Perinatal outcome of singleton siblings born after assisted reproductive technology and spontaneous conception: Danish national sibling-cohort study

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Objective: To compare the perinatal outcome of singleton siblings conceived differently.
Design: National population-based registry study.
Setting: Denmark, from 1994 to 2008.
Patient(s): Pairs of siblings (13,692 pairs; n = 27,384 children) conceived after IVF, intracytoplasmatic sperm injection (ICSI), frozen embryo replacement (FER), or spontaneous conception subcategorized into five groups according to succession: [1] IVF-ICSI vs. spontaneous conception (n = 7,758), [2] IVF-ICSI vs. FER (n = 716), [3] FER vs. FER (n = 34), [4] IVF-ICSI vs. IVF-ICSI (n = 2,876), and [5] spontaneous conception vs. spontaneous conception (n = 16,000).
Intervention(s): Observations were obtained from national registries.
Main Outcome Measure(s): Birth weight, gestational age, low birth weight (<2,500 g), preterm birth (<37 weeks' gestation) and perinatal deaths.
Result(s): Mean birth weight was 65 g (95% confidence interval [CI], 41–89] lower in all assisted reproductive technology children compared with their spontaneously conceived siblings. FER children were 167 g (95% CI, 90–244] heavier than siblings born after replacement of fresh embryos. The difference in birth weight between firstborn and second born sibling depended on order of conception method. Higher risk of low birth weight with (odds ratio [OR], 1.4; 95%CI, 1.1–1.7] and preterm birth (OR, 1.3; 95% CI, 1.1–1.6] was observed in IVF/ICSI compared with spontaneous conception.
Conclusion(s): When differentiating between order and mode of conception, it seems that assisted reproductive technology plays a role in mean birth weight and risk of low birth weight and preterm birth. Birth weight was higher in siblings born after FER compared with fresh embryos replacement. (Fertil Steril® 2010;■:■–■. ©2010 by American Society for Reproductive Medicine.)

Key Words: Perinatal outcome, singleton siblings, maternal factors, ART

The use of assisted reproductive technology (ART) is increasing all over the world. In Denmark, 4% of recent birth cohorts are conceived by IVF, intracytoplasmic sperm injection (ICSI), or frozen embryo replacement (FER) (1). It is well documented that infants born after ART, even singletons, have a poorer perinatal outcome than spontaneously conceived children (2–4). It has been shown that the infertility characteristics of the parents may influence the perinatal outcome (5, 6). In addition, ART itself may also influence the perinatal outcome negatively.

Romundstad et al. (7) conducted a sibling analysis comparing birth weight, gestational age, and the risk of perinatal mortality in siblings born after ART and spontaneous conception. The conclusion was that parental stigmata, rather than the technique, were likely to cause the adverse perinatal outcomes among ART children.

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Children born after FER have a higher birth weight and fewer adverse perinatal outcomes than do children born after fresh IVF-ICSI (8–12). Some of the explanation may be that women who benefit from cryopreservation have a good prognosis, with a good ovarian reserve and response to controlled ovarian stimulation (COS). Embryos surviving cryopreservation and thawing may be of better quality than some of the embryos used for fresh embryo transfer. The uterine environment after COS may also be less optimal for implantation and early placentation (13).

The objective of this study was to compare pregnancy outcome in two consecutive singleton siblings conceived differently. By keeping the parental factors constant, we aimed to clarify whether the parental factors leading to infertility or the reproductive technology per se cause the adverse perinatal outcome found among ART singletons.

MATERIALS AND METHODS

We used data from the Danish Medical Birth Register, IVF Register, and Causes of Deaths Register. Women treated with ART who had given birth to a singleton after IVF, ICSI, or FER from January 1, 1994, to December 31, 2006, were identified from the IVF Register. All women who had given birth to two singletons with the following four sibling combinations representing conception mode were included: cohort A, IVF-ICSI vs. spontaneous

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TABLE 1

Background characteristics of the mothers and their children from cohorts A (IVF-ICSI vs. spontaneous conception [n = 7,758]), B (IVF-ICSI vs. FER (n = 716]), C (FER vs. FER [n = 34]), D (IVF-ICSI vs. IVF-ICSI [n = 2,876]), and E (spontaneous conception vs. spontaneous conception [n = 16,000]).

