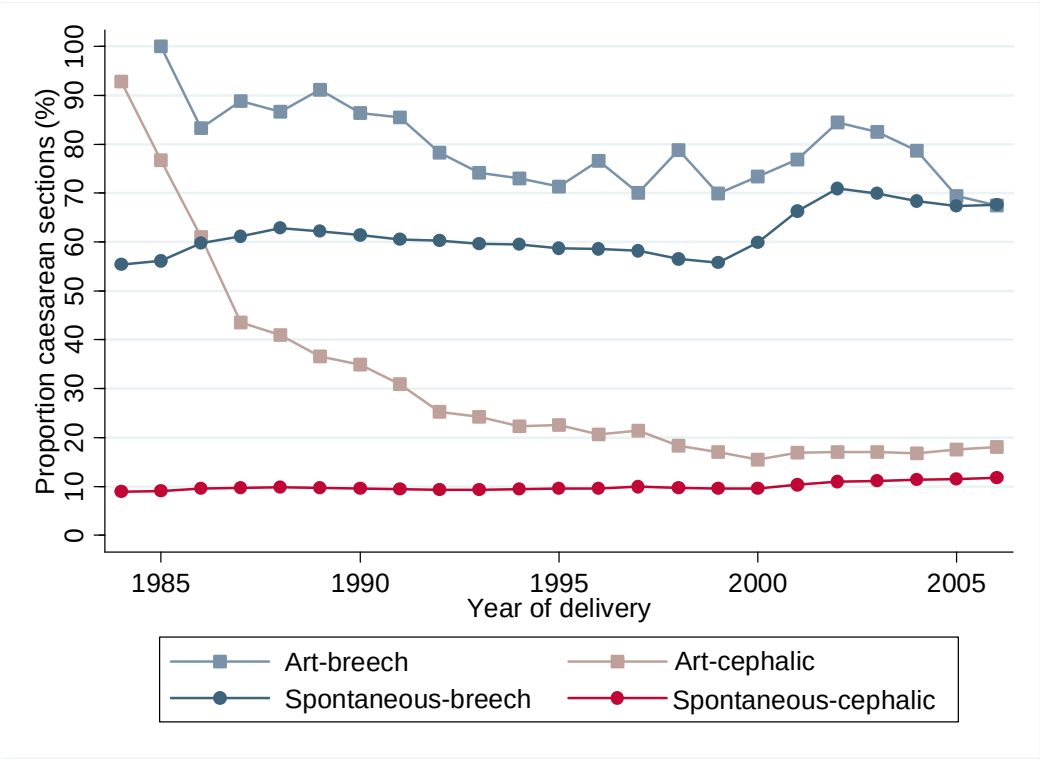
Using the sib-ship comparisons, however, the difference in mean birth weight was only 9 g (-18 to 36), and in gestational age, the difference was 0.6 days (-0.5 to 1.7) The odds ratios for small for gestational age was fully attenuated to 0.99 (0.62 to 1.57) in the sib-ship comparisons, and the odds ratio for perinatal mortality was 0.36 (0.20 to 0.67). The latter estimate should, however, be interpreted with caution due to a potential bias.

Paper III.

Assisted fertilisation and breech delivery: risks and obstetric management

Compared to women with spontaneously conceived singleton pregnancies in the total population, we found that breech presentation occurred nearly 50 percent more often in ART singleton pregnancies (crude RR, 1.48, 95% CI 1.34-1.64). After adjustment for relevant confounding factors, however, this difference was fully attenuated (RR 0.97, 95% CI 0.88-1.07). The most important contributors to the attenuation were shorter length of gestation and lower parity in the ART pregnancies. In a time trend analyses, we found that for both breech and cephalic presentation, the rates of caesarean section in ART births are approaching the rates of the spontaneously conceived (Figure 10).

Figure 10. Proportion of caesarean sections (three years moving averages) in singleton pregnancies after assisted fertilisation (ART) and spontaneous conception (spontaneous) according to breech and cephalic presentation and by year of delivery



GENERAL DISCUSSION

The main results may be summarised as follows

• Assisted fertilisation is associated with an increased risk of placenta previa

• Singletons born after ART have lower mean birth weight, mean gestational length is shorter and there is an increased risk of prematurity and small for gestational age babies as compared to the spontaneously conceived singletons in the general population. However, these outcomes did not differ between singletons of women who had conceived both spontaneously and after assisted fertilisation.

• The increased risk of breech presentation in singleton pregnancies after assisted fertilisation is fully attenuated after adjustment for parity, gestational length and maternal age

• The caesarean rates of ART singletons are approaching the rates of the general population, for both breech and cephalic presentation.

Strengths of the study

Relevant group for comparison

Previously, various approaches to explain the gap between ART and spontaneously conceived pregnancies have been done. The recurring objection has been the identification of relevant comparison groups. This challenge was pointed out already in 1991[96] and later by others [22, 107, 121]. The principal strength of our analyses is the novel analytical approach in which the risk of placenta previa and adverse perinatal outcomes in singleton siblings within the same mother were studied (paper I and II). In this design, maternal factors are kept relatively constant between the ART and the spontaneously conceived pregnancies.

In general, the ultimate study design to evaluate the effect of medical treatment is a randomised controlled trial (RCT). Brought forward to this scenario, the fictitious setting would be to randomise healthy fertile couples to two groups. Group A would be randomised

for assisted fertilisation and group B for spontaneous conception. Then differences in pregnancy complications and perinatal outcomes would be compared between the “exposed” and the “unexposed” groups. However, this design is for obvious reasons not feasible in the context of ART. Fertile couples would presumably be opposed to volunteer for fertility treatment and ethical approval for this impracticable study would not be achieved.

As a second best option we introduced a study design using sib-ship comparisons of outcomes among mothers who had delivered babies both after spontaneous conception and after assisted fertilisation. Thus, we identified mothers with two consecutive singleton pregnancies registered with different mode of conception (i.e. natural and assisted).

In general, factors such as biological (genetically), life style, and socio-economical situation are relatively constant during a woman’s reproductive course. Thus, the major strength of this novel design used in this thesis is the relatively constancy of maternal and paternal factors.

In the sib-ship analyses, order of mode of conception may be important (i.e whether the ART pregnancy precedes the spontaneous conceived or vice versa). Thus, women who seek and achieve successful infertility treatment prior to spontaneous conception may differ from women who seek infertility treatment subsequent to a successful spontaneous pregnancy. It is therefore important to consider if differences in the order of mode of conception could be important in the interpretation of results.

Change of partner from one pregnancy to the next may also be a threat to the interpretation of results. In order to study the paternal influence, we restricted the analyses to those registered with the same father, but this did not change the results.

Wide range of relevant potential confounders available

Information on a wide range of relevant confounding factors enabled us to study the association of the outcome variable and disentangle the importance of different covariates. Maternal age and parity are the single most important confounders in these studies. In the adjusted analyses we have controlled for these potential confounders and also for other factors. In paper III, gestational length and parity were the most important contributors to mediate the association between ART and the increased risk of breech presentation.

Population based cohort study

The unselected population based registration gives information on more than 98 % of all deliveries in Norway after 16 weeks of gestation [119]. In these studies we have included

births with a gestational length of 22 weeks and more. The mandatory and unselected notification to the medical birth registry insures representativeness as the entire population is reported to the registry. In addition, these studies benefit from the general advantage of the cohort study design by the temporality criterion (effect follows cause in time) and by its relative immunity to bias in selection and misclassification.

Limitations of the study

It would have been of interest to have additional information on other factors with potential confounding effects. Information of particular interest would be maternal height and weight before and during pregnancy, as well as menstrual data and time to pregnancy.

An important weakness of the sib-ship analyses is the limited statistical power. For certain comparisons in Study II, for example, few observations (i.e. births < 32 weeks and perinatal mortality) preclude any firm conclusions.

In order to study rare outcomes in more detail larger studies are needed. In our studies we have not evaluated risk of malformations related to assisted fertilisation. Most malformations are rare, and substantially larger studies are needed to study these outcomes with sufficient precision.

Internal validity

The internal validity may be reduced by systematic errors, which broadly can be classified into three general types: *selection bias, information bias and confounding.*

Selection bias

Selection bias results from procedures in the selection or inclusion of subjects to a study which leads to effect estimates that differ from estimates based on the entire population. Therefore, the groups that one wishes to compare may not be representative.

The reporting from the delivery units to the MBRN is mandatory and considered to be virtually complete for the Norwegian population. Selection bias is therefore not likely to constitute a serious threat to the internal validity of the present studies. Still, in the sib-ship analysis of perinatal mortality in study II, selection bias seemed to operate. Women who had experienced perinatal death after a spontaneously conceived pregnancy were three times more likely to conceive by ART in the next pregnancy compared to women without this experience. This suggests that a perinatal death may influence the tendency for a couple to seek fertility treatment, and that this treatment is provided. Since a perinatal death could indicate an inherent tendency for adverse pregnancy outcome the results related to perinatal mortality after ART should be interpreted with caution. Statistically, this was indicated by the interaction test related to order of mode of conception.

Information bias

Information bias results from incorrect determination or measurement of exposure, outcome, or both. The effect of information bias depends on the type of bias. If information is obtained differently for the groups that are compared, one may not easily predict the direction of the bias. Differential information biases may thus go in all directions, either causing under-estimates, or over-estimates of effect. By contrast, random differences in how information is collected, or random measurement error, will typically cause a non-differential misclassification pattern that tends to obscure or attenuate real differences. In a cohort study, information about outcome is usually obtained in the same way for exposed (ART) and unexposed (spontaneous) women. If outcome information were obtained differently, depending on mode of conception, this would be a threat to the validity of the study. For the studies in the present thesis, gestational age was obtained differently for ART and spontaneously conceived pregnancies before 1998. If the use of LMP for the spontaneously conceived resulted in a systematically different measure of gestational age compared to ART pregnancies, this could have resulted in information bias. However, the results did not differ by the different methods, suggesting that information bias caused by different methods of classifying length of gestation, was not a source of bias.

For many couples who struggle with infertility, there is a psychological burden involved, and for some there might be an increased need for closer surveillance by the

attending health care professionals. This in turn, may lead to a more rigorous and active intervention during pregnancy and delivery for ART women. Information bias can therefore not be excluded in studies involving ART. However, information from both groups (ART and spontaneously conceived) was collected under similar circumstances and the outcomes in the present study are not easily influenced by subjective means. Therefore the internal validity of our studies is not likely to be seriously impaired by information bias. As the use of this technology is becoming increasingly more common, a more conventional management related both to surveillance during pregnancy and to obstetric management during labour in ART pregnancies may also be assumed.

Confounding

As in all observational studies, the possible role of uncontrolled or residual confounding must be considered. A confounder must be a risk factor for the outcome of interest and simultaneously be associated with the exposure under study. Also, a confounder must not be affected by the exposure or by the disease, and a confounder must not be an intermediate link in the chain of causation between exposure and outcome.

When there is bias in selection or information in a study, irreparable damage usually occurs. By contrast, when confounding is present, this bias can be corrected, provided that confounding was anticipated and the necessary information related to these factors is collected. Some factors that were considered as potential confounders in this thesis include maternal age, parity, year of birth, duration between pregnancies, smoking and education. Previous caesarean sections were evaluated as a confounder in paper I, as it is related to both ART and placenta previa

There are several techniques for controlling confounding.

Restriction In study number I, II and III; mothers younger than 20 years or mothers with parity beyond 5 were excluded. This was done for better comparability between the groups as no mothers in the ART group were younger than 20 years or registered with a parity of 5 or higher.

In study II, all analyses were repeated after excluding pregnancies that occurred before 1988, because of incompleteness in the registration before that year (sensitivity analyses).

Matching — Most previous studies on pregnancy complications and perinatal outcome after assisted fertilisation have used matched controls for comparisons mostly because of lack of data of the whole spontaneously conceived population. In our studies, data for the entire population were available and therefore, there was no need for matching.

Stratification — Stratified analyses were done for combinations of calendar period of birth, maternal age, and parity in order to assess interaction and confounding.

Precision/chance:

The precision of various estimates reported in a study is mainly related to the size of the study population and the frequency of the exposure and outcome. In general, there are two ways to increase precision, either by increasing the sample size or by more precise measurements. For most outcomes we had sufficient power to estimate clinically important differences. Still, in the sib-ship analyses there was limited power to study perinatal mortality and the risk of prematurity before 32 weeks of gestation (extreme prematurity).

Mechanisms

In Study I, we found that the increased risk of placenta previa in ART pregnancies may be related to the reproductive technology. We were not able to study the potential underlying mechanism for this association. However, one possible explanation for the increased risk could be that site of embryo transfer in the uterine cavity, but to study the importance of site, the depth of transfer from the internal os must be recorded.

In Study II, the differences in perinatal outcome between ART and spontaneously conceived pregnancies that were observed in the general population were not present in the sib ship comparisons. This indicates that there is no direct link between the reproductive

technology and the adverse outcome. The observed difference between ART and spontaneous conception that we found in the total population, may rather be mediated by the underlying infertility of the mother or the couple.

Generalizability

It is an important objective of epidemiological studies to obtain estimates of effect that are valid for relevant target populations (Rothman 2008). The population based nature of these studies secures that the study population is representative as it includes a broad spectre of the couples who achieved pregnancy after assisted fertilisation in Norway. The higher maternal age and lower parity among ART mothers compared to the women who conceived naturally in the general population are in line with previous studies from different countries [122]. Further, the distribution of causes of infertility/indications for fertility treatment is in accordance with that of other countries [22-24]. Therefore, it seems reasonable to assume that the characteristics of the Norwegian infertile couples are comparable to infertile couples in other countries.

It is, however, important to realise that changes in various components of the reproductive technology (stimulation medications, embryo culture media, cryo protector etc.) may influence the outcome of ART. Therefore, the results of the current study may become less relevant with time.

CONCLUSIONS

1) We conclude that there is an increased risk of placenta previa in pregnancies following assisted fertilisation. The increased risk seems to be directly related to the reproductive technology. We suggest that the depth of embryo transfer may be important, and recommend that future studies should include measurements of depth of embryo transfer.

2) We found that adverse perinatal outcomes occurred more often among singletons in ART pregnancies compared to perinatal outcomes after spontaneous conception in the general population. However, these differences were absent in the sib-ship analyses. We conclude that the differences that we observed in the general population may be attributable to the factors that lead to infertility rather than to factors related to the reproductive technology.

