EDITORIAL

Maternal diabetes and the fetal heart

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Heart 2006;92:1019–1021. doi: 10.1136/hrt.2005.083840

Maternal diabetes mellitus significantly affects the fetal heart and fetal–placental circulation in both structure and function. The influence of pre-conceptional diabetes begins during embryonic development in the first trimester, with altered cardiac morphogenesis and placental development. It continues to have an influence on the fetal circulation through the second and third trimesters and into the perinatal and neonatal period

Hypertrophic cardiomyopathy observed in the infant of the diabetic mother is characterised by thickening of the inter-ventricular septum, and to a lesser extent the ventricular free walls. It is observed in infants of diabetic mothers whether or not there is reasonable metabolic control.^{1,2} Fortunately, most affected infants are clinically asymptomatic and have resolution of the hypertrophy within months, presumably as there is no further exposure to the abnormal intrauterine milieu. The development of hypertrophic cardiomyopathy is believed to occur as a consequence of both fetal hyperinsulinaemia and the normally increased expression and affinity of insulin receptors which leads to the proliferation and hypertrophy of cardiac myocytes.^{3,4} Given the presence of this pathology whether or not there is reasonable metabolic control, it has been postulated that fluctuations in glucose values rather than basal state may be more important determinants of fetal cardiac and general somatic growth in maternal diabetes.⁵

EVOLUTION OF FETAL MYOCARDIAL CHANGES IN MATERNAL DIABETES

The timing of development of the myocardial changes in the infant of the diabetic mother has been well demonstrated by fetal echocardiography. Fetal echocardiographic investigations suggest the onset of hypertrophy occurs even before 20 weeks of gestation with documentation of increased ventricular septal thickening relative to fetuses in non-diabetic pregnancies.^{1,6,7} There is accelerated growth of the fetal heart in the mid and third trimesters compared to fetuses of non-diabetic pregnancies, even when adjusted for fetal weight. Unlike other forms of fetal cardiomyopathy, hypertrophic cardiomyopathy associated with maternal diabetes is not typically associated with the evolution of cardiovascular compromise before birth.⁸

While the timing of onset is somewhat controversial, differences in fetal ventricular inflow and outflow velocities suggest, in addition to changes in form, there is altered fetal

myocardial function in maternal diabetes from the late first and mid trimesters. Fetuses of diabetic pregnancies have been shown to have an accelerated increase in maximum and mean temporal velocities across atrioventricular valves through gestation relative to normal pregnancies.⁹ Increased left and right ventricular outputs adjusted for fetal weight have also been observed.⁹ Lower right atrioventricular valve inflow E (early diastole)/A (atrial systole) velocity ratios have been demonstrated, particularly later in gestation.^{10,11} Of these parameters, only lowered E/A wave ratio has been shown to be associated with worse maternal glycaemic control, which may be indirectly due to changes in fetal heart rate, ventricular wall thickness and haematocrit.¹²

Using tissue Doppler techniques to assess long-axis atrial and ventricular function, in this issue of *Heart* Gardiner and colleagues found absolute age related values of ventricular systolic and diastolic long-axis function to be greater in fetuses of diabetic mothers which they postulated reflects improved age-related cardiac performance.¹³ They demonstrated a significant increase in myocardial shortening velocities and long-axis amplitude of motion of the left ventricular and septal free wall. Late lengthening myocardial velocities in the left and right ventricular free walls were also significantly increased, possibly in keeping with improved ventricular diastolic performance, despite the presence of increased ventricular and septal wall thickness. While such parameters may be consistent with better age related cardiac performance, the long-axis indices of ventricular function have also been shown to be affected by changes in preload and afterload¹⁴ which may at least in part be the reason for a pattern of progressive increase with gestation. In normal and diabetic pregnancies there is a progressive decrease in placental vascular resistance with gestation and thus decrease in fetal ventricular afterload. Furthermore, the combined ventricular output increases with gestation concomitant with fetal growth.¹⁵ In diabetic pregnancies, an accelerated increase in biventricular outputs relative to fetuses of non-diabetic mothers and fetal weight likely contribute to the differences in myocardial velocities demonstrated by Gardiner *et al*¹³ compared to non-diabetic controls.

