

Infertility, infertility treatment, and congenital malformations: Danish national birth cohort

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Abstract

Objectives To examine whether infertile couples (with a time to pregnancy of > 12 months), who conceive naturally or after treatment, give birth to children with an increased prevalence of congenital malformations.

Design Longitudinal study.

Setting Danish national birth cohort.

Participants Three groups of liveborn children and their mothers: 50 897 singletons and 1366 twins born to fertile couples (time to pregnancy ≤ 12 months), 5764 singletons and 100 twins born to infertile couples who conceived naturally (time to pregnancy > 12 months), and 4588 singletons and 1690 twins born after infertility treatment.

Main outcome measures Prevalence of congenital malformations determined from hospital discharge diagnoses.

Results Compared with singletons born to fertile couples, singletons born to infertile couples who conceived naturally or after treatment had a higher prevalence of congenital malformations—hazard ratios 1.20 (95% confidence interval 1.07 to 1.35) and 1.39 (1.23 to 1.57). The overall prevalence of congenital malformations increased with increasing time to pregnancy. When the analysis was restricted to singletons born to infertile couples, babies born after treatment had an increased prevalence of genital organ malformations (hazard ratio 2.32, 1.24 to 4.35) compared with babies conceived naturally. No significant differences existed in the overall prevalence of congenital malformations among twins.

Conclusions Hormonal treatment for infertility may be related to the occurrence of malformations of genital organs, but our results suggest that the reported increased prevalence of congenital malformations seen in singletons born after assisted reproductive technology is partly the result of the underlying infertility or its determinants. The association between untreated infertility and congenital malformations warrants further examination.

Introduction

About 10-20% of couples who are trying to become pregnant have a waiting time to pregnancy longer than 12 months, the clinical definition of infertility in most industrialised countries.¹ An increasing number of couples seek treatment for infertility.² Children conceived after assisted reproductive technology have an excess of congenital malformations compared with children conceived spontaneously,³⁻⁵ but little research has been devoted to attempting to separate the effect of assisted reproductive technology from that of infertility itself. In a recent review, Rimm et al pointed out that previous studies on the topic have lacked a comparison group of children born to infertile couples who conceived naturally.⁵ Using a large cohort of

Danish couples, we estimated the prevalence of congenital malformations as a function of infertility and its treatment.

Methods

We did the study within the Danish national birth cohort.⁶ From June 1997 to February 2003, 85 381 women (92 892 pregnancies) responded during the first or second trimester to the first of four scheduled telephone interviews. Women were asked if their pregnancy was planned and how long they had tried to become pregnant before succeeding. If they reported a time to pregnancy of six months or longer, participants were asked if they or their male partner had received any infertility treatment. Couples who reported a time to pregnancy of less than six months were classified as not treated. We identified three groups of planned pregnancies: 52 380 conceived by fertile couples (time to pregnancy ≤ 12 months), 5910 conceived naturally by infertile couples (> 12 months), and 5564 conceived by infertile couples after infertility treatment. If a woman reported that she or her male partner had received infertility treatment, she was then asked which one (or more) of six specified treatments they received (see bmj.com). We linked the cohort to pregnancy outcomes by using the national hospital register and the medical birth register.^{7,8} After exclusions, 61 249 singletons and 3156 twins remained available for analysis. Diagnoses on congenital malformations are recorded in the national hospital register.⁷

Statistical analysis

We calculated hazard ratios for a diagnosis of congenital malformations by using regression models, with follow-up starting from the date of birth and ending at the time of the first diagnosis of a malformation, death, or the end of follow-up (9 November 2004). We did separate analyses for singletons and twins. We tested the effect of time to pregnancy on malformations. Potential confounders included maternal age at conception, pre-pregnancy body mass index, smoking, alcohol intake, coffee consumption, and occupational status.

Results

The median follow-up time was four years from the time of birth. Compared with singletons born to fertile couples, singletons born to infertile couples had a higher prevalence of congenital malformations, regardless of treatment (table 1). Among singletons

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Table 1 Congenital malformations in singletons according to time to pregnancy (TTP) and infertility treatment