	Cohort A		Cohort B				
	IVF-ICSI (%)	Spontaneous conception (%)	IVF-ICSI (%)	FER (%)	Cohort C (%)	Cohort D (%)	Cohort E (%)
Maternal age (y)							
18–29	935 (24)	758 (19)	62 (17)	44 (12)	2 (6)	480 (17)	9,168 (58)
30–34	1,805 (46)	1,621 (42)	150 (42)	128 (36)	15 (44)	1,000 (35)	4,326 (28)
35–39	1,001 (26)	1,235 (32)	128 (36)	160 (45)	16 (47)	1,230 (43)	1,982 (13)
>40	140 (4)	266 (7)	17 (5)	25 (7)	1 (3)	152 (5)	156 (1)
Parity							
0	2,612 (67)	763 (20)	261 (73)	82 (23)	15 (44)	1,402 (49)	2,136 (14)
≥1	1,266 (33)	3,101 (80)	96 (27)	275 (77)	19 (56)	1,477 (51)	13,620 (86)
Year of birth							
1994–1998	634 (16)	743 (19)	77 (22)	43 (12)	5 (15)	543 (19)	6,354 (40)
1999–2002	1,361 (35)	993 (26)	151 (42)	133 (37)	16 (47)	1,058 (37)	5,790 (37)
2003–2006	1,886 (49)	2,144 (55)	129 (36)	181 (51)	13 (38)	1,281 (44)	3,614 (23)
ART method							
IVF	2,597 (67)		243 (68)			1,755 (61)	
ICSI	1,091 (28)		93 (26)			987 (34)	
IVFICSI	193 (5)		21 (6)			140 (5)	

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conception; cohort B, IVF/ICSI vs. FER; cohort C, FER vs. FER; and cohort D, IVF-ICSI vs. IVF-ICSI. Subsequently, all established pregnancies were traced in the Medical Birth Register, where information on gestational age, birth weight, and adverse perinatal outcomes was collected. A fifth cohort of siblings in which both children were conceived after spontaneous conception—cohort E, spontaneous conception vs. spontaneous conception—was randomly selected from the Medical Birth Register. The personal identification number, which is unique for all Danish citizens, makes it possible to follow the children and their mothers through the different national health registries.

Cohort A: Siblings Born after IVF-ICSI vs. Spontaneous Conception (n = 7,758)

A total of 3879 women conceived a singleton both after IVF-ICSI and spontaneous conception. If a woman had given birth to a spontaneously conceived child, both before and after the ART child, the birth preceding the ART birth was chosen.

Cohort B: Siblings Born after IVF-ICSI vs. FER (n = 716)

A total of 358 women delivered two singletons conceived after IVF-ICSI and FER, respectively. All women who had given birth to two singletons conceived after FER (cohort C, FER vs. FER; n = 34) or two IVF-ICSI singletons (cohort D, IVF-ICSI vs. IVF-ICSI; n = 2876) were also identified. A control group of spontaneously conceived siblings (cohort E, spontaneous conception vs. spontaneous conception; n = 16,000) was randomly selected from the Danish Medical Birth Register.

We included all singletons from the sibling combinations as described previously from January 1, 1994, to December 31, 2006. To be able to record spontaneously conceived siblings born after the ART siblings delivered late in the study period, we included data on spontaneously conceived siblings born until June 30, 2008.

Mortality was defined as stillbirth (death after 22 weeks' gestation), neonatal death (death at birth until day 28), and death within the first year of life, excluding day 0–28. Analysis on total death includes all three periods.