3) The increased risk of breech presentation in singleton pregnancies after assisted fertilisation is not caused by the reproductive technology, but seems to be mediated by lower parity and shorter gestational length in ART pregnancies.

4) Differences in obstetric management of singleton ART pregnancies is approaching the conventional management of spontaneously conceived singletons.

The reproductive technology does not seem to add a substantial extra burden beyond the inherent pre-existing infertility as judged from the perinatal outcomes that we have studied. It should be emphasized that further studies of pregnancy complications and perinatal outcome in ART pregnancies are warranted as there are persisting uncertainties.

FUTURE PERSPECTIVES

Demographers have recently argued that assisted fertilisation will be a useful tool to maintain a minimum of net maintenance of the population. In this perspective, both the short and long term safety effects on children and mothers are important, and research and careful monitoring of outcomes are essential. New medications used for controlled ovarian hyper-stimulation, changes of media used for embryo culture and a rapid development of both vitrification and cryopreservation of embryos are examples of the plethora of important variables that must be observed and continuously evaluated.

Over the last years there has been a growing concern that ART may influence imprinting in humans. Because the absolute incidence of imprinting disorders is small (<1:12,000 births), large cohort studies of children born after ART are needed to evaluate whether there is an association between ART and imprinting disorders. There are some indications that ART children may differ metabolically from spontaneously conceived children [123, 124]. These studies are suggesting an imprinting effect of ART also in human, and this warrant properly controlled and sufficiently large studies that compare ART children and spontaneously conceived children in order to evaluate any potential unintended effects of the reproductive technology.

In epidemiological studies of rare outcomes, low statistical power due to few observations is a common weakness. In the Nordic countries, registrations of pregnancies and births after assisted fertilisation have been recorded. After an initiative from a Danish group, a Nordic collaboration group with delegates from Denmark, Sweden, Finland and Norway has been established. The intention is to set up a Nordic database with pooling of data that include all ART pregnancies, deliveries and neonates from all the participating countries. A large number of ART pregnancies and children enables rare, but important outcomes to be studied with sufficient statistical power. The Nordic collaboration is of crucial importance and will presumably contribute to the highlighting of where further research and debate within the field of reproductive medicine are needed.

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Increased risk of placenta previa in pregnancies following IVF/ICSI; a comparison of ART and non-ART pregnancies in the same mother

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BACKGROUND: The risk of placenta previa may be increased in pregnancies conceived by assisted reproduction technology (ART). Whether the increased risk is due to factors related to the reproductive technology, or associated with maternal factors, is not known. METHODS: In a nationwide population-based study, we included 845 384 pregnancies reported to the Medical Birth Registry of Norway between 1988 and 2002 and compared the risk of placenta previa in 7568 pregnancies conceived after assisted fertilization, with the risk in naturally conceived pregnancies. To study the influence of ART more directly, we compared the risk of placenta previa between consecutive pregnancies among 1349 women who had conceived both naturally and after assisted fertilization. Odds ratios (OR), adjusted for maternal age, parity, previous Caesarean section and time interval between pregnancies were estimated using logistic regression. RESULTS: There was a six-fold higher risk of placenta previa in singleton pregnancies conceived by assisted fertilization compared with naturally conceived pregnancies [adjusted OR 5.6, 95% confidence interval (CI) 4.4–7.0]. Among mothers who had conceived both naturally and after assisted fertilization, the risk of placenta previa was nearly three-fold higher in the pregnancy following assisted fertilization (adjusted OR 2.9, 95% CI 1.4–6.1), compared with that in the naturally conceived pregnancy. CONCLUSIONS: The use of ART is associated with an increased risk of placenta previa. Our findings suggest that the increased risk may be caused by factors related to the reproductive technology.

Key words: assisted reproduction technology/placenta previa/population study/sibling comparisons

Introduction

Placenta previa, placentation in the lower segment of the uterine cavity, is associated with serious maternal and adverse fetal outcomes, including haemorrhage, prematurity and increased perinatal morbidity and mortality (McShane *et al*., 1985; Ananth *et al*., 1989). Its aetiology remains unclear, but several studies have reported higher frequencies of placenta previa in pregnancies of women with advanced maternal age, multiparity and previous Caesarean delivery and abortion (Faiz and Ananth, 2003). Lifestyle factors such as smoking and cocaine abuse during pregnancy have also been related to the increased risk of placenta previa (Handler *et al*., 1994; Ananth *et al*., 1996). In a meta-analysis of complications related to assisted reproduction, the investigators reported three-fold higher risk of placenta previa associated with the treatment (Jackson *et al*., 2004). The result was, however, based on six small studies, with only 39 cases of placenta previa in 1610 pregnancies conceived by assisted fertilization.

The comparison group in the studies included in the meta-analysis has been women with naturally conceived pregnancies from the general population. However, these studies have not been able to separate effects of unfavourable maternal factors from factors that may be related to the reproduction technology. Worldwide, an increasing proportion of pregnancies are conceived by assisted fertilization, and therefore, possible iatrogenic side effects of the treatment should be clarified.

In this study, we first contrasted the prevalence of placenta previa in pregnancies following assisted fertilization with the prevalence in naturally conceived pregnancies. Second, we attempted to separate the influence of maternal factors from that of the assisted reproduction technology (ART) by studying women who had conceived both naturally and after assisted fertilization. Among these women, we compared the risk of placenta previa between consecutive pregnancies, where one sibling was conceived spontaneously and the other after

assisted fertilization. We hypothesized that if a pregnancy following assisted fertilization was more likely to result in placenta previa, the increased risk could be attributed to the ART and not only to maternal factors.

Materials and methods

Data were derived from the Medical Birth Registry of Norway. This nationwide registry was established in 1967 and comprises records from more than 2×10^6 deliveries (Irgens, 2000). Information on each pregnancy is based on standardized forms completed by midwives within 1 week of delivery. The reporting is mandatory and covers virtually all births in Norway. The form gives information related to the mother's health before and during pregnancy, complications during pregnancy and at delivery and perinatal data of the child.

From all fertility clinics in Norway, the Medical Birth Registry also receives separate notification of pregnancies conceived after assisted fertilization. This reporting is also mandatory and includes information related to the use of ART, notably IVF, ICSI and cryopreservation of embryos. In all these methods, fertilization occurs *in vitro*, and the resulting embryos are transferred to the uterus. Information on the date of embryo transfer, the number of embryos transferred and the number of fetuses with ongoing heart activity confirmed by ultrasound at gestational weeks 7–8 is also recorded. In this study, we did not include the induction of ovulation or insemination as methods of ART. Norwegian ART clinics have since mid-1990s almost exclusively replaced a maximum of two embryos. Fetal reduction is virtually never performed in Norway.

We used data for the period 1988–2002, comprising 882 040 pregnancies. According to recommendations from the WHO, we restricted the analyses to pregnancies where the length of gestation was 22 weeks or more and offspring birthweight was at least 500 g, resulting in 3607 excluded pregnancies. There were no pregnancies after assisted fertilization among mothers younger than 20 years of age or with parity of five or higher. Therefore, we excluded all pregnancies among mothers below 20 years of age (n = 29 998) and parity of five or more (n = 1802). We also excluded 335 triplet pregnancies (137 after assisted fertilization), 19 quadruplet pregnancies (six after assisted fertilization) and 895 pregnancies with missing data on the length of gestation and birthweight. This left 845 384 deliveries among 502 840 women; 832 490 were singletons, and 5581 (0.7%) of the singleton pregnancies were conceived after assisted fertilization. Among 12 894 twin pregnancies, 1987 (15.4%) were conceived after treatment with ART.

Consecutive pregnancies in the same mother

In the study population of 502 840 women, 1349 women were registered with two consecutive singleton pregnancies, where one sibling was delivered after spontaneous conception and the other was delivered after ART. If the mothers had given birth to more than two singletons, we used the two first consecutive births eligible for the sibling comparison. Thus, among 2698 deliveries, 1349 children were conceived spontaneously and 1349 after ART. Among the pregnancies, 762 (56%) of those conceived by ART preceded the naturally conceived pregnancy.

Placenta previa

Ultrasound screening is routinely offered to all pregnant women in Norway around week 18 of gestation. Approximately 98% of all pregnant women attend this ultrasound examination (Backe, 1997), and depending on the findings, some of these women are followed up throughout pregnancy with repeated ultrasound examinations. When placenta previa is detected at the routine screening, the condition has to be verified at the follow-up examination around week 32 and subsequently confirmed at birth to be reported to the Medical Birth Registry. In births before the follow-up scan at week 32, the diagnosis is based on verification at birth. The standardized form sent to the Medical Birth Registry does not differentiate between placenta previa *marginalis* and placenta previa *totalis*.

Statistical analysis

First, we used information from the general population of pregnant women and compared the risk of placenta previa between naturally conceived pregnancies and pregnancies conceived after assisted fertilization. Second, we restricted the analysis to consecutive pregnancies of singletons among mothers who had delivered both after spontaneous conception and after the use of assisted reproductive technology.

To account for the dependencies of pregnancies delivered by the same mother, we adjusted the SE for intra-group dependencies (Williams, 2000). We also used generalized estimating equation (GEE) and conditional logistic regression (Carlin *et al*., 2005). The three techniques produced similar results, and we only present the results from the logistic regression analyses.

In the analyses, we evaluated possible confounding by other factors and adjusted for maternal age (20–29, 30–34, 35 years and older), parity (0, 1, 2 or higher), time interval between births (<3 years, ≥3 years), period of birth (5-year categories), previous Caesarean sections, sex of offspring and marital status. Stratified analyses were performed for combinations of period, maternal age and parity. In supplementary subanalyses, we adjusted for maternal smoking (before and during pregnancy) and the level of education. For the analyses, we used SPSS for Windows (Version 13, Chicago, IL, USA) and Stata (Version 9, College Station, TX, USA).

Results

Placenta previa in the general population of pregnant women

Women who gave birth after the use of ART were older and had fewer previous births than women who delivered after spontaneous conception (Table I). They also smoked less, but the level of education did not differ between the groups. Among 845 384 pregnancies, 1949 (0.23%) were diagnosed with placenta previa; 1910 in singleton pregnancies and 39 in twin pregnancies. The overall prevalence of placenta previa was fairly stable from 1988 to 2002, but in pregnancies following assisted fertilization, the prevalence was consistently higher throughout the period compared with spontaneously conceived pregnancies. Before any adjustments were made, the crude prevalence of placenta previa in naturally conceived singleton pregnancies was 0.22% as compared with 1.59% in singleton pregnancies conceived after assisted fertilization (Table I). In twin pregnancies, the corresponding proportions were 0.21 and 0.81%.

Adjustment for potentially confounding factors did not substantially alter the association between the use of ART and the occurrence of placenta previa (Table II). Thus, the odds ratio (OR) for singleton pregnancies was 5.6 [95% confidence interval (CI) 4.4–7.0] after adjustment for maternal age, parity, interval between deliveries, the year of delivery, the history of Caesarean section, offspring sex and marital status. In a separate subgroup analysis, we could also adjust for maternal smoking and the level of education, but the results were not

Table I. Maternal characteristics of pregnancies conceived by assisted fertilization and spontaneously conceived pregnancies in Norway, 1988–2002[a]

	Singleton pregnancies, *n* (%)		Twin pregnancies, *n* (%)	
	Assisted fertilization	Spontaneous conception	Assisted fertilization	Spontaneous conception
Maternal age (years)				
20–29	1036 (18.6)	493 403 (59.7)	428 (21.5)	5501 (50.4)
30–34	2601 (46.6)	235 609 (28.5)	999 (50.3)	3692 (33.8)
35–39	1883 (33.7)	97 897 (11.8)	560 (28.2)	1714 (15.7)
40+	61 (1.1)	7715 (0.9)	7 (0.4)	90 (0.8)
Parity				
0	3962 (71.0)	341 917 (41.3)	1388 (69.8)	4297 (39.4)
1	1457 (26.1)	301 642 (36.5)	543 (27.3)	4025 (36.9)
≥2	162 (2.9)	183 350 (22.2)	56 (2.8)	2656 (23.6)
Previous Caesarean section				
No	5319 (95.3)	765 050 (92.5)	1889 (95.1)	10 083 (92.4)
Yes	262 (4.7)	61 859 (7.5)	98 (4.9)	824 (7.6)
Smoking during pregnancy[b]				
Yes	261 (10.3)	30 834 (14.2)	83 (8.8)	447 (14.0)
No	1782 (70.0)	137 986 (63.6)	647 (68.9)	2008 (62.7)
Unknown	502 (19.7)	48 052 (22.2)	209 (22.3)	746 (23.3)
Method				
IVF[c]	4033 (72.3)	–	1533 (77.2)	–
ICSI[c]	981 (17.6)	–	305 (15.3)	–
Unknown	567 (10.2)	–	149 (7.5)	–
Placenta previa	89 (1.59)	1821 (0.22)	16 (0.81)	23 (0.21)

[a]Restricted to pregnancies among mothers 20 years or older with five or less previous births.
[b]Smoking data restricted to pregnancies after November 1998.
[c]Including thawed embryo replacements.

