Multiple pregnancies in Norway, 1967-2008

The influence of assisted reproductive technologies

Anne Tandberg

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  University of Bergen, Norway

- The Medical Birth Registry of Norway

  Norwegian Institute of Public Health, Bergen

- Section for Gynecology and Obstetrics

  The Department of Clinical Medicine

  University of Bergen, Norway

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Abstract

Background: Multiple pregnancies have increased risk of certain adverse outcomes as preterm birth, low birthweight and higher perinatal mortality rate compared to singleton pregnancies. Data from industrialized countries during the last 20-30 years indicate rising incidences and have therefore been of major concern. The objective of the present thesis was to assess trends, incidence and outcome of multiple pregnancies in Norway during four decades with special focus on maternal age, assisted reproductive technologies (ART) and the mother's own gestational age and birthweight-by-gestational age.

Methods: Three population based cohort studies were all based on data from the Medical Birth Registry of Norway. Data were derived from cross-sectional-, sibship- and generational data files provided by linkage of the mothers' unique identification number and the infants' day of birth. Outcomes for twins and triplets were compared with those for singletons and estimated for the periods before (1967-1987) and after (1988-2006) information on ART was available in the registry. Contingency tables, stratification, generalized linear models and logistic regressions were used to calculate statistical associations.

Results: *Incidence:* The total twin birth rate in Norway increased from 1.1% in 1967 to 1.9% in 2004. Restricted to spontaneously conceptions, the rate reached 1.6% in 2004. A rise in the total triplet rate was observed from the last part of the eighties and through the nineties, followed by a steep decline from year 2000.

The likelihood to conceive with twins increased with the mother's own birthweight, but was unchanged by her gestational age at birth.

Perinatal outcome: The gestational age declined and the cesarean section rate increased in both twin- and triplet pregnancies from the first to the second period. The perinatal mortality rate improved considerably, but was still ten-fold higher in triplets and four times higher in twins compared to singletons in the last period. A proportion of ten

percent of the triplets were very preterm born (≤28 weeks), and did partly explain the higher mortality rate for these infants.

The mother's own gestational age and birthweight-by-gestational age had significant impact on the outcome of her reproduction, especially in twin pregnancies. If the mother herself was born at 27-31 weeks, she had four times higher relative risk of losing one or both of her twins compared to term born mothers. Term born mothers with birthweight-by-gestational age z-score <-2, also had a high mortality risk in twin offspring.

Conclusions: The twin birth rate in Norway has increased nearly 50% during the last decades, even when pregnancies from ART are excluded. The perinatal mortality rates for twins have declined considerably during the same period, but a less favourable improvement is observed for triplets. A twin pregnancy is a high-risk pregnancy if the mother herself is born preterm or is growth restricted at birth. Factors leading to preterm birth or growth restriction in one generation seem to affect reproduction outcome in the next generation, and is clearly revealed in a twin pregnancy.

List of publications

1. Tandberg A, Bjørge T, Børdahl PE, Skjaerven R. **Increasing twinning rates in Norway, 1967-2004: The influence of maternal age and assisted reproductive technology (ART).** Acta Obstet Gynecol Scand.2007;86(7):833-9

2. Tandberg A, Bjørge T, Nygård O, Børdahl PE, Skjaerven R. **Trends in incidence and mortality for triplets in Norway 1967-2006: The influence of assisted reproductive technologies.** BJOG 2010;117(6):667-75.

3. Tandberg A, Melve KK, Nordtveit TI, Bjørge T, Skjaerven R. **Maternal birth characteristics and perinatal mortality in twin offspring. An intergenerational population-based study in Norway 1967-2008.** BJOG 2011;Epub Date 11/02/04.

Definitions and abbreviations

ART: Assisted reproductive technologies are defined as procedures in which a woman's ovaries are stimulated, her eggs surgically removed, combined with sperm and returned to the woman's uterus.

AID: Assisted insemination by donor.

AIH: Assisted insemination by husband.

Dizygous (DZ) twins: Dizygotic twins occur when two eggs are fertilized by two different sperms and implant in the uterus within the same menstrual cycle. These twins will be no more similar genetically than any siblings and they may have like or unlike gender.

FER: Frozen embryo replacement.

FSH: Follicle stimulating hormone.

Gestational age: The duration of pregnancy.

ICSI: Intra cytoplasmatic sperm injection.

Infertility: Infertility is the inability to conceive a child after two years of regular sexual intercourse without contraception.

Intergenerational factors: Conditions experienced by one generation that affect the pregnancy outcomes in the next generation.

IVF: In Vitro Fertilisation.

MBRN: The Medical Birth Registry of Norway.

Monochorionic: When monozygotic twins are contained in a shared chorion, they are referred to as monochorionic. The chorion is the outer membrane of the sac surrounding a fetus in utero.

Monozygous (MZ) twins: Monozygous twins occur when a single egg is fertilized to form a zygote, but this zygote split into two separate, but identical embryos. MZ twins are genetically identical and look alike.

Parity: The number of times a woman has given birth.

Perinatal mortality: Death of the fetus from ≥22 gestational weeks until ≤ 6 days after birth.

Stillbirth: The World Health Organisation defines stillbirth as fetal death after gestational week 22 and before birth. This definition is used in Paper 2. In Paper 3, we included all stillbirths from 16 completed weeks of gestation as recorded in MBRN.

Twins: Refer to two individuals who have shared the same uterus and are being born within the same day or next.

Zygote: A zygote is the cell formed by the union of a male sex cell (a sperm) and a female sex cell (an ovum). The zygote develops into an embryo following the instruction encoded in its genetical material, the DNA.

Statistical abbreviations:

CI: Confidence interval

OR: Odds ratio

RR: Relative risk

SD: Standard deviation

1. Introduction

1.1 Multiple births

The most common event in human reproduction is the birth of a single infant. Multiple births are relatively rare, but contribute to a significant proportion of pregnancy complications such as preterm birth, perinatal morbidity and mortality.[1 2] As twins and higher order pregnancies are much less frequent than singleton pregnancies, related research papers are limited in numbers. Multiples are often excluded from study populations or reported in subgroups to avoid introduction of bias.[3 4] Establishment of nationwide health registries has, however, facilitated epidemiological research in cohort designs with appropriate sample sizes for studies of twins and higher order multiples.

There are two types of twinning; dizygotic (DZ) and monozygotic (MZ). The rate of MZ twins has been remarkably constant among spontaneously conceived twin pregnancies throughout the world,[5 6] and is about 3-4 per 1,000 pregnancies.[7-10] The variations of the twinning rate have been confined to DZ twinning. DZ twinning is repeated in families, and genetic analysis is beginning to identify genes contributing to these events.[11] Other factors predisposing to DZ twinning include maternal age, ovarian hyperstimulation and the use of assisted reproductive technologies (ART). The mechanism of MZ twinning is still poorly understood and is considered to be a spontaneous or random event.[11] Dependent on which day after fertilization the separation of the zygote into two embryos occurs (day 1-14), the twins will more or less share membranes and placenta. The later the separation occurs, the greater are the risks for complications. MZ twins are genetically alike and have always the same gender. However, their intrauterine experience may be different and mechanical defects (amniotic band syndrome), circulation disturbances and delivery complications may affect only one of the twins.[7]

A multiple pregnancy represents a high-risk situation for the mother as well as the fetuses. The main maternal complications are pregnancy-induced hypertension, pre-eclampsia, ante- and postpartum bleeding, gestational diabetes and assisted and surgical delivery.[12 13 14] These complications are more frequent among twin pregnancies and

have a significant impact on the outcomes of twins such as preterm delivery, perinatal morbidity and mortality.[15 16]

Preterm delivery is the major contributor for adverse perinatal outcome in multiple pregnancies.[17 18] Placental failure and intrauterine growth restriction (IUGR), growth discordance and severe preeclampsia may lead to iatrogenic preterm birth, either medically induced or by cesarean section.[19] Excessive stretch of the myometrium due to increased fetal and placental mass is associated with elevated production of prostaglandins and upregulation of proteins that mediate ripening of the cervix with onset of delivery as consequence.[20] Infections in cervix uteri, chorioamnionitis[21] and idiopathic vaginal bleeding[22] are also pathological processes that may initiate preterm delivery.

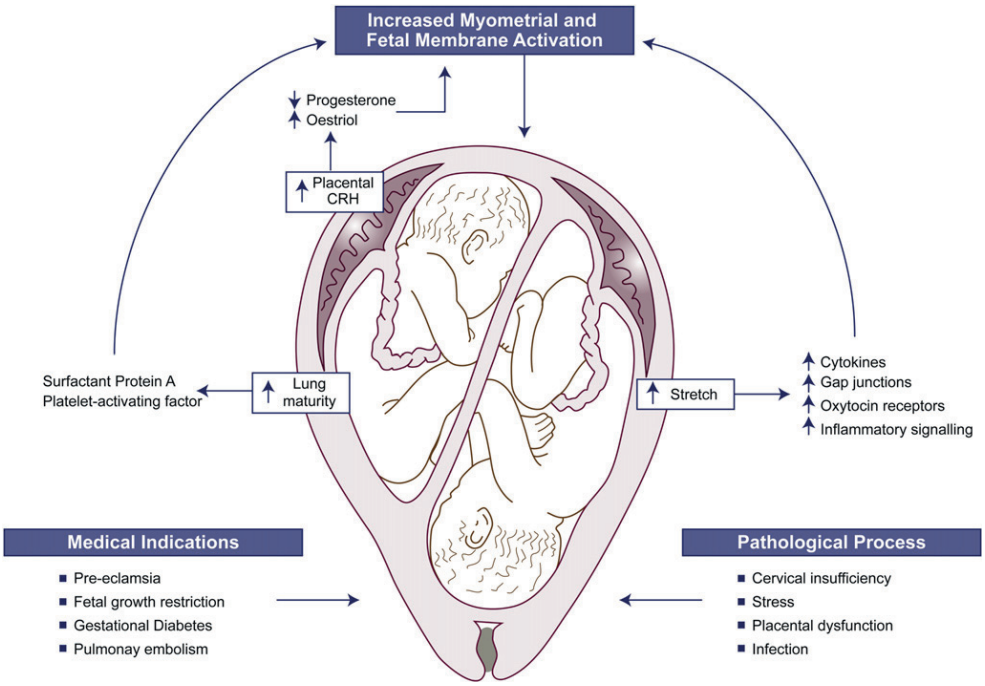

Figure 1: Potential mechanisms leading to preterm birth in multiple pregnancies.

