CONGENITAL HEART DISEASE

Increased periconceptual maternal glycated haemoglobin in diabetic mothers reduces fetal long axis cardiac function

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Objective: To compare ventricular long axis function in fetuses of diabetic mothers (FDM) with contemporaneously studied normal controls (N) and to assess the effect of pre-pregnancy diabetic control on these measurements.

Design: Long axis function was compared in 41 FDM and 159 N fetuses in a cross sectional observational study.

Setting: Fetal medicine unit.

Methods and results: Echocardiography confirmed structural normality. Pulsed wave valvar Doppler velocimetry, lengthening and shortening myocardial velocities, and amplitude of ventricular long axis movement were recorded at the base of the left and right ventricular free walls and septum. Periconceptual diabetic control was assessed by haemoglobin A1c (HbA1c) in early pregnancy. Doppler and myocardial velocities were negatively related and myocardial thickness was positively related with HbA1c. In both cohorts all variables except mitral and tricuspid late filling (A wave) velocities were dependent on gestational age. FDM gestational age related values were higher for most variables and robust analysis of covariance showed significantly different maturation patterns in mitral valve E:A ratio ($p = 0.036$) and pulmonary velocity ($p = 0.04$), late lengthening myocardial velocities (left $p = 0.016$ and right $p = 0.066$), left myocardial shortening velocities ($p = 0.008$), and left free wall ($p = 0.03$) and septal ($p = 0.04$) amplitude of motion. FDM septal thickness was significantly increased throughout gestation ($p < 0.0001$).

Conclusion: Periconceptual diabetic control influences fetal cardiac performance and myocardial hypertrophy but, unlike the pathophysiology of adult ventricular hypertrophy, is accompanied by functional adaptation. It is unlikely to explain the increased rate of late stillbirth observed in diabetic pregnancies.

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The fetal heart is a target organ for the congenital effects of pre-existing maternal diabetes. Cardiac anomalies and myocardial hypertrophy are about three times more prevalent in the offspring of women with diabetes.^{1,2} These fetuses have a fivefold greater risk of being stillborn than do infants in the general population.³ Fetal death of unknown aetiology occurs, even with maternal euglycaemia and satisfactory antepartum assessment, and its occurrence in late gestation suggests a disturbance of cardiovascular adaptation.⁴

Although the role of maternal glucose control in late stillbirth is debatable, increased maternal glycated haemoglobin (HbA1c) concentration is reported to alter embryonic and later fetal growth.^{5,6} Also, the relation between HbA1c concentrations and the extent of cardiac abnormalities is controversial.^{7,8} The general consensus, however, is that myocardial hypertrophy, macrosomia, and neonatal hypoglycaemia are related to maternal diabetic control with cardiac hypertrophy a response to fetal hyperglycaemia and hyperinsulinaemia, even when measures of maternal control are optimal.⁹ A diabetic cardiomyopathy has been proposed as a unique entity that is characterised by localised septal hypertrophy and accompanying cardiac dilatation¹⁰; newborns may show severe but transient cardiorespiratory symptoms, more usually related to lung pathology. Cardiac hypertrophy resolves postnatally and is therefore considered relatively benign.¹¹ However, the role of cardiac hypertrophy and altered fetal autonomic function in late stillbirth remain to be determined.¹²

Previous studies have used conventional imaging techniques, minor axis M mode, and filling velocities. One disadvantage is that ventricular minor axis function is usually preserved in the fetal heart until there is overt myocardial dysfunction. Furthermore, ventricular filling velocities are affected by heart rate, packed cell volume, and myocardial thickness, all of which may be increased in fetuses of diabetic mothers (FDM).¹³ In contrast, long axis function has been shown to be a sensitive indicator of early ventricular dysfunction in adults and is technically easy to perform in the fetus, as recordings are made at the mitral and tricuspid annulus levels.¹⁴ We have described gestational age related reference ranges for long axis function in the normal fetus and it has been used to assess ventricular function in both children and fetuses showing reduced myocardial velocities at the tricuspid annulus in fetal heart failure.^{15–18}

The objectives of this study were to compare ventricular long axis function in FDM with contemporaneously studied normal controls (N) and to assess the effect of pre-pregnancy diabetic control on these measurements.

PATIENTS AND METHODS

Study population

Forty one singleton fetuses of diabetic pregnancies (FDM) were studied cross sectionally from 17 weeks to term.