Table II. Odds ratio (OR) of placenta previa in pregnancies after assisted fertilization versus spontaneous conception adjusted for maternal age at birth, parity, duration between pregnancies, calendar period of birth and previous Caesarean section by plurality[a]

	Singletons					Twins				
	N	Cases	Crude OR	Adjusted OR	95% confidence interval (CI)	*n*	Cases	Crude OR	Adjusted OR	95% CI
Spontaneous conception	826 909	1821	1.0	1.0	Reference	10 907	23	1.0	1.0	Reference
Assisted fertilization	5581	89	7.3	5.6	4.4–7.0	1987	16	3.8	2.9	1.5–5.8
Maternal age										
20–29	494 439	711	1.0	1.0	Reference	5929	6	1.0	1.0	Reference
30–34	238 210	692	2.0	1.8	1.6–2.0	4691	21	4.4	3.4	1.3–8.9
35+	99 841	507	3.5	2.9	2.6–3.3	2274	12	5.2	3.7	1.3–10.8
Parity										
Para 0	345 879	591	1.0	1.0	Reference	5685	16	1.0	1.0	Reference
Para 1	303 099	750	1.4	1.2	1.0–1.3	4568	16	1.2	0.9	0.3–2.7
Para 2+	183 512	569	1.8	1.1	1.0–1.3	2641	7	0.9	0.7	0.2–2.0
Time between births										
Para 0[b]	345 879	591	–	–	–	5685	16	–	–	–
<3 years	213 974	485	1.0	1.0	Reference	2827	6	1.0	1.0	Reference
>3 years	272 637	834	1.4	1.1	1.0–1.3	4382	17	1.8	1.5	0.6–3.9
Year of birth										
1988–1992	278 813	588	1.0	1.0	Reference	3548	8	1.0	1.0	Reference
1993–1997	282 386	617	1.0	1.0	0.9–1.1	4347	15	1.5	1.3	0.5–3.0
1998–2002	271 291	705	1.1	1.0	0.9–1.2	2641	16	4	1.0	0.4–2.2
Previous Caesarean section										
No	770 369	1670	1.0	1.0	Reference	11 927	6	1.0	1.0	Reference
Yes	62 121	240	1.8	1.4	1.2–1.6	922	33	2.4	2.2	0.8–5.9

[a]Analysis restricted to pregnancies among mothers giving birth at age 20 or older and with five or less previous births. SE corrected for intra-group dependencies.
[b]Dropped because of collinearity with parity.

substantially different from the main results (data not shown). In twin pregnancies, the adjusted OR was 2.9 (95% CI 1.5–5.8).

We analysed different methods of assisted reproduction separately and found that the increased risk of placenta previa was fairly similar for IVF and ICSI. Compared with the spontaneously conceived pregnancies, the prevalence was six-fold higher in IVF pregnancies (adjusted OR 6.3, 95% CI 4.9–8.1) and four-fold higher in ICSI pregnancies (adjusted OR 4.4, 95% CI 2.5–7.8). In pregnancies after the replacement of thawed embryos, the numbers were too small to study any effects (three cases of placenta previa among 227 singleton pregnancies).

Table III. Characteristics of pregnancies complicated by placenta previa after assisted fertilization and spontaneous conception in Norway from 1988 to 2002 by plurality[a]

	Singletons		Twins	
	Assisted fertilization (*N* = 89)	Spontaneous conception (*N* = 1821)	Assisted fertilization (*N* = 16)	Spontaneous conception (*N* = 23)
Mean gestation in days (SD)	259.0 (20.2)	258.4 (23.3)	245.0 (16.0)	238 (23.0)
Mean birthweight in kg (SD)	2838 (638)	2904 (777)	2370 (716)	2507 (661)
Caesarean section (%)	96.6	85.1	100	87.0

[a]Restricted to pregnancies among mothers giving birth at age 20 or older and with five or less previous births.

In cases of placenta previa, mean gestational age and mean birthweight were fairly similar in pregnancies after naturally conception and after assisted fertilization, whereas Caesarean delivery was more frequent if the pregnancy was conceived after assisted fertilization (Table III). Thus, the proportion of Caesarean section was 96.6% in singleton pregnancies with placenta previa as compared with 85.1% in spontaneously conceived pregnancies. To avoid the possibility that placenta previa was reported more often in pregnancies after assisted fertilization (potential surveillance bias), we restricted the diagnosis of placenta previa to pregnancies with Caesarean delivery. However, the results were similar to those of the main analysis, showing six-fold higher prevalence (OR 6.3, 95% CI 4.9–7.9) of placenta previa associated with assisted fertilization.

We also stratified the analysis according to the calendar period of birth (1988–1992, 1993–1997 and 1998–2002), parity and maternal age, but the results did not substantially differ across strata of these variables.

Comparison of consecutive sibling pregnancies

In the study population, 1349 women had delivered singletons both after natural conception and after assisted fertilization (Table IV). In pregnancies following assisted reproduction, women were slightly older but had fewer previous births and previous Caesarean sections than when the same women delivered after spontaneous conception. The crude prevalence of placenta previa was 2.0% in pregnancies conceived by ART as compared with 0.7% in pregnancies following natural conception, suggesting approximately three-fold higher prevalence. After adjustment for maternal age, parity and previous Caesarean section, placenta previa was nearly three times more likely to occur in pregnancies following assisted fertilization (OR = 2.9, 95% CI 1.4–6.1) compared with spontaneously conceived sibling pregnancies (Table V).

In additional analyses, we studied the association with placenta previa in pregnancies where the first child was conceived spontaneously and in pregnancies where the first child was conceived by assisted fertilization. After adjustment for maternal age and previous Caesarean section, the results showed a positive association with placenta previa regardless of whether the first (OR 2.5, 95% CI, 0.5–12.5) or the second pregnancy (OR 2.6, 95% CI 0.4–16.8) was conceived by the use of ART.

Table IV. Maternal characteristics of consecutive singleton pregnancies among women who have given birth both after assisted fertilization and after spontaneous conception

	Assisted fertilization (*N* = 1349), *n* (%)	Spontaneous conception (*N* = 1349), *n* (%)
Maternal age at birth (years)		
20–29	254 (18.8)	461 (34.2)
30–34	676 (50.1)	489 (36.3)
35+	419 (31.1)	399 (29.6)
Parity		
0	675 (50.0)	537 (39.8)
1	617 (45.7)	704 (52.2)
≥2	57 (4.2)	108 (8.1)
Previous Caesarean section		
No	1225 (90.8)	1138 (84.4)
Yes	124 (9.2)	211 (15.6)
Method		
IVF	961 (71.2)	–
ICSI	194 (14.4)	–
Unknown	194 (14.4)	–
Smoking during pregnancy[a]		
Yes	57 (9.9)	51 (11.5)
No	402 (69.4)	302 (68.0)
Unknown	120 (20.7)	91 (20.5)
Placenta previa	27 (2.0)	10 (0.7)

[a]Smoking data restricted to pregnancies after November 1998.

Discussion

By comparing consecutive pregnancies, where the mother conceived spontaneously in one pregnancy and after assisted fertilization in the other, it seems reasonable to attribute differences in pregnancy complications to the reproduction technology rather than to maternal factors. Consequently, the nearly three-fold higher risk of placenta previa that we observed in the pregnancy following assisted fertilization may largely be attributed to factors related to the reproduction technology.

Within the large, unselected population, we found that placenta previa occurred six times more often in singleton pregnancies after assisted reproduction compared with naturally conceived pregnancies. In this setting, the higher prevalence of placenta previa is most likely due to a combination of maternal factors and factors related to the ART.

Previously, a few small studies have examined the association between assisted fertilization and the risk of placenta previa (Howe *et al*., 1990; Tan *et al*., 1992; Tanbo *et al*., 1995; Verlaenen *et al*., 1995; Reubinoff *et al*., 1997; Koudstaal *et al*., 2000; Shevell *et al*., 2005). Most studies found that placenta previa is more common after assisted reproduction. Six of

Table V. Odds ratio (OR) of placenta previa in consecutive singleton pregnancies among women who have given birth both after assisted fertilization and after spontaneous conception

	Women	Placenta previa	Crude OR	AdjustedOR[a]	95% confidence interval
Spontaneous conception	1349	10	1.0	1.0	Reference
Assisted fertilization	1349	27	2.7	2.9	1.4–6.1
Order of mode of conception					
Spontaneous first					
Spontaneous conception	587	3	1.0	1.0	Reference
Assisted fertilization	587	17	5.8	2.6	0.4–16.8
Assisted fertilization first					
Spontaneous conception	762	7	1.0	1.0	Reference
Assisted fertilization	762	10	1.4	2.5	0.5–12.5

[a]Adjusted for maternal age at birth, parity and previous Caesarean section.

these studies were included in a meta-analysis of complications after assisted fertilization (Jackson *et al*., 2004). The joint results indicated three-fold higher risk of placenta previa in pregnancies after assisted fertilization compared with naturally conceived pregnancies. However, the analysis was only based on 39 cases of placenta previa in 1610 pregnancies following assisted fertilization. However, no study could distinguish between the impact of maternal factors and factors related to the reproduction technology.

Our study includes an unselected nationwide population with compulsory reporting of all births to the Medical Birth Registry of Norway. The unique identification number of every citizen in the country enables pregnancies conceived after assisted fertilization to be identified and linked to pregnancy outcome. Information on potentially confounding factors, such as parity, maternal age and previous Caesarean section, allows us to adjust for these factors in the statistical analysis, and in a subset of the population, the information on the level of education and smoking could also be taken into account.

Although complete previa (‘*totalis*’) tends to be associated with more severe bleeding and an absolute indication for Caesarean section, a less severe degree of placenta previa (‘*marginalis*’) may also cause life-threatening haemorrhage and may therefore be regarded as clinically important even though the site of placentation allows vaginal delivery (Ghourab, 2001). Thus, we included all cases of placenta previa regardless of the mode of delivery in the primary analysis. In a secondary analysis, we restricted the diagnosis of placenta previa to Caesarean section deliveries. This restriction provided a slightly stronger association between ART and the risk of placenta previa (OR = 6.3), and the adjusted OR of 5.6 obtained in the primary analysis may be considered as a more conservative estimate.

Except for one extra ultrasound examination in weeks 7–8 of pregnancy, women who conceive after assisted fertilization attend the standard programme for prenatal care in Norway. Specially trained midwives perform the routine ultrasound examination at 17–18 weeks of gestation, and virtually, all pregnant women in the country attend this examination (Backe, 1997). If prenatal surveillance was more rigorous for women who received assisted fertilization, one consequence could be that placenta previa would be diagnosed more often in the assisted fertilization group than among women who conceived spontaneously. To reduce a possible diagnostic bias, we restricted the diagnosis of placenta previa to cases that were registered after Caesarean deliveries. However, this did not attenuate the strong positive association with assisted fertilization. Twins constitute another group that receives close surveillance, regardless of whether the pregnancy is conceived spontaneously or after assisted fertilization. However, the higher frequency of placenta previa in twin pregnancies conceived by reproduction technology strengthens the validity of our findings and suggests that placenta previa is not diagnosed systematically different between the groups.

Nonetheless, women who seek infertility treatment represent a selected group of women. By using naturally conceived pregnancies from the general population as comparison, one cannot readily distinguish the impact of maternal factors from factors related to ART. By comparing consecutive pregnancies among women who have delivered after both assisted fertilization and spontaneous conception, one may, at least partly, solve this problem because confounding by maternal and environmental factors is less likely. The results for consecutive siblings, showing three-fold higher risk of placenta previa associated with assisted fertilization, suggest that a substantial proportion of the increased risk may be attributed to ART.

The underlying mechanism for this effect is not clear. In assisted fertilization, drugs are utilized to induce multiple follicular development. Fertilization and embryo development take place outside the body, and embryos enter the uterine cavity through the cervix by mechanical means.

The stimulation protocol used in assisted reproduction frequently results in very high levels of gonadal steroids that induce morphological and structural changes and disturbed expression of relevant genes in the endometrium (Horcajadas *et al*., 2005). These effects are thought to be global, and given the current knowledge, this effect on the endometrium is not likely to contribute to a higher risk of placenta previa.

It is well documented that fertilization and embryo culture *in vitro* can change key metabolic pathways in the embryo (Leese *et al*., 1998). These effects may interfere with implantation and early embryo development, but it is difficult to explain how the changes could result in more frequent implantation in the lower segment of the uterus.

In ART, embryos are placed in the uterine cavity by the transcervical route using a catheter. This procedure may induce uterine contraction, possibly due to the release of prostaglandins after mechanical stimulation of the internal cervical os (Fraser, 1992; Fanchin *et al*., 1998; Mansour, 2005). It has

been demonstrated that as much as 15% of replaced embryos may be totally expelled from the uterus (Poindexter *et al*., 1986). It is conceivable that these mechanically induced uterine contractions could lead to higher frequencies of implantation in the lower uterine segment and thereby increase the risk of placenta previa. Another study reported that 80% of embryos were implanted in the area in which they were transferred (Baba *et al*., 2000), suggesting that the site of replacement could be particularly important. Also, lower deposition in the uterine cavity may improve the rate of successful implantation (Waterstone *et al*., 1991; Coroleu *et al*., 2002), and preference now tends to be lower replacement of the embryo. To evaluate whether the risk of placenta previa may be attributed to the depth of embryo replacement, however, the transfer distance from both the internal cervical os and the uterine fundus should be monitored and systematically recorded.

In summary, the risk of placenta previa in pregnancies following assisted reproductive treatment is considerably higher than in pregnancies following natural conception. Our results suggest that factors directly related to the reproduction technology contribute to the increased risk.

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Effects of technology or maternal factors on perinatal outcome after assisted fertilisation: a population-based cohort study

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Summary

Background **Research suggests that singleton births following assisted fertilisation are associated with adverse outcomes; however, these results might be confounded by factors that affect both fertility and pregnancy outcome. We therefore compared pregnancy outcomes in women who had singleton pregnancies conceived both spontaneously and after assisted fertilisation.**

Methods **In a population-based cohort study, we assessed differences in birthweight, gestational age, and odds ratios (OR) of small for gestational age babies, premature births, and perinatal deaths in singletons (gestation ≥22 weeks or birthweigh ≥500 g) born to 2546 Norwegian women (>20 years) who had conceived at least one child spontaneously and another after assisted fertilisation among 1 200 922 births after spontaneous conception and 8229 after assisted fertilisation.**

Findings **In the whole study population, assisted-fertilisation conceptions were associated with lower mean birthweight (difference 25 g, 95% CI 14 to 35), shorter duration of gestation (2·0 days, 1·6 to 2·3) and increased risks of small for gestational age (OR 1·26, 1·10 to 1·44), and perinatal death (1·31, 1·05 to 1·65) than were spontaneous conceptions. In the sibling-relationship comparisons, the spontaneous versus the assisted-fertilisation conceptions showed a difference of only 9 g (–18 to 36) in birthweight and 0·6 days (–0·5 to 1·7) in gestational age. For assisted fertilisation versus spontaneous conception in the sibling-relationship comparisons, the OR for small for gestational age was 0·99 (0·62 to 1·57) and that for perinatal mortality was 0·36 (0·20 to 0·67).**

Interpretation **Birthweight, gestational age, and risks of small for gestational age babies, and preterm delivery did not differ among infants of women who had conceived both spontaneously and after assisted fertilisation. The adverse outcomes of assisted fertilisation that we noted compared with those in the general population could therefore be attributable to the factors leading to infertility, rather than to factors related to the reproductive technology.**

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Introduction

An increasing number of women in more developed countries are delaying childbearing until an age when their fertility is reduced. This tendency, together with technological advances and greater accessibility to fertility treatment, has led to increased use of assisted-reproduction technologies. Of mounting concern, however, is that assisted fertilisation is associated with an increased risk of adverse perinatal outcomes.[1] The causes of this increase have been the subject of much controversy—is the reproductive technology to blame or could the adverse outcomes be attributed to factors related to the infertile couple? Although the higher prevalence of twins and triplets associated with assisted fertilisation accounts for much of the increased risk,[1–5] singletons conceived after assisted fertilisation are at higher risk of low birthweight, preterm delivery, and perinatal death than are spontaneously conceived singletons,[1–4,6–9] suggesting that the technology, and not the factors contributing to infertility, might cause differences in risk.

