

CONGENITAL HEART DISEASE

Cardiovascular malformations in infants of diabetic mothers

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Objective: To compare the prevalence at live birth and the spectrum of cardiovascular malformations in infants born to diabetic mothers with pre-existing diabetes with that in infants of non-diabetic mothers.

Design: Prospective study of all live births in the resident population of one health region, with recording of details of the outcome of all pregnancies of women with pre-existing diabetes and of all live born babies with cardiovascular malformations.

Results: In the six years 1995–2000 there were 192 618 live births in the study population. Cardiovascular malformations were confirmed in 22 of 609 (3.6%) babies with diabetic mothers and in 1417 of 192 009 (0.74%) babies with non-diabetic mothers. The odds ratio for a cardiovascular malformation with maternal diabetes was 5.0 (95% confidence interval 3.3 to 7.8). Combination of these results with previous reports and comparison with the spectrum of cardiovascular malformations in infants of non-diabetic mothers shows a greater than threefold excess of transposition of the great arteries, truncus arteriosus, and tricuspid atresia.

Conclusions: Pre-existing maternal diabetes is associated with a fivefold increase in risk of cardiovascular malformations. Transposition of the great arteries, truncus arteriosus, and tricuspid atresia are overrepresented to produce a substantial excess of these malformations.

Congenital cardiovascular malformations form the most prevalent group of birth defects, affecting around 6–8 per 1000 live births.¹ In most cases the cause is unknown although some are genetic in origin and a few are known to have an environmental cause. Only 1% of cases are caused by maternal diseases.² Maternal diabetes is known to have a teratogenic effect on the cardiovascular system with a reported risk of malformation in published studies of 1.7–4.0%.^{3–8} A prospective population based study of live born infants of diabetic mothers has not previously been reported. Our aim in this study was to determine the prevalence at live birth of structural cardiovascular malformations in babies born to mothers with pre-existing diabetes and to compare the findings in babies of non-diabetic mothers.

METHODS

Population base

We based the study on the population of the former Northern Health Region of England, which comprised the counties of Cumbria, Northumberland, Tyne & Wear, Cleveland, and Durham. All babies with suspected congenital heart disease from 15 of the 16 health districts are referred to a single paediatric cardiology centre. Babies from the small health district of South Cumbria are referred elsewhere for geographical reasons and they were excluded from the study.⁹ The population is stable and geographically well defined with a recent average live birth rate of around 32 000 a year.

Study population

We included in this study all live born babies whose mothers had pre-existing diabetes and who were born between 1 January 1995 and 31 December 2000. The data were cross referenced with the paediatric cardiology database to identify all those with a cardiovascular malformation. The Northern Diabetic Audit was set up in 1993 to collect data prospectively on the outcome of all pregnancies in women with pre-existing diabetes. Its design and findings have been reported

previously.¹⁰ All terminations of pregnancy for fetal heart defects also were noted.

Denominator population

The Regional Paediatric Cardiology Database has registered all congenital cardiovascular malformations in live born children within the former Northern Health Region since 1985 with prospective ascertainment since 1990.⁹ We identified all babies born alive with a cardiovascular malformation to non-diabetic mothers between 1 January 1995 and 31 December 2000. The Office for National Statistics provided data on the regional birth rate in the same period. Although this study concentrated on pregnancies ending in live birth, termination of pregnancy for fetal heart disease was also noted in the non-diabetic denominator population from data provided by the Northern Congenital Abnormality Survey.¹¹

In a separate retrospective investigation we obtained details of the pregnancies of all mothers of babies with transposition live born between 1985 and 2000 from data held at the Northern Congenital Abnormality Survey.¹¹

Case definition

In common with most previous epidemiological studies we defined a cardiovascular malformation as a "gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional importance".¹² We limited ascertainment to cases diagnosed before the baby was 12 months old, as the majority of significant structural heart disease has presented by this age.¹³ We included only live born infants, as the natural history of cardiovascular malformations in the fetus is unclear.¹ We excluded babies with diabetic cardiomyopathy, as this is often a self limiting problem with no clinical consequence and is not a structural malformation of the heart. We also excluded from the study babies with mild physiological pulmonary artery branch stenosis, persistent foramen ovale, persistent ductus in prematurity, atrial septal defect undergoing spontaneous closure in infancy, isolated cardiac arrhythmia, isolated bicuspid aortic valve, mitral valve

Table 1 Cardiovascular malformations in live born babies with diabetic and non-diabetic mothers

	Diabetic	Non-diabetic	Total
CVM	22	1417	1439
Normal	587	190592	191179
Total	609	192009	192618

CVM, cardiovascular malformation.

prolapse without mitral regurgitation, isolated dextrocardia, and cardiac tumours.

