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Risk of stillbirth and infant deaths after assisted reproductive technology: a Nordic study from the CoNARTaS† group

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STUDY QUESTION: Is the risk of stillbirth and perinatal deaths increased after assisted reproductive technology (ART) compared with pregnancies established by spontaneous conception (SC)?

SUMMARY ANSWER: A significantly increased risk of stillbirth in ART singletons was only observed before 28 + 0 gestational weeks.

WHAT IS KNOWN ALREADY: The current literature indicates that children born after ART have an increased risk of perinatal death. The knowledge on stillbirth in ART pregnancies is limited.

STUDY DESIGN, SIZE, DURATION: A population based case–control study.

PARTICIPANTS/MATERIALS, SETTING AND METHODS: A total of 62 485 singletons and 29 793 twins born after ART in Denmark, Finland, Norway and Sweden, from 1982 to 2007, were compared with 362 798 spontaneously conceived (SC) singletons and 132 181 twins.

MAIN RESULTS AND THE ROLE OF CHANCE: The adjusted rate ratio for stillbirth at gestational weeks 22 + 0 to 27 + 6 was 2.08 [95% confidence interval (CI) 1.55–2.78] for ART versus SC singletons. After 28 + 0 gestational weeks there was no significant difference in the risk of stillbirth between ART and SC singletons. ART twins had a lower risk of stillbirth compared with SC twins, but when restricting the analysis to opposite-sex twins and excluding all monozygotic twins, there was no significant difference between the groups. Singletons conceived by ART had an overall increased risk of early neonatal death (adjusted odds ratio 1.54, 95% CI 1.28–1.85) and death within the first year after birth (1.45, 1.26–1.68). No difference regarding these two parameters was found when further adjusting for the gestational age [(0.97, 0.80–1.18) and (0.99, 0.85–1.16), respectively]. ART twins had a lower risk of early neonatal and infant deaths than SC twins, but no difference was found when restricting the analyses to opposite-sex twins.

LIMITATIONS, REASON FOR CAUTION: We were not able to adjust for potential confounders, such as a prior history of stillbirth, induction of labour, body mass index or smoking.

WIDER IMPLICATIONS OF THE FINDINGS: The risk of stillbirth in ART versus SC singletons was only increased for very early gestational ages (before 28 weeks). This might indicate that the current clinical management of ART pregnancies is sufficient regarding prevention of stillbirth during the third trimester.

†Committee on Nordic ART and Safety.

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Key words: stillbirth / assisted reproductive technology / infant death / preterm birth / small-for-gestational age

Introduction

The current literature indicates that children born after assisted reproductive technology (ART) are at an increased risk of perinatal death compared with spontaneously conceived children. The studies are limited by the relatively small numbers of stillbirth and infant deaths (Westergaard *et al.*, 1999; Wisborg *et al.*, 2010; Pandey *et al.*, 2012). Children born after ART carry an overall increased risk of preterm birth and low birthweight, which is partly explained by parental characteristics and partly explained by the ART treatment itself (Helmerhorst *et al.*, 2004; Jackson *et al.*, 2004; Romundstad *et al.*, 2008; Henningsen *et al.*, 2010; Pinborg *et al.*, 2012). We aimed to investigate the prevalence and risks of stillbirth and infant deaths in a large common Nordic cohort of ART singletons and twins. The purpose was to assess the risk of stillbirth in ART pregnancies by gestational age.