However, separation of the effects of the reproductive technology from those of factors leading to infertility is difficult and some conditions (eg, fibroids, uterine malformations, and hormonal disorders) can affect both fertility and pregnancy outcome.[10] In outcome studies of singleton pregnancies conceived with assisted fertilisation, the comparison group has generally consisted of spontaneously conceived singleton controls or spontaneously conceived pregnancies in the general population.[1–3,5–9] In these studies, differences in outcomes cannot be easily attributed to factors leading to the infertility or to features of the reproductive technology.

We have attempted to address the problem of comparability by keeping maternal factors as constant as possible. We compared outcomes of two consecutive singleton pregnancies—ie, one conceived after assisted fertilisation and the other after spontaneous conception, assuming that maternal factors are fairly constant in pregnancies within the same mother. For comparison with previous studies we also studied differences in fetal outcomes of spontaneously conceived singleton

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	Assisted fertilisation (N=8229)	Spontaneous conception (N=1 200 922)
Year of birth		
1984–89	298 (4%)	300 565 (25%)
1990–94	1178 (14%)	281 112 (23%)
1995–99	2236 (27%)	278 317 (23%)
2000–06	4517 (55%)	340 928 (28%)
Maternal age (years)		
20–29	1549 (19%)	715 374 (60%)
30–34	3770 (46%)	342 195 (28%)
≥35	2910 (35%)	143 353 (12%)
Parity*		
0	5600 (68%)	475 124 (40%)
1	2202 (27%)	440 664 (37%)
≥2	427 (5%)	285 134 (24%)
Smoking during pregnancy†		
No	3839 (87%)	267 483 (79%)
Intermittent	73 (2%)	7874 (2%)
Regular	499 (11%)	62 316 (19%)
Unknown	685 (··)	58 520 (··)
Caesarean section	1983 (24%)	150 691 (13%)
Induction of labour	1228 (15%)	130 290 (11%)
Type of ART procedure		
IVF fresh embryo	5738 (70%)	··
IVF frozen embryo	332 (4%)	··
ICSI fresh embryo	1807 (22%)	··
ICSI frozen embryo	98 (1%)	··
Unknown	254 (3%)	··
Indication for fertility treatment‡		
Male factor	881 (39%)	··
Endometriosis	219 (10%)	··
Tubal factor	447 (21%)	··
Ovulation dysfunction	251 (11%)	··
Unexplained	433 (19%)	··
Other	15 (1%)	··

Data are number (%). ART=assisted reproductive technology. IVF=in-vitro fertilisation. ICSI=intracytoplasmic sperm injection. *Restricted to five or fewer previous births. †Percentages based on pregnancies after November, 1998. ‡Percentages based on pregnancies from 2002–05.

Table 1: **Characteristics of singleton pregnancies conceived spontaneously and after assisted fertilisation**

pregnanciess in the general population and the outcomes of those born after the use of assisted fertilisation.

Methods

Study population

For the **Medical Birth Registry of Norway** see http://www.mfr.no

We used data from the Medical Birth Registry of Norway, which had records of more than 2·2 million births between 1967 and 2006. Information about each pregnancy was recorded on standard forms by midwives or doctors within 1 week of delivery for all deliveries after 16 weeks of gestation. The record included information about the mother's health before and during pregnancy, complications during pregnancy, and at birth, and characteristics of the child within the first week after delivery. The Medical Birth Registry is routinely linked to the Statistics Norway database, to obtain information on infant mortality, through the unique identification number of every Norwegian citizen.

All fertility clinics in Norway report detailed information about pregnancies achieved with assisted fertilisation to the Medical Birth Registry. Provision of this information is mandatory, and the database is considered to be virtually complete from 1988 onwards and includes information on method of fertilisation, notably in-vitro fertilisation or intracytoplasmic sperm injection, and whether the replaced embryos were fresh or cryopreserved. Additionally, information is provided on the date of embryo replacement, number of embryos transferred, and the number of fetuses with heart activity confirmed by ultrasonography during the first trimester. Information on indications for fertility treatment was available only for 2002–05. We used data from 1 305 228 births that occurred from January, 1984, to the end of June, 2006. We excluded 39 473 multiple pregnancies and 935 pregnancies with missing data on plurality. In accordance with the WHO recommendations,[11] analyses were restricted to pregnancies in which the duration of gestation was 22 weeks or longer, or birthweight was at least 500 g, resulting in 5957 exclusions. We also excluded 45 676 pregnancies in which the mother was younger than 20 years, and 4036 pregnancies in women with parity of six or more. Of the remaining total of 1 209 151 singleton deliveries among 665 883 women, 1 200 922 (99%) were conceived spontaneously and 8229 (1%) were conceived after assisted fertilisation.

Sibling-relationship analyses

Of those women who had given birth to a singleton infant after assisted fertilisation, 2546 had also delivered a singleton infant after spontaneous conception. In 1426 (56%) of these sibling relationships, the assisted-fertilisation pregnancy preceded that with spontaneous conception. In the other 1120 (44%) cases, the spontaneously conceived pregnancy preceded the pregnancy achieved by assisted fertilisation. We had valid information about the duration of the gestation for 2204 (87%) of these pairs of siblings.

Variables

Low birthweight (small for gestational age) was defined as less than the weight 2 SD below mean adjusted for gestational age and offspring sex. Duration of gestation was calculated from information obtained during routine ultrasonography in pregnancy weeks 17–19. If such information was not available, we used the last menstrual period to estimate gestational age of the spontaneously conceived pregnancies, whereas the date of embryo transfer was used to calculate it in assisted-fertilisation pregnancies. In cases of unreported or unrealistic

birthweights (ie, >6 SD from expected birthweight for gestational age and offspring sex), the gestational age was recorded as missing.[12] In total, data on duration of gestation were missing in 73 936 (6%) pregnancies. Perinatal mortality was defined as stillbirth after 22 weeks of pregnancy or as death within the first 7 days of life after 22 or more completed weeks of gestation. Information about deaths that occurred from 7 days until 1 year was extracted from a link between the Norwegian Medical Birth Registry and Statistics Norway. Time between births was calculated as that from the delivery of a child until the estimated conception of a subsequent pregnancy. If two fetuses were seen during ultrasonographic examination in the first trimester, but only a singleton was born in this pregnancy, we defined this child as a survivor of vanishing twins.

The study was approved by the regional committee for Medical Research Ethics in Norway, and by the internal review board of the Medical Birth Registry of Norway.

Statistical analysis

Mean birthweight and mean gestational age were estimated with a random-effects linear regression model, adjusted for maternal age (20–29 years, 30–34 years, and 35 years and older), parity (0, 1, or 2 or more), sex of the offspring, time between pregnancies (<18 months, 19–35 months, and ≥36 months), and year of delivery (1984–89, 1990–94, 1995–99, and 2000–06). Odds ratios, comparing outcomes of assisted fertilisation and spontaneously conceived pregnancies, were estimated in relation to delivery of a small for gestational age child; delivery before 32 weeks or 37 weeks of gestation; and perinatal death. We used a random-effects logistic regression analysis to account for deliveries within the same mother. In these analyses we adjusted for maternal age, parity, offspring sex, time between pregnancies, and year of delivery. Stratified analyses were done for combinations of year of birth, maternal age, and parity. In the comparison of siblings born to women after both assisted fertilisation and spontaneous conception, we assessed whether order of mode of conception modified the results by testing for interaction between the type and order of conception. Because the Registry data for assisted fertilisation are considered to be complete only from 1988 onwards, we repeated the analyses with pregancies before that year excluded. We used Stata (version 9.2) for the statistical analyses.

Role of funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The proportion of children born after assisted fertilisation increased throughout the study (table 1). Compared with women in the general population who had spontaneously conceived pregnancies, those with assisted-fertilisation pregnancies were on average older and had fewer previous births; also, the proportion of smokers was lower, and induced labour and caesarean sections were more common in pregnancies following assisted fertilisation (table 1).

Crude mean birthweight was higher in spontaneously conceived singletons in the general population than in singletons born after assisted reproductive technology (table 2; webtable 1). After adjustment for gestational age, maternal age, parity, offspring sex, year of birth, and time from a previous birth to conception of a subsequent pregnancy, the crude birthweight difference was reduced (table 2).

See Online for webtable 1

In the sibling-relationship comparison of singletons born to women who had one child after spontaneous conception and another after assisted fertilisation, crude mean birthweight was slightly greater in the spontaneously conceived group than in the assisted-reproduction-technology group. In the adjusted analyses, the difference between the groups was negligible. In the sibling-relationship comparisons, order of mode of conception did not affect the differences in birthweight (table 2).

To show the known effect of parity on birthweight, we restricted the analysis to women who had given birth to

	Singletons in the general population			Consecutive-singleton siblings			
	Spontaneous	Assisted fertilisation	Difference (95% CI)*	Spontaneous	Assisted fertilisation	Difference (95% CI)	p value†
Number with valid gestational age	1 127 739	7474	..	2204	2204	..	..
Crude birthweight (g)	3555 (0·6)	3424 (7·8)	131 (118 to 145)	3538 (13·0)	3451 (14·0)	87 (49 to 125)	..
Adjusted birthweight (g)‡	3564 (1·1)	3539 (5·4)	25 (14 to 35)	3574 (22·0)	3566 (21·0)	9 (−18 to 36)	0·85
Crude gestational age (days)	280·1 (0·01)	276·4 (0·2)	3·7 (3·4 to 4·0)	278·7 (0·3)	276·7 (0·3)	2·0 (1·0 to 2·9)	..
Adjusted gestational age (days)§	278·9 (0·03)	276·4 (0·2)	2·5 (2·1 to 2·8)	278·5 (0·8)	277·2 (0·7)	1·3 (0·3 to 2·4)	..
Adjusted gestational age (days)¶	280·7 (0·03)	278·7 (0·2)	2·0 (1·6 to 2·3)	280·3 (1·1)	279·7 (1·2)	0·6 (−0·5 to 1·7)	0·50

Data are mean (SE), unless otherwise indicated. *Between spontaneous and assisted-fertilisation pregnancies. †For interaction between order and type of conception (spontaneous *vs* assisted fertilisation). ‡Adjusted for gestational age, maternal age, parity, offspring sex, year of birth, and time from previous birth to conception. §Adjusted for maternal age, parity, offspring sex, year of birth, and time from previous birth to conception. ¶Adjusted as § and restricted to spontaneous deliveries (inductions and caesarean deliveries are excluded).

Table 2: **Birthweight and gestational age of singletons in the general population and of consecutive-singleton siblings conceived spontaneously and after assisted fertilisation**

See Online for webtable 2

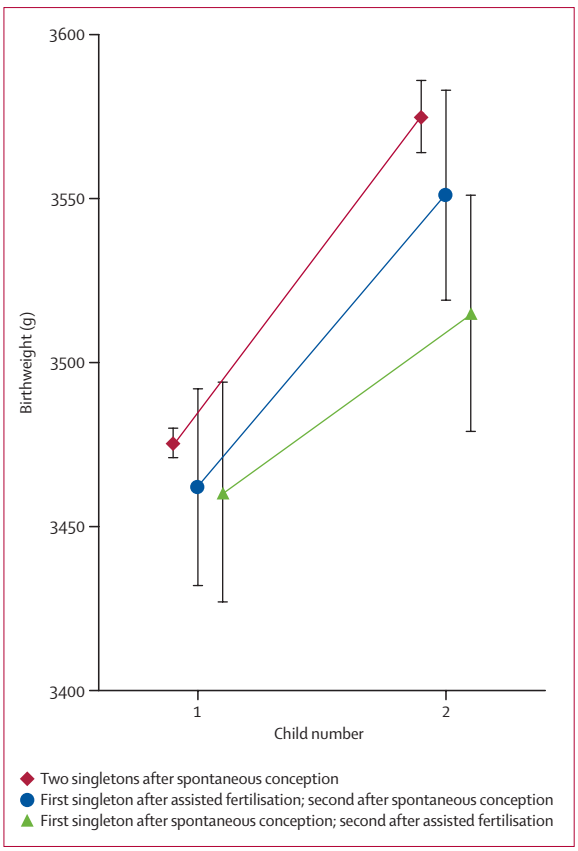

Figure: **Adjusted mean birthweight of singletons in families with two children only**
Data adjusted for maternal age, parity, offspring sex, year of birth, change of partner, and time from previous birth to conception. Error bars represent 95% CIs. Two singletons after spontaneous conception (191732 families), first assisted fertilisation and second spontaneous (916 families), and first spontaneous conception and second assisted fertilisation (728 families).

two singletons only, and stratified according to mode of conception (figure). Birthweight consistently increased from the first to the second pregnancy, independently of the type of conception. In the sibling-relationship comparisons of women who had conceived both spontaneously and after assisted fertilisation, birthweights did not differ substantially within each parity group (figure).

In the general population, crude mean gestational age was slightly longer for singleton children conceived spontaneously than for those conceived after assisted fertilisation (table 2). After adjustment for maternal age, parity, offspring sex, year of birth, and time from a previous birth to conception, the crude difference was reduced. Restriction of the analysis to spontaneous deliveries (excluding caesarean and induced deliveries that accounted for 275447 [23%] of 1209151 deliveries) resulted in a further reduction in the difference in gestational age (table 2).

In the comparison of consecutive siblings, the adjusted gestational age was shorter after conception with assisted reproduction technology than after spontaneous conception. The difference was reduced further by exclusion of induced and caesarean deliveries. The interaction test (between type and order of conception) did not imply inconsistency related to order of mode of conception.