Abbreviations: FDM, fetuses of diabetic mothers; HbA1c, glycated haemoglobin; N, normal controls

Ventricular function was compared with that of 159 N. Subjects were excluded from the N group for maternal hypertension, renal disease, and drug ingestion and from both study groups for fetal aneuploidy or congenital malformation (at anomaly scan) or if growth restriction developed (< 5th centile). Ten of the diabetic mothers studied had insulin dependent diabetes mellitus (secondary to pancreatic islet β cell destruction) and 31 had non-insulin dependent diabetes mellitus (defect in insulin secretion with or without insulin resistance). All mothers were taking insulin throughout the pregnancy. Periconceptual diabetic control was assessed by the HbA1c measurements taken at booking. Neonatal outcome was assessed by birth weight, Apgar scores, and the need for intensive care. The study was approved by the Imperial College School of Medicine, Hammersmith, Queen Charlotte's and Chelsea and Acton hospitals' research ethics committee. All subjects gave informed consent to participate in the study.

Echocardiography

All fetuses were studied with an Acuson Sequoia 512 echocardiograph with a curvilinear 6C2 probe (Siemens Medical Solutions, Acuson Division, Mountain View, California, USA). The fetal heart was fully examined, including Doppler, to confirm normality.¹⁹ Right and left ventricular long axis function of the fetus was assessed with myocardial Doppler velocities and maximum amplitude of the atrioventricular ring displacement from M mode recordings as described previously.¹⁵ Early (E) and late (A) diastolic filling velocities were measured with the pulsed wave Doppler sample volume at the tips of the left and right atrioventricular valves. Fetal heart rate was measured from the mean of three Doppler recordings through the aortic valve. Long axis shortening and lengthening tissue Doppler velocities were recorded at the basal segment of the left, septal, and right sided myocardial segments. The maximum displacement between the onset of systole and onset of diastole was recorded in the left and right free wall and septal segments measured from the apex of the heart to its base with the M mode cursor positioned at the left and right atrioventricular rings and the septum. With the fetal heart orientated in the parasternal long axis view the M mode cursor was placed at the tips of the mitral valve and tricuspid valves to measure left ventricular free wall and septal thickness, and right ventricular free wall thickness, respectively.

All results are presented as the mean of three consecutive recordings of each measurement, which were stored on magneto-optical disc for digital data measurement. Measurements were made off line with the investigators blinded to individual case status to assess reproducibility, which has been reported elsewhere.¹⁵

Statistical analysis

All data were analysed with SPSS version 12 (SPSS Inc, Chicago, Illinois, USA) and SPLUS 6.0 (Insightful Corporation, Seattle, Washington, USA). We used the same methods as in a previous publication describing gestational reference ranges for fetal cardiac variables showing that some variables change more slowly in the third trimester.¹⁵ Piecewise linear robust analysis of covariance models were fitted allowing for the possibility of a different mean or a different slope for increasing gestational age between N and FDM patients before and after 30 weeks' gestation. When slope slopes did not differ after 30 weeks, the models were refitted without these extra terms. The MM robust regression procedure (SPLUS Robust library) was used with the 90% efficiency setting as the default. When marginal differences appeared at this default setting, the models were refitted at

80% efficiency to see whether the significance improved or disappeared. Only robust marginally significant differences are reported here.

To explore the effects of periconceptual maternal HbA1c on fetal cardiac function in the FDM cohort we also used robust regression with gestation and HbA1c as independent predictors. The Mann-Whitney test was used to compare maternal demographics and neonatal outcomes between groups. Significance was taken at the $p < 0.05$ level.

RESULTS

Maternal and birth data

Maternal demographics and neonatal outcome are given as median (range) unless otherwise stated. There were no significant differences in maternal age (non-diabetic mothers 31 (19–36) v diabetic mothers 34 (24–40) years) or parity (1 (0–3)). Two non-diabetic and four diabetic mothers had a previous stillbirth. Gestational age at delivery of FDM was significantly less (37.5 (34–38) v 39 (34–41) weeks, $p = 0.02$) because of elective induction of labour at 38 weeks. Birth weight was similar (FDM 3219 (2204–4040) g v N 3350 (1904–4240) g) and neonatal condition was good with Apgar scores > 8 in all cases. No baby was polycythaemic (packed cell volume ≥ 0.65) or required neonatal intensive care. The median HbA1c was 6.7 (4.7 to 13.9) g% in the diabetic cohort. No differences were observed in the variables recorded in FDM between women with insulin and women with non-insulin dependent diabetes.

A previous study that used the same operators assessed interobserver variability for myocardial tissue velocities at 5–7% and maximum long axis amplitude of motion at 10–14% with lower intraobserver variability (at 3–4% and 6–11%, respectively); thus, measurements generally fell below the acceptable level of 12%.¹⁵

Relation of periconceptual HbA1c and cardiac function

Doppler flow and myocardial velocities were negatively related with HbA1c—that is, higher HbA1c values were associated with reduced myocardial and flow velocities. These were significant in four left sided or septal measures of long axis function: late lengthening velocities at the left free wall ($p < 0.0001$), shortening velocities in the septum ($p = 0.025$), and the maximum long axis amplitude of motion of the atrioventricular ring at the left free wall ($p = 0.063$) and in the septum ($p = 0.039$). Fetal myocardial thickness was positively but non-significantly related with HbA1c in all cases according to robust regression analysis.