Methods

Data sources

We used a Nordic population-based cohort of ART singletons ($n = 62\,485$) and twins ($n = 29\,793$) from Denmark, Finland, Norway and Sweden (Supplementary data, Fig. S1). The national registers were initiated in 1982 in Sweden, in 1988 in Norway, in 1990 in Finland and in 1995 in Denmark. The data were included from the year that each national ART register was established until December 2007 (Henningsen *et al.*, 2011). Only live births and stillbirths with a gestational age of 22 + 0 weeks or more were included. The ART live births and stillbirths included singletons and twins born after *in vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI) and frozen embryo transfer. Data regarding the method of ART conception were available from all of the Nordic countries except Finland. The ART singletons were matched 1:4 with a control group of spontaneously conceived (SC) children from their country. The matching criteria were parity (0 versus ≥1), year of birth and country but not plurality. The ART twins were compared with a control group consisting of all SC twins born within the study period obtained from each country without matching. In the original data set, when the controls for singletons were randomly matched on parity, year of birth and country, twin children could be included. We then excluded all of the singleton controls that were twins, so the control singleton population was not exactly four times larger than the ART singleton population. This resulted in ART singletons being compared strictly with SC singletons and ART twins being strictly compared with SC twins. Treatments with ovulation induction and intrauterine insemination were recently recorded in the Nordic ART registers. Consequently, we were unable to identify children conceived after these techniques, and some of these children will be present among the controls. Children conceived by these fertility treatments only account for a small percentage of the national birth cohorts and include a limited number of children in the SC group. Our database includes data on stillbirths from gestational weeks 22 + 0, but only Finland and Norway registered stillbirths this early throughout the whole study period. In April 2004, Denmark changed the definition of stillbirth from gestational weeks 28 + 0 to week 22 + 0. Because Sweden only started registering stillbirths from gestational weeks 22 + 0 in July 2008, Sweden only contributes stillbirths after gestational weeks 28 + 0.

Early neonatal death was defined as death within the first 0–6 days after birth. Perinatal death was defined as stillbirth (≥22 weeks) plus early neonatal death. Infant death was defined as death within the first year after birth. Low birthweight was defined as a birthweight of <2500 g, and very low birthweight was defined as <1500 g. Preterm birth was defined as delivery before 37 weeks of gestation, and very preterm birth was defined as delivery before 32 weeks of gestation. Small-for-gestational age (SGA) was defined as <2 standard deviations from the expected mean birthweight at a specific gestational age. Large-for-gestational age (LGA) was defined as >2 standard deviations from the expected mean birthweight at a specific gestational age. SGA and LGA were calculated using Marsal's formula (Marsal *et al.*, 1996). In the analyses on perinatal outcomes, we excluded all stillbirths (singletons, $n = 1653$; twins, $n = 2142$) and children with missing or outlying values of birthweight or gestational age (Supplementary data, Fig. S2).

The study was approved by the Data Protection Agencies and the register keeping authorities in each participating country. Permission from the ethical committees was required in Norway and Sweden, but was not in Denmark or Finland for register research.

Permission was given from the Regional Ethical Committee in Sweden (Dnr 023-09, T431-09) and in Norway (REK 2010/1909-11).

Statistical analysis

The prevalences of adverse perinatal outcomes and mortality in ART and SC children were compared in logistic regression models, and birthweights and gestational ages were compared in general linear models. All of the analyses were carried out separately for singletons and twins. To compare the incidence of stillbirth in ART and SC children at specific gestational age intervals, the fetuses-at-risk approach was used to estimate the differences in incidence as rate ratios (RRs). All of the analyses were adjusted for the matching criteria: mother's parity (0 versus ≥1), year of birth (1 year categories) and country. They were then adjusted for the confounding factors of maternal age (<30; 30–34; 35–39; ≥40) and child's sex in the multivariable analyses. The analyses on early neonatal, perinatal and infant deaths were further adjusted for the gestational age. Mortality within the first year after birth was illustrated in Kaplan–Meier plots stratified by plurality and the mode of conception. All of the regression analyses of twin data were adjusted for correlation within twin pairs, e.g. using generalized estimating equations to fit the logistic regression models. All of the results shown are based on the combined Nordic data. Diagnostic plots of the residuals were used to verify the adequacy of the general linear models. The statistical tests were declared significant for a two-sided *P*-value not exceeding 0.05. All of the analyses were performed using SAS statistical software, version 9.1 (SAS Institute).

Results

Background characteristics

The women pregnant after ART were on average older than the women who conceived spontaneously and were more likely to deliver by Caesarean section (Table I). The estimated adjusted mean birthweight was 65 g

Table I Background characteristics of the mothers and births after ART and SC according to singletons and twins.

