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Original Article

Assisted conception and the risk of CHD: a case–control study

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Abstract Epidemiological studies suggest a higher prevalence of congenital malformations in children conceived through assisted reproductive technologies. There are a few studies that address CHD specifically and most have examined data from registries. We examined the relationship between CHD and assisted conception using data collected in a specialist paediatric cardiac service in the United Kingdom.

Between April, 2010 and July, 2011, the parents of children attending paediatric cardiology clinics at the Royal Brompton Hospital, London, were invited to complete a questionnaire that enquired about the nature of their child's conception, the route for their original referral, and a number of potential confounding exposures. "Cases" were defined as children diagnosed with one or more carefully defined CHDs and "controls" as those with normal hearts.

Of 894 new attendees with complete data, half of them were cases (n = 410, 45.9%). The overall prevalence of assisted conception was 5.4% (n = 44). Logistic regression analysis demonstrated a non-significant increase in the crude odds for the use of assisted reproduction (odds ratio 1.21, 95% confidence interval 0.66–2.22) in this group. After adjustment for gestation, parity, year of birth, and maternal age, the odds ratio reduced (odds ratio 0.95, 95% confidence interval 0.48–1.88). Increased rates of assisted conception were observed in a number of CHD subgroups, although no significant differences were found.

These findings do not suggest an overall association between CHD and assisted reproduction in this population.

Keywords: Heart defects; congenital; assisted reproductive technologies; ovulation induction; in vitro fertilisation

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An estimated one in 50 births in the United Kingdom are conceived through assisted reproductive technology,[1] a proportion that has risen steeply over the past 20 years. The associated risks of multiple pregnancy, low birth weight, and prematurity are well documented, but there is concern over the potential for an increased risk of congenital abnormalities in children conceived in this way as well;[2] however, the extent of any such risk is unclear as the available relevant evidence is limited, not entirely consistent, and prone to methodological limitations.[3] It is also unclear whether any risk lies in the treatment itself or reflects the indication(s) for its use. Using a figure derived from a Danish study of the effect of subfertility on the rates of major congenital malformation,[4] Rimm et al reported a meta-analysis[5] that attempted to account for the possibility that children of subfertile couples could be at an increased risk of major malformation in part because of the various underlying causes of their parents' subfertility. After adjustment, the summary odds ratio for major malformations fell from 1.29

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(95% confidence interval 1.01–1.67) to 1.01 (95% confidence interval 1.82–1.23), highlighting the difficulty in quantifying any risk.

With the exception of two case–control studies,[6,7] the published literature on this topic uses cohort or registry data[6,8–16] often with a few cases of individual abnormalities. This is particularly so for cardiac malformations that, although among the commonest of all congenital malformations, are rare events. Only one study, a case–control analysis of data from the Paris Registry of Congenital Malformation,[6] has focussed on CHD, reporting that the use of assisted reproductive technology was higher for children with cardiac rather than any other malformation (4.7 versus 3.6%, $p = 0.008$), although not when restricted to singleton pregnancies. The use of a control group with other abnormalities in the Paris study makes it difficult, however, to assign any measure of absolute risk to assisted reproductive technology. In this study, we report the findings of a case–control study of congenital cardiac abnormalities identified from a specialist clinic setting using healthy controls from the same clinic, and to our knowledge is the first study in this field to use such a design.

Material and methods

Recruitment

Between April, 2010 and July, 2011, the parents of children attending the Paediatric Cardiology Outpatient Clinic at Royal Brompton Hospital, London, United Kingdom, were invited to complete a brief, confidential questionnaire. Children were referred to the clinic for further investigation of a heart murmur, cardiac symptoms, or family history of heart conditions. The questionnaire enquired about the nature of their child's conception, the route of their, original, referral to the clinic, and a number of potential confounding factors. We analysed this information using a case–control approach.

Patients were eligible if they were "new" – that is, those who had never attended the clinic before. Cases were defined as (new) children who were diagnosed in the clinic with one or more carefully defined CHDs. Controls were (new) children seen at the clinic during the same time period who had normal hearts.

Informed consent was obtained from the parents, and the study was approved by Charing Cross Research Ethics Committee.

