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

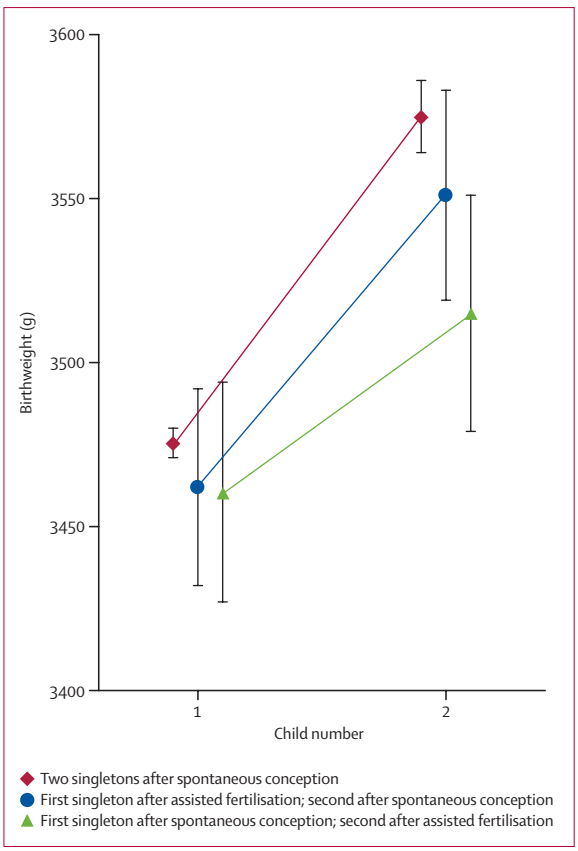

Figure: **Adjusted mean birthweight of singletons in families with two children only**
Data adjusted for maternal age, parity, offspring sex, year of birth, change of partner, and time from previous birth to conception. Error bars represent 95% CIs. Two singletons after spontaneous conception (191732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