Maternal characteristics	Singletons		Twins	
	ART (n = 62 485)	SC (n = 362 798)	ART (n = 29 793)	SC (n = 132 181)
Age (years) (±SD)[a], no. of births (%)	33.3 ± 4.1[†]	28.4 ± 5.1	32.6 ± 3.9[†]	30.0 ± 4.9
<30	11 358 (18.2)	215 830 (59.5)	6508 (21.9)	61 570 (46.6)
30–34	26 433 (42.3)	102 878 (28.4)	13 613 (45.7)	46 280 (35.0)
35–39	20 719 (33.2)	37 324 (10.3)	8628 (29.0)	21 145 (16.0)
≥40	3975 (6.4)	6766 (1.9)	1044 (3.5)	3258 (2.5)
Parity, no. of births (%)				
0	41 435 (66.4)	256 127 (70.8)	19 650 (66.1)	41 057 (31.1)
≥1	21 011 (33.7)	105 809 (29.2)	10 061 (33.9)	91 124 (68.9)
Birth characteristics				
Birthweight, g (±SD)[a]	3442 ± 631[†]	3503 ± 563	2522 ± 621[†]	2563 ± 619
Gestational length, days (±SD)[a]	276.3 ± 15.7[†]	278.8 ± 13.1	254.1 ± 20.7[†]	256.0 ± 20.4
Child's sex, no. of children (%)				
Male	32 143 (51.5)	185 584 (51.2)	15 264 (51.4)	66 943 (50.7)
Female	30 310 (48.5)	177 020 (48.8)	14 468 (48.7)	65 105 (49.3)
Mode of delivery, no. of births (%)				
Vaginal	46 053 (77.2)	311 141 (85.8)	14 496 (51.0)	78 135 (59.1)
Caesarean	13 610 (22.8)	51 657 (14.2)	13 943 (49.0)	54 046 (40.9)
Year of birth, no. of births (%)				
1982–1987	106 (0.2)	583 (0.2)	35 (0.1)	9418 (7.1)
1988–1992	2272 (3.6)	16 683 (4.6)	1451 (4.9)	22 638 (17.1)
1993–1997	10 758 (17.2)	70 291 (19.4)	6743 (22.6)	31 654 (24.0)
1998–2002	19 916 (31.9)	122 781 (33.8)	11 676 (39.2)	32 852 (24.9)
2003–2007	29 433 (47.1)	152 460 (42.0)	9888 (33.2)	35 619 (27.0)

[a]Means ± standard deviation (SD).
[†]$P < 0.001$ for comparisons between the assisted conception group and the spontaneous-conception group.

(95% CI, 60–70) lower in the ART singletons and 24 g (16–33) lower in the ART twins compared with their spontaneously conceived counterparts. The estimated adjusted mean gestational age was 2.3 days (2.1–2.4) shorter for the ART singletons and 0.5 days (0.2–0.7) shorter for the ART twins. The proportion of twins among the ART children reached a maximum of 38.6% in 1993. For many years this remained relatively stable, but from 2002 an annual decline was seen, with the lowest ART twin rate observed in 2007 when 20.8% of the Nordic ART children were twins. Sweden had the lowest national ART twin rate, and 10.6% of the Swedish ART children born in 2007 were twins (data not shown).

Perinatal outcomes

The ART singletons had a significantly higher risk of low birthweight, with an adjusted odds ratio (OR) of 1.58 (95% CI, 1.51–1.64), and a significantly higher risk of preterm birth, with an OR of 1.55 (1.50–1.61), compared with the SC singletons. The difference in the risk of very low birthweight and very preterm birth was higher (Table II). The singletons born after ART had an adjusted OR of 1.16 (1.11–1.22) of being SGA. The singletons conceived after IVF had a significantly higher risk of low birthweight and preterm and very preterm birth compared with the singletons conceived after ICSI (data not shown). The ART twins had a significantly lower risk of low birthweight, very low birthweight and being born SGA than the spontaneously conceived twins. When restricting the analyses to opposite-sex twins only and eliminating all monozygotic twins, there was no statistically significant difference in the risk of being born with a low or very low birthweight between the ART and SC twins (Table II).

Stillbirth, gestational age and maternal age

We assessed the risk of stillbirth in the ART singletons at specific gestational age intervals. The ART singletons carried a significantly higher risk of stillbirth during gestational weeks 22 + 0 to 27 + 6 compared with the SC singletons, adjusted RR 2.08 (95% CI, 1.55–2.78). Beyond gestational weeks 28 + 0, there was no significant difference in the risk of stillbirth between the ART and SC singletons (Table III). The ART twins had a lower risk of stillbirth compared with the SC twins until gestational weeks 40. Beyond 40 weeks of gestation the stillbirth risk was similar in ART and SC twins (data not shown). When restricting this analysis to opposite-sex twin children only, we found no significant differences in the risk of stillbirth for any gestational age intervals. In the total singleton cohort (ART + SC), women aged 35 years or more had an increased risk of stillbirth from gestational weeks 28, compared with women aged 30–34 years. The adjusted ORs were 1.36 (1.15–1.60) for women aged 35–39 years and 1.55 (1.14–2.09) for women aged 40 years or more.