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Twins and triplets have higher risks of birth defects than singleton pregnancies.[23-26] Three large and detailed studies have shown similar effects on the malformation rates in multiples, although the studies had differences in definitions and inclusion criteria.[23 25 26] A weighted meta-analysis estimated an overall increase in the risk of a birth defect in twins to be 30 % higher than in singletons (OR 1.3;1.02-1.64).[27] Some studies have examined this result further for differences by zygosity or chorionicity and malformation rates.[26 28] Subgroup analysis revealed that the proportion of malformations was not significantly different between singletons and DZ twins, whereas the rate for MZ twins was five-fold higher than for singletons.[28] Probably 10% of MZ twins are born with a birth defect.[7] In triplets, the malformation rate is estimated by some investigators to be about four times as high as in singletons.[29 30] In a large Japanese study, 3.7% of triplets had a birth defect compared with 1.5% in singletons and 2.2% in twins.[31]

Twin-twin transfusion syndrome occurs in 10-20% of all MZ, monochorionic twin pregnancies and these twins have a survival rate of only 69-90%.[32-34] The syndrome is caused by the formation of circulation disorders (vascular anastomosis) in the monochorionic placenta which enables the blood circulation of the two twins to communicate and create inter-twin hemodynamic imbalance.[33 35]

A vaginal twin delivery is an obstetric challenge due to complicated assessment during labour, malpresentation of the fetuses and high risk of cord prolapse. At term, the second born twin has a threefold higher risk of delivery related death than first born twin mostly due to anoxia. A British study from 2007 suggested planned cesarean section of twins in order to prevent these deaths.[36] The study estimated that 264 twin cesarean sections had to be performed to prevent one death.[37]

1.2 Incidence

The spontaneous twinning rates vary considerably throughout the world and between populations. The lowest rates have been reported from Japan (6-9 twin births per 1,000 births). Europe, America and most countries in Africa and Asia have intermediate rates (9-20 per 1,000), while the highest rates have been found in rural populations in Nigeria

(27-54 per 1,000).[38-40] The rates of spontaneous twinning declined in many western countries during the 20th century with the lowest incidence in the mid-1970s. The rate at that time was 11 per 1,000 in Finland, 10 per 1,000 in Denmark and 9 per 1,000 in Norway and Sweden.[41] The U-shaped curve with the lowest incidence in the mid-1970s is not fully understood,[39 41-44] and the rates increased gradually until the mid-1980s, followed by a more rapid increase from 1990 to 1996.[41 45] The most pronounced rise was observed in Denmark, where the rate increased 2.2-fold in the period 1970-2003, from 10 to 22 per 1,000 births.[46 47] Based on data from "Division of Vital Statistics, USA "[48], researchers have annually described the multiple birth rates in the US until 2005.[49 50] They reported that the twin birth rate increased until 2004 and was unchanged in 2005. The actual data are missing in these reports, but another study from the same Vital Statistics calculated the twin birth rate to be19 per 1,000 births in 1990 and 29 per 1,000 in 2000. The proportion of multiple births from ART in the US was estimated at 13.6% in 2000.[51]

In industrialized countries where ART was available, there was a dramatic rise in incidence of triplet pregnancies from the late eighties until the late nineties. In Denmark, the triplet rate increased from 1.44 per 10,000 births during 1980-88 to 6.08 per 10,000 in 1994.[46] In Norway, the increase was reported to be 9-fold from1972 to 1994, but the data in the cited paper are based on the Population Statistics in Norway and does not seem to be complete.[45] The epidemic increases in the triplet rates were similar in other European and Asian countries. In the US, the increase was 5-fold from1980 to 1997 and declined annually from 1998, and the contribution of ART-triplets to the total of triplet births was 42.5% in 2000.[51 52]

In this century, it has been the aim of the European Society of Human Reproduction (ESHRE) to reduce the multiple gestation rates caused by ART, and single embryo transfer (SET) programmes are now implemented in most fertility clinics in Europe. As a result, the twin birth rates have declined in many European countries during the last 5 years, particularly in the Nordic countries.[53]

1.3 Maternal age and parity

Already in 1865, the Scottish obstetrician Matthew Duncan was aware of the relation between increasing maternal age and increasing twinning rates.[54] The documentation of increasing twinning rates with advancing maternal age is numerous and convincing.[41 43 55] The lowest rates are found among women less than 20 years, and women 35-39 years have the highest rates. In recent years, women in western countries postpone having children to a later stage in life, which is a substantial contributor to the increasing twinning rates. In Norway, the mean maternal age regardless of parity, has increased from 26 years in 1967 to 30 years in 2008.[56] This is a paradox because of the general decline in fecundity by age. One hypothesis is that serum level of the follicle stimulating hormon (FSH) secreted by the pituitary gland, increases because of a decline in the ovarian feedback. As a result of the higher FSH level, more than one follicle complete their final maturation and multiple ovulations are likely to occur.[57-59]

The theory that women who conceive with twins were more fertile than other women was proposed in the early 70ies.[60] The background for this idea was the higher rate of twinning with higher parity in the period before the availability of effective contraception. MacGillivray et al. concluded in a study that the association between twinning and parity was largely due to the maternal age effect.[61] A case control study, including all twin mothers in Denmark in 1984-85, found no association between parity and DZ twinning, and a negative association between parity and MZ twinning.[55] Another Danish cohort study found that subfertile women had a low rate of twins,[62] and women who conceived more quickly, had a higher DZ twinning rate.[63] During the last decades, birth rates have declined in most part of the world. Norwegian women have on average one child less than they did in the 60ies.[64] Consequently, higher parity cannot be a substantial contributor to the increasing twinning rates during the last twenty years.

Other factors that affect the occurrence of twinning are genetic predisposition, maternal height and body mass index,[62] diet[65] and psycho-social stress.[38]

1.4 Fecundity and infertility

Fecundity is the biologic ability to conceive a live birth. Fecundity and infertility is highly associated. The incidence of reduced fecundity is difficult to estimate and few population based data sources are available. However, in the Mother and Child Cohort Study[66] it is possible to estimate "time to pregnancy" because the mothers report how many months it took for her to conceive. One study from the Mother and Child Cohort presented a significant trend of reduced fecundity by increasing male body mass index.[67] Another cohort study from Denmark showed reduced fecundity in overweight and obese women.[68] Fertility rates decline with advancing age, and older couples will need longer time to conceive than younger couples.[69 70] Other risk factors of reduced fecundity is smoking,[71] sexually transmitted infections, reduced frequency of intercourse, somatic co-morbidity and high stress level.[72] In a retrospective study, including 3,000 women, the infertility rate was estimated at 16.1% (95% CI: 14.6-17.6).[73] In about a third of all infertile couples, the causes of infertility originate from female factors, one third concerns the male and one third is unexplained. There are often overlap between categories, and one couple may suffer from combinations of several fertility lowering factors.

1.5 Assisted reproductive technologies (ART)

In the literature, there are different forms of fertility treatments included in the term assisted reproductive technologies (ART). The method used for fertilisation is dependent on the infertility factor and previously failed treatment cycles. In unexplained infertility, tubal disease, ovulation disorder and endometriosis, in vitro fertilization (IVF) is used. Intracytoplamatic sperm injection (ICSI) is used in male infertility with reduced sperm quality. Surplus embryos can be cryopreserved and replaced in subsequent treatment cycles (FER). Hormonal stimulation with assisted insemination by partner (AIH) is used in couples with ovulation disorder or unexplained infertility and the pregnancy rate is 5-10% per cycle.[74] Artificial insemination by donor (AID) is used for severe reduced sperm quality.

The first baby conceived in vitro by assisted reproductive technologies (ART) was born in 1978 and she has now become a mother herself.[75] The use of ART is increasing world-wide, and, in 2005, the proportion of children born after assisted fertilisation was 2.8% in Norway, 2.9% in Sweden and 3.5% in Denmark.[53] In 2010, as many as 4.5 million babies have been born world-wide after ART treatment.[76] The mean proportion of multiple births among ART pregnancies in 16 European countries was 22% in 2005.[53] To compare, in pregnancies from spontaneous conceptions the multiple rate varies from 0.9 to 2.7%.[41 45] In Norway, the multiple rate from ART-pregnancies has declined from 30% in 2000 to 12% in 2008.[74]

1.6 Differences in perinatal outcome between non-ART and ART

Several studies have shown that ART pregnancies are associated with more frequent adverse perinatal outcomes compared to pregnancies conceived naturally.[77 78] Firstly, the outcomes of ART are influenced by the background characteristics of people being treated by ART to achieve a pregnancy; maternal age, nulliparity and a history of infertility. Secondly, the ART technique itself involves gametes, zygotes and implantation processes, and the consequences are not fully understood. One recently published study suggested that the problems of adverse outcome in ART singletons were related to the underlying infertility rather than the reproductive technology itself.[79] Another study compared the outcome of 2,239 singleton ART children with that of 6,343 singleton offspring to subfertile women who finally conceived spontaneously. The ART group had significantly higher risk of preterm birth and low birthweight.[80]

The proportion of 25-35% multiple pregnancies in ART treatment has been the main reason for the adverse pregnancy outcome in ART compared to those naturally conceived with a multiple rate of 1.5-2.5%. However, comparing perinatal outcome between spontaneous and ART conceived twin pregnancies have been assessed by several authors and two systematic reviews are available.[47 78] In the review from Helmerhorst et al.[78], ten matched studies with twin pregnancies were included. Three[81-83] of the ten studies were able to control for zygosity.