Classification of CHD

Diagnoses, recorded by the cardiologist during the clinic visit, were obtained from the patient's medical notes. We devised a "blinding" process whereby the information related to the diagnosis of CHD was collected independently of the information provided by the parent. In total, 20 subcategories of CHD were pre-defined by two paediatric cardiologists on the basis of a modification of previous classifications used in the UK Northern regional studies[17] and when creating a risk adjustment model for CHD using the International Paediatric and Congenital Cardiac Code.[18] Cardiomyopathy, acquired heart disease, and isolated arrhythmia diagnoses were also recorded. In addition, we re-examined our data using the classification and grouping of anomalies used in the analysis of the Paris Registry[6] as a direct comparison.

Assisted reproductive technology: assisted conception

Assisted reproductive technology was defined as any of the following procedures or treatments: ovulation induction, intrauterine insemination, in vitro fertilisation, or intracytoplasmic sperm injection.[19]

Potential confounders

We collected information on potential confounding factors including maternal age, year of birth, parity, and prematurity. We assigned to each family an index of socio-economic status (SOC2000)[20] using paternal occupation or, where this was not available, maternal occupation.

Statistical analyses

Associations between categorical variables were investigated using χ^2 tests or, where numbers were low, Fisher's exact test. For continuous variables, the t test was used, unless the data were not normally distributed for which non-parametric tests were adopted (Mann–Whitney). We used unconditional logistic regression analysis to test the degree of association between assisted conception and CHD, while adjusting a priori for maternal age as a continuous variable, parity, none versus one or more previous births, year of birth, and gestation. Diagnoses of cardiomyopathy, acquired heart disease, and arrhythmia were analysed separately. Exposure was initially assessed as "any assisted reproduction technology" and then as in vitro fertilisation or intracytoplasmic sperm injection, excluding ovulation induction and intrauterine insemination; analysis was repeated for singletons only.

All statistical tests were two sided, and a p-value of <0.05 was considered as statistically significant. All analyses were conducted using STATA version 11 (College Station, Texas, United States of America).

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Results

Of the 2834 eligible patients, 541 (19.1%) declined to take part, and for 38 patients (1.3%) we failed to collect data. Of the remaining 2255 (79.6%), 899 were new attendees. We did not have diagnostic information for one child, and four children were further excluded as they did not provide enough relevant information, leaving 894 new patients for analysis. Of these, 410 were defined as cases and 408 as controls. The remainder were patients with other types of heart disease: 19 (2.1%) children with cardiomyopathy, 30 (3.4%) with an arrhythmia, and 27 (3.0%) with acquired heart disease. The overall prevalence of assisted conception was 5.4% – 11 ovulation induction, three intrauterine insemination, 16 in vitro fertilisation, 11 intracytoplasmic sperm injection, and three in vitro fertilisation/intracytoplasmic sperm injection combination.

Cases tended to be younger, more likely to be born with other medical conditions, more likely to have been born by caesarean section, and to have a lower birth weight compared with controls (Table 1). No associations were found between case status and maternal age, family history of heart problems, or family socio-economic status. Maternal diabetes, of which 78% was gestational, was not associated with being a case. Questions addressing referral patterns showed that cases were more likely to be detected on a scan before birth or by heart murmur and less likely than controls to have been detected by symptoms of palpitations, fainting, or by family history.

Mothers who used assisted methods of conception were older (34.2 (5.3) years versus 30.8 (6.0) years, $p < 0.001$), were more likely to be in the highest socio-economic group than those who conceived naturally (72.7 versus 52.3%, $p = 0.015$), and more likely to have had their child's heart problem detected on an antenatal scan (20.5 versus 9.7%, $p = 0.022$). They were also less likely to have had any previous live births (18.2 versus 51.4%, $p < 0.001$)

Table 1. Characteristics of cases and controls.