Table II Perinatal outcomes in children born after ART and SC stratified by singletons, twins and opposite-sex twins only.

	ART, *n* (%)	SC, *n* (%)	OR,[a] [95 CI]	OR,[b] [95 CI]
Birthweight <2500 g				
Singletons	3748 (6.1)	13 234 (3.7)	1.73 [1.66–1.79]	1.58 [1.51–1.64]
All twins	12 579 (43.0)	51 534 (39.9)	0.90 [0.87–0.93]	0.89 [0.86–0.93]
Opposite-sex twins	6163 (43.0)	16 878 (37.0)	1.02 [0.97–1.07]	1.01 [0.95–1.06]
Birthweight <1500 g				
Singletons	860 (1.4)	2227 (0.6)	2.32 [2.14–2.51]	2.05 [1.88–2.24]
All twins	1968 (6.7)	8122 (6.3)	0.83 [0.77–0.90]	0.85 [0.79–0.92]
Opposite-sex twins	972 (6.8)	2659 (5.8)	0.88 [0.79–0.98]	0.91 [0.81–1.02]
Preterm birth <37 weeks				
Singletons	5172 (8.4)	19 234 (5.4)	1.63 [1.58–1.69]	1.55 [1.50–1.61]
All twins	13 685 (46.6)	54 689 (42.5)	1.02 [0.92–1.14]	1.06 [0.95–1.18]
Opposite-sex twins	6697 (46.7)	17 921 (39.6)	1.11 [0.98–1.26]	1.14 [1.00–1.29]
Very preterm birth <32 weeks				
Singletons	975 (1.6)	2615 (0.7)	2.22 [2.10–2.39]	2.05 [1.89–2.22]
All twins	2469 (8.4)	9330 (7.3)	0.87 [0.75–1.01]	0.96 [0.84–1.09]
Opposite-sex twins	1206 (8.4)	3054 (6.8)	0.88 [0.76–1.03]	0.98 [0.84–1.13]
Small-for-gestational age <2 SD				
Singletons	2326 (3.8)	10 929 (3.1)	1.28 [1.23–1.34]	1.16 [1.11–1.22]
All twins	4407 (15.1)	20 225 (15.9)	0.83 [0.80–0.86]	0.79 [0.76–0.83]
Opposite-sex twins	2179 (15.4)	6511 (14.4)	0.94 [0.89–1.00]	0.90 [0.85–0.96]
Large-for-gestational age >2 SD				
Singletons	2140 (3.5)	10 944 (3.1)	1.10 [1.05–1.15]	1.04 [0.99–1.09]
All twins	153 (0.5)	681 (0.5)	1.29 [1.04–1.61]	1.30 [1.03–1.63]
Opposite-sex twins	85 (0.6)	264 (0.6)	1.31 [0.96–1.79]	1.32 [0.96–1.82]

Stillbirths were excluded from the analyses.
[a]Adjustments for parity (0 versus ≥1) and year of birth.
[b]Adjustments for parity (0 versus ≥1), year of birth, maternal age, child's sex and country.

Table III Rate ratios for the incidence of stillbirth at different gestational age intervals for singletons conceived after ART and SC.

	ART stillbirths, *n* (%)	SC stillbirths, *n* (%)	ART fetuses at risk	SC fetuses at risk	RR[a] [95 CI]	RR[b] [95 CI]
22 + 0–27 + 6 weeks	77 (0.26)	209 (0.12)	29 736[c]	177 412[c]	2.19 [1.68–2.86]	2.08 [1.55–2.78]
28 + 0–31 + 6 weeks	44 (0.07)	203 (0.06)	61 846	358 757	1.29 [0.93–1.79]	1.28 [0.89–1.82]
32 + 0–36 + 6 weeks	53 (0.09)	296 (0.08)	61 180	356 766	1.06 [0.79–1.42]	0.94 [0.69–1.28]
37 + 0–39 + 6 weeks	61 (0.11)	294 (0.09)	56 939	339 833	1.23 [0.93–1.62]	1.07 [0.79–1.45]
40 + 0–41 + 6 weeks	48 (0.16)	240 (0.12)	30 812	198 285	1.28 [0.94–1.75]	0.98 [0.70–1.38]
≥42 + 0 weeks	9 (0.18)	48 (0.13)	4916	35 704	1.34 [0.66–2.73]	0.79 [0.37–1.66]