Compared with the general population, the adjusted odds ratio (OR) for premature delivery (ie, before 37 weeks of gestation) was 1·69 (95% CI, 1·55–1·85) in pregnancies conceived after assisted fertilisation (table 3; webtable 2); premature delivery before 32 weeks of gestation was more than twice as common (2·21, 1·89–2·59) after assisted fertilisation. In the sibling comparisons of mothers who had given birth both after assisted fertilisation and spontaneous conception, the adjusted OR for delivery before gestational week 37 was 1·20 (0·90–1·61). Before 32 weeks', the adjusted OR was 1·26 (0·68–2·32) for pregnancies after assisted fertilisation compared with spontaneous conceptions. The frequency of premature delivery (ie, before 37 weeks of gestation) was similar in the sibling-relationship comparisons, irrespective of the order and type of conception (table 3).

Compared with the general population, the risk of being born small for gestational age was 26% higher for singleton pregnancies after assisted fertilisation than in those after spontaneous conception (table 3). However, among women who had delivered after both assisted fertilisation and spontaneous conception, the frequency of small for gestational age did not differ between siblings, and the order of mode of conception did not change this association (table 3).

In the general population, perinatal mortality in singletons was 7·2 per 1000 births (95% CI, 7·0–7·4) compared with 9·5 per 1000 births (7·5–11·8) following assisted fertilisation. The higher perinatal mortality after assisted fertilisation was due to a higher frequency of stillbirths (6·6 *vs* 5·2 per 1000 births) and early (0–6 days after delivery) neonatal mortality (2·9 *vs* 2·0 per 1000 births). From 7 days to 1 year after birth, mortality did not differ between the groups (OR 1·00, 0·61–1·56). The crude association (1·32, 1·05–1·65) of perinatal death with assisted fertilisation was not attenuated after multivariable adjustment for potentially confounding factors, including history of a previous perinatal death (1·31, 1·05–1·65, table 3).

In the sibling-relationship comparisons, 40 perinatal deaths occurred in pregnancies after spontaneous conception (16 per 1000 births, 95% CI 11–21), and 21 occurred after conception with assisted fertilisation (8 per 1000 births, 5–13). This difference was not altered substantially after adjustment for parity, year of birth, and maternal age (table 3). However, the difference in perinatal mortality was strongly affected by the order of mode of conception—ie, crude perinatal mortality was four times higher (OR 4·31, 1·93–9·60) in spontaneously conceived pregnancies that preceded those after assisted fertilisation, but no clear mortality difference was seen if

	Singletons in the general population			Consecutive-singleton siblings			
	Spontaneous	Assisted fertilisation	Odds ratio (95% CI)	Spontaneous	Assisted fertilisation	Odds ratio (95% CI)	p value*
Number at risk with valid gestational age	1127739	7474	..	2204	2204	..	..
Delivery <37 weeks	60535 (5%)	728 (10%)	1·69 (1·55–1·85)†	144 (7%)	205 (9%)	1·20 (0·90–1·61)†	0·67
Small for gestational age‡	26162 (2%)	231 (3%)	1·26 (1·10–1·44)†	52 (2%)	53 (2%)	0·99 (0·62–1·57)†	0·18
Number at risk of perinatal death	1200922	8229	..	2546	2546	..	..
Perinatal deaths	8647 (1%)	78 (1%)	1·31 (1·05–1·65)§	40 (2%)	21 (1%)	0·36 (0·20–0·67)§	<0·0001

Data are number (%), unless otherwise indicated. *For interaction between order and type of conception (spontaneous *vs* assisted fertilisation). †Adjusted for maternal age, parity, offspring sex, year of birth, and time from previous birth to conception. ‡Defined as birthweight for gestational age and sex less than the value 2 SD below mean. §Adjusted for maternal age, parity, offspring sex, year of birth, time from previous birth to conception, and previous perinatal death.

Table 3: **Risk of adverse outcomes in singletons in the general population and in consecutive-singleton siblings conceived spontaneously and after assisted fertilisation**

the assisted-fertilisation pregnancy preceded the spontaneous pregnancy (p<0·0001 for interaction).

When we investigated this finding further, we noted that the proportion of subsequent assisted-fertilisation births in women who had a perinatal death after a spontaneously conceived pregnancy was about three times higher (75 [0·66%] of 11378 *vs* 1587 [0·23%] of 688404) than in those with no history of a perinatal death in a previous pregnancy.

The adjusted mean birthweight was slightly less after in-vitro fertilisation than that after intracytoplasmic sperm injection (difference 15 g, 95% CI –12 to 41; table 4), and the adjusted mean gestational age was 276·0 days for in-vitro fertilisation and 276·3 days for intracytoplasmic sperm injection pregnancies. After exclusion of caesarean and induced deliveries, gestational length was slightly increased with both methods of assisted fertilisation (difference 0·3 days, –0·7 to 1·3; table 4).

There were no substantial differences between the in-vitro fertilisation and intracytoplasmic sperm injection groups in the risks of being born small for gestational age, preterm delivery before 37 weeks of gestation, or perinatal death (table 4).

In a separate analysis we studied whether the use of frozen embryos (after in-vitro fertilisation and intracytoplasmic sperm injection) could have affected these findings; however, the results remained unchanged after we excluded these pregnancies (data not shown).

In a subanalysis restricted to the period after 1998, information about smoking habits and previous abortions was available but adjustment for these factors did not substantially change the associations between mode of conception and perinatal outcomes. We also restricted the analyses to sibling relationships with the same father, but the results remained nearly unchanged (data not shown). In a subanalysis of 2276 pregnancies for which we had information on indication for fertility treatment we noted no substantial differences in birthweight (overall p=0·20), but there was some statistical evidence that mean gestational age varied according to indication (overall p=0·05). The largest difference was between ovulatory dysfunction and male factor (webtable 3).

	In-vitro fertilisation*	Intracytoplasmic sperm injection*
Birthweight (g)†	3558 (3528–3588)	3573 (3540–3601)
Gestational age (days)	277·2(276·0–278·4)	277·5(276·2–278·8)
Small for gestational age‡§	1·00	0·91 (0·64–1·31)
Delivery <37 weeks†	1·00	0·85 (0·69–1·05)
Perinatal death¶	1·00	0·96 (0·5–1·81)

Data are mean (95% CI) or odds ratio (95% CI). *Fresh and frozen embryos. †Adjusted for maternal age, parity, offspring sex, year of birth, and time from previous birth to conception. ‡Restricted to spontaneous deliveries and adjusted for maternal age, parity, offspring sex, year of birth, and time from previous birth to conception. §Defined as birthweight for gestational age and sex less than the value 2 SD below the mean. ¶Adjusted for maternal age, parity, offspring sex, year of birth, time from previous birth to conception, and previous perinatal death.

Table 4: **Risk of adverse outcomes in singletons after in-vitro fertilisation and intracytoplasmic sperm injection**

In a separate analysis, exclusion of singleton survivors from vanishing twins did not change the results (data not shown).

Discussion

Assisted fertilisation was not associated with increased risk of low birthweight, premature delivery, delivery of a small for gestational age infant, or perinatal mortality among women who conceived singletons both spontaneously and after the use of assisted fertilisation technology. The increased risks associated with assisted fertilisation compared with spontaneously conceived pregnancies in the general population were substantially attenuated when we took into account the effect of possible confounding factors.

The main strength of our study was the novel analytic approach of sibling-relationship comparisons. We were able to control for a wide range of potential confounding factors in the multivariable analyses. The large sample size, including information about all pregnancies in Norway during a long period, enabled us to study rare outcomes. Nevertheless, our study had little statistical power to analyse births that occurred before 32 weeks of gestation, and to study perinatal mortality among women who had conceived both spontaneously and after assisted fertilisation. Among women who received fertility

See Online for webtable 3

treatment outside Norway, some pregnancies following assisted fertilisation could have been misclassified as spontaneously conceived. Since assisted fertilisation is strongly associated with twin pregnancies, we explored this possibility by assessing the proportion of twin births among children conceived spontaneously by women who had also undergone assisted fertilisation in Norway. The proportion of twins born to mothers with only spontaneous pregnancies was 1·5%, compared with 25·0% in assisted-fertilisation pregnancies. In spontaneously conceived pregnancies among mothers who also had delivered after assisted fertilisation, however, the proportion of twin pregnancies was 2·5%, indicating a 1% excess of twin births. This excess could be explained by misclassification of about 4%, and this would have little effect on our findings. The completeness of the assisted-fertilisation pregnancy data reported to the Medical Birth Registry before 1988 is unknown. Therefore, we did a sensitivity analysis by restricting the analyses to deliveries after 1987; however, the results remained nearly identical.

Four meta-analyses[5–8] of perinatal outcomes in singleton pregnancies, found that, compared with spontaneously conceived singletons in the general population those born after assisted fertilisation are about twice as likely to be born preterm, are nearly three times more likely to weigh less than 1500 g, and have about 50% higher risk of being born small for gestational age.[5–7] Evidence from previous studies suggests that perinatal mortality might be higher after assisted fertilisation.[1–3,5–7]

Assisted fertilisation and spontaneously conceived pregnancies in the general population might not be similar.[1] For example, studies of couples with reduced fertility who eventually conceived spontaneously, show higher risk of adverse perinatal outcomes than those without fertility problems.[13–17] Consequently, outcomes might differ between pregnancies conceived spontaneously and after assisted fertilisation because of factors attributable to the underlying infertility, and not to the reproductive technology. Previous studies that have assessed effects of the reproductive technology on pregnancy outcomes could therefore be biased.

We used two separate approaches in our study. First, we used the traditional method used by other population-based studies and compared assisted-fertilisation pregnancies with those that were conceived spontaneously in the general population. With this approach, our findings corresponded to those reported in the meta-analyses.[5–8] Additionally, however, we identified women who had given birth both after spontaneous conception and after assisted fertilisation. With this approach, we compared the outcomes of siblings—ie, one pregnancy conceived spontaneously and the other after assisted fertilisation. In this way, maternal factors could be kept constant. Therefore, the differences could be attributed to the reproductive technology rather than to the underlying infertility.[18]

Nonetheless, a woman's need for assisted fertilisation could be associated both with the reason for her infertility and, with previous pregnancy outcomes. For example, complications in a spontaneous pregnancy could affect subsequent fertility and could lead to complications during subsequent pregnancies. This indication for assisted fertilisation might create a selection bias. We therefore assessed whether order of mode of conception made any difference to the sibling comparisons. We report no evidence that the tendency to seek subsequent fertility treatment was affected by birthweight, length of gestation, risk of small for gestational age, and prematurity in the previous pregnancy. The tests for interaction between order of mode of delivery and type of conception (assisted fertilisation or spontaneous) provided no evidence of such an order effect.

The sibling comparisons of perinatal mortality, however, suggested that this particular event could change the tendency to seek subsequent fertility treatment. If the spontaneous pregnancy occurred first, perinatal mortality was higher in the spontaneous pregnancies than in the pregnancies following assisted fertilisation, whereas no difference was seen if the assisted-fertilisation pregnancy occurred first. We explored this finding further, and noted that women who had had a perinatal death in a spontaneously conceived pregnancy were three times more likely to seek fertility treatment afterwards than those who had not. Therefore, a perinatal death could indicate an inherent tendency for adverse pregnancy outcomes or could have a strong effect on subsequent fertility. Differences in perinatal mortality should therefore be interpreted with caution, both in comparisons of siblings and in those of assisted-fertilisation and spontaneously conceived pregnancies in the general population. We did not do sibling-relationship comparisons among women who had given birth both after spontaneous and assisted conception for the method of fertilisation because of low statistical power.

As shown in animal studies, the reproductive technology might induce phenotypical effects. For example, in-vitro fertilisation, and in-vitro culture and cryopreservation tend to result in large calf syndrome in ruminants.[19] Gestational duration and birthweight are increased in animals born after assisted fertilisation. This effect has been attributed to premature transcription of genes associated with embryonic growth factors, including the insulin-like growth factor-2 system.[20] Assisted reproduction in rodents tends to result in reduced fetal growth and small for gestational age offspring.[21,22]

One suggested mechanism for this effect is dysregulation of key regulatory pathways of embryonic growth.[23] Our study does not include data that allow interpretation of molecular mechanisms, but the absence of evidence for an effect on birthweight or gestational age associated with assisted fertilisation is reassuring.

Use of fertility treatment is increasing in all European countries, and the proportion of babies born after assisted fertilisation now exceeds 5% in some Nordic countries.[24] Elucidation of the potential risks associated with the use of reproductive technology is therefore important. Although the increased prevalence of twins and triplets associated with assisted fertilisation can explain most of the increases in the rates of adverse pregnancy outcomes,[1–5] singletons born after the use of such technology do worse than those conceived spontaneously.[1–3,5–9] Whether this difference in adverse outcomes is due to the reproductive technology or to factors related to the underlying infertility is not clear.[13–17]

In our study, birthweight, gestational age, and risks of small for gestational age infants and preterm delivery did not differ among siblings born to women who had conceived both spontaneously and after assisted fertilisation. The adverse outcomes of assisted fertilisation that we recorded in comparisons with spontaneous pregnancies in the general population could therefore be caused by the underlying infertility, rather than to factors related to the reproductive technology.

Contributors

LBR and PRR conceived and planned the study, analysed the data, and wrote the report. AS and VD conceived the study, and revised the report. RS conceived the study, supervised the analysis, and revised the report. DG interpreted the findings and wrote the report. LJV planned the study, analysed the data, and wrote the report.

Conflict of interest statement

We declare that we have no conflict of interest.

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Assisted fertilization and breech delivery: risks and obstetric management

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BACKGROUND: Previous studies have suggested that assisted reproduction technology (ART) is associated with increased risk of breech presentation. We investigated whether factors that tend to differ between ART and spontaneously conceived pregnancies may explain the higher risk of breech deliveries associated with ART.

MATERIAL AND METHODS: In this population-based cohort study, we included 1 209 151 singleton pregnancies reported to the Medical Birth Registry of Norway between 1984 and 2006 and compared the risk of breech presentation in 8229 ART pregnancies with that in spontaneously conceived pregnancies. Risk ratios (RR), adjusted for maternal age, parity, gestational length and year of birth, were estimated using binominal regression, and we describe differences and time trends in obstetric management for breech and cephalic presentations after ART compared with management of spontaneously conceived pregnancies.