DZ twin pregnancies have more favourable outcome than MZ, and zygosity is considered to be a major confounder in comparisons between ART and non-ART twins. Only 3-5% of ART twin pregnancies are MZ versus about 30% of spontaneous conceptions.[84] In the review[78], summary results for the included studies showed that relative risk of perinatal mortality was significantly lower in ART twins than among those naturally conceived (RR 0.58, 95% CI: 0.44-0.77). In a national cohort study from Denmark,[85] no difference in perinatal mortality was found between ART and non-ART twins when only DZ twins were included. A recently published study [86] compared outcome of ART twins with non-ART twins of unlike sex. ART twins had higher risk of preterm birth, low birthweight and perinatal death. In addition, ART twins had longer birth admission and were more likely to be admitted to a neonatal intensive care unit.

1.7 Intergenerational studies

Intergenerational studies explore the transmission of characteristics between one generation and the next. The highly cited Barker hypothesis says that "undernutrition in utero permanently changes the body's structure, function and metabolism in ways that lead to coronary heart disease in later life".[87-89] An interpretation of the Barker hypothesis is that an individual's intrauterine experience will influence on health over the life course, including reproduction and pregnancy outcomes. Age at menarche, regularity of menstrual cycles and polycystic ovary syndrome are reproductive factors in women that will affect pregnancy outcome, and subsequently the offspring health in the next generation.[90]

Family members across generations share both genes and socioeconomic positions. Half of the fetal genes are provided by the mother and half by the father. In addition, a mother will affect her fetus through the intrauterine environment during pregnancy, which again is dependent on the mother's genes, health, nutrition, behaviour and socioeconomic position.[91] The primordial oocytes in a female are created in her fetal life, and her intrauterine experience might affect the quality (imprinting process) of her gametes with implications for the next generation.[92]

The recurrence of birthweight from a mother to her offspring is well established.[93-96] The familial recurrence of preterm birth and the relative contributions of maternal and fetal genotypes to the risk of preterm delivery was explored in an intergenerational study using the same source population as in the present thesis. The results from this study suggested that inherited risk factors may contribute to preterm delivery, but probably only through the mother.[91]

In the literature, we found one intergenerational study with focus on outcome of twinning as end point.[97] The study concluded with a weak, but positive relation between maternal birthweight and twin offspring gestational age and a strong relation to total twin birthweight. However, the sample size was small, with only 131 mother-twin pair units included.

Studies on the association between a mother's birth characteristics and perinatal mortality in her offspring are few and for singletons only.[98 99] In 1997, Skjærven et al. published a study with generational data from 104,105 mother-offspring units from the time period 1967-1994. The main finding was that a mother's birthweight did influence the perinatal mortality of her own babies, but only if her birthweight was below 2,000 gram.[99] A follow-up study by Nordtveit et al., with 520,794 mother-offspring units from 1967-2006, was published in 2010. The authors concluded that a mother's gestational age, and not her birthweight, was significantly associated with perinatal mortality in the offspring, while there was no such association for the father.[98] Twin pregnancies were excluded from these studies.

1.8 Background of the present thesis:

Increasing incidence of multiple pregnancies worldwide has been related to more widespread use of ART. However, very few studies have been able to distinguish between pregnancies from spontaneous conception and ART in the presentation of the incidence rates. Our nationwide, population based birth registry with linkage to the ART Registry, made it possible to present the multiple incidence rates from spontaneous conception and ART separately.

Several studies have investigated the differences in pregnancy complications and perinatal results between twin pregnancies and singleton pregnancies.[1 2] Many investigators have also compared twin pregnancies from ART with those of spontaneous conceptions.[47 78 81 85] However, publications on triplet studies are sparse, and based on small numbers or samples from different databases,[17 100-103] with the risk of introducing selection and information bias. Hence, our main focus in Paper 2 was to investigate outcome parametres of triplets relative to twins and singletons. The Medical Birth Registry of Norway (MBRN) with birth records on every child born in Norway from 1967-2006 was a unique data source for cohort studies of triplets.

The mother affects her fetus through the intrauterine environment which is influenced by maternal genes, nutrition status, behaviour and smoking, but also through her own experience as a fetus. Results from a previous study showed that very preterm born mothers experienced a three-fold increased risk of a perinatal loss in their singleton offspring compared to term born mothers.[98] A twin pregnancy is a stressful condition for the mother and can reveal the underlying relationship of maternal birth characteristics and birth outcome even more clearly than single pregnancies. Due to our large data samples we were able to apply the Barker hypothesis of early origin of adult disease[86] in a reproductive context with maternal birth characteristics as exposure for outcome in a twin pregnancy.

2. Aims of the present thesis

The overall aim was to investigate the incidence, causes and consequences of multiple pregnancies based on data from the Medical Birth Registry of Norway.

The specific aims were to:

- Assess the increasing twinning rates in Norway during the last 40 years, and evaluate the impact of maternal age and ART (Paper 1).
- Describe the secular changes in incidence rates, birthweights, gestational age and perinatal mortality for triplets relative to twins and singletons during the last 40 years in Norway, with a particular focus on the influence of ART (Paper 2).
- Investigate if maternal preterm birth and intrauterine growth restriction were related to perinatal mortality of twin offspring in the next generation (Paper 3).

3. Material and methods

3.1 Data sources

The Medical Birth Registry of Norway (MBRN).

The registry was established in 1967 by the Directorate of Health in order to monitor birth defects and other maternal and perinatal health problems, and to conduct epidemiological research on causes and consequences of perinatal problems.[104] Later, similar birth registries were established in the other Nordic countries. At present, MBRN is one of the largest medical data sources in the world, comprising high quality data for a 44-year period. The registry is based on compulsory notification of every birth and late abortion in the country from 16 weeks of gestation onwards. By 2008, 2.46 million births have been registered. A standardized notification form is used to collect data on demographic variables, maternal health before and during pregnancy, previous reproductive history, complications during pregnancy and delivery and pregnancy outcomes. The form is completed by a midwife based on the hospital record and the pregnancy record, and sent to MBRN within the 9th day post partum or at discharge from the hospital. For neonates transferred to the neonatal intensive care unit, the form is completed by the physicians there. The notification form was almost unchanged during 1967-1998. A more detailed version was introduced in1999, including ultrasound gestational age determination and maternal smoking habits (Appendix 1-2).

The Population Registry provides identification numbers to all individuals soon after birth. All records in the MBRN are routinely linked with the Population Registry in order to identify missing birth notifications for live births and for information on all later registrations of infants that die.

The ART Registry

Since 1988, the MBRN has received a separate notification on central clinical variables following ART (Appendix 3). The different methods of reproductive technologies (IVF, ICSI and FER) are reported exclusively. Only procedures that involves fertilization outside the body is registered, consequently not AIH and AID. The duration and causes

of infertility, number of treatment cycles and number of transferred embryos are also reported. Finally, the presence and numbers of vital embryos seen at the first sonographic examination in the 7^{th}-8^{th} gestational week are noted. The registration is based on the mother's personal identification number after a written informed consent. The positive response rate is almost 100% among the pregnant couples. The ART registry record is linked with the compulsory birth record using the mother's unique personal identification number. All the eleven public and private Norwegian fertility-clinics report compulsory to the ART registry. By 2008, data on 18,011 pregnancies, including 3,294 twin pregnancies and 137 triplet pregnancies, have been registered in the ART registry. In addition, a proportion of women pregnant by ART-treatment abroad are registered as an ART pregnancy (yes /no) on the birth record constituting 1,259 (6.5%) of all ART pregnancies, including 226 pairs of twins in the period 1988-2008.

3.2 Methods

All three studies are population based cohort studies. In Paper 1, we used data from 1967-2004, and 27,849 multiple births and late abortions were identified, including 494 set of triplets and 30 sets of quadruplets. The multiple birth rates were described as rate per 100 births. For the investigation of time trends, the study period was divided into two, 1967-87 and 1988-2004. This cut point was chosen because the registration of ART pregnancies started in 1988. Detailed descriptions of the placentae with membranes were not noted in MBRN. Consequently, we used Weinberg's method to estimate the zygosity in the different time periods and by conception.[105 106]

In Paper 2, the source population consisted of all live births and stillborns in Norway from the 16th week of gestation onwards in the time period 1967-2006. Births with gestational age 16-21 weeks were excluded from the analyses of birthweight, gestational age and perinatal mortality, but were included in the incidence rates. After exclusions, the study population consisted of 2,118,584 singletons, 55,149 twins and 1,344 triplets.

Paper 2

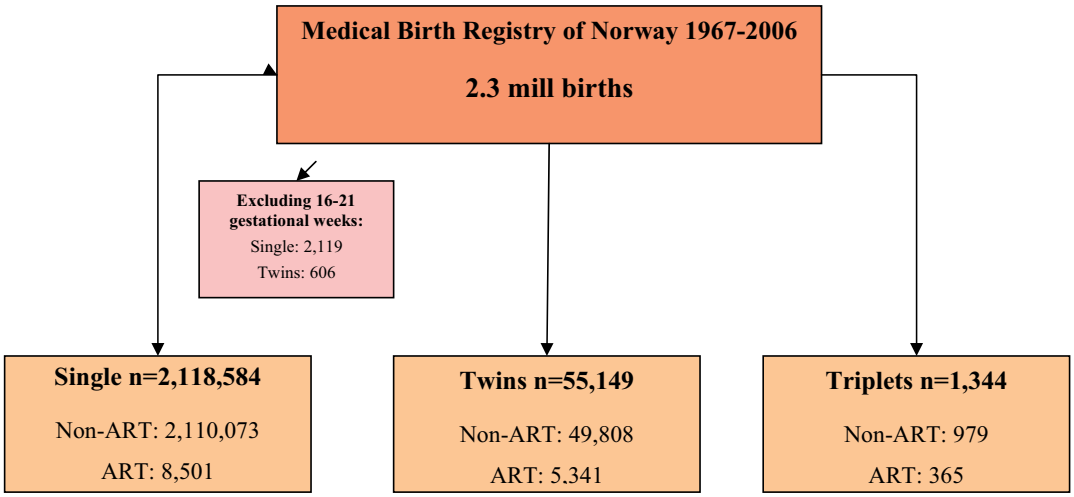


Figure 2. Flow chart of included births in Paper 2.