[a]RRs adjusted for parity (0 versus ≥1) and year of birth.
[b]RRs adjusted for parity (0 versus ≥1), year of birth, maternal age, child's sex and country.
[c]Due to differences in the registration of stillbirth between the Nordic countries during the study period, only Finland, Norway and Denmark from April 2004 contributed data on stillbirths before gestational weeks 28 + 0.

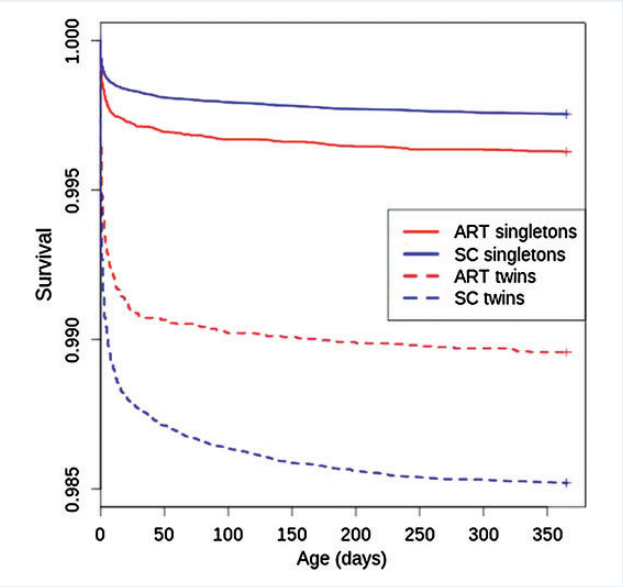

Figure 1 Kaplan–Meier curves for the death of a live born child within the first year after birth among ART singletons and twins compared with spontaneously conceived singletons and twins.

Early neonatal and infant deaths

The difference in the incidence of death within the first year after birth according to plurality and the mode of conception is illustrated in Fig. 1. The Kaplan–Meier plot shows that ART singletons have an overall increased risk of death within the first year after birth. For twins, the opposite phenomenon was observed. SC twins had a higher risk. For singletons, the adjusted ORs for early neonatal and infant deaths in ART versus SC were 1.54 (95% CI, 1.28–1.85) and 1.45 (1.26–1.68), respectively. When further adjusting for gestational age, there was no statistically significant difference between the groups: 0.97 (0.80–1.18) and 0.99 (0.85–1.16), respectively (Table IV). The sub-analyses comparing IVF and ICSI singletons showed no significant differences in the risk of early neonatal, perinatal or infant deaths (data not shown). For the ART twins, the adjusted OR of early neonatal death was 0.75 (0.63–0.89) and the adjusted OR of infant death was 0.76 (0.66–0.88). In the opposite-sex twin analyses, twins born after ART or SC had similar risks of early neonatal and infant deaths (Table IV).

Discussion

Our cohort comprised >92 000 children conceived after ART born over 25 years in four countries, allowing us to investigate rare but important outcomes, such as stillbirth and perinatal deaths. Few previous studies have investigated the association between ART and stillbirth, but these report an increased risk of stillbirth and perinatal deaths for ART singletons (Westergaard *et al.*, 1999; Wisborg *et al.*, 2010; Pandey *et al.*, 2012). Regarding ART twins, two studies found a lower risk of stillbirth and perinatal deaths than in spontaneously conceived twins (Dhont *et al.*, 1999; McDonald *et al.*, 2010). The main finding in this large Nordic collaborative study is that the risk of stillbirth is only significantly increased in ART singleton pregnancies during the late second trimester. From gestational weeks 28 + 0, the risk of stillbirth was not significantly increased in ART singletons compared with SC singletons. ART twins had a lower risk of stillbirth until gestational weeks 40 compared with SC twins. From gestational weeks 40, there was no significant difference between ART and SC twins, but this can likely be explained by the rather small sample sizes in the late gestational weeks. ART singletons had a significantly increased crude risk of early neonatal and infant deaths, but after adjusting for gestational age and taking the contribution of preterm birth into account, the results were not statistically significant. ART twins had a lower risk of stillbirth, early neonatal, perinatal and infant deaths compared with SC twins. This is likely caused by the lower rate of monozygotic ART twins because there was no difference between opposite-sex ART and SC twins.