Because treatment with ovulation induction, intrauterine insemination, or both was not yet recorded in the Danish IVF Register during the study period, there may be children born after these techniques among the children recorded as spontaneous conception. This possibility might cause the spontaneous conception group of children to have a slightly worse perinatal outcome, thereby resulting in a smaller difference in birth weight (IVF-ICSI children vs. spontaneously conceived siblings) than their true difference. The proportion of these children is approximately 2%, although this percentage might be higher among our group of women who at one point in their life exhibited a need for fertility treatment (14). Information on the type of cryopreservation and day of embryo transfer is not available in the Danish IVF Register, but during the study period the majority of Danish clinics practiced slow freezing combined with day 2 embryo transfer.

According to Danish legislation, studies based solely on register data and with no personal involvement of the participants do not require approval from an ethical committee. Therefore, approval from an institutional review board, which in Denmark would be the local ethical committee, was not necessary for this study. Permissions to obtain data from the registers were achieved by the Danish Data Protection Agency (J.no. 2008-41-2319) and the Danish National Board of Health (J.no. 7-505-29-935).

Statistical Analysis

Differences in mean birth weight between siblings were estimated in a linear mixed effects ANOVA model accounting for repeated deliveries within the same mother. Multivariate analysis adjusted for maternal age (<30, 30-34, 35-39, ≥40), parity (0, or ≥1), year of birth (1994-1998, 1999-2003, 2004-2008) and offspring sex. In order to report estimated mean birth weights and gestational ages in the adjusted analyses, we chose male children born by a nulliparous mother, aged 30-34, between year 1999 and 2003 as the reference group. To estimate the risks for low birth weight, very low birth weight, preterm birth, very preterm birth, stillbirth and perinatal death we used a multiple logistic regression model for paired data with similar adjustments as in the linear mixed effects models.

Diagnostic residual plots assessed the fit of the linear models. In all of the models interaction between all pairs of confounders were tested, but none

TABLE 2

Neonatal characteristics of the children from cohort A (IVF-ICSI vs. spontaneous conception) and cohort B (IVF-ICSI vs. FER).

	IVF-ICSI vs. spontaneous conception sibling cohort (n = 7,758)				IVF-ICSI vs. FER sibling cohort (n = 714)			
Outcome	**IVF-ICSI**	**Spontaneous conception**	**Diff. (95% CI)**	***P* value**	**IVF-ICSI**	**FER**	**Diff. (95% CI)**	***P* value**
Birth weight, crude	3,442 ± 11	3,556 ± 10	114 (93–134)	<0.0001	3,443 ± 35	3,645 ± 33	202 (132–271)	<0.0001
Birth weight, adjusted[a]	3,501 ± 17	3,566 ± 20	65 (41–89)	<0.0001	3,522 ± 52	3,689 ± 60	167 (90–244)	<0.0001
Birth weight, adjusted[b]	3,589 ± 14	3,637 ± 17	48 (28–68)	<0.0001	3,602 ± 46	3,725 ± 53	123 (55–191)	0.0004
Gestational age, crude	276.6 ± 0.3	277.2 ± 0.2	0.6 (0.1–1.1)	0.03	277.6 ± 0.9	277.8 ± 0.8	0.2 (−1.5, 1.9)	0.82
Gestational age, adjusted[a]	277.6 ± 0.4	279.0 ± 0.5	1.4 (0.7–2.0)	<0.0001	278.2 ± 1.2	279.7 ± 1.4	1.5 (−0.3, 3.3)	0.10

Note: Data are mean ± SE. Diff. = difference (birth weight).

[a] Adjustments are made for maternal age, parity, year of birth, and sex. As mean birth weight and gestational age depend on these factors, the estimated mean values are reported for a male child born by a nulliparous mother, 30–34 years old, between 1999 and 2002.

[b] Adjustments are made for maternal age, parity, year of birth, sex, and gestational age. As mean birth weight depend on these factors, the estimated mean birth weight is reported for a male child born at term (≥37 weeks' gestation) by a nulliparous mother, 30–34 years old, between 1999 and 2002.