In Paper 3, we used data from 1967-2008. Offspring were linked to their mothers by the unique national identification number, providing data on 778,978 mother-offspring units. Mothers born as multiples themselves and mothers with missing gestational age and birthweight were excluded. Records with unlikely birthweight, judged by birthweight-by-gestational age Z-scores, were also excluded. After exclusions, the study population comprised 9,426 mother-twin pair units. The mothers were born during 1967-1991 and the offspring were born during 1982-2008.

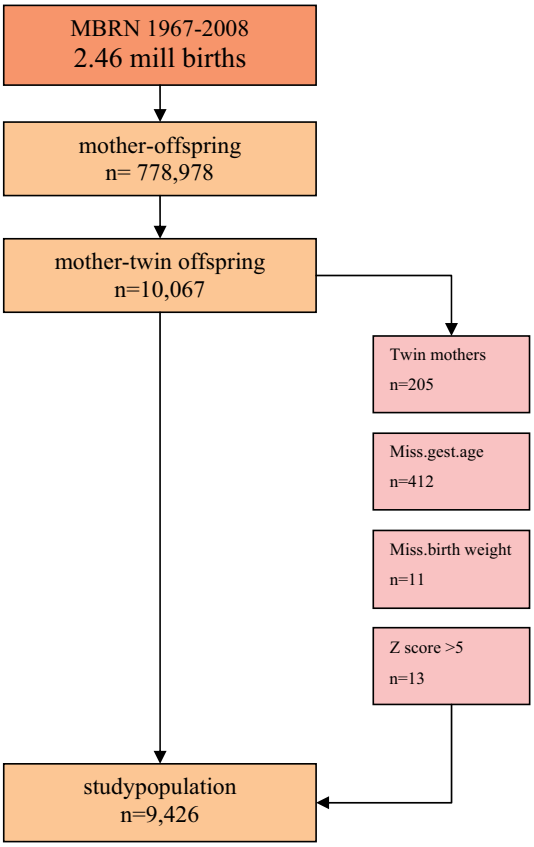


Figure 3. Flow chart of included births in Paper 3.

3.3 Exposure, outcome and confounding variables

The incidence rate of twin pregnancies was estimated as the number of twin pregnancies per 100 births by year of birth.

The incidence rate of triplet pregnancies was estimated as the number of triplet pregnancies per 10,000 births by year of birth, and accumulated into five-year categories in graphs.

Perinatal mortality was defined as the total number of fetal deaths from 22 weeks of gestation in Paper 2 and 16 weeks in Paper 3, until ≤6 days after birth. In Paper 3, the main outcome was perinatal mortality in one or both twins in a pair.

ART was evaluated by stratification in all papers, and as effect-modifying variable in Paper 3.

Gestational age: Gestational age estimation was based on the last reported menstrual period (LMP). From 1999, ultrasonographic gestational age estimation was reported in addition, but only used if LMP was missing (2.5%). In ART pregnancies, the date of embryo transfer was used to calculate the length of gestation. In Paper 2, gestational age was missing in 5.4% of singletons, 4.7% of the multiple pregnancies and in 8.5% of the pregnancies from ART. In records with missing gestational age, cases with birthweight ≥500 gram were included in the analyses of incidence, mean birthweight and total perinatal mortality. In Paper 3, mothers with missing gestational age (4.2%) were excluded. In the twin offspring generation, the gestational age of the firstborn twin was used. The mother's gestational age at birth divided into five categories was the main exposure in Paper 3.

Preterm delivery: Preterm delivery was defined as birth before 37 completed weeks or 259 days of gestation.[107] In Paper 2, we redefined the preterm definition as birth ≤ 10^{th} percentile of gestational age separately for the three plurality categories. In Paper 3, gestational age at birth for the index mothers were divided into five categories (27-31, 32-34, 35-36, 37-42 and 43+ weeks).

Z-scores for birthweight by gestational age: Conversion of the absolute birthweight (X_i) by gestational age to a standardized score (Z_i), represented in units of standard deviations, following the formula:

$$Z_i = (X_i - X_{mean})/SD$$

X_{mean} and SD are mean and standard deviation of birthweight for a specific gestational age in whole weeks.

Birthweight discordance in twins and triplets: Calculated as the difference between the largest and the smallest infant's weight, divided by the largest infant's weight.

Maternal age: Maternal age at delivery was categorized into five-year age groups (<20, 20-24, 25-29, 30-34, 35-39 and 40+ years) and used as exposure in Paper 1 and confounder in Paper 2. Maternal age was effect-modificator in Paper 1.

Parity was defined as the number of children previously born to a woman, and was evaluated as confounder in Paper 1 and Paper 3. Data were missing in 1.5% of the births.

The study period was mainly divided into two, before (1967-87) and after (1988 -2004 (2006 in Paper 2)) the start-up of the ART registry in MBRN. Most analyses in Paper 1 and 2 were stratified by these two time periods, but further subdivided into five-year periods in the estimation of incidences.

The study unit was twin pregnancies in Paper 1. In Paper 2, the individual infants were the units in the analyses of gestational age, birthweight and perinatal mortality. Measurements of birthweight discordance were assessed using a triplet sibship data file. In Paper 3, the outcome units were twin pairs organized as sibships. We considered it as an event if one or both of the twins died.

3.4 Statistical analyses:

Associations between exposures and outcomes were estimated using relative risks (RR) and odds ratios (OR) with 95% confidence intervals (95% CI) in 2x2 tables and logistic regression, respectively.

Mean values of subgroups were compared by t-tests and proportions by chi square tests.

Potential confounders were evaluated in contingency tables, stratification and logistic regression.

RR models in Paper 3 were calculated using generalized linear models with log-link rather than logit-link as in logistic regression.

Effect modifications were evaluated with specific interaction terms in general linear and logistic regression models (Paper 1 and 3).

Deviation from linearity was tested using "goodness of fit" between a model with a linear trend and a model with categorical factors rendering a chi-square test.

The Z-scores were based on current 'birthweight for gestational age standards' in Norway based on tabled data as presented by Skjærven et al.[108]

P-values <0.05 were considered statistically significant (Paper 2 and 3).

Estimation of zygosity was calculated using the Weinberg's method (Paper 1). The DZ twinning rate was estimated as twice the number of opposite sex twin pairs. This number was subtracted from the total number of twins to identify the MZ rate.[105]

We used the statistical software packages SPSS version 15.0 (SPSS Inc., Chicago, Illinois) and STATA Statistical Software, Release 9.0 (StataCorp LP, College Station, Texas).

Graphs were created in SigmaPlot10, Systat Software Inc**.** (SSI), San Jose, California.

4. Summary of results

4.1 Incidence

During the total study period 1967-2006, 2.18 million pregnancies were registered in the MBRN. Of these, 27,575 were twin pregnancies and 448 were triplet pregnancies with gestational age >22 weeks. ART was registered from 1988, and overall 12,509 pregnancies were conceived by ART, including 2,964 twin pregnancies and 151 sets of triplets to the end of the study period.

The total twinning rate was stable at 1.0-1.1% from 1967 to1988 and increased thereafter to 1.9% in 2004, a yearly increase of 3.3%. Restricted to spontaneously conceived twin pregnancies, the rate reached 1.6% in 2004. A rise in the total triplet rate was also observed from the last part of the eighties. After excluding ART pregnancies, the incidence was still doubled from the start to the end of the study period.

In Paper 3, the likelihood to conceive with twins was studied in relation to maternal birth characteristics. The relative risk to conceive with twins was dependent on the mother's birthweight, but not on her gestational age at birth.

The increase of the twinning rate from the first (1967-1987) to the second (1988-2004) time period was significant in all maternal age strata with an interaction between maternal age and time period (p= 0.003) (Figure 4, left). In spontaneous conceptions, the chance to conceive with twins increased up to age 38, followed by a strong decreasing trend. In ART twin pregnancies, the distribution of twin pregnancies by age was different from spontaneous conceptions, with the highest risk among women 25-30 years and a steep decline thereafter.

The age-specific non-ART triplet rate was not dependent on maternal age to the same extent with an almost stable rate among women 30-40 years. However, similar to twins, there was an increase in all gestational age categories in triplets from the first to the last period (Figure 4, right).

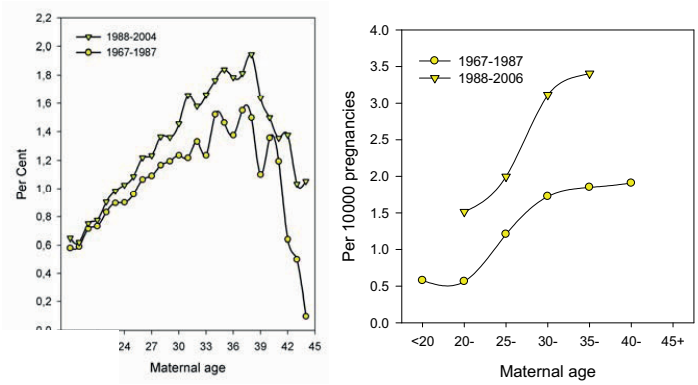


Figure 4. Twinning (left) and triplet (right) rates by maternal age in two periods among non-ART pregnancies.

4.2 Birthweight, gestational age and perinatal mortality

Birthweight was unchanged over time in the very preterm categories (≤28 weeks), but increased in the last time period by advancing gestational ages in all plurality categories. The mean gestational age declined in both twin and triplet pregnancies from the first to the second period. The cesarean section rate increased substantially in the same period. The perinatal mortality rate in twins improved slightly, but was unchanged in triplets relative to singletons over time, although the overall perinatal mortality rates improved significantly.