Statistical analysis

Statistical analysis was limited to calculation of the odds ratio for comparison of risk of malformation in diabetic pregnancies.¹⁴

RESULTS

During the six years 1995–2000 there were 192 618 live births in the study population. In 192 009 babies born to non-diabetic mothers, there were 1417 with a cardiovascular malformation diagnosed before the age of 12 months, a prevalence at live birth of 7.4 per 1000 (0.74%). In 609 babies live born to diabetic mothers, there were 22 with cardiovascular malformations, a prevalence at live birth of 36 per 1000 (3.6%). Table 1 gives the details. The odds ratio for a cardiovascular malformation in the offspring of diabetic mothers compared with the non-diabetic population was 5.0 (95% confidence interval (CI) 3.3 to 7.8).

Table 2 gives details of the specific cardiovascular malformations in infants of diabetic mothers in our study population and in five previous reports.^{3–5,8} Table 3 compares the spectrum of cardiac defects in maternal diabetes derived from the six studies in table 2 with results from our own non-diabetic population. The methodological differences between previous reports make this an approximation only and detailed statistical comparison is inappropriate. Because our own data for offspring of non-diabetic mothers relate to 1995–2000, table 3 also includes the percentage distribution of various specific cardiovascular malformations as described in a recent analysis by Hoffman¹ of 35 reports of the descriptive epidemiology of cardiac defects published in 1964–1998. It is worthy of note

that transposition of the great arteries, tricuspid atresia, and truncus arteriosus are seen three or more times more frequently than expected in the infants of diabetic mothers than in either our own data from non-diabetic mothers or in Hoffman's compiled data.

Few babies in table 2 had tricuspid atresia or truncus arteriosus. However, transposition accounts for 14.4% of all heart defects, which have a prevalence at live birth of 36 per 1000, giving a prevalence of transposition of 518 per 100 000. This compares with 4.3% of 7 per 1000 in the non-diabetic population, a prevalence of 30 per 100 000. Thus, there is a roughly 17-fold excess of transposition in live born babies of mothers with pre-existing diabetes.

To investigate further the link between maternal diabetes and transposition we retrospectively investigated all mothers of babies with transposition who were live born in 1985–2000 from data held at the Northern Congenital Abnormality Survey. There were 180 babies with transposition in that 16 year period, of whom 5 (2.8%, 95% CI 0.9% to 6.4%) had mothers who could be identified retrospectively as having pre-existing diabetes. Given that only 609 of 192 618 (0.32%, 95% CI 0.29% to 0.34%) mothers in the six years of our main study had diabetes, this confirms the increased risk of transposition in infants of diabetic mothers.

All women in the Northern Diabetic Audit have diabetes before conception. In the six years of this study there were 774 pregnancies, of which 609 resulted in live birth: 562 of 609 (92%) women were treated with insulin throughout the pregnancy and 552 of 609 (91%) had insulin dependent diabetes.

There were 24 pregnancies in diabetic women with a fetal or postnatal recognition of a cardiovascular malformation. One ended in an early spontaneous abortion, no pregnancies were terminated, and there was one antepartum stillbirth. Both dead fetuses had left atrial isomerism. A diagnosis of a cardiovascular malformation was confirmed or suspected antenatally in 10 of 22 (45%) pregnancies resulting in live birth. During the same time 92 pregnancies were terminated with cardiovascular malformations (53 with isolated cardiac defects, 17 with multiple malformations, and 22 with associated chromosomal abnormalities).

DISCUSSION

Although the increased risk of cardiovascular malformations associated with maternal diabetes is recognised, this is the

Table 2 Details of cardiovascular malformations in live born babies with maternal diabetes in the present and previous reports