Malformations	No (%) singletons born to fertile couples (TTP≤12 months) (group A; n=50 897)	Singletons born to infertile couples who conceived naturally (TTP>12 months) (group B; n=5764)			Singletons born to infertile couples who received infertility treatment (group C; n=4588)				
		No (%)	Hazard ratio (95% CI) with group A as reference*		No (%)	Hazard ratio (95% CI) with group A as reference*		Hazard ratio (95% CI) with group B as reference*†	
			Crude	Adjusted‡		Crude	Adjusted‡	Crude	Adjusted‡
All§	2564 (5.0)	344 (6.0)	1.19	1.20 (1.07 to 1.35)	307 (6.7)	1.35	1.39 (1.23 to 1.57)	1.13	1.17 (1.00 to 1.36)
Nervous system	78 (0.2)	19 (0.3)	2.16	2.01 (1.21 to 3.34)	15 (0.3)	2.14	2.16 (1.23 to 3.80)	0.99	1.18 (0.59 to 2.35)
Eye, ear, face, and neck	180 (0.4)	30 (0.5)	1.48	1.45 (0.98 to 2.15)	19 (0.4)	1.20	1.20 (0.74 to 1.94)	0.81	0.84 (0.47 to 1.51)
Circulatory system	494 (1.0)	71 (1.2)	1.27	1.25 (0.97 to 1.61)	53 (1.2)	1.20	1.21 (0.91 to 1.62)	0.94	0.92 (0.64 to 1.32)
Respiratory system	92 (0.2)	9 (0.2)	0.86	0.77 (0.38 to 1.53)	11 (0.2)	1.33	1.21 (0.64 to 2.28)	1.54	1.76 (0.72 to 4.32)
Cleft lip/palate	117 (0.2)	16 (0.3)	1.21	1.15 (0.68 to 1.95)	5 (0.1)	0.47	0.48 (0.19 to 1.18)	0.39	0.38 (0.14 to 1.06)
Digestive system	187 (0.4)	33 (0.6)	1.56	1.51 (1.04 to 2.19)	24 (0.5)	1.43	1.44 (0.94 to 2.22)	0.92	0.94 (0.55 to 1.60)
Genital organs	172 (0.3)	15 (0.3)	0.77	0.81 (0.48 to 1.38)	30 (0.7)	1.96	2.03 (1.37 to 3.01)	2.54	2.32 (1.24 to 4.35)
Urinary system	175 (0.3)	21 (0.4)	1.06	1.07 (0.68 to 1.69)	24 (0.5)	1.53	1.45 (0.94 to 2.24)	1.44	1.34 (0.74 to 2.43)
Musculoskeletal system	1142 (2.2)	158 (2.7)	1.23	1.27 (1.07 to 1.51)	147 (3.2)	1.45	1.54 (1.29 to 1.83)	1.18	1.23 (0.98 to 1.55)
Other malformations	199 (0.4)	27 (0.5)	1.20	1.20 (0.80 to 1.80)	28 (0.6)	1.57	1.63 (1.09 to 2.44)	1.31	1.34 (0.78 to 2.30)
Chromosomal abnormalities	98 (0.2)	8 (0.1)	0.72	0.68 (0.33 to 1.41)	10 (0.2)	1.14	0.98 (0.50 to 1.89)	1.57	1.51 (0.59 to 3.87)

*Cox regression.

†Analysis restricted to infertile couples.

‡Adjusted for maternal age at conception, pre-pregnancy body mass index, smoking, alcohol intake, coffee consumption, and occupational status.

§Children with two or more malformations counted once for all congenital malformations but counted for each malformation in relevant subgroup.

born to infertile couples who conceived naturally, we saw an increased prevalence of malformations of the nervous system, digestive system, and musculoskeletal system. Singletons born to couples who received infertility treatment had a similar pattern, as well as a higher prevalence of malformations of genital organs and “others” (see extra table on bmj.com for results on detailed diagnoses with two-digit codes in ICD-10). When we restricted the analysis to singletons born to infertile couples, we saw an excess only of genital organ malformations associated with treatment (table 1). Among singletons born to untreated couples, prevalence of congenital malformations increased with increasing time to pregnancy (table 2).

Compared with singletons born to fertile couples, children born after intracytoplasmic sperm injection, in vitro fertilisation, intrauterine insemination, hormonal treatment, or surgery had an increased prevalence of congenital malformations, with hazard ratios between 1.31 and 1.85. When we restricted the analysis to infertile couples, only intracytoplasmic sperm injection was associated with a significantly higher overall prevalence of congenital malformations (hazard ratio 1.57, 95% confidence interval 1.11 to 2.23). We saw a significantly increased prevalence of genital organ malformations (4.39, 1.58 to 12.21) and musculoskeletal system malformations (1.67, 1.01 to 2.76).

Twins had an overall higher prevalence of congenital malformations than singletons (7.0% *v* 5.2%; $P < 0.0001$). However, we saw no significant association with infertility, infertility treatment, or type of treatment.