While placental vascular resistance based on umbilical arterial Doppler velocimetry may not be altered in diabetic pregnancies in the absence of growth restriction and maternal hypertension,¹⁶ even average for gestational age infants of diabetic pregnancies show increased placental size relative to fetal weight compared to placentae of uncomplicated pregnancies.¹⁷ Type 1

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Published Online First
12 May 2006

pregestational diabetes in particular is associated with increased fetal-placental angiogenesis with increased total placental capillary volume, surface area and length.¹⁸ Both increased biventricular output relative to fetal weight and consequent changes in ventricular long-axis function may reflect differences in placental blood flow in addition to the baseline differences in general somatic growth. Thus, as Gardiner and colleagues¹³ have suggested, their findings could reflect an adaptive fetal cardiovascular process rather than a myopathic process. Evaluation of the isovolumic acceleration in fetuses of diabetic pregnancies may provide additional insight into the actual systolic performance of the fetal heart unrelated to loading conditions.¹⁴

INFLUENCE OF POOR MATERNAL METABOLIC CONTROL ON THE FETAL HEART

While others have largely reported lack of correlation between fetal cardiac functional changes and maternal glycaemic control, Gardiner and colleagues report a significant inverse relationship between myocardial and flow velocities and HbA1c values.¹³ Experimental and clinical studies have documented maternal diabetes-induced changes in fetal metabolic and circulatory homeostasis which are at least in part due to hyperglycaemia. In maternal diabetes, the fetus increases its oxidative metabolism, becoming more hypoxic.¹⁶ The increased placental weight as well as polycythaemia, which is common in infants of diabetic mothers, may represent positive adaptive mechanisms which protect the fetus from hypoxaemia. Interestingly, large for gestational age infants, usually found in less well-controlled maternal diabetes, have placental weights that are comparable to the placenta of average for gestational age infants from non-diabetic women.¹⁷ This subset of fetuses among diabetic pregnancies are at highest risk for intrauterine death which may be a consequence of inadequate adaptation to the pathophysiological influences of less well-controlled maternal diabetes. While not as yet investigated, it is possible that worse glycaemic control directly or indirectly hinders normal accelerated growth of the placenta in response to hypoxaemia resulting in less relative placental growth and less change in myocardial and flow velocities. In addition to the histological changes in the placenta, late gestation animal models have demonstrated that hyperglycaemia results in a reduction in the percentage of the cardiac output that is distributed to the placenta, with redistribution of the output to the body, heart, renal, adrenal and splanchnic circulations.¹⁹ Such change, if chronic, may alter the adaptive placental growth relative to the growth of the fetus, despite the stimulus of hypoxaemia. This could ultimately be manifested by less of an increase in cardiac output and thus less significant increases in long-axis ventricular function parameters. Lack of sufficient adaptation may lead to worsening hypoxaemia and acidaemia resulting in greater compromise and potential for acute fetal loss. Reduced fetal heart rate variability and frequency of accelerations observed in third trimester fetuses of diabetic mothers,²⁰ which have suggested less mature autonomic function, may occur as a consequence of the chronic hypoxaemia, and may further contribute to an inability to adapt acutely and chronically to the ill-effects of hyperglycaemia.