	Pederson <i>et al</i> 1964 ³	Rowland <i>et al</i> 1973 ²	Mills <i>et al</i> 1988 ⁶	Ferencz <i>et al</i> 1990 ⁷	Becerra <i>et al</i> 1990 ⁸	This study 2003	Total
HLH	0	0	0	2	0	0	2(1.6%)
MA	0	0	1	0	0	0	1(0.8%)
TA	2	1	0	1	0	0	4(3.2%)
DIV	0	0	0	0	0	1	1(0.8%)
PA	0	1	0	0	1	2	4(3.2%)
CAT	1	1	1	2	0	0	5(4.0%)
AVSD	0	0	0	2	0	1	3(2.4%)
TGA	3	3	5	2	2	3	18(14.4%)
ToF	2	0	0	5	0	2	9(7.2%)
VSD	3	3	8	10	5	6	35(28.0%)
AS	0	0	1	1	0	0	2(1.6%)
PS	1	1	1	1	0	3	7(5.6%)
CoA	1	3	2	2	0	3	11(8.8%)
ASD	0	2	1	2	2	1	8(6.4%)
PDA	2	1	0	0	0	0	3(2.4%)
Misc	0	3	1	5	3	0	12(9.6%)
Total	15	19	21	35	13	22	125(100)

AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CAT, common atrial trunk; CoA, coarctation of the aorta; CVM, cardiovascular malformations; DIV, double inlet ventricle; HLH, hypoplastic left heart; MA, mitral atresia; Misc, miscellaneous; PA, pulmonary atresia; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TA, tricuspid atresia; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; VSD, ventricular septal defect.

Table 3 Comparison of frequency of individual cardiovascular malformations in live born babies of non-diabetic mothers

	CVM in offspring of non-diabetic mothers (%)	Overall CVM Hoffman (%)	CVM in maternal diabetes (%)*
HLH	1.5	2.8	1.6
MA	0.3	–	0.8
TA	0.4	–	3.2
DIV	0.4	1.3	0.8
PA	2.0	–	3.2
CAT	0.9	1.4	4.0
AVSD	5.0	3.8	2.4
TGA	4.3	4.4	14.4
ToF	4.5	5.2	7.2
VSD	51.8	32.4	28.0
AS	2.2	3.9	1.6
PS	7.1	7.0	5.6
CoA	3.4	4.8	8.8
ASD	7.3	7.5	6.4
PDA	5.7	6.8	2.4
Misc	3.9	–	9.6

*Summarised from six studies in table 2.

Individual malformations with the most notable excess in infants of diabetic mothers are shown in bold.

first prospective population based study to compare the prevalence at live birth of congenital heart disease in infants of mothers with pre-existing diabetes with that in infants of non-diabetic mothers. We have found a significant excess of cardiovascular malformations with an odds ratio of 5.0. However, the total number of cardiovascular malformations in babies with diabetic mothers in our study is small (22) and so precludes detailed analysis of individual diagnoses. To overcome this we combined our findings with those in previous publications containing sufficient data for analysis.^{3–5,8}

Pedersen and colleagues⁵ reported malformations visible to “the naked eye” present on clinical examination in the offspring of diabetic mothers born in 1926–1963. No data relating to cardiovascular malformations are given in the original report but Rowe and colleagues¹⁵ provided the data from Pedersen’s study cohort in 1981. Rowland and associates⁵ reported a population based study of diabetic pregnancy but included both still births and post-infant ascertainment of congenital heart disease up to the age of 7 years in 1973. Mills and colleagues⁶ reported a case–control study of malformations of infants of diabetic mothers in 1988. The abnormalities reported were apparently detected by a single examination at three days of age, although the diagnoses included anomalous origin of the left coronary artery from the pulmonary artery, coarctation of the aorta, and atrial septal defect, malformations that are not usually apparent at this early age. Ferencz and colleagues⁷ in 1990 reported a case–control study of congenital heart disease, so the denominator of normal babies of diabetic mothers was not available. “Overt” diabetes was present in 0.5% of mothers of babies with heart defects but four of 35 mothers denied ever taking insulin and there was no means of validating the diagnosis. Ferencz and colleagues⁷ reported an excess of cases of double outlet right ventricle, a diagnostic category not used in any of the other studies. Double outlet right ventricle defines one part of a malformation, which is of importance when contemplating surgical repair, but it does not have a constant definition^{16,17} and does not define an anatomically or physiologically distinct group of malformations.¹⁷ It includes diagnoses that may otherwise be described as transposition of the great arteries, tetralogy of Fallot, etc. Unlike most other studies, that of Ferencz and colleagues⁷ did not find an excess of babies with transposition of the great arteries, possibly as a result of the use of double outlet right ventricle as a diagnostic category. Becerra and associates⁸ reported a case–control study of babies with birth defects in 1990. Their study group also included stillbirths and because this was a case–control

study the number of normal babies born to diabetic mothers is unknown.