Placental dysfunction and fetal growth restriction are well known causes for stillbirth (Surkan *et al.*, 2004). After stratification for SGA in the analyses on risk of early neonatal, perinatal and infant deaths, ART singletons with normal growth still had a higher risk compared with normal growth SC singletons (data not shown). Among SGA singletons alone, there was no significant difference in the risk of early neonatal, perinatal and infant deaths between the ART and SC singletons, indicating that being SGA overrules the characteristics of being conceived by ART. Maternal obesity, advanced maternal age and maternal smoking are well-known risk factors for stillbirth (Smith and Fretts, 2007; Flenady *et al.*, 2011). When considering the effect of maternal age in our singleton population, we found that women aged 35 years or older were at an increased risk of stillbirth compared with women younger than 35 years in the pooled analyses of ART and SC singletons. Because information on body mass index and maternal smoking has only recently been available in the Nordic registers, we were unfortunately unable to investigate the impact of these confounders on our population. Nordic studies have estimated that the prevalence of obese women with pregnancies conceived after ART is approximately the same as that of the background population and that half as many of the women who conceive after ART smoke compared with the women pregnant after spontaneous conception (Kallen *et al.*, 2010a; Pinborg *et al.*, 2011). The increased risk of stillbirth is probably not related to obesity or smoking among the women pregnant after ART in our study, but the risk of stillbirth might be underestimated because of the confounding effects of smoking and BMI. Whether the finding of a similar risk of stillbirth in ART versus SC singletons beyond weeks 28 can be explained by a possible increased incidence of induction of labour and a higher Caesarean section rate in ART pregnancies cannot be ruled out. This seems unlikely to be the entire explanation, because induction of labour generally only occurs at gestational ages close to term and only potentially influences the stillbirth rate in the late third trimester.

The increased risk of early neonatal and infant deaths in ART singletons might be partially explained by the increased incidence of preterm birth among ART children, and gestational age is important when considering plausible causes of perinatal death. The causal pathways of preterm birth and stillbirth are still widely unknown. It is not clear if stillbirth leads to preterm birth or if the opposite is true (Basso and Wilcox, 2010; Wilcox *et al.*, 2011). Caution should be taken when we adjust for gestational age in the risk analyses of ART versus SC conception and stillbirth. Gestational age can act as a mediator (part of the causal pathway) and as a confounder. In this study, the risk of stillbirth was assessed according to the number of 'fetuses at risk' at a specific gestational age (our analyses

Table IV Risk of early neonatal death, perinatal death and infant death among children conceived after ART versus SC.

	ART, *n* (%)	SC, *n* (%)	OR[a] [95 CI]	OR[b] [95 CI]	OR[c] [95 CI]
Early neonatal death[d]					
Singletons	171 (0.27)	623 (0.17)	1.64 [1.38–1.94]	1.54 [1.28–1.85]	0.97 [0.80–1.18]
All twins	289 (0.97)	1714 (1.30)	0.70 [0.60–0.82]	0.75 [0.63–0.89]	0.82 [0.69–0.97]
Opposite-sex twins	140 (0.96)	466 (1.02)	0.82 [0.64–1.06]	0.85 [0.65–1.12]	1.03 [0.79–1.36]
Perinatal death[e]					
Singletons	493 (0.79)	1962 (0.54)	1.48 [1.34–1.64]	1.31 [1.18–1.47]	0.83 [0.73–0.94]
All twins	604 (2.02)	3546 (2.68)	0.69 [0.62–0.78]	0.66 [0.58–0.74]	0.63 [0.56–0.72]
Opposite-sex twins	351 (2.41)	1028 (2.25)	0.94 [0.80–1.10]	0.77 [0.64–0.93]	0.87 [0.72–1.07]
Infant death[f]					
Singletons	276 (0.44)	1103 (0.30)	1.50 [1.31–1.71]	1.45 [1.26–1.68]	0.99 [0.85–1.16]
All twins	398 (1.33)	2486 (1.88)	0.70 [0.61–0.80]	0.76 [0.66–0.88]	0.80 [0.70–0.92]
Opposite-sex twins	187 (1.29)	684 (1.50)	0.81 [0.66–0.99]	0.85 [0.68–1.06]	0.94 [0.76–1.18]