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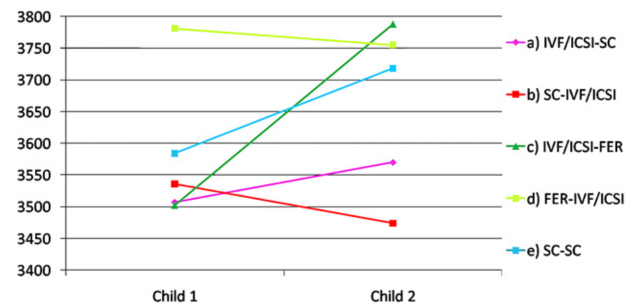
FIGURE 1

Birth weight* (in grams) in siblings from cohorts A (IVF-ICSI vs. spontaneous conception), B (IVF-ICSI vs. FER), and E (spontaneous conception vs. spontaneous conception). *a*, Child number one is conceived after IVF-ICSI, and child number two after spontaneous conception (n = 5,984). *b*, Child number one is conceived after spontaneous conception, and child number two after IVF-ICSI (n = 1,774). *c*, Child number one is conceived after IVF-ICSI, and child number two after FER (n = 550). *d*, Child number one is conceived after FER, and child number two after IVF-ICSI (n = 166). *e*, Child number one and child number two are conceived after spontaneous conception (n = 16,000).
*Adjustments are made for maternal age, parity, year of birth, and sex. As mean birth weight depends on these factors, the estimated mean values are reported for a male child born by a nulliparous mother, 30–34 years old, between 1999 and 2002.



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were found meaningful to include in the analyses. Analyses were performed with SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Demographics

Background characteristics of mothers and children from all five cohorts are listed in Table 1.

Cohort A: Siblings Born after IVF-ICSI vs. Spontaneous Conception (n = 7,758)

When adjusting for known confounders (maternal age, parity, year of birth, and offspring sex) children born after spontaneous conception were 65 g heavier than their siblings born after IVF-ICSI (Table 2). Most of the siblings had the same father (92%). We found the correlation in birth weight between siblings with the same father to be stronger (rho = 0.45) than when the children shared only the same mother (rho = 0.39). Either way, correlation this did not have a significant influence on the child's birth weight (data not shown). Birth weight increased from child number one to child number two regardless of order and mode of conception in the crude analyses. After statistical adjustments, this was not the case when the spontaneously conceived sibling preceded an IVF-ICSI sibling, because a decline in birth weight of 62 g (95% CI, –8, 132; P=0.07) was found from child number one to child number two (Figure 1). Mean gestational age was 1.4 days longer in spontaneously conceived children versus their IVF-ICSI siblings (Table 2). The proportion of children born with low birth weight (<2500 g) or preterm birth (before 37 weeks' gestation) was significantly higher among

TABLE 3

Risk of adverse perinatal outcome in siblings born after IVF-ICSI fresh ET vs. spontaneous conception (cohort A, n = 7,758).

	IVF-ICSI	Spontaneous conception	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)[a]	*P* value
Low birth weight (<2,500 g)	213 (5.5%)	147 (3.8%)	1.5 (1.2–1.8)	<0.0001	1.4 (1.1–1.7)	0.01
Very low birth weight (<1,500 g)	47 (1.1%)	41 (1.1%)	1.1 (0.8–1.7)	0.48	1.1 (0.6–1.8)	0.84
Gestational age <37 wk	281 (7.1%)	217 (5.6%)	1.3 (1.1–1.6)	0.0007	1.3 (1.1–1.6)	0.01
Gestational age <32 wk	47 (1.1%)	41 (1.1%)	1.1 (0.8–1.7)	0.48	1.1 (0.7–1.8)	0.75

[a] Adjustments are made for maternal age, parity, year of birth, and sex.

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the children born after IVF/ICSI than among their spontaneously conceived siblings (Table 3).