RESULTS: Breech presentation occurred nearly 50% more often in ART singleton pregnancies than in spontaneously conceived singletons [crude RR: 1.48, 95% confidence interval (CI): 1.34–1.64], but after adjustment for potentially confounding factors the difference was fully attenuated (RR: 0.97, 95% CI: 0.88–1.07). The most important contributors to the attenuation were parity and length of gestation. In general, Caesarean sections and induced deliveries were more likely in ART pregnancies, but over the study period, the proportion of Caesarean sections in ART pregnancies gradually approached that of spontaneously conceived pregnancies.

CONCLUSION: Increased risk of breech presentation in pregnancies after ART is mediated by lower parity and shorter gestational length. In general, the obstetric management of women with ART pregnancies is gradually approaching the ordinary surveillance of pregnant women.

Key words: assisted reproduction technology / breech presentation / singletons / Caesarean section / population study

Introduction

The safety of assisted fertilization has been scrutinized since assisted reproduction technology (ART) was introduced with the first successful pregnancy in 1978 (Steptoe and Edwards, 1978). It has been shown in many studies that ART pregnancies are associated with higher risk of complications and adverse perinatal outcomes compared with spontaneously conceived pregnancies (Helmerhorst *et al.*, 2004; Jackson *et al.*, 2004; McDonald *et al.*, 2005; Pinborg, 2005). However, the results of recent research suggest that problems related to ART in singleton pregnancies are more likely to be caused by the underlying infertility than by the reproduction technology (Romundstad *et al.*, 2008).

There is some evidence that breech presentation occurs more often in pregnancies following assisted fertilization (Frydman *et al.*, 1986; Frydman *et al.*, 1989; Antoine *et al.*, 1990; Heijnsbroek *et al.*, 1995; Isaksson *et al.*, 2002; Zadori *et al.*, 2003; Ombelet *et al.*, 2005), but it is unclear to which degree the excess risk can be attributed to the technology or to other factors associated with assisted fertilization. The aetiology of breech presentation is not fully understood, but the condition has been linked to prematurity, a first pregnancy, advanced maternal age, a previous breech presentation, placenta previa and uterine anomalies (Hofmeyr and Hannah, 2001; Lin, 2004).

In general, the obstetric management of ART pregnancies seems to differ from that of spontaneously conceived pregnancies. Typically, deliveries are more likely to be induced in ART pregnancies, and the rate of Caesarean sections is considerably higher (Kallen *et al.*, 2005). Breech presentation is strongly associated with delivery by Caesarean section, but it is not known if the obstetric management

of breech deliveries of ART pregnancies differs from that of spontaneously conceived pregnancies.

In this population study, we have therefore assessed whether mode of conception (assisted versus spontaneous) was associated with the risk of breech presentation, and whether the clinical management of breech presentations differed according to the mode of conception.

Materials and Methods

Study population

We used data on singleton births registered from 1984 to 2006 at the Medical Birth Registry of Norway (www.mfr.no). The registry is population based and comprises data on virtually all births in Norway since 1967. The attending midwife or obstetrician fills in information on standardized forms regarding the mother's health before and during pregnancy, complications during pregnancy and at delivery and length of gestation at birth. Information on the child includes birth size, and events recorded during the first week of life, including referral to a neonatal intensive care unit (NICU). All fertility clinics report all pregnancies after assisted fertilization to the registry, and the information includes details on methods used for fertilization (IVF or ICSI), the number of embryos transferred and whether the embryo replaced is fresh or thawed after cryopreservation. Result of first trimester ultrasound scans is also reported. The registry does not have information on pregnancies after inseminations or ovulation inductions.

The analyses were restricted to singleton pregnancies with length of gestation of 22 weeks or more and offspring birthweight of at least 500 g (World Health Organization recommendations, http://www.who.int/making_pregnancy_safer/publications/neonatal.pdf). There were no ART pregnancies among mothers younger than 20 years of age, or in women with parity of five or higher. To achieve comparable groups, mothers younger than 20 years and women with parity of five or higher in the spontaneously conceived group were excluded. The study population, including criteria for inclusions and exclusions, is illustrated in Fig. 1 (flow chart) and has previously been described in more detail (Romundstad *et al.*, 2008). Briefly, the study population included 1 209 151 singleton pregnancies among 665 883 women (Fig. 1). Among these pregnancies, 1 200 922 (99%) were conceived spontaneously and 8229 (1%) were conceived after assisted fertilization.

Variables

Parity was divided into three categories (0, 1 or 2 or more). Length of gestation at birth was calculated from information obtained during routine ultrasonography in pregnancy weeks 17–19. If this information was not available, we used the last menstrual period to calculate the gestational age among women who conceived spontaneously, whereas the date of embryo transfer was used to determine the gestational age in pregnancies with assisted fertilization. In cases of unreported gestational age or unrealistic birthweights for gestational age and offspring sex (i.e. >6 SD from expected), gestational length was set to missing (Skjaerven *et al.*, 2000). Data on gestational age were missing in 73 936 (6%) pregnancies. Interval between births was calculated as the time period from the previous delivery until estimated conception of the index pregnancy. We used referral to an NICU as an indicator of perinatal morbidity. Due to a revision of the notification form to the Medical Registry of Norway in 1999, there was a change in the reporting of breech presentations. Until 1998 breech delivery was recorded as a specific complication of delivery (specified in the instructions in the form), but thereafter, breech presentation was ticked off in a specific checkbox.

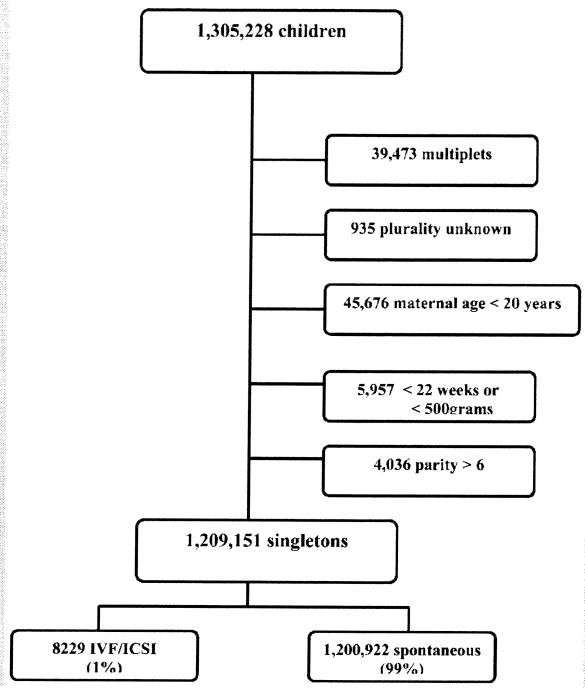

Figure 1 Flow chart of the study population from the medical birth registry of Norway (1984–2006).

Statistical analysis

We compared the risk of breech presentation in pregnancies conceived after assisted fertilization and spontaneously conceived pregnancies, using a binomial regression model, and present the differences in risk as risk ratios (RR) with the corresponding 95% confidence intervals (95% CI). To account for correlated outcomes within the same mother, we computed the robust standard error. In the analyses, we controlled for potential confounding by maternal age (20–29 years, 30–34 years, 35 years and older), parity (0, 1, 2 or higher) and year of delivery (1984–1989, 1990–1994, 1995–1999 and 2000–2006). We also evaluated the gestational age in six categories (22–27 weeks, 28–32 weeks, 33–36 weeks, 37–39 weeks, 40–41 weeks and 42+ weeks) as a potential mediating factor. In supplementary analyses we controlled for time interval between pregnancies (no previous birth, <18 months, 19–35 months, ≥36 months). We used STATA for Windows (version 10, College Station, Texas, USA) for the statistical analyses.

Results

The risk of breech presentation was fairly stable throughout the study period, both for pregnancies conceived after assisted fertilization and for spontaneously conceived pregnancies, but risk for breech presentation was consistently higher in ART pregnancies (Table I). In both groups, breech delivery occurred more often in first time pregnancies and in pregnancies with low gestational age.

Among 8229 singleton ART pregnancies, gestational age was reliably recorded in 7474 pregnancies. Among these, 372 (5.0%) were breech deliveries, and among ART pregnancies with delivery before 28 weeks of gestation, 42.3% presented with breech,

Table I Number and proportion of breech deliveries by pregnancy characteristics in 1200 922 spontaneous and 8229 ART pregnancies in Norway, 1984–2006.[a]

	ART		Spontaneous conception	
	Breech/total	(%)	Breech/total	(%)
Year of birth				
1984–1989	22/298	7.4	9483/300 565	3.2
1990–1994	55/1178	4.7	9113 /281 112	3.2
1995–1999	118/2236	5.3	9166 /278 317	3.3
2000–2006	224/4517	5.0	12 624/340 928	3.7
Maternal age (years)				
20–29	70/1549	4.5	23 531/715 374	3.3
30–34	198/3770	5.2	11 631/342 195	3.4
35+	151/2910	5.2	5224/143 353	3.6
Parity				
0	336/5600	6.0	21 648/475 124	4.6
1	60/2202	2.7	11 738/440 664	2.7
2 or more	23/427	5.4	7000/285 134	2.5
Gestational age (weeks)[b]				
22–27	22/52	42.3	950/4003	23.7
28–32	16/162	9.9	1411/9629	14.7
33–36	41/514	8.0	3273/46 905	7.0
37–39	206/2898	7.1	18 194/395 137	4.6
40–41	73/3265	2.2	11 516/537 009	2.1
42+	14/583	2.4	2610/135 058	1.9
Method used for fertilization				
IVF	306/6070	5.0	–	–
ICSI	95/1811	5.0	–	–
Unknown	19/254	7.5	–	–

[a]Restricted to pregnancies among mothers 20 years or older with five or less previous births.
[b]Data restricted to pregnancies with valid data on gestational age.

compared with 23.7% among spontaneously conceived pregnancies (Table I). Among ART pregnancies, there was no difference in the risk of breech presentation between the IVF group and the group conceived with ICSI (Table I). **SQ1**

The crude RR of breech presentation in ART compared with spontaneously conceived pregnancies was 1.48 (95% CI: 1.34–1.64), but after adjustment for maternal age, parity and calendar period of birth this association was reduced to 1.04 (Table II), and further adjustment for length of gestation fully attenuated the association (adjusted RR: 0.97, 95% CI: 0.88–1.07). Of these factors, parity and length of gestation contributed most to the attenuation. Similarly, in a stratified analysis restricted to nulliparaous women delivering at term (>36 weeks), we found no association between ART and risk of breech presentation, RR = 1.03 (95% CI: 0.91–1.16). In additional analyses we also controlled for time interval between pregnancies, but this did not alter the results.

Among a total of 419 breech singletons conceived by ART, 77.6% were delivered by Caesarean section, and the corresponding proportion of Caesarean sections in spontaneously conceived singletons was 61.6% (Table III). The proportion of breech presentations that resulted in elective Caesarean sections substantially differed between the groups. In ART pregnancies, 42.5% of breech presentations were delivered by elective Caesarean section, compared with 26.0% among spontaneously conceived pregnancies (risk difference, 16.5%). Adjustment for maternal age, calendar period and parity reduced this difference to 12.3% (95% CI: 7.5–17.0%). There was, however, no clear difference between the groups in frequency of acute Caesarean deliveries after breech presentation. **SQ2**

Throughout the study period, there was a general and consistent increase in the rate of Caesarean sections in spontaneously conceived pregnancies, whereas the proportion of Caesarean sections in ART pregnancies decreased over time; gradually approaching the rates of Caesarean section in spontaneously conceived pregnancies (Fig. 2). Similar time-related patterns, with gradually smaller differences in the frequency of Caesarean sections between ART and spontaneously conceived pregnancies, were observed for both breech and cephalic presentations. The frequency of induction of labour was 14.9% in the ART group and 10.8% in the spontaneously conceived group. These proportions were fairly stable over time (data not shown).

The use of epidural anaesthesia (EDA) in breech deliveries did not differ by mode of conception (Table III), but in pregnancies with cephalic presentation, EDA was more common in ART compared with spontaneously conceived pregnancies (25.9 versus 14.1%, crude risk difference, 11.8%). After adjustment for maternal age, calendar period, gestational length and parity, this difference was attenuated to 4.3% (95% CI: 3.4–5.3%).

In general, perinatal mortality was slightly higher after breech compared with other presentations (overall risk difference, 0.6%, 95% CI: 0.6–0.7%). This difference was greater in ART than in spontaneously conceived pregnancies (Table III). Breech presentations also resulted in transferral to the NICU, but slightly more often following ART than spontaneously conceived pregnancies (22.3 versus 20.4%). **SQ3** After adjustment for potentially confounding factors the risk difference was 2.2% (95% CI: −2.9 to 7.4%). Following cephalic presentations, 13.1% of the newborns in the ART group were referred to the NICU, compared with 9.1% of singletons conceived after spontaneous conception (adjusted risk difference, 3.1%, 95% CI: 2.1–4.1%).

Discussion

The crude risk of breech presentation was higher in ART compared with spontaneously conceived pregnancies, but after adjustment for maternal parity and length of gestation, the difference between the groups was fully attenuated. Previous studies have reported increased risk of breech presentation related to ART (Frydman *et al.*, 1986; Zadori *et al.*, 2003; Ombelet *et al.*, 2005; Poikkeus *et al.*, 2007), but the studies were typically small, and failed to take potentially confounding factors into account in the analysis.

Certain factors have been consistently associated with breech delivery, and in our study, approximately 24% of fetuses with delivery before 28 weeks of gestation were in the breech position; compared with 2% of pregnancies with post-term delivery (Table I). During the third trimester there is a spontaneous internal version of the fetus presenting in breech to a cephalic presentation. Therefore, it is possible that increasing size traps the fetus into the head down position, and

Table II RR of breech presentation in singleton pregnancies after ART versus spontaneous conception, crude and adjusted for maternal age at birth, parity and calendar period of birth.[a]

	n	Cases	Crude RR	Adjusted model RR	Additional adjustment for gestational age RR	95% CI
Spontaneous conception	1 127 741	37 954	1.0	1.0	1.0	Reference
ART	7474	372	1.48	1.04	0.97	0.88–1.07
Year of birth						
1984–89	276 394	8627	1.0	1.0	1.0	Reference
1990–94	257 263	8347	1.03	1.02	1.02	0.99–1.05
1995–99	258 701	8625	1.05	1.05	1.03	1.00–1.06
2000–06	342 857	12 727	1.18	1.14	1.08	1.05–1.11
Maternal age (years)						
20–29	667 484	21 983	1.0	1.0	1.0	Reference
30–34	328 794	11 250	1.04	1.26	1.24	1.21–1.26
35+	138 937	5093	1.12	1.45	1.36	1.32–1.41
Parity						
para0	453 088	20 749	1.0	1.0	1.0	Reference
para1	415 580	11 052	0.58	0.55	0.56	0.55–0.58
para2+	266 547	6525	0.54	0.46	0.46	0.45–0.48
Gestational age (weeks)						
22–27	4055	972	11.17	–	10.50	9.90–11.15
28–32	9791	1427	6.79	–	6.32	6.00–6.66
33–36	47 419	3314	3.26	–	3.09	2.98–3.21
37–39	398 035	18 400	2.16	–	2.17	2.12–2.22
40–41	540 274	11 589	1.0	–	1.0	Reference
42+	135 641	2624	0.90	–	0.88	0.85–0.92

[a]Analysis restricted to pregnancies among mothers giving birth at age 20 years or older, with five or less previous births and with valid data on gestational age. Standard error corrected for correlated outcomes within the same mother.