Gestational changes in fetal long axis function

All variables, except late filling mitral and tricuspid A waves, were dependent on gestational age. FDM had increased absolute gestational age related values for most variables compared with controls. Table 1 shows the centiles for the variables studied with a comparison between FDM and N subdivided by gestational age before and after 30 weeks. The effects of gestational age and maternal diabetes were further assessed by using robust analysis of covariance.

Doppler velocimetry

Gestational related maturation differed significantly between FDM and N in the ratio between early and late mitral valve filling velocities (mitral valve E:A, $p = 0.036$) and the maximum velocity of flow through the pulmonary valve ($p = 0.04$). These differences were more pronounced after 30 weeks' gestation (table 2).

Table 1 Centiles for cardiac variables in a gestation related comparison of cardiac function in fetuses of diabetic (FDM) and non-diabetic mothers (normal controls; N)

		Centiles					
		Gestation <30 weeks			Gestation ≥30 weeks		
		Fetus type	25	50	75	25	50
Doppler velocimetry							
Mitral valve early filling (m/s)	N	0.264	0.299	0.339	0.329	0.366	0.410
	FDM	0.245	0.280	0.327	0.369	0.380	0.491
Mitral valve late filling (m/s)	N	0.424	0.474	0.520	0.436	0.503	0.547
	FDM	0.386	0.460	0.508	0.431	0.472	0.560
Mitral valve filling velocity ratio	N	0.573	0.635	0.705	0.704	0.748	0.811
	FDM	0.563	0.633	0.708	0.704	0.842	0.933
Tricuspid valve early filling (m/s)	N	0.300	0.354	0.395	0.365	0.400	0.441
	FDM	0.273	0.300	0.329	0.359	0.440	0.496
Tricuspid valve late filling (m/s)	N	0.480	0.511	0.579	0.489	0.559	0.608
	FDM	0.429	0.476	0.552	0.490	0.575	0.704
Tricuspid valve filling velocity ratio	N	0.605	0.667	0.727	0.667	0.729	0.803
	FDM	0.573	0.630	0.700	0.689	0.772	0.790
Aortic valve (maximum systolic) (m/s)	N	0.530	0.630	0.730	0.640	0.745	0.850
	FDM	0.471	0.530	0.589	0.660	0.732	0.984
Pulmonary valve (maximum systolic) (m/s)	N	0.422	0.490	0.559	0.516	0.573	0.643
	FDM	0.372	0.445	0.492	0.583	0.617	0.747
Myocardial velocities							
Left free wall early lengthening (m/s)	N	0.041	0.050	0.056	0.060	0.068	0.079
	FDM	0.041	0.047	0.056	0.072	0.080	0.083
Left free wall late lengthening (m/s)	N	0.075	0.090	0.108	0.089	0.098	0.119
	FDM	0.079	0.093	0.104	0.108	0.136	0.163
Left free wall shortening (m/s)	N	0.050	0.059	0.067	0.062	0.072	0.082
	FDM	0.045	0.050	0.060	0.076	0.086	0.113
Septal early lengthening (m/s)	N	0.041	0.045	0.050	0.049	0.057	0.065
	FDM	0.040	0.044	0.049	0.057	0.060	0.074
Septal late lengthening (m/s)	N	0.063	0.075	0.086	0.078	0.086	0.097
	FDM	0.080	0.084	0.097	0.079	0.095	0.121
Septal shortening (m/s)	N	0.040	0.050	0.057	0.054	0.063	0.073
	FDM	0.046	0.050	0.056	0.054	0.076	0.085
Right free wall early lengthening (m/s)	N	0.050	0.060	0.069	0.060	0.069	0.082
	FDM	0.046	0.051	0.061	0.072	0.087	0.099
Right free wall late lengthening (m/s)	N	0.092	0.110	0.124	0.104	0.119	0.142
	FDM	0.089	0.101	0.115	0.118	0.134	0.152
Right free wall shortening (m/s)	N	0.056	0.065	0.076	0.067	0.080	0.094
	FDM	0.061	0.064	0.079	0.074	0.092	0.107
Amplitude at atrioventricular ring							
Left free wall amplitude (mm)	N	0.349	0.405	0.463	0.498	0.570	0.660
	FDM	0.313	0.390	0.493	0.590	0.640	0.793
Septal amplitude (mm)	N	0.300	0.370	0.441	0.390	0.467	0.555
	FDM	0.278	0.351	0.448	0.405	0.620	0.694
Right free wall amplitude (mm)	N	0.478	0.567	0.655	0.700	0.791	0.936
	FDM	0.472	0.520	0.636	0.724	0.950	1.059
Myocardial measurements							
Left free wall (mm)	N	1.600	2.100	2.400	2.650	3.100	3.65
	FDM	1.700	1.800	2.700	3.100	3.700	4.68
Septum (mm)	N	1.800	2.100	2.400	2.925	3.300	3.60
	FDM	1.600	2.000	2.750	3.625	4.200	4.50
Right free wall (mm)	N	1.700	2.200	2.475	3.100	3.200	3.475
	FDM	1.550	2.000	2.700	3.350	3.800	4.350
Heart rate (beats/min)	N	140	146	151	132	140	146
	FDM	141	147	153	133	140	148