	New patients		
Characteristics	Controls (n = 408) n (%)	Cases (n = 410) n (%)	p value
The child			
Male	215 (52.7)	206 (50.2)	0.483
Age in years (median, range)	3.5 (0–19)	0.5 (0–19)	<0.001
Multiple birth	20 (4.9)	26 (6.3)	0.372
Child born with extracardiac abnormalities	99 (24.3)	131 (32.0)	0.014
Source of referral to clinic			
GP	94 (23.0)	53 (12.9)	
Hospital	291 (71.3)	343 (83.7)	<0.001
Other	23 (5.6)	14 (3.4)	
The mother			
Age in years (mean, SD)	30.7 (6.1)	31.3 (5.9)	0.154
Heart condition	32 (7.8)	23 (5.6)	0.206
Diabetes (any)	24 (5.9)	21 (5.1)	0.633
Other children	279 (68.4)	264 (64.4)	0.227
Previous live births			
None	217 (53.2)	194 (47.7)	0.115
One or more	191 (46.8)	213 (52.3)	
The pregnancy			
Folic acid supplement	331 (84.0)	354 (88.1)	0.099
Gestation (median)	40 (24–44)	39 (26–42)	0.001
Caesarean section	133 (32.6)	171 (41.8)	0.006
Special Care Baby Unit	61 (15.5)	155 (38.6)	<0.001
Birth weight (kg)	3.24 (0.76)	3.04 (0.80)	<0.001
The father			
Age in years (mean, SD)	33.9 (6.8)	34.8 (7.0)	0.073
Heart condition	26 (6.6)	22 (5.5)	0.505
Blood relation to mother	23 (6.4)	15 (4.3)	0.197
Occupational Category (SOC2000)*			
1–3	198 (50.8)	221 (56.1)	
4–5	101 (25.9)	94 (23.9)	0.310
6–9	91 (23.3)	79 (20.1)	

*SOC2000 1–3 managerial professional and technical, SOC2000 4–5 administrative and skilled, SOC2000 6–9 service, sales, process, plant, production, and elementary occupations

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and more likely to have a multiple birth (43.2 versus 3.5%, $p < 0.001$).

Table 2 shows the prevalence of assisted reproductive technologies in cases, controls, and for each subgroup of CHD. Compared with controls, cases were more likely to have been conceived using assisted methods of conception than controls; however, the difference was small and was not statistically significant (5.9 versus 4.9%, $p = 0.545$). Increased rates of assisted conception were observed in a number of individual CHD subgroups, the highest among those with a functionally univentricular heart (16.7%), pulmonary vein anomalies (14.3%), tetralogy of Fallot and related anomalies (11.1%), and atrial septal defects (10.1%), but the numbers in each group were small and none of the differences were statistically significant. Increased rates were also observed in those with cardiomyopathy (15.8%).

Crude and adjusted associations between CHD and assisted conception are shown in Table 3. Odds ratios are shown for assisted reproductive technologies with and without ovulation induction. There was a small but not significant association between assisted conception and CHD (odds ratio 1.21, 95% confidence interval 0.66–2.22). The magnitude of association decreased after adjustment for confounders (odds ratio 0.95, 95% confidence interval 0.48–1.88). When the analysis was restricted to singletons, the adjusted odds ratio was higher but

Table 2. Prevalence of Assisted Reproductive Technology in controls, CHD cases, and subgroups.

Category	n	ART [n (%)]	p value
Structurally normal heart (reference)	408	20 (4.9)	(ref)
Any CHD (1–20)	410	24 (5.9)	0.546
Subgroups of CHD			
Functionally univentricular heart	6	1 (16.7)	0.270
Pulmonary vein anomalies including anomalous connections	7	1 (14.3)	0.307
Tetralogy of Fallot and related anomalies (excluding pulmonary atresia)	18	2 (11.1)	0.237
Atrial septal defects	69	7 (10.1)	0.081
Other congenital heart malformations	35	3 (8.6)	0.413
Ventricular septal defects	108	7 (6.5)	0.512
Atrioventricular septal defects: partial or complete	16	1 (6.3)	0.563
Aortic arch obstruction or interruption	17	1 (5.9)	0.585
Patent arterial duct	25	1 (4.0)	1.000
TGA + ventricular septal defect (VSD) or double outlet right ventricle – TGA type	3	0 (0.0)	1.000
Common arterial trunk	3	0 (0.0)	1.000
Pulmonary atresia + VSD	4	0 (0.0)	1.000
Transposition of great arteries (TGA) with intact ventricular septum	16	0 (0.0)	1.000
Tricuspid valve anomalies	4	0 (0.0)	1.000
Mitral valve anomalies	9	0 (0.0)	1.000
Hypoplastic left heart syndrome	1	0 (0.0)	1.000
Pulmonary valve related anomalies	42	0 (0.0)	1.000
Pulmonary valve atresia – including intact ventricular septum	2	0 (0.0)	1.000
Aortic valve anomalies	22	0 (0.0)	1.000
Subaortic stenosis	3	0 (0.0)	1.000
Cardiomyopathy	19	3 (15.8)	0.075
Acquired heart disease (excluding cardiomyopathy)	27	3 (11.1)	0.164
Arrhythmia alone	30	0 (0.0)	1.000
Tarabit et al subgroups			
Functionally univentricular CHD	7	1 (14.3)	0.307
Anomalies of the great arteries	27	3 (11.1)	0.164
Anomalies of the atria and interatrial communications	69	7 (10.1)	0.081
Cardiac neural crest defects and double-outlet right ventricle without ventricular hypoplasia	31	3 (9.7)	0.216
Anomalies of venous connections	11	1 (9.1)	0.437
Ventricular septal defects	108	7 (6.5)	0.512
Isolated atrioventricular septal defects	16	1 (6.3)	0.563
Malformations of the atrioventricular valves and atrioventricular connections	29	1 (3.5)	1.000
Malformations of the outflow tracts and ventriculoarterial connections	126	3 (2.4)	0.316
Anomalies of heart position	4	0 (0.0)	1.000
Anomalies of coronary vessels	3	0 (0.0)	1.000
Discordant atrioventricular connections	2	0 (0.0)	1.000
TGA, heterotaxy syndrome and discordant atrioventricular connections	21	0 (0.0)	1.000