We obtained similar results when we restricted our analyses to firstborn children or to children born at term (data not shown).

Discussion

Malformations in offspring

Singletons born to infertile couples, regardless of treatment, had a higher prevalence of congenital malformations than did children born to couples with a time to pregnancy of ≤ 12 months, and the prevalence of congenital malformations increased with increasing time to pregnancy. We may have underestimated the risk of some congenital malformations, as we had no data on malformations for miscarriages, induced abortions after prenatal screening, or stillbirths. Infertile couples are more likely to have been offered prenatal screening if they receive treatment. However, we obtained similar results after excluding Down’s syndrome and neural tube defects.

We found an increased prevalence of congenital malformations in singletons born after infertility

Table 2 Overall congenital malformations in singletons conceived spontaneously or after treatment, according to time to pregnancy

Time to pregnancy (months)	Singletons conceived spontaneously			Singletons conceived after treatment for infertility		
	No	No (%) with malformations	Adjusted hazard ratio (95% CI)*	No	No (%) with malformations	Adjusted hazard ratio (95% CI)*
0-2	28 039	1317 (4.7)	1.00	–	–	–
3-5	13 096	712 (5.4)	1.16 (1.06 to 1.27)	–	–	–
6-12	9 762	535 (5.5)	1.17 (1.06 to 1.30)	625	34 (5.4)	1.00
>12	5 764	344 (6.0)	1.29 (1.14 to 1.45)	3963	273 (6.9)	1.34 (0.94 to 1.92)
Test for trend			$P < 0.0001$			$P = 0.107$

*Cox regression; adjusted for maternal age at conception, pre-pregnancy body mass index, smoking, alcohol intake, coffee consumption, and occupational status.

treatment, which is consistent with three recent meta-analyses that showed a 30-40% excess.³⁻⁵ Our results are also consistent with a previous Danish study in which a crude relative prevalence of 1.41 (0.96 to 2.09) was estimated for singletons after in vitro fertilisation.⁹ However, when we restricted the analysis to singletons born to infertile couples, treatment was associated with an increased prevalence only of genital organ malformations. This increase may be explained by the use of ovulation inducing drugs. Although infertile couples who conceive naturally may differ from those who seek infertility treatment, they are a more appropriate reference group than fertile couples.

All conventional forms of infertility treatment correlated with a higher prevalence of congenital malformations, but this remained significant only for intracytoplasmic sperm injection when the underlying infertility was taken into account. Intracytoplasmic sperm injection is generally offered to couples with male infertility.⁹ The increased prevalence of malformations among singletons born after intracytoplasmic sperm injection may be confounded by the indication for treatment. Compared with twins born to fertile couples, twins born after infertility treatment did not show a higher prevalence of congenital malformations, as previously reported.^{5 10}

Study methods

Selection bias may have affected our estimates if participation was associated with the exposure as well as the outcome. This is unlikely as we recruited participants before the outcome of the pregnancy was known. The prevalence of congenital malformations in our study was slightly higher than previously reported.⁹ We believe that this illustrates the importance of having a longer follow-up time to allow malformations to be diagnosed. Despite the large sample size, the number of children with specific malformations was small. We therefore grouped congenital malformations by organ systems. We lacked power to detect small increases in the prevalence of specific malformations. At the same time, a "positive" finding for a specific malformation should be interpreted with caution because we tested many associations. We excluded some minor malformations or malformations that are often misdiagnosed or related to preterm birth, and we used only hospital discharge diagnoses with documented high quality (predictive value = 88.2%; completeness = 89.9%).¹¹

Conclusions

Our results indicate that, in order to properly evaluate the effects of assisted reproductive technology, infertile patients who conceived spontaneously should be used as a reference. Infertile couples should be offered prenatal screening, and research should be devoted to finding the mechanisms behind the association between congenital malformations and infertility or subfertility.

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What is already known on this topic

Infertile or subfertile couples who conceive naturally have a high risk of adverse pregnancy outcomes, such as preterm delivery, stillbirth, and neonatal death

Singletons born to infertile couples after infertility treatment have a higher prevalence of congenital malformations, including hypospadias, than singletons conceived naturally

What this study adds

Infertility or subfertility seems to be associated with an increased prevalence of congenital malformations in offspring

The increased prevalence of congenital malformations seen in singletons born after infertility treatment is partly confounded by the indication for treatment

To assess the side effects of assisted reproductive technology, children conceived naturally by infertile couples are a more appropriate comparison group than children conceived naturally

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