Combining our findings with those previously reported, the excess of cardiovascular malformations in infants of diabetic mothers is confirmed (table 2). Although methodological differences between previous reports preclude detailed statistical analysis, the more than threefold excess of diagnoses such as transposition of the great arteries, truncus arteriosus, and tricuspid atresia, coupled with the fivefold excess of cardiovascular malformations overall, implies that these specific malformations are perhaps at least 15 times more prevalent than in offspring of non-diabetic pregnancies.

In a case–control study of infants with “conotruncal” defects (which included truncus arteriosus, tetralogy of Fallot, transposition of the great arteries, and double outlet right ventricle) in Atlanta, Adams and colleagues¹⁸ found an increased risk associated with maternal diabetes with an odds ratio of 5.6 overall (7.1 for truncus arteriosus and 9.1 for transposition of the great arteries). However, there was no validation of the diagnosis of diabetes (only four of six mothers admitted to taking “medication”) and there was no separation of pre-existing diabetes and gestational diabetes. Although Adams and colleagues¹⁸ confirm the excess of transposition of the great arteries and truncus arteriosus, there is little justification for grouping conotruncal defects together, as they are different types of malformations and are unlikely to have a common cause.

Studies of antenatal echocardiography and diabetic pregnancy also report an excess of cardiovascular malformations. Gladman and colleagues¹⁹ identified fetal heart disease in seven of 328 diabetic pregnancies. Four pregnancies resulted in live birth, giving a prevalence at live birth of congenital heart disease of 1.2%. The authors concluded that “the incidence of fetal cardiac abnormalities is low and not significantly related to maternal diabetic control”. Meyer-Wittkopf and colleagues²⁰ reported a prevalence of fetal cardiac abnormalities of 3.1% in diabetic mothers. Five babies were live born, giving a live birth prevalence of 1.5%. The authors concluded that the “increased risk” of cardiovascular malformation in infants of diabetic mothers was an indication for fetal echocardiography.

In common with previous studies, ours included babies with persistent ductus arteriosus and atrial septal defect recognised in infancy. Both of these are usually asymptomatic in the infant or young child and both are more commonly recognised beyond infancy. In a previous study we found that 47% of cases of persistent ductus arteriosus and 41% of atrial septal defects were diagnosed in children in the first 12 months of

life compared with 80% of all other cardiovascular malformations.¹³ Infants born to diabetic mothers may be subjected to greater scrutiny and may therefore be more likely to have asymptomatic cardiovascular malformations recognised. Despite that, it can be seen from table 3 that atrial septal defect and persistent ductus are not overrepresented in the spectrum of cardiovascular malformations.

In this study we did not assess the quality of control of diabetes during pregnancy because of the lack of standardisation of normal haemoglobin A_{1c} assays in different laboratories in the region until recently.¹⁰

Our prospective population based study of infants of diabetic mothers has confirmed the increased risk of cardiovascular malformations and the greatly increased risk of some specific malformations, notably transposition of the great arteries. It supports existing recommendations that all pregnant women with diabetes should be offered a specialist fetal echocardiogram.²⁰ This advice is reinforced by published evidence that antenatal diagnosis of transposition leads to an improved postnatal outcome.²¹

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FROM BMJ JOURNALS

Patients admitted to a district general hospital with unstable angina are disadvantaged compared with those admitted to a tertiary centre

Please visit the *Heart* website [www.heartjnl.com] for a link to the full text of this article.

Patients with unstable angina or non-ST elevation myocardial infarction (NSTEMI) admitted to a district general hospital (DGH) waited over two and a half times longer for angiography and twice as long for revascularisation than those admitted to the local tertiary cardiac centre.

As the conditions carry a significant mortality and trials have shown prognostic benefit for early investigation and revascularisation in "high risk" patients with these diagnoses, equity of access to care should be a cornerstone of the NHS.

The authors studied 95 patients admitted to DGHs who were subsequently transferred to the Manchester, UK, Heart Centre at Manchester Royal Infirmary (MRI). They compared their progress with a similar number admitted directly to the Infirmary under the care of general physicians (internists) but later transferred to the cardiac team. There were no important baseline differences, except that the DGH patients were less likely to have had a previous revascularisation procedure.

The greatest part of the delay was while patients waited for transfer. Selection bias resulted from the perceived advantage of an MRI patient transferring to cardiac services thereby freeing up a much needed general medical bed. The principle of equal access demands that tertiary centres should be allowed to work independently of bed pressures created elsewhere in their parent hospital.

▲ *Postgraduate Medical Journal* 2003;**79**:93–98