ART = assisted reproductive technology

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Table 3. Logistic regression analyses of the association between CHD and assisted reproductive technologies.

	All				Singletons only			
	n	ART [n (%)]	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	n	ART [n (%)]	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
All methods of assisted conception								
Reference, normal heart	408	20 (4.9)	ref	ref	388	11 (2.8)	ref	ref
All CHD	410	24 (5.9)	1.21 (0.66–2.22)	0.95 (0.48–1.88)	384	14 (3.7)	1.30 (0.58–2.89)	1.07 (0.45–2.58)
All methods of assisted conception excluding OI and IUI								
Reference, normal heart	404	16 (4.0)	ref	ref	385	8 (2.1)	ref	ref
All CHD	400	14 (3.5)	0.88 (0.42–1.83)	0.75 (0.33–1.70)	379	9 (2.4)	1.15 (0.44–3.00)	1.02 (0.36–2.92)

ART = assisted reproductive technology; IUI = intrauterine insemination; OI = ovulation induction; OR = odds ratio; 95% CI = 95% confidence intervals

*Adjusted for mother's age, gestation, year of birth, and parity

not statistically significant (odds ratio 1.07, 95% confidence interval 0.45–2.58). No important findings were seen when excluding ovulation induction or intrauterine insemination. An analysis of a subset of case and controls, restricted to those >2 years of age at the time of visit, produced similar odds ratios (data not shown).

We repeated the analysis for the groups outlined by Tararbit et al.[6] We found increased rates of assisted conception in a number of groups, although none of these were significant (Table 2). In the analysis by Tararbit et al, a significant increase in the prevalence of assisted reproduction technologies was seen for those with malformations of the outflow tracts and ventriculo-arterial connections compared with controls (5.6 versus 3.6%, p = 0.003); this was not seen in our analysis (2.4 versus 4.9%, p = 0.316). Similar prevalences of assisted conception in those with ventricular septal defects were seen in both our study and the study by Tararbit et al (6.5 and 5.0% respectively), although our results were not significant.

Discussion

We did not, in this study, detect an overall association between CHD and the use of assisted reproduction technology. We did find a higher prevalence of assisted conception in several CHD subgroups – functionally univentricular heart, pulmonary vein anomalies, tetralogy of Fallot and related anomalies, and atrial septal defects – but the number of cases in each were small and the differences were not statistically significant. Our results were adjusted for a priori cofounders, and we found no evidence of further confounding. After adjustment, our odds ratio reduced, suggesting that there was confounding by factors related to the underlying indication for assisted conception.

Of the previous published literature, where heart malformations had been included in the analysis, nine studies reported a positive association,[6–12,14,16] although three of these did not adjust for potentially confounding variables.[9,11,14] The study of the Paris Registry,[6] the largest of all, found an association between assisted reproductive technologies and CHD (odds ratio 1.3, 95% confidence interval 1.0–1.6). The odds were increased when excluding those with chromosomal abnormalities (odds ratio 1.4, 95% confidence interval 1.1–1.7); however, the odds ratios reduced when restricting the analysis to singletons, suggesting that the effect may be partially due to multiple pregnancy as the authors admit. We were unable to demonstrate any significant associations, using a control group consisting of children with no congenital cardiac abnormalities, when re-analysing our data using the Paris congenital heart malformation groupings, which were designed to capture genetic or putative embryological factors.