MATERNAL DIABETES AND EVOLUTION OF CONGENITAL HEART DISEASE

While improvements in fetal surveillance and perinatal management have led to a reduction in diabetes related complications including perinatal mortality, the incidence of associated congenital anomalies remains high relative to the general population. Congenital heart defects occur in up to 8.5 per 100 live births of infants of diabetic mothers.²¹ The congenital heart defects identified in offspring of diabetic

mothers include double-outlet right ventricle, truncus arteriosus, transposition of the great arteries, ventricular septal defect, and hypoplastic left heart syndrome.^{22–23} The exact teratogenic mechanism of maternal diabetes is not fully defined and is likely multifactorial. High maternal haemoglobin A1c values during early pregnancy are associated with increased risk of malformations.²⁴ Multiple biochemical and signal transduction pathways are known to be modified in the presence of hyperglycaemia, which include reduction in cellular levels of myoinositol and arachidonic acid and increases in production of reactive oxygen species.²⁵ Hyperglycaemia has a direct influence on the proliferation and migration of neural crest cells which are critical in the development of the heart and brain.²⁶ However, experimental work has shown not only increased glucose values but also that values of triglycerides, β -hydroxybutyrate, branched chain amino acids, and creatinine correlate positively with increased resorption rates and malformation rates among affected pregnancies.²⁷ Maternal diabetes is associated with induction of placental genes associated with chronic stress and inflammation,²⁸ and recent investigations have even implicated a potential role for inflammation in the evolution of maternal diabetes-induced embryopathy.²⁹ Finally, the finding that altered fetal heart function has been observed as early as 12–14 weeks^{10–30} and is more prevalent where there is worse metabolic control¹⁰ could suggest a haemodynamic influence, even in the first trimester, which may contribute further to the evolution of structural pathology. Flow and tissue Doppler investigations in the first trimester may ultimately elucidate the role of haemodynamic changes in the evolution of the fetal cardiac embryopathy of maternal diabetes.

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IMAGES IN CARDIOLOGY

doi: 10.1136/hrt.2005.073221

“Crush” and “reverse crush” technique to treat a complex left main stenosis

An 82-year-old man presented for elective coronary angiography. He had recent onset exertional dyspnoea and nitrate-responsive chest pain. ECG showed left bundle branch block; systolic function was preserved at echocardiography.

The left anterior descending coronary artery (LAD) had significant ostial stenosis with calcification; the left circumflex (LCX) had critical ostial disease of the predominant atrioventricular vessel, with a severe stenosis of an early marginal branch (panel A). Coronary surgery was discussed but the patient elected to have percutaneous intervention.

An 8 French JL 4.0 guide catheter, 5000 iu of heparin, and abciximab bolus were used. The LAD and LCX were wired using BMW wires. Predilatation was performed in both branches using a 2.5 × 12 mm Maverick balloon. Modified T-stenting with “crushing” to LCX-LAD was performed. The co-dominant LCX was treated as the main vessel. A 3.5 × 23 mm Cypher was placed in the LCX and a 3.0 × 18 mm Cypher in the LAD, with the LCX stent covering the entire left main stem (panel B).

The LAD stent was inflated first at 12 atm (panel C). The stent balloon and wire were removed and the LCX stent was deployed at 18 atm, crushing the proximal part of the LAD stent (panel D). The LAD was then re-accessed using a Wizdom wire and the struts were opened with a 2.5 mm Maverick balloon. The first obtuse marginal branch (OM1) was then wired using a Wizdom wire and predilated with the 2.5 balloon.

Dr Colombo’s “reverse crushing” technique was used to treat the LCX-OM1 bifurcation. A further 3.0 × 13 mm Cypher was placed in OM1, the proximal 2 mm protruding into the proximal LCX, and a 3.5 × 20 Quantum balloon was placed in the LCX (panel E). The OM1 stent was deployed first at 12 atm, pinning the LCX balloon in position (panel F), then the wire and balloon were removed. The Quantum balloon was then inflated at 16 atm, crushing the proximal part of the OM1 stent (not shown). The LAD wire was removed and the vessel was rewired and predilated, to make sure no struts were protruding into its lumen. The final result is shown in panel G. Panel H depicts the final position of the three stents used.

A combination of “crush” and “reverse crush” techniques was used to ensure complete coverage of a very complex, trifurcating LM lesion in an elderly patient. By treating the

LCX as the main vessel and inflating the LAD stent first, we ensured that the crushed part of the stent was not restricting access to the OM1.

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