The gestational age specific mortality was highest for singletons and lowest for triplets in the gestational age categories 23-31 weeks. Using relative gestational age, triplets had higher perinatal mortality rate than twins and singletons in all percentiles. Triplets, twins and singletons had different gestational age distributions at birth and a proportion of 10 % of triplets were born before 28 weeks. The mortality rate for triplets before this stage in pregnancy duration was 50%, but fell to 3.8% for 28 weeks and above.

Perinatal mortality in triplets was calculated in relation to birthweight discordance and stratified by gestational age. When gestational duration was ≥28 weeks,

a weight discordance of ≥40% between the largest and smallest triplet had severe impact on mortality (RR 14.7; 6.7-32.2).

Relative risk of perinatal death was marginally lower in ART twins compared to non-ART twins. We could not demostrate a similar effect for triplets.

4.3 Perinatal mortality according to maternal birth characteristics

Perinatal mortality in twins was estimated with maternal birth characteristics as exposure (Paper 3). In the study population of 9,426 mother-and-twin pairs, 3.7% of the mothers were preterm born. Mothers born at 27-31 weeks had four times higher relative risk of losing one or both of her twins compared to term born mothers (RR 3.82; 1.56-9.36). There was a linear trend between maternal gestational age and perinatal mortality in twin offspring (test for deviation of linearity; χ^2 =0.3, 2df, P>0.5).

Mothers born preterm and in need for ART treatment had the highest risk of a perinatal loss (RR 4.07; 2.13-7.78), with a significant interaction between the mothers gestational age and ART (p= 0.033).

To separate the effect of intrauterine growth restriction from the effect of prematurity on the offspring perinatal mortality, we analysed term mothers in strata of birthweight-by-gestational age z-scores. Mothers born with z-score 1-2 had the most favourable outcome, while serious growth retarded mothers (z <-2) experienced the highest mortality in twin offspring.

Relative risk of a perinatal loss was higher in all preterm gestational age categories for mothers who delivered twins compared to singletons, with a significant interaction between maternal gestational age and plurality (p=0.003). Similarly, the effect of maternal birthweight (Z-scores) in term mothers interacted significantly with plurality (p= 0.024).

5. Discussion

5.1 Methodological considerations

The present studies have methodological strengths and limitations. This section will discuss to what extent the limitations may have influenced the findings in the thesis.

Validity and precision are key concepts in this evaluation. Validity means the absence of systematic errors, and it is divided into internal and external validity. Internal validity is divided into selection bias, information bias and confounding. External validity refers to whether the results can be generalized to other populations. Precision means the absence of random errors. The best way to assure high precision is to increase the study sample size.[109 110]

The study design: The present three studies were all historic cohort studies. Norway has a stable population with little emigration,[111] and the cohorts used in the papers were drawn from population based compulsory registries with a negligible problem of loss to follow-up. Twin- and triplet-pregnancies are rare events, and the present cohort design was therefore the best way to obtain valid and precise estimates because of the large sample size. In paper 3, however, there was a selection of the source population by design since only those who had reproduced were included in the second generation.

Validity: Since the source population used in the present studies is nation-wide and the birth registry is compulsory, selection bias is unlikely for the main exposures in all the three papers. The knowledge about adverse perinatal outcome could impossibly influence the plurality. Our main outcome in Paper 2 and 3 was perinatal mortality, and a follow-up time of only one week after birth secured a low dropout rate. However, in Paper 3, the follow-up time of the included index mothers was inadequate. The mothers were born during 1967-1990, and only the oldest cohort of the mothers had completed their reproduction, while the youngest had just started family building.

In Paper 3, we excluded mothers who themselves were born as twins. Recurrence of twinning itself is complicating the data and our interpretations. We know that twins on average are born earlier and are smaller for gestational age than singletons. Individuals

born as multiples must be biologically different either by the unique intrauterine experience or genetically, possibly through fetal programming.[112] Twin mothers paradoxically have offspring as large as singleton mothers even though they are smaller at birth.[113 114] To avoid selection bias, we found it most correct to exclude these mothers from the study population. However, we repeated the analyses of perinatal mortality by maternal gestational age (Paper 3, Table 2) and maternal birthweight-by-gestational age (Paper 3, Table 4) in twin offspring with all mothers included. There was a small reduction in the risk of perinatal mortality in the most preterm category, indicating that twin mothers born preterm had a slightly more favourable outcome. In the analyses of birthweight-by-gestational age, the inclusion of twin mothers to the mothers under exposure had no effect on the results.

Information bias: Bias is systematic error that results from incorrect measurement or classification of the exposure or outcome.[110] The ART registry reports only ART pregnancies from treatment conducted at fertility clinics in Norway. However, infertile Norwegian couples also receive ART treatment abroad, most frequently in Denmark and Sweden. Through contact with 12 infertility clinics in Denmark and Sweden, we found less than 40 ART twin pregnancies after treatment abroad yearly in the period 1988-2004. Excluding these pregnancies, the spontaneous twinning rate was marginally lower. In Paper 2, we estimated 3-4 ART triplet pregnancies conceived abroad yearly, about 10% of the total. Consequently, the incidence rate of non-ART and ART triplets might be biased. Perinatal outcomes were, however, similar for non-ART and ART triplets and were not affected by information bias.

Gestational age is an important variable in perinatal epidemiology. In the MBRN, the gestational age estimation was based on the last menstrual period (LMP). From 1999, ultrasonographic gestational age estimations were reported in addition. In ART pregnancies, the day of embryo transfer was used to calculate the length of gestation. In Paper 2 and 3, we used LMP for gestational age estimations and the ultrasonographic findings only if LMP was missing (2.5%). This was done to avoid the implications of changing from one method to another. The validity of the gestational age registered in the birth register has been assessed, and was considered to be 90-98% satisfactory.[115]

Hence, information bias caused by different methods of estimating length of gestation is not likely.

Records with obviously misclassified gestational age were also excluded in Paper 2 and 3, based on birthweight by gestational age Z-scores above 4 and 5, respectively.

The registration of twins and triplets in sibship data files has some challenges. Twin pairs and triplet sets are linked, but they do not necessarily have the same gestational age. In some cases, intrauterine death in one of the fetuses has occurred early in the pregnancy, and the surviving twin is delivered at a later date. Some of these births are classified as a multiple births, but only one birth record exists. In our data, we had more twin individuals than twin pairs, but due to the large sample size, this sort of bias was not believed to distort the results in our study. Most pregnancies with vanishing twins are classified as single birth, because the demise of the fetus happened at a very early stage. The true incidence of vanishing twin is difficult to assess. Anyway, in a review from 1996, it was suggested that if two embryos are seen in the first trimester, the loss rate is 7.3% of spontaneous conceptions.[116]

In the present thesis, we tested the effect of potential confounders as maternal age and time periods by adjustments in logistic regression models and by stratification.

Confounding: Confounding is defined as confusion of effects, implying that the effect of the exposure variable is mixed with the influence of another variable.[110] In Paper 1 and 2, the use of fertility enhancing drugs was considered as an important confounder for the spontaneous twin- and triplet rate. The use of clomiphene citrat and gonadotrophins for ovulation induction was not registered in MBRN or elsewhere. We were not able to evaluate its effect on the results, and therefore we introduced the concepts “non-ART pregnancies” and “ART pregnancies”.

In Paper 1, the high impact of aging on the risk of twinning was considered to be a confounder. Thus, we stratified the multiple pregnancy rates by maternal age. In Paper 2, we adjusted for maternal age in five age categories and time periods.

In Paper 2 and 3, the differences in the outcome from spontaneous conceptions and ART pregnancies were compared. Gestational age and birthweight was lower for ART pregnancies in all the three plurality categories and might explain some of the higher risk of perinatal mortality in ART pregnancies since preterm birth is the main reason for perinatal mortality.[17 78] Higher level of anxiety and concern during pregnancy, among both the infertile couple and the physician, might lead to more frequent doctor visits and consequently a more active and earlier intervention in ART pregnancies. We suggest that iatrogen induction of delivery is a confounder to the lower gestational age in ART multiples.

In Paper 3, characteristics of the grandmother as age, parity and socio-economic conditions were evaluated as confounders for the outcome of her grandchildren. However, adjustments did not change the results, and we decided to present the crude values. The parity of the index mother had an independent effect on the outcome of her twin pregnancy, but was not associated with her own gestational age and was therefore not considered to be a confounder in Paper 3.[117]

The causes for reduction in perinatal mortality may be due to improvements in clinical treatment or simply a result of secular changes with better nutrition, better economy and in general better health care in the population. To quantify the effects from the different sources is difficult.

Effect modifications: In Paper 1, there was an interaction between maternal age and time period after excluding ART pregnancies. In other words, the association of the increasing multiple rates by age was significantly stronger in the last time period. A possible explanation is the trend in the last period to delay birth of first child to ages where the risk of spontaneous conception with twins is higher.[41 57]

In Paper 3, the cause behind the effect modification of ART and preterm born mothers to perinatal mortality in twin offspring is not obvious. ART twin pregnancies are mostly DZ, and one should expect more favourable outcome compared to spontaneous twinning which is a mixture of MZ and DZ. However, the adverse effect of the underlying

infertility itself might have contributed more strongly than zygosity to the outcome of these ART pregnancies.

The interaction between perinatal mortality in offspring, maternal birth characteristics and plurality is biological plausible because of the larger demand in a twin pregnancy compared to a single pregnancy.