Myocardial velocities

The late lengthening myocardial velocities in the left ($p = 0.016$) and right ($p = 0.066$) free walls were significantly increased in FDM, although the maturational increases seen in the right decreased after 30 weeks (fig 1). Left free wall myocardial shortening velocities ($p = 0.008$) and the maximum long axis amplitude of motion in the left free wall ($p = 0.03$) and septum ($p = 0.041$) (fig 2, table 2) were significantly increased.

Cardiac wall thickness

Increased septal growth was evident in FDM from early gestation ($p < 0.0001$). The thickness of the right and left free wall increased during gestation in FDM but differences in the right were only marginally significant ($p = 0.091$) and in the left did not reach significance (table 2).

Fetal heart rate

Fetal heart rate fell by 0.7 beats/gestational week in controls and by 0.6 in FDM. Robust regression, incorporating gestational age and the effects of HbA1c into the model, showed no significant differences between the cohorts.

DISCUSSION

Findings and mechanisms

This study provides new information on cardiac function in FDM as shown by measures of long axis cardiac function that were not apparent previously.^{8 20 21} We have shown for the first time a relation between periconceptual diabetic control and myocardial velocities and cardiac growth in pregnancy in a cohort of reasonably well controlled diabetic mothers. Poorer periconceptual diabetic control was related to reduced myocardial velocities and increased myocardial thickness.

Table 2 Robust analysis of covariance: models* for cardiac variables showing a significant maturational difference in FDM

		Intercept	Intercept FDM	Slope N	Slope N30	Slope FDM	Slope FDM30	Error
Doppler velocimetry								
Mitral valve filling velocity ratio	Coeff	0.038	0.232	0.016†	-0.019†	-0.010	0.039†	0.089
Pulmonary valve (maximum systolic)	Coeff	0.130	0.069	0.013†	-0.017†	-0.005	0.044†	0.097
Myocardial velocities								
Left free wall late lengthening	Coeff	0.098†	-0.031	0.001†		0.002†		0.022
Left free wall shortening	Coeff	0.055†	-0.026†	0.001†		0.001†		0.012
Right free wall late lengthening	Coeff	0.154†	-0.072†	0.001†	0.002	0.003†	-0.009†	0.025
Amplitude at atrioventricular ring								
Left free wall	Coeff	0.135	-0.100	0.016†		0.006†		0.089
Septal amplitude	Coeff	-0.056	0.137	0.012†	-0.002	-0.007	0.039†	0.097
Myocardial measurements								
Right ventricular free wall	Coeff	0.013	-0.389	0.108†		0.028†		0.401
Septum	Coeff	0.195	-0.715†	0.114†		0.043†		0.388

*Parameters in the models: intercept (intercept of regression line with y axis (N group)); slope N (rate of change of variable with gestation (N group)); slope N30 (slope after 30 weeks, if different (N group)); intercept FDM (correction to intercept for FDM group); slope FDM (correction to slope N (for FDM group)); slope FDM30: (correction to slope N30 after 30 weeks, if different (for FDM)); error (robust estimate of scale for residuals that can be used to calculate 95% confidence limits); †p<0.05.

The long axis fibres function to maintain ejection fraction and, by increasing atrial volume in systole, augment ventricular output. Myocardial velocities and amplitude of motion correlate well with ejection fraction and are reduced with ventricular dilatation, myocardial ischaemia, or restrictive disease.

Figure 1 Comparison of gestational changes in diastole, showing late lengthening myocardial tissue velocities at the (A) right (TDI RA) and (B) left (TDI LA) atrioventricular ring in fetuses of mothers without (normal controls (N); circles) and with diabetes (FDM; triangles).

Glucose control was good in this motivated group of pregnant women and there was no macrosomia (> 90th centile for gestational age) compared with the 24% reported in previous studies, yet maturational differences in long axis cardiac function and growth were seen in FDM.²⁰

We have previously described normal age related changes in fetal long axis cardiac function and myocardial thickness.¹⁵ In the present study we report that absolute gestational age related values tend to be