ICSI children were an average of 52 g heavier (95% CI, –1, 105; P=0.06) than IVF children in the adjusted analyses. Seemingly, their risk of low birth weight was reduced compared with the IVF children (1.5% vs. 3.9%), although not significantly (adjusted odds ratio [OR], 0.82; 95% CI, 0.55–1.24; P=0.35). Likewise, preterm birth was less frequent in the ICSI children (2.0% vs. 5.4%) although not significantly (adjusted OR, 0.83; 95% CI, 0.58–1.19; P=0.31.

The stillbirth rate was similar in IVF-ICSI and their spontaneously conceived siblings. Neonatal mortality and death within the first year of life occurred only in the group of spontaneously conceived children. A total of 46 deaths occurred after spontaneous conception, and 19 occurred after ART. The crude OR of total death was 2.4 (95% CI, 1.4–4.2; P=0.0008) among spontaneous conception children. After adjustments, the total mortality rate was increased sevenfold (adjusted OR, 7.1; 95% CI, 3.0–16.7; $P < 0.0001$) among the spontaneously conceived children compared with their ART siblings. This difference was clearly influenced by the order of mode of conception, because the crude total mortality was fivefold higher (OR, 5.4; 95% CI, 3.0–9.8; $P < 0.0001$) if the spontaneously conceived pregnancy preceded the ART pregnancy.

Cohort B: Siblings Born after IVF-ICSI vs. FER (n = 716)

In the adjusted analyses, an average difference of 167 g (95% CI, 90–244; $P < 0.0001$) was found between the two groups. The FER children were the heaviest (Table 2). A decrease in birth weight of 26 g (95% CI, –197, 250; P=0.82) was found from firstborn to second born child in the adjusted analysis when the FER child preceded the IVF-ICSI sibling. If the firstborn was IVF-ICSI and the second born was FER, birth weight increased by 286 g (95% CI, 92–480; $P < 0.004$; Fig. 1); 1.5% (n = 11) of the FER children were born with low birth weight, compared with 2.8% (n = 20) of their IVF-ICSI siblings (adjusted OR, 0.5; 95% CI, 0.3–1.1; P=0.18). The risk of preterm birth was also lower (adjusted OR, 0.5; 95% CI, 0.3–1.0; P=0.06) among the children born after FER than IVF-ICSI, although it was not statistically significant.

Cohort C: Siblings Born after Two FER conceptions (n = 34)

The difference in birth weight from child number one to child number two was 231 g (95% CI, 36–497; P=0.09) in the crude analysis, and 454 g (95% CI, 15–923; P=0.06) after adjustment.

Cohort D: Sibling Born after Two IVF-ICSI conceptions (n = 2,876)

A crude increase in birth weight of 121 g (95% CI, 84–159; $P < 0.0001$) was found from child number one to child number two. This difference was 110 g (95% CI, 60–159; $P < 0.0001$) after adjustments; 5.7% (n = 163) of the children were born with LBW, and 7.3% (n = 210) were preterm.

Cohort E: Siblings Born after Two Spontaneous Conceptions (n = 16,000)

The difference in birth weight in the crude analysis was 133 g (95% CI, 108–159; $P < 0.0001$), and after adjustments it was 134 g (95% CI, 105–163; $P < 0.0001$; Fig. 1). LBW was found among 3.9% (n = 303) of children, and preterm birth was found among 4.9% (n = 382).

DISCUSSION

By conducting sibling analyses, we have used a new approach to evaluate the perinatal health of singleton siblings born by the same mother but after different modes of conception. The sibling analyses make it possible to evaluate the influence of different modes of conception on birth weight in singletons, while the maternal characteristics are maintained steady; therefore, the pure influence of conception method without interference of maternal factors can be assessed. Spontaneously conceived children were an average of 65 g heavier than their ART siblings and had a lower risk of LBW and preterm birth. Children born after FER were 167 g heavier than their siblings conceived after fresh ET, and no statistical significant differences were found regarding the risk of LBW or preterm birth.