Table III Characteristics of breech and cephalic deliveries after ART and spontaneous conception in Norway from 1984–2006.[a,b]

	ART, *n* = 419	Breech			Cephalic	
		Spontaneous conception, *n* = 40 386	Adjusted[d] risk difference, % (95% CI)	ART, *n* = 7415	Spontaneous conception, *n* = 1124 616	Adjusted[d] risk difference, % (95% CI)
Caesarean section (%)	325 (77.6)	24 875 (61.6)	7.4 (3.3 to 11.4)	1473 (19.9)	111 008 (9.9)	6.5 (5.6 to 7.4)
Elective (%)	178 (42.5)	10 511 (26.0)	12.3 (7.5 to 17.0)	452 (6.1)	32 084 (2.9)	3.5 (3.0 to 4.1)
Acute (%)	120 (28.6)	9710 (24.0)	1.9 (−2.8 to 6.5)	935 (12.6)	57 667 (5.1)	5.7 (5.0 to 6.5)
Urgency not given (%)	27 (6.4)	4654 (11.5)	1.8 (−2.4 to 5.9)	86 (1.2)	21 257 (1.9)	0.1 (0.0 to 0.2)
Epidural (%)	134 (32.0)	13 118 (32.5)	−1.3 (−5.7 to 3.0)	1917 (25.9)	158 969 (14.1)	4.3 (3.4 to 5.3)
Perinatal deaths (%)	16 (3.8)	1218 (3.0)	1.4 (−0.4 to 3.1)	58 (0.8)	7146 (0.6)	0.2 (0.0 to 0.4)
Transmitted to NICU[c] (%)	56 (22.3)	2697 (20.4)	2.2 (−2.9 to 7.4)	544 (13.1)	29 217 (9.1)	3.1 (2.1 to 4.1)

[a]Restricted to singleton pregnancies among mothers giving birth at age 20 years or older and with five or less previous births.
[b]Other presentations than breech and cephalic were excluded, *n* = 36 315 (395 ART and 35 920 spontaneous pregnancies).
[c]Data restricted to pregnancies after November 1998.
[d]Adjusted for maternal age at birth, parity, and calendar period of birth.

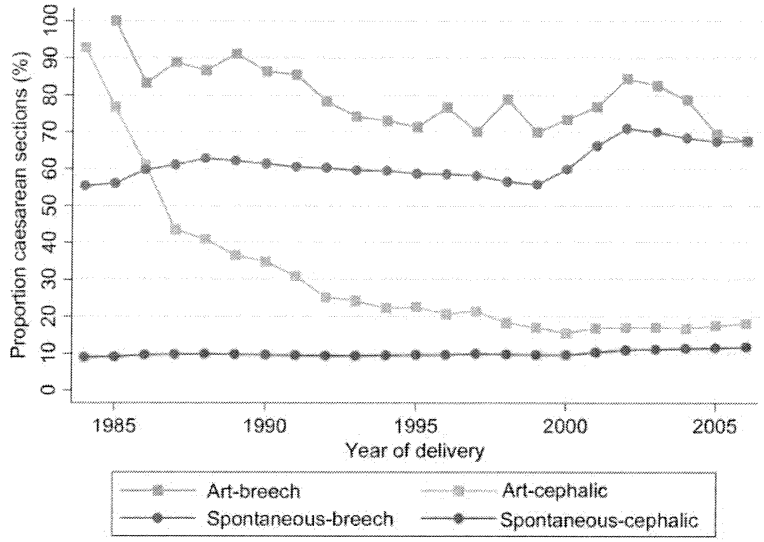

Figure 2 Proportion of Caesarean sections (3-year moving averages) in singleton pregnancies after ART and spontaneous conception (spontaneous) according to breech and cephalic presentation and by year of delivery.

pregnancies with early delivery may simply recruit more breech presentations before the head is turned down. ART pregnancies tend to be first-time deliveries and have shorter length of gestation, and these factors may largely explain the higher crude risk of breech deliveries associated with ART.

In general, breech presentation increases the risk of adverse perinatal outcomes (Danielian *et al.*, 1996). Our findings confirm this; breech deliveries were associated with higher perinatal mortality and morbidity compared with cephalic presentations, regardless of whether the pregnancy was spontaneously conceived or conceived by assisted fertilization.

The main strengths of this study include its population-based design, the large number of observations, and comprehensive information on potentially confounding factors. Nonetheless, we did not have information on some factors that are both related to breech presentation and to fertility treatment, including uterine malformations such as didelphus, septa and bicorn, and uterine leiomyoma (Lin, 2004; Biderman-Madar *et al.*, 2005). Taking these factors into account, however, is not likely to alter the results substantially. Similarly, breech presentations may recur from one generation to the next (Nordtveit *et al.*, 2008). We did not have information on familial predisposition in this study, but familial predisposition to breech delivery is not likely to be associated with infertility treatment, and information on recurrence would probably not have disturbed our results. The reporting of breech presentation changed in 1998. However, it is unlikely that this change would lead to differential reporting according to the mode of conception (ART or spontaneous).

The differential evaluation of gestational age for ART (date of embryo transfer) and spontaneously conceived (first day of last menstrual period) before 1998 may introduce a bias. However, when we restricted the analysis to pregnancies (both ART and spontaneous) in which gestational age were determined by ultrasound, the results remained unchanged.

Over time, there was a gradual shift towards vaginal deliveries of ART singleton pregnancies, whereas in spontaneously conceived pregnancies, there was an increase in Caesarean sections for both breech and cephalic presentations. Thus, rates of Caesarean section in the two groups have approached each other during the study period. A similar time-related reduction in Caesarean sections in ART pregnancies has been observed by others (Kallen *et al.*, 2005), but to our knowledge, no previous study has reported Caesarean section rates according to breech and cephalic presentations.

The optimal mode of delivery for breech presentations is controversial. In a randomized trial among women with breech presentation (the Term Breech Trial), perinatal death and neonatal morbidity were lower during the first 6 weeks of life among those who were randomized to planned Caesarean delivery compared with women randomized to planned vaginal delivery (Hannah *et al.*, 2000). It has been suggested that the use of Caesarean section in the management of breech presentation has increased as a consequence of that study (Pasupathy *et al.*, 2008), and our results appear to confirm this, both for ART and spontaneously conceived pregnancies.

Indications for Caesarean sections are typically diverse; some will be performed as an elective procedure, whereas others may be due to an acute obstetric situation. Nonetheless, it appears that interventions are more likely in ART than in spontaneously conceived pregnancies, with higher rate of Caesarean sections in the ART group. We found that the rate of elective Caesarean sections for breech deliveries was considerably higher in the ART group, and the rate of acute Caesarean sections for cephalic deliveries was also higher in the ART group. These findings indicate that ART pregnancies are subjected to a more active obstetric management. The higher tendency to intervene may to some extent explain why ART pregnancies have slightly shorter length of gestation (Romundstad *et al.*, 2008).

For most couples with fertility problems, there is a psychological burden involved (Schmidt, 2006), and in many regions of the world,

treatment adds a substantial economical burden for the couples. These factors may also explain why these pregnancies are subjected to closer surveillance than spontaneously conceived pregnancies. Possibly, more cautious surveillance may result in higher rates of obstetric interventions. However, the use of ART has become increasingly more common, and our results show that the management of ART pregnancies is gradually approaching the conventional care of spontaneously conceived pregnancies.

In summary, our results show that the higher risk of breech presentation in singleton pregnancies conceived by ART was fully attenuated after controlling for differences in parity, maternal age and length of gestation, i.e. factors that tend to differ between ART and spontaneously conceived pregnancies. The results also suggest that the obstetric management of singleton ART pregnancies is approaching the conventional management of spontaneously conceived singletons.

Funding

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APPENDIXES

Melding til MFR av graviditet etter foretatt IVF/ICSI

Fylles ut av avdelingen for alle behandlinger ved første ultralydundersøkelse

Avdeling/institusjon

Ikke skriv her

Kvinnens navn og adresse

På grunn av optisk lesning av skjemaene må fødselsnummer påføres her selv om det eventuelt også står på påklistret merkelapp.

Fødselsnummer

Infertilitetsårsak
(Kryss evt. i flere rubrikker)

1 ☐ Tubarfaktor
2 ☐ Endometriose
3 ☐ Ovulasjonsforstyrrelse
4 ☐ Sædfaktor
5 ☐ Annet, spesifiser:
6 ☐ Uforklarlig

Hovedårsak til infertiliteten?
(Kryss kun av i én rubrikk)

1 ☐ Tubarfaktor
2 ☐ Endometriose
3 ☐ Ovulasjonsforstyrrelse
4 ☐ Sædfaktor
5 ☐ Annet
6 ☐ Uforklarlig

Ikke skriv her

Hvor lenge har paret vært infertilt (antall år)? år

Metode ved dette forsøket:
1 ☐ IVF ferskt embryo
2 ☐ IVF frosset embryo
3 ☐ ICSI ejakulat ferskt embryo
4 ☐ ICSI ejakulat frosset embryo
5 ☐ ICSI-MESA ferskt embryo
6 ☐ ICSI-MESA frosset embryo
7 ☐ ICSI-TESA ferskt embryo
8 ☐ ICSI-TESA frosset embryo
9 ☐ Annet

Antall embryoer innsatt ved dette forsøket:

Hvor mange ganger innsatt embryo, inkludert dette forsøket, ved egen institusjon:

Hvor mange ganger innsatt embryo ved annen institusjon:

Dato for innsettelse:

Dato for første ultralydundersøkelse:

Status ved første ultralydundersøkelse:
1 ☐ Graviditet, pågående
2 ☐ Gravid utenfor livmoren
3 ☐ Spontan abort
4 ☐ Annet, spesifiser:

Ikke skriv her

Antall fostre:

Antall fostre med sikker hjerteaksjon:

Bes innsendt til MFR straks etter første ultralydundersøkelse

Dato, stempel og underskrift

Bording AS 06.08

16319

HELSEKORT FOR GRAVIDE

Godkjent av Helsedirektøren

Den gravides eksemplar, leveres fødeavdelingen ved fødselen.

MOR: Fødselsnr. (11 siffer)

Navn

Adresse | Telefon

Postnr. | Poststed

FAR: Fødselsnr. (11 siffer)

Navn

Adresse

Stilling/yrke

Sivilstand
- ☐ Gift
- ☐ Samboer
- ☐ Ugift/enslig
- ☐ Annet

Utdanning (høyest fullførte)
- ☐ Grunnskole
- ☐ Videregående
- ☐ Høyere utd.

Yrke - aktiv utenfor hjemmet siste 6 mnd. ☐ Ja ☐ Nei

Stilling/yrke

Type bedrift

Statsborgerskap: Mor | Far

Trossamfunn: Mor | Far

Tidligere svangerskap

Antall | Spont.ab. | Lef. f. | Prov.ab. | Dødfødt | Ex. u.

Merknader (Årstall, fødested, flerfødsler, fødselsvekt, svangerskapsvarighet, komplikasjoner, operative forløsninger)

Tidligere sykdommer
- ☐ Intet spesielt
- ☐ Hjertesykdom
- ☐ Hypertensjon
- ☐ Nyre/urinv.
- ☐ Diabetes
- ☐ Allergi
- ☐ Epilepsi
- ☐ Gyn. sykd./opr.
- ☐ Psykisk sykdom
- ☐ Annet, se merkn.

Arvelige sykd.
- ☐ Ingen kjente
- ☐ Ja, se merkn.
- ☐ Foreldre i slekt

Livsvaner — Dagl. | Av og til | Aldri
- Alkoholforbruk ☐ ☐ ☐
- Røyking ☐ ☐ ☐
- ☐ Stoffmisbruk

Ant. sigaretter daglig: Ved 1. kontroll: ☐ Ved ca. 36. uke: ☐

Faste medikamenter
- ☐ Daglig
- ☐ Av og til
- - hvilke, se merknader

Rubella vaksinert
- ☐ Ja
- ☐ Nei

Merknader

Aktuelle svangerskap

S.m.

Termin

☐ Sikker ☐ Usikker

Korrigert termin

Når korrigert

Klinisk status, dato

Uterus svarer til uker

Cor/pulm/mammae

Cyt.pr. res. , ref.

Blodprøver

Dato

Luesprøve

ABO

Rh ☐ pos. ☐ neg.

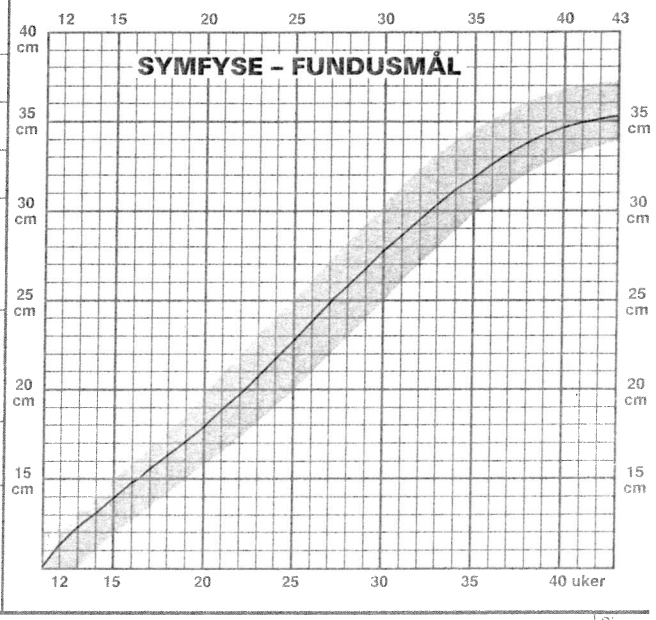
Blodtype antistoff ☐ Nei ☐ Ja, se merkn.