Consistent with our results, studies from Finland and Belgium failed to find significant associations.[13,15] In contrast, three studies from North America reported significant relationships[7,9,16] between assisted conception and cardiovascular defects. Kallen et al,[12] a Swedish population-based study found an increase in the odds of major cardiovascular defects (odds ratio 2.1, 95% confidence interval 1.6–2.8) and also an increased risk of ventricular or atrial septal defects without major cardiovascular defects. More recently, a cohort study based in Australia[8] also found increased risks of cardiovascular abnormalities (odds ratio 1.36, 95% confidence interval 1.08–1.72). The data were collected from a registry of births and two IVF clinics and included defects detected within 1 year of birth.

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Our study used a different design to those previously published and included over 400 cases of CHD, which is higher than other studies.[9,10,13–16] The information that can be obtained from records of birth registry studies is limited, and despite large numbers overall the majority of these studies have small numbers of cases of heart malformations.

The difficulties in studying associations between congenital abnormalities and assisted reproductive technologies have been discussed by Schieve et al[3] who highlight the problem of ensuring an adequate sample size when both assisted reproductive technologies and CHD are relatively rare events. By using a specialist clinic setting, we ensured a high number of children with CHD; we elected to study only children who were newly referred to the clinic, because the reasons why patients continue to be seen in a cardiac clinic are complicated and usually related to the presence of ongoing disease. Participants had, by definition, survived long enough to attend a hospital clinic; consequently, it is possible that our approach missed an association between assisted reproductive technologies and particularly severe forms of CHD or serious congenital malformations diagnosed antenatally where the family elected not to continue the pregnancy. Although only a very small proportion of children with CHD die of their condition, or from a related one, during pregnancy or shortly after birth, in the United Kingdom, up to 57% of parents decide not to continue the pregnancy after the diagnosis has been made of a severe form of CHD[21] such as hypoplastic left heart syndrome or where there is an associated chromosomal anomaly. On the other hand, our study included children across a range of ages, minimising the chance of missing undiagnosed cases as has been reported in around 25% of congenital malformations at discharge from hospital after birth;[22] studies based on birth registries using data recorded at birth, or, occasionally, up to one year of age, are likely to miss a proportion of CHD. Conversely, it is also possible that children are diagnosed with minor abnormalities at birth, which may normalise over the first year of life. We failed to collect information for about one-fifth of eligible children, in most cases because their parent(s) did not wish to take part in the study. This may have introduced some selection bias, but we were not permitted to investigate this in detail. We selected our control population with care, by sampling non-cases from the same clinic, in this way minimising any bias that might arise from increased scrutiny of those born through assisted conception. Controls were defined as those who were found to have a normal heart after referral for investigation of an audible, "innocent", murmur or a family history of congenital cardiac disease.

Finally, although we incorporated into our study a process through which the ascertainment of "exposure" – assisted conception – was made separately from allocation of case status, and parents were unaware of the diagnosis when completing the questionnaire, we cannot be sure that the cardiologists who made the diagnosis were unaware of the method of conception.

We note that the overall prevalence of assisted reproductive technologies in our study population was higher (5%) than the national figure (2%) reported by the UK Human Fertilisation & Embryology Authority.[1] It is possible that some mothers who have fertility treatment in order to conceive have higher rates of antenatal investigation than mothers who have conceived naturally. Others have argued against this,[7,10,13] but in our population children conceived through assisted reproductive technologies were more likely to have their CHD detected on the antenatal scan, suggesting that they had been more closely monitored. In one US study,[7] septal defects were the only cardiac anomaly associated with assisted conception (adjusted odds ratio 2.1, 95% confidence interval 1.1–4.0); although ascertainment bias was ruled out for most of the other, non-cardiac, defects analysed, the authors suggested that the identification of septal defects may have been linked to increased scrutiny. If CHD in naturally conceived children tends to be detected at a later date, then it is possible that registry studies may overestimate any risk of assisted reproductive technologies. Restricting our sample to those who were aged over two years at the time of their visit did not alter our findings. Using a case–control analysis, we failed to find any convincing evidence of an overall increased risk of CHD in children conceived through assisted reproductive technologies. Although these findings are reassuring, there remains some uncertainty over the issue and over the question of whether any increases in risk reported elsewhere are reflective of the risk inherent in assisted reproductive technologies or in the medical indication(s) for it.[8]

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Conflicts of Interest

None.

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