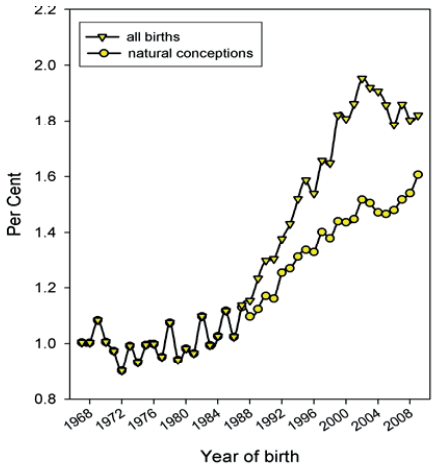
Generalisability: The data in this thesis came from a compulsory register from a nationwide population and selection bias and skewness is unlikely. The twinning rates vary among populations throughout the world and both genetic and environmental factors are involved in addition to different use and practise of assisted reproduction. The results concerning incidence rates for twins and triplets in Papers 1 and 2 are therefore most likely to be valid only for western countries since socio-economic conditions, urbanisation, nutrition, health care and the availability of ART are almost similar in these countries. Perinatal outcome of preterm infants are also dependent on the level of obstetrics and neonatal medical care in addition to the general living standard. Our results are therefore limited to populations with the same health care standards.

The findings that perinatal outcome in a twin pregnancy is dependent on the mothers birth characteristics is probably of a more biological origin, and can be generalised to other populations.

Presision: Due to the enormous amount of data in MBRN, the precision was high in most analysis in all three papers in this thesis. However, in Paper 3, we had few cases of mothers in the very preterm category, but the results of mortality in the twin offspring from these mothers are robust and justified in tests of linearity. In Paper 2, we had too few cases to study gestational age specific perinatal mortality of triplets after stratification by ART and non-ART conceptions. Since the registry was nationwide, it was impossible to increase the sample size without linking similar registries from the other Scandinavian countries. Such collaboration has started recently.

5.2 Discussion of specific results and comparison with other studies

Rising twin birth rates is not unique for Norway. Denmark has observed a 2.4 fold increase[118] and Sweden a 1.7 fold increase in the same time period.[119] This is partly explained by the liberal access to infertility treatment and includes both ART and other hormonal stimulation of the ovaries. In our data, there was still a significant increase after excluding ART twin pregnancies. We think this is partly due to a rising use of hormonal ovarian stimulation, but also to advancing maternal age in the population. We have now extended the time period in Figure 1, Paper 1 to cover five more years (2005-09). The spontaneous twin birth rate continues to increase, while the total incidence declines. The latter is probably due to the implementation of single embryo policy in ART (Figure 5).



**Triplet pregnancies excluded*
and mothers with missing personal identification numbers were included.

Figure 5. Twin birth rates by year of birth, Norway, 1967-2009. All twin births and births restricted to natural conception.

In the same way, the incidence of triplets in Norway was more than three-fold in the time period 1988-2000 compared with the previous twenty-year period, mostly due to insertion of three embryos in ART treatment.[120] Guidelines for number of embryos

transferred were changed in Norway like most European countries around the turn of the century,[53] and explain the decline in the triplet rate from 2000 onwards. These findings have parallels in the international literature in countries were ART treatment is available.[49 121] However, excluding pregnancies from ART, the incidence rate of non-ART triplet pregnancies was still more than doubled during the forty year period 1967-2002. So, even if the number of embryos can be strictly controlled in ART treatment, increased use of fertility enhancing drugs might probably further contribute to the rise of twins- and triplet rates.

In Paper 3, we found that the prevalence of twin pregnancies in our study population was independent of the mother's gestational age, but increased with maternal birthweight and birthweight-by-gestational age z-scores. The findings are in accordance with a study using the Danish National Birth Cohort (1996-2002), in which twinning were used as a marker of fecundity. The authors reported more than a doubling in the twin birth rate if the mother was born at term, had a birthweight herself > 4.500 gram and a pre-pregnancy body mass index of <25 kg/m^2.[122] In our study, we were not able to evaluate the effect of body mass index.

Maternal age is one of the most important factors influencing the twinning rate with a higher risk of twins with advancing age.[41 57] The rise of the twinning rate up to maternal age 38-39 years was most pronounced in the last time period, with a significant interaction between maternal age and time period (p= 0.003). The increase in the mean maternal age during the study period indicates that women in a modern Nordic society postpone having their children to a later stage in life. Hence, the shift in maternal age distribution explains the enhanced risk of twinning by advancing maternal age in the last time period. Other studies support these findings.[11 41] The paradox that twinning rates are increasing while fecundity is declining by maternal age, is explained with impaired feedback control from the aging ovary to the pituitary gland. The rising concentrations of the follicle stimulating hormone FSH by age will lead to multifollicular development and subsequent ovulation of two or more oocytes.[11 57 58]

The likelihood of achieving a twin pregnancy in the ART cohort declined from 31% in the age group 25-29 years to 12% at ages 40-42, although two embryos were transferred if available. This finding underlines the nature of infertility itself, with higher frequency of poor oocyte quality and impaired uterine implantation rate, occurring at an earlier stage among infertile women. A Danish study estimated that one in 10 ART-singleton deliveries originates from a twin pregnancy in which one twin had died after week 8 of gestation ("vanishing twin").[123] The study population was from 1995-2001 when double embryo transfer was standard. The high frequency of vanishing twins underlines the high risk of a fetal loss in ART pregnancies.

The impact of parity on the twinning rate is discussed by several authors. Allen et al. proposed that women who conceived with twins were more fertile, and the higher risk of twinning with increasing parity did follow as a consequence.[60] Others think that the association of parity and twinning rates is strongly confounded by maternal age. These authors investigated data from the period 1951-83, when large families were still relatively common.[5] We wanted to clarify the parity effect in our study, and stratified the time trend analysis of incidence by maternal age into primipara (first pregnancy) and para 1+ (subsequent pregnancies in the same woman). The strong increase in twin births in the last period in women 30-40 years occurred among primiparae. These data are now presented in Figure 6. The finding is in accordance with the combination of a general postponing of childbearing, declining fertility by age and excess use of ovulating inducing drugs in this age group.

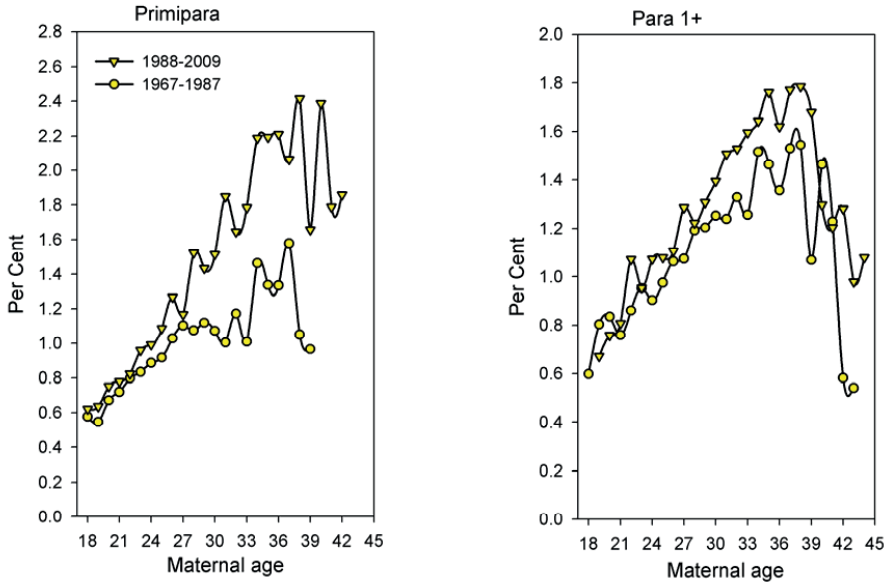


Figure 6. Twin birth rate by maternal age and main study periods excluding assisted reproductive technology (ART). Left panel: 1st pregnancies. Right panel:2nd and subsequent pregnancies.

We were able to quantify the number of twin births from hormonal stimulation combined with assisted insemination by husband (AIH) or donor (AID). These treatments and pregnancies are nominally, compulsory reported to the Directorate of Health and Social Affairs.[124] Nine twin births after AIH/AID were reported in Norway in 2008. In other studies, it is estimated that 17-32% of non-ART twins are born after fertility enhancing therapies with or without inseminations.[125 126]

Most of the rise in the twin birth rates is caused by DZ twins.[11] By using Weinberg's method,[106] we found a small increase in the risk of DZ twinning in the non-ART twin pregnancies (Paper 1). During the period 1990-2004, the number of ART twins to the total twin birth rate was considerable (25%). The accepted knowledge that one third of twin pregnancies in a population were MZ and two third were DZ [5-7] was shifted towards a higher proportion of DZ twins. DZ pregnancies have fewer

complications than do MZ, and the described shift might have biased our results of improvement in perinatal mortality for all twins.

In our study, the individual birthweight-by-gestational age of triplets was similar to twins until 32nd weeks of gestation, but fell below singletons from week 28. Physiological adaption to the limited uterine capacity is one reason for the blunted growth curve, but intrauterine growth restriction as a result of competition for nutrients is also important for the lower birthweight-by-gestational ages. After prematurity, fetal growth restriction is the most important contributor to perinatal mortality in triplet pregnancies.[17 127] We found that birthweight discordance within a triplet set had less impact on perinatal mortality when gestational age was 22-27 weeks compared to ≥ 28 weeks, probably because of the overall high mortality rate in these extremely preterm infants. When gestational age passed 27 weeks, birthweight discordance ≥40% represented a high risk of death for the smallest fetus. It would have been correct to adjust for chorionisity in these analyses, but data were lacking.

Perinatal mortality in multiples: In Paper 2, epidemiological aspects of triplet pregnancies were described with a special focus on perinatal mortality. No publications were previously based on this large database on triplets, except one study of birthweight percentiles in multiples covering the years 1967-1995.[128] Use of gestational-age-specific mortality rates showed that triplets had lower mortality than singletons and twins from the lowest gestational age categories up to 32-34 weeks, while the overall relative risk of perinatal mortality for all triplets was ten times higher than for all singletons. The same mortality curve pattern was shown in a study from the Swedish Medical Birth Registry, covering the years 1982-1995.[129] This usual approach represents a biased relation since only a small number of singletons are born preterm, including highly selected and vulnerable infants. When we used relative gestational ages based on the distribution of gestational ages at birth in percentiles, triplets had a higher perinatal mortality than twins and singletons in all percentiles of gestational age. This observation is in accordance with the overall mortality results and clinical experience. We found a markedly better survival for triplets after the 28th week of gestation, corresponding to

the 10th percentile (from 50% to 97% survival), and we suggest this gestational age as a relative preterm definition in triplets instead of the traditional 37 weeks.