The data were stratified by singletons, twins and opposite-sex twins only.
[a]ORs adjusted for parity (0 versus ≥1) and year of birth.
[b]ORs adjusted for parity (0 versus ≥1), year of birth, maternal age, child's sex and country.
[c]ORs adjusted for parity (0 versus ≥1), year of birth, maternal age, child's sex, country and gestational age.
[d]Early neonatal death is defined as death within the first week after birth.
[e]Perinatal death is defined as stillbirth ≥22 + 0 weeks and death within the first week after birth.
[f]Infant death is defined as the death of a live born child within the first year after birth.

used all live fetuses at a given gestational age as the denominator) as suggested by several others (Yudkin *et al.*, 1987).

Twins are at a much higher risk of preterm birth than singletons, because twins share the uterus. Preterm twin deliveries are more often triggered by mechanical causes. Preterm birth in singletons might more often be caused by underlying pathology. Another explanation for the increased risk of early neonatal death seen in singletons conceived after ART is the negative effects of a vanishing twin on the surviving co-twin, which is subsequently classified as a singleton gestation. With a twin delivery rate of ~25%, it has been estimated that ~1 in 10 ART singletons is the result of a pregnancy that started as a twin gestation. ART singletons with a vanished co-twin have an increased risk of preterm birth and of being born small-for-gestational age. In some studies, this has been found to be a predictor of intrauterine death (Gardosi *et al.*, 1998; Pinborg *et al.*, 2005; Pinborg *et al.*, 2007). With the increasing use of elective single embryo transfer in Nordic countries, this phenomenon is expected to decline, but in the present cohort a large part of the ART singletons were born after double embryo transfers. This was confirmed by the high twin rates throughout most of the study period. We found no difference or a decreased risk of several adverse perinatal outcomes for ART twins compared with SC twins. This could be related to the low proportion of monozygotic twins among ART twins or to the heterogeneity of the twin control population in this study, because twins born after SC and twins conceived after non-ART fertility treatments, such as ovulation induction in anovulatory infertility and controlled ovarian stimulation with intrauterine insemination, were included in the control group. A non-negligible proportion of the control twins were born by subfertile women and might be affected by their parents' impaired reproductive characteristics or by the intrauterine insemination treatment, including mild ovarian stimulation. These factors would tend to reduce the difference between the groups. We used Weinberg's differential rule based on the number of opposite-sex twin sets and estimated the rate of monozygotic twins in our ART population as ~3.5 versus 32% in our twin control population (Weinberg, 1902). This is in agreement with other studies (Pinborg *et al.*, 2004; Aston *et al.*, 2008). Women pregnant with monozygotic twins are at risk of twin-to-twin-transfusion syndrome and are at risk of several complications, including perinatal loss or twin demise (Mosquera *et al.*, 2012). For all outcomes, the significant difference between the ART and SC twins disappeared when comparing opposite-sex twins only and, excluding all of the monozygotic twins.

Based on the findings of this study, the explanation of the increased risk of early neonatal death among ART singletons is partially a consequence of the higher preterm birth rate. The causes of preterm birth among ART singletons remain unclear. Studies have reported a negative effect of parental subfertility, even in women who conceive spontaneously, and the time to pregnancy as an indicator of reproductive impairment has been shown to be important for the outcomes (Romundstad *et al.*, 2008; Kallen *et al.*, 2010b).

Our study combines data on mortality in the early stages of life in ART children from the Nordic countries, providing a comprehensive population of infants born after ART with high external validity. This allowed us to make a robust estimate of the prevalence of stillbirth and infant deaths adjusted for several potential confounders. Because we found no increased risk of stillbirth at term for ART singletons or twins, we have no argument for altering the current clinical guidelines regarding the management of ART pregnancies at term, including the strategy of the medical induction of labour.

Authors' roles

All of the authors planned the study and discussed the data and the results. A.A.H. merged the data, performed the analyses and drafted the manuscript. J.L.F. contributed to the data analyses. All of the

authors were involved in finalizing the manuscript and approved the final version. The authors have agreed upon the listing of authors.

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Conflict of interest

No conflict of interest was reported.

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