Studies have analyzed children born after ART and found an increased risk of adverse perinatal outcomes in the ART population compared with spontaneously conceived children (2–4). Because there are many differences between women who conceive spontaneously and women who conceive by ART, it may not be fair to make a direct comparison between these two groups. Differences in age and parity, confounders such as smoking, BMI, and maternal educational level, and underlying infertility characteristics are known to influence the delivery outcome (8, 15). In Sweden, a recent study on almost 9000 women with endometriosis showed an increased risk of preterm delivery in singletons, regardless of the use of ART (16). Our group of mothers differs from the ART mothers in general. They have given birth to more than one child, and some of them have also given birth to a spontaneously conceived child. This could limit our sibling mothers to women treated for mild infertility, and therefore our findings might not be representative for the general ART population.

Subfertile women do not only have a difficulty in conceiving and carrying the pregnancy to term; they also carry an increased risk of adverse outcomes, including perinatal death (5, 6). We found the total mortality rate to be higher among the spontaneously conceived children. When differentiating between firstborn and second-born children, we found a fivefold increased risk of death among the spontaneously conceived children preceding their ART sibling than vice versa. Women with a child conceived spontaneously before an ART child belong to a selected subgroup of women with a high proportion of earlier experienced perinatal mortality. The high prevalence of perinatal death among the spontaneously conceived children is not believed to represent characteristics related to the mode of conception, but is more likely to be explained by an increased use of ART when trying to conceive after having experienced perinatal death. Earlier sibling studies have found that the proportion of subsequent ART births in women who have experienced perinatal death after a spontaneous pregnancy was threefold higher than in those with no history of perinatal death in a previous pregnancy (7).

Previously, only one study on perinatal outcome in ART used sibling analysis (7). In the Norwegian analyses, researchers included 2,546 singleton ART deliveries and their spontaneously conceived siblings, and they compared differences in birth weight, gestational age, risk of preterm birth, and perinatal deaths. In their adjusted analyses, they found a consistent increase in birth weight from child number one to child number two, independently of mode and order of conception. Children born after FER were not analyzed separately, but were pooled with children born after fresh IVF-ICSI and compared with their spontaneously conceived siblings. This analysis might explain some of the differences between the studies and could partly explain the favorable outcome of the Norwegian ART group, because it has been shown that FER children have an average birth weight of 200 g more than children born after fresh IVF/ICSI (9, 10, 12).

Strengths and Limitations

One strength of this study is the large sample size (n = 27,384) of singleton siblings conceived by different modes of conception during a 13-year study period. A limitation of the study is the lack of adjustment for confounders such as smoking and time to pregnancy. Because some of our sibling cohorts are small (e.g., cohort C), the statistical power in these analyses is limited.

In accordance with earlier reports on FER children, we found a higher mean birth weight compared with children born after fresh IVF-ICSI (10, 12). In agreement with a large Australian study, our sibling analysis demonstrated that the effects of cryopreservation seem to operate within the same woman. Therefore, the positive cryo effect must be explained by factors other than a positive selection of women and embryos alone (9). Because a frozen-thawed embryo is normally replaced in either a natural or artificial cycle with E_2 and P support, it has been speculated that the more natural uterine environment is favorable for early placentation and embryogenesis (13). The effect of COS has been hypothesized to be associated with low birth weight in children born after fresh IVF, but a recent German study including data on more than 32,000 IVF children found it unlikely that ovarian stimulation affected birth weight in IVF pregnancies (17).

Our findings show that although maternal factors are kept constant, differences in perinatal outcomes can still be found among siblings born after different conception methods. Our results are reassuring in regard to the safety of ART, because the differences found in birth weight between siblings conceived after ART versus spontaneous conception might be only statistically relevant and not clinically relevant. Still, our study suggests that the etiology behind the adverse outcomes in ART conceptions is multifactorial and is related to both the ART technology and the parental characteristics.

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