Another strategy to calculate the risk of perinatal mortality in multiples would have been to use the "fetuses-at-risk" approach were stillbirths and deaths within the first week of life should be reported separately.[130 131] In the "fetuses at risk" model, the denominator in the calculation of risks is the number of ongoing pregnancies, i.e. the undelivered.[132] In recent years, this approach is suggested to be superior to the traditional stratification on gestational age-specific perinatal mortality with all live births and stillbirths as denominator. Proponents argue that the etiology of stillbirths and early neonatal death has changed, because of fewer early neonatal deaths caused by asphyxia and advances in neonatal medicine. In addition, the classification of stillbirths versus livebirths in the extremely preterm was more inaccurate in the past and differed temporarily and geographically, which justified the combined category "perinatal mortality".[130] Some believe that the hazard of perinatal mortality (the instantaneous risk) at each gestational age is more realistic obtained when derived from a denominator consisting of all individuals at risk of a given outcome. Applying this approach leads to the conclusion that mortality rates increase steadily with advancing gestational age especially after week 34-35. Using gestational age-specific stillbirths as nominator and all undelivered fetuses as denominator are indicators of short-time risk only.[133]

It has not been a tradition in publications from MBRN to use the "fetuses-at-risk" approach in perinatal mortality issues.[134-136] One exception is a recently published study with recurrence of stillbirth as the main focus.[137] In our study (Paper 2 and 3), we found it most appropriate to use the conventional definition of gestational age-specific mortality. Firstly, we used data from 1967 onwards, and the merged category "perinatal death" was a more reliable variable than division in stillbirth and early neonatal death for the first decades. Secondly, the "fetuses-at-risk" approch is based on singletons, and we studied risks of perinatal mortality in multiples. It is not clear if the same stillbirth risk measures can be used in multiple pregnancies with one stillbirth and one surviving co-twin. However, data were analysed according to "the fetuses-at-risk model", and obtained in Figure 7.

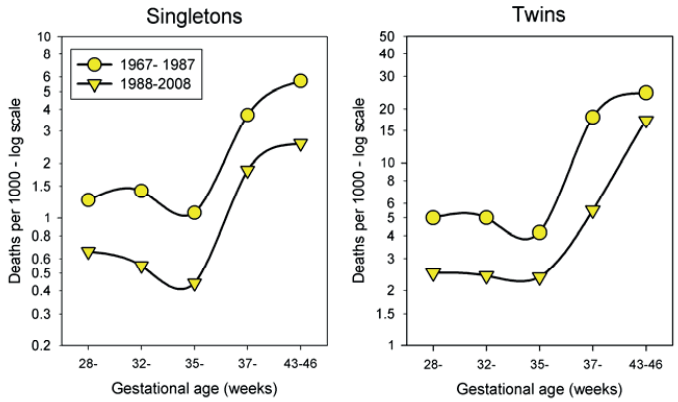


Figure 7. Stillbirth per gestational week, singletons and twins. Norway.

We found that although death rates have improved for singletons, twins and triplets in the past 40 years, the relative risk of perinatal mortality for triplets was still 10 times higher than for single births in the last time period (1988-2004) compared to the first (1967-1987). The delayed improvement in mortality for triplets may be a result of the higher proportion of very preterm births in addition to birthweight discordance. 16% of the triplet sets in our study population had severe forms of discordance (Paper 3, Table 4), which is significantly associated with both stillbirth and deaths during the first days of living.[17 138] Unfortunately, death causes were not routinely available in MBRN.

*Intergenerational effects on perinatal mortality in twins***.** The increased risk of perinatal death in twin offspring to mothers born preterm or growth retarded were higher for twin offspring than previously shown for singleton offspring.[98] Perinatal mortality in twin offspring has not been evaluated in intergenerational studies previously, and our results add a novel adverse consequence of being born preterm or with impaired fetal growth. We were looking at possible causes to understand how maternal gestational age might affect perinatal mortality in twin offspring. Preterm delivery is the most important cause of perinatal death overall,[139] and we already know that preterm mothers are at increased

risk of having preterm singleton offspring.[91] To explore this further, the material of twin offspring were divided into preterm (≤36 weeks) and term born (≥ 37 weeks), and perinatal mortality was analysed by maternal gestational age. There was a four-fold higher risk of perinatal deaths in the preterm twin offspring if the mother also was born preterm (27-31 weeks) compared to term (RR 3.7; 1.2-11.2). No such association was found when the twin offspring were born at term.

The association of low gestational age and increased perinatal mortality in offspring could be genetic, but not necessarily. Being born preterm could also produce long-term physical defects with impaired development and function of the reproductive organs.[140] [141] The defect will be revealed more clearly in a twin pregnancy because of the higher physical demand in such gestations. In contrast, women exposed to intrauterine growth restriction might have an increased risk of epigenetic modulations with persistent change in genetic expression, and the intergenerational association is more likely to be transmitted by genes.[142] The consequences of birth characteristics in one generation with unfavourable perinatal outcome in the next generation are probably caused by heterogeneity of unknown risk factors. The effect-modification of ART on twin offspring mortality in the preterm born mothers can only be a part of this picture.

A genuine new finding was that women delivered at term, but with low birthweight-by-gestational age, experienced increased perinatal mortality among their twin offspring compared to women with more optimal weight-by-gestation. Intrauterine growth restriction is associated with increased risk of developing adult onset disease, such as type 2 diabetes, renal insufficiency, cardiovascular disease and fatty liver.[142] The mechanism behind this life course approach is so far poorly understood. Because of "the brain-sparing effect", other organs than the brain, myocardium and adrenal glands will be hypoperfused in situations with chronic hypoxia. The subsequent long-term consequences of deficient development of the uterus and ovaries in fetal life are unknown.[143] Also, it has been suggested that intrauterine growth restriction interrupts developmental processes and may produce persistent changes in gene expressions. Such epigenetic modulations may play important roles for a woman's ability to meet the increased physiological demands of a twin pregnancy.

It has previously been suggested that pregnancy is a physiological stress-test that reveals latent chronic disease.[140 144] The Barker hypothesis indicates that an individual's birthweight is associated with cardiovascular disease in later life. Pregnancy complications as preeclampsia and gestational diabetes are also highly associated with cardiovascular disease.[145 146] These studies lead to the idea that a woman predisposed to cardiovascular disease because of unfavourable birth characteristics are probably more exposed to pregnancy complications and subsequent adverse perinatal outcome of her twin offspring. Because the index mothers are born 1967-1990, the incidence of cardiovascular disease is still expected to be low, but studies on this endpoint will be conducted in the future.

The impact of ART: ART pregnancies have been associated with higher risk of pregnancy complications and adverse perinatal outcomes compared to naturally conceived pregnancies. Several systematic reviews have been published comparing singletons[77 78 147] and twins.[47 78 86 118] The reviews indicate around two-fold increase in risk of perinatal mortality in ART singletons compared with singletons conceived spontaneously.[77] The results for comparison of twins by mode of conception are more conflicting. Some studies are confounded by zygosity, and the relative risk of adverse outcome in ART twins will be reduced because of the low proportion of MZ twins. In a recent study from Australia,[86] ART twins were compared with unlike-sex twins from spontaneous conception in an effort to compare groups of homogenous zygosity. The ART twins had doubled risk of preterm birth, low birthweight and perinatal death (RR 2.2; 1.1-4.6). On the other hand, Pinborg et al. did not observe any effect on perinatal outcome when they restricted their analyses to unlike sex twins.[118] In Paper 2, outcome of twins pregnancies were compared according to mode of conception. ART twins had lower risk of perinatal mortality compared to non-ART twins in the period 1988-2006, similar as other studies.[78 81] We have now, in retrospect, dichotomized spontaneously conceived twin pairs in same and unlike sex, and repeated the analyses of perinatal mortality risk for these subgroups (Table 1). Relative risk for a perinatal loss was 1.33 (1.05-1.69) in ART twins compared to unlike sex non-ART twins. These results are more consistent with the observation that infertility itself is an independent risk factor for adverse pregnancy outcome as seen in ART singletons.

Table 1. Relative risk of perinatal mortality in A: like sex spontaneously conceived twins (All MZ+DZ) and B: ART twins (mostly DZ) with unlike sex spontaneously conceived twins (DZ) as reference.

	Twin pairs	Perinatal mortality	
A. Spontaneous:	n	n (%)	RR (95%CI)
Unlike sex (DZ)	9094	149 (1.64)	1.00 (ref)
Like sex (MZ+DZ)	19324	652 (3.37)	2.10 (1.75-2.51)
Total	28418	801 (2.81)	
B**. ART** (≈DZ)	5856	127 (2.17)	1.33 (1.05-1.69)

Recent research suggests that some of the problems with adverse pregnancy outcome in ART pregnancies are related to biological factors and consequences of being infertile.[79] In addition, efforts have been made to identify possible iatrogenic effects on the children conceived by the use of in vitro technologies. The influence of the procedure itself, such as the culture medium and the ovulation hyperstimulation on fetal growth and development, has been an ongoing debate. A major topic is disturbed genomic imprinting.[148] Beckwith–Wiedemann syndrome is an overgrowth disorder present at birth, characterized by a large tongue, abdominal wall defect and increased growth. The incidence is 1/ 15,000 births. Children conceived through ART have a three- to four-fold increased chance of developing Beckwith–Wiedemann syndrome.[149] The epigenetic changes that underlie the syndrome are well defined, but other imprinting disorders that lead to low birthweight and IUGR have not been identified. Data from animal studies show direct links between ART procedures, DNA methylation and disruption of genomic imprinting.[150 151] A project with data and blood samples from the Norwegian Mother and Child Cohort Study[152] is now being planned to study the relationship between infertility, ART, birth outcomes and epigenetic variations.