Ref.

Rubella antistoff ☐ ikke påvist ☐ påvist

Ref.

Sv.sk.kurs ☐ Nei ☐ Ja



Før svangerskap Høyde	Vekt		BT	Hb	Urin	Ødem 0/1/2/3	*Leie/ Be-veg.	Fl./ min,	Med. +/ –	Arb. utenf. hjem.
Dato	Uke	Vekt								

Ultralyd
- ☐ Nei
- ☐ Ja

Ant. ganger

Notater | Sign.

Sendt (dato/ sign.)

Fødeavd. /

Statistikk /

/

Oppsummering - spesielle komplikasjoner

- ☐ Blødn. ≤ 12. uke
- ☐ Blødn. 13.–28. uke
- ☐ Blødn. ≥ 29. uke
- ☐ Hb ≤ 10,0 g/dl
- ☐ Hb ≥ 13,5 g/dl etter 20 uker
- ☐ Hypertensjon alene
- ☐ Preeklampsi lett
- ☐ Preeklampsi alvorl.
- ☐ Glukosuri
- ☐ Virusinf.
- ☐ Annet

Henvist/innlagt
- ☐ Sykehus
- ☐ Spes. poliklin.
- ☐ Operert

Merknader | Sign

*Leie: H = hodeleie, S = sideleie, T = tverrleie
Beveg.: B = bevegelig, F = festet

Opplysningene gis på frivillig basis

Kontinuasjonsark: ☐ Nei ☐ Ja

Registreringsskjema fra 1967-1998

STATENS HELSETILSYN
Postboks 8128 Dep.
0032 OSLO

Medisinsk registrering av fødsel

Sendes 9. dag etter fødselen til fylkeslegen (stadsfysikus) i det fylket der moren er bosatt.

Merk: Det skal fylles ut blankett for hvert barn (foster). Dør barnet etter fødselen, skal det også fylles ut legeerklæring om dødsfall, og/eller dødsfallet meldes til skifteretten (lensmannen).

Barnet

Barnet var 1 ☐ Levende født 2 ☐ Dødfødt foster | Født dag, mnd., år | Klokkeslett | Personnr. | Skriv ikke her

1 ☐ Enkel 2 ☐ Tvilling 3 ☐ Trilling 4 ☐ Firling | Kjønn 1 ☐ Gutt 2 ☐ Pike

Etternavn, alle fornavn (bare for levendefødte)

Fødested. Navn og adresse på sykehuset/fødehjemmet | Kommune

Faren

Etternavn, alle fornavn | Født dag, mnd., år | Bostedskommune

Moren

Etternavn, alle fornavn. Pikenavn | Født dag, mnd., år

Bosted. Adresse | Kommune

Ekteskapelig status 1 ☐ Ugift 6 ☐ Samboende 2 ☐ Gift 3 ☐ Enke 4 ☐ Separert 5 ☐ Skilt | Ekteskapsår (gifte)

Antall tidligere fødte (før denne fødselen) | Levende fødte | Av disse i live | Dødfødte

Er moren i slekt med faren? 1 ☐ Nei 2 ☐ Ja. Hvilket slektskapsforhold.

Morens helse før svangerskapet

1 ☐ Normal 2 ☐ Sykdom (spesifiser):

Siste menstruasjons første blødningsdag

Morens helse under svangerskapet

1 ☐ Normal 2 ☐ Komplikasjoner (spesifiser):

Ble fødselen provosert

1 ☐ Nei 2 ☐ Ja

Inngrep under fødselen

1 ☐ Nei 2 ☐ Ja (spesifiser):

Inngrepet utført av 1 ☐ Lege 2 ☐ Jordmor

Komplikasjoner i forbindelse med fødselen

1 ☐ Nei 2 ☐ Ja (spesifiser):

Fostervann, placenta og navlesnor

1 ☐ Normalt 2 ☐ Patologisk (spesifiser):

Barnets tilstand

Bare for levende fødte. Tegn på asfyksi? 1 ☐ Nei 2 ☐ Ja | Apgarscore etter 1 min. | etter 5 min.

For levende fødte og dødfødte. Tegn på medfødt anomali, på skade eller sykdom? 1 ☐ Nei 2 ☐ Ja. Hvilke:

Lengde (i cm) | Hode-omkr. (i cm) | Vekt (i g) | For døde innen 24 timer Livet varte i | Timer | Min

For dødfødte. Døden inntrådte 1 ☐ Før fødselen 2 ☐ Under fødselen
Dødsårsak:

Seksjon? 1 ☐ Nei 2 ☐ Ja

Alvorlige arvelige lidelser i slekten

1 ☐ Nei 2 ☐ Ja Sykdommens art og hos hvilke slektninger:

Sted (sykehusets stempel) | Dato | Jordmor | Lege

IK - 1002.

50 000. 5.96. SKM GRAFISK

Melding om avsluttet svangerskap etter 12. uke – Fødsel, dødfødsel, spontanabort

Se utfyllingsinstruks for blanketten på baksiden

MFR

Sosial- og helsedirektoratet

A – Sivile opplysninger

Institusjonsnr: | Institusjonsnavn

Fødsel utenfor institusjon: ☐ Hjemme, planlagt ☐ Hjemme, ikke planlagt ☐ Under transport ☐ Annet sted

Mors fulle navn og adresse

Pikenavn (etternavn):

Mors sivilstatus: ☐ Gift ☐ Ugift/enslig ☐ Annet ☐ Samboer ☐ Skilt/separert/enke

Slektskap mellom barnets foreldre? ☐ Nei ☐ Ja Hvis ja, hvorledes:

Mors bokommune

Fars fødselsdato | Fars fulle navn

Mors fødselsnr:

B – Om svangerskap og mors helse

Siste menstr. 1. blødn.dag | ☐ Sikker ☐ Usikker

Mors tidligere svangerskap/fødte: Levendefødte | Dødfødte (24. uke og over) | Spontanabort/Dødfødte (12.–23. uke) | Spontanaborter (under 12. uke)

Ultralyd utført? ☐ Nei ☐ Ja UL termin:

Annen prenatal diagnostikk? ☐ Nei ☐ Ja, angi type:

Patologiske funn ved prenatal diagnostikk? ☐ Nei ☐ Ja, hvis bekreftet – spesifiser

Spesielle forhold før svangerskapet: ☐ Intet spesielt
☐ Astma ☐ Allergi ☐ Tidligere sectio ☐ Res. urinveisinfeksjon ☐ Kronisk nyresykdom ☐ Kronisk hypertensjon ☐ Reumatoid artritt ☐ Hjertesykom ☐ Epilepsi ☐ Diabetes type 1 ☐ Diabetes type 2 ☐ Annet, spesifiser i «B»

Regelmessig kosttilskudd: ☐ Nei — Før sv.sk. / I sv.sk.
Multivitaminer ☐ ☐
Folat/Folsyre ☐ ☐

Spesielle forhold under svangerskapet: ☐ Intet spesielt
☐ Blødning < 13 uke ☐ Blødning 13–28 uke ☐ Blødning > 28 uke ☐ Glukosuri ☐ Svangerskapsdiabetes ☐ Hypertensjon alene ☐ Preeklampsi lett ☐ Preeklampsi alvorlig ☐ Preeklampsi før 34. uke ☐ HELLP syndrom ☐ Eklampsi ☐ Hb < 9.0 g/dl ☐ Hb > 13.5 g/dl ☐ Trombose, beh. ☐ Infeksjon, spes. i «B»

☐ Annet, spesifiser i «B»

Legemidler i svangerskapet: ☐ Nei ☐ Ja – spesifiser i «B»

Spesifikasjon av forhold før eller under svangerskapet:

B

Røyking og yrke
Forutsetter mors samtykke – se rettledning på baksiden

☐ Skriftlig orientering gitt til mor ☐ Samtykker ikke for røykeoppl.

Røykte mor ved sv.sk. begynnelse? ☐ Nei ☐ Daglig ☐ Av og til Ant. sig. dagl.:

– ved sv.sk. avslutning? ☐ Nei ☐ Daglig ☐ Av og til Ant. sig. dagl.:

Mors yrke ☐ Samtykker ikke for yrkesoppl. ☐ Ikke yrkesaktiv ☐ Yrkesaktiv heltid ☐ Yrkesaktiv deltid

Mors yrke

Bransje:

C – Om fødselen

Leie/presentasjon: ☐ Normal bakhode ☐ Sete ☐ Tverrleie ☐ Avvikende hodefødsel ☐ Annet, spesifiser i «C»

Fødselstart: ☐ Spontan ☐ Indusert ☐ Sectio

Ev. induksjonsmetode: ☐ Prostaglandin ☐ Oxytocin ☐ Amniotomi ☐ Annet, spesifiser i «C»

Indikasjon for inngrep og/eller induksjon ☐ Komplikasjoner som beskrevet nedenfor ☐ Fostermisdannelser ☐ Overtid ☐ Annet, spesifiser i «C»

Inngrep/tiltak: ☐ Ingen
☐ Utskj. tang, hodeleie ☐ Annen tang, hodeleie ☐ Vakuumekstraktor ☐ Episitomi

Fremhj. ved setefødsel: ☐ Vanlig fremhjelp ☐ Uttrekning ☐ Tang på etterk. hode

Sectio: Var sectio planlagt før fødsel? ☐ Nei ☐ Ja
☐ Utført som elektiv sectio ☐ Utført som akutt sectio

Spesifikasjon av forhold ved fødselen/andre komplikasjoner

C

Komplikasjoner: ☐ Ingen
☐ Vannavg. 12–24 timer ☐ Vannavg. > 24 timer ☐ Mekaniske misforhold ☐ Vanskelig skulderforløsning ☐ Placenta previa ☐ Abruptio placentae ☐ Perinealruptur (grad 1-2) ☐ Sphincterruptur (gr. 3-4) ☐ Blødn.> 1500 ml, transf. ☐ Blødning 500–1500 ml ☐ Eklampsi under fødsel ☐ Navlesnorfremfall ☐ Truende intrauterin astyksi ☐ Risvekkelse, stimulert ☐ Langsom fremgang ☐ Uterus atoni ☐ Annet:

Anestesi/analgesi: ☐ Ingen
☐ Lystgass ☐ Petidin ☐ Epidural ☐ Spinal ☐ Pudendal ☐ Infiltrasjon ☐ Paracervical blokk ☐ Narkose ☐ Annet:

Placenta: ☐ Normal ☐ Hinnerester ☐ Ufullstendig ☐ Infarkter
☐ Koagler ☐ Utskrapning ☐ Manuell utherting
Placenta-vekt

Navlesnor ☐ Normal ☐ Velamentøst feste ☐ Marginalt feste ☐ Karanomalier
☐ Omslyng rundt hals ☐ Annet omslyng ☐ Ekte knute
Navlesnor-lengde:

Fostervann ☐ Normal ☐ Polyhydramnion ☐ Oligohydramnion ☐ Misfarget ☐ Stinkende, infisert ☐ Blodtilblandet

Komplikasjoner hos mor etter fødsel ☐ Intet spesielt ☐ Feber > 38.5° ☐ Trombose ☐ Eklampsi post partum ☐ Mor overflyttet ☐ Mor intensivbeh. ☐ Sepsis ☐ Annet, spesifiser

D – Om barnet

Fødselsdato | Klokken

Pluralitet: ☐ Enkelttfødsel ☐ Fierfødsel
For flerfødsel: Nr. | Av totalt

Kjønn: ☐ Gutt ☐ Pike
Ved tvil spesifiser i «D»
For dødfødte: ☐ Usikkert kjønn

Barnets vekt: . Hode-omkrets:

Total lengde: Eventuelt sete–issemål:

Apgar score: 1 min 5 min

Barnet var: ☐ Levendefødt ☐ Dødfødt/sp.abort Oppgi dødsårsak i «D»

For dødfødte: ☐ Død før fødsel ☐ Død under fødselen ☐ Ukjent dødstidspunkt

For dødfødte, oppgi også: ☐ Død før innkomst ☐ Død etter innkomst

Levendefødt, død innen 24 timer: Livet varte: Timer Min.

Død senere (dato): Klokken

Overfl. barneavd. ☐ Nei ☐ Ja Dato:

Overfl. til

Indikasjon for overflytting: ☐ Respirasjonsproblem ☐ Prematur ☐ Medfødte misd. ☐ Perinatale infeksjoner ☐ Annet, spesifiser

Neonatale diagn.: (Fylles ut av lege/pediater) ☐ Intet spesielt
☐ Hypoglyk. (< 2 mmol/l) ☐ Medf. anemi (Hb < 13.5 g/dl) ☐ Hofteleddsdyspl. beh. m/pute ☐ Transit. tachypnoe ☐ Resp. distress syndr. ☐ Aspirasjonssyndrom ☐ Intrakraniell blødning ☐ Cerebral irritasjon ☐ Cerebral depresjon ☐ Abstinens ☐ Neonatale kramper ☐ Konjunktivitt beh. ☐ Navle./hudinf. beh. ☐ Perinat. inf. bakterielle ☐ Perinat. inf. andre ☐ Fract. claviculae ☐ Annen fraktur ☐ Facialisparese ☐ Plexusskade

Behandlingskoder: ☐ Systemisk antibiotika ☐ Respiratorbeh. ☐ CPAP beh.

Icterus behandlet: ☐ Lysbehandlet ☐ Utskifting
Årsak: ☐ ABO uforlik. ☐ RH immunisering ☐ Fysiologisk ☐ Annen årsak

Tegn til medfødte misdannelser: ☐ Nei ☐ Ja

Spesifikasjon av skader, neonatale diagnoser og medfødte misdannelser – utfylles av lege

D

☐ Kryss av hvis skjema er oppfølgingsskjema

Jordmor v/fødsel:

Jordmor v/utskrivning:

Utskrivningsdato
Mor:
Barn:

Protokollnr.: /

Lege:

Lege barsel/barneavd:

IS-1002 6893. 11.03. Andvord Grafisk.