The focus on safety aspects in the ART treatment and the complications associated with multiple pregnancies, have led to changes in the embryo transfer policy. In Scandinavia, single embryo transfer (SET) has now been the main rule during the last five years for the first and second treatment cycles if top-quality embryos are available. Combined with the transfer of frozen-thawed embryos, the cumulative pregnancy rate is acceptable.[53 153-157] Evaluation of an infertility clinic's quality is no longer only based on "pregnancy rate" but rather "one healthy child to term". The twinning rate among ART-pregnancies in Norway is reduced by two third in the time period 2003-2008, as the SET program gradually has been implemented.[74]

6. Conclusions

The twin birth rate in Norway has increased significantly in all age groups during the last four decades. Advancing maternal age and frequent use of ART cannot alone explain this increase, and excess use of ovulation stimulating drugs may be additive.

The triplet rate rises almost three-fold in the nineties, but declines in this century probably due to reduction in numbers of embryo transferred in ART-treatment. However, the spontaneous triplet rate has more than doubled during the last twenty-five years probably also because of ovulation stimulating drugs. The perinatal mortality has improved considerably during the study period, but is still ten-fold more frequent in triplets and four times more frequent in twins compared to singletons during the last twenty years. A proportion of 10% of the triplets are born before gestational week 28 and these very preterm births partly explain the poorer outcome in triplets. The perinatal mortality is similar in ART and non-ART triplets. In twins, the mortality is marginally higher for non-ART compared to ART twins, zygosity unconsidered.

There is a significantly higher risk of perinatal loss in twin offspring when the mother is born preterm or growth retarded herself, indicating that a woman's birth characteristics reflects her reproductive capacity, especially in a twin pregnancy. Our results add new knowledge to the identification of risk factors and will improve the understanding of the biological mechanisms in multiple pregnancies.

7. Implications and future research

7.1 Prevention of multiple pregnancies

Multiple pregnancies are considered to be a rare, but a natural variant in human reproduction, and our research has contributed to increased knowledge about incidence and perinatal outcome of such pregnancies. The general improvement in neonatal medicine has not included multiples to the same extent as singletons, and the increasing twin birth rate should be an important concern in health care and policy. Thus, decisions in order to limit the occurrence of multiple pregnancies will be beneficial not only for the individual, but also in a health economic perspective. Due to implementation of SET in ART treatment, the contribution of twin pregnancies from ART is already considerably lowered, and will probably continue to fall. The use of hormonal drugs for ovulation induction and the following multiple pregnancies should be monitored more carefully and registered in birth records and health registries.

7.2 Improving the outcome

We have identified different categories of multiple pregnancies with especially high risk profiles of poor outcomes. A main implication of this thesis should therefore be implementation of national standardized protocols for monitoring the high risk groups:

a) Triplet pregnancies
b) Twin pregnancies where the mother was preterm or growth-retarded herself at birth

Standardized protocols should include distinct criteria on the frequency and content of the controls and that they should take place in central hospitals. The protocols should also clearly include criteria for when additional diagnostic examinations should be performed and when intervention with delivery induction or cesarean section is necessary. Parameters associated with unfavourable outcomes should be searched for. Research aiming to identify predictive factors that contribute to preterm births should be given high priority and will be valuable not only for the child at risk, but also through

generations. New predictors believed to detect women with multiple pregnancies at risk of preterm delivery include ultrasonographic measurements of cervical length and cervicovaginal fetal fibronectin.[20 158] Introduction of these parameters in pregnancy monitoring should be considered. Overweight and obese women have increased risks of preterm birth, and maternal body mass index at the start of pregnancy should also be noted in the MBRN.[159]

Because pregnancy outcomes are less favourable in MZ twins than DZ twins, determination of zygosity by sonography in early pregnancy (before 12th week) would be of value. Decisions of zygosity with DNA tests on like sex twin-pairs at birth might also be introduced and clinical relevance evaluated.

7.3 Future perspectives

Our focus during this work has been different aspects of multiple pregnancies limited to the data available in MBRN. Follow-up studies on long-term outcome in multiples require linkage to other datasources like the Mother and Child Cohort Study[152] and the Cause of Death Registry.[160] Rare events as congenital malformations in multiples, childhood cancer and safety aspects of ART children should be searched for in larger databases like the Nordic collaboration already initiated: The Committee on Nordic Assisted Reproductive Technology and Safety (ConARTAS).

Intergenerational associations give rise to ideas about shared genetic causes, but also that medical decisions and treatments, lifestyle and socio-economic positions in our time will influence health through generations.

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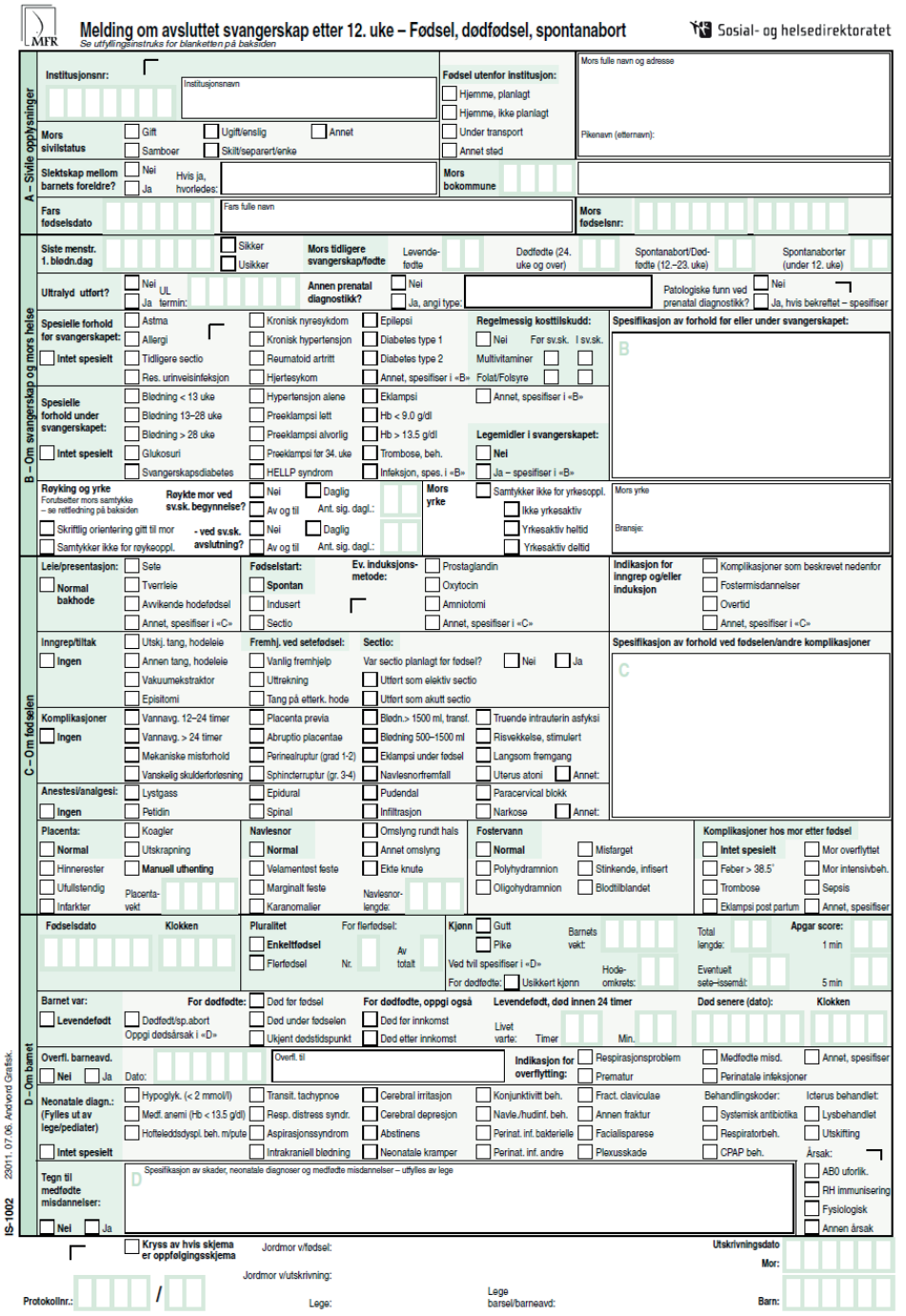
Appendices 1-3



MFR

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

Se utfyllingsinstruks for blanketten på baksiden

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 ☐ Samboer ☐ Ugift/enslig ☐ Skilt/separert/enke ☐ Annet

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 ☐ ☐

Spesifikasjon av forhold før eller under svangerskapet: B

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»

Røyking og yrke
Forutsetter mors samtykke – se nettledning 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 ☐ Episiotomi

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 asfyksi ☐ 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 uthenting
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: ☐ Enkeltfødsel ☐ Flerfødsel — 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
For dødfødte: ☐ Dødfødt/sp.abort — Oppgi dødsårsak i «D»
☐ 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: ☐ AB0 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:

Lege:

Lege barsel/barneavd:

Utskrivningsdato — Mor: — Barn:

Protokollnr.: /

IS-1002 2301. 07.06. Arkivord Grafisk.

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:

50 000. 5.96. SEM GRAFISK

Sted (sykehusets stempel) | Dato | Jordmor | Lege

IK - 1002.

Melding til MFR av graviditet etter foretatt IVF/ICSI

Fylles ut av avdelingen for alle behandlinger ved første ultralydundersøkelse

Ikke skriv her

Avdeling/institusjon

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:

Ikke skriv her

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

Antall fostre:

Antall fostre med sikker hjerteaksjon:

Bes innsendt til MFR straks etter første ultralydundersøkelse

Dato, stempel og underskrift

Bording AS 04.09

19079

Errata

- **Paper 3**, page 2, paragraph 4: The sentence: “Records with obviously misclassified gestational age were also excluded based on z-scores for birthweight-by-gestational age above 4 (n=15, 0.1%)” should be “…z-scores for birthweight-by-gestational age above 5 (n=13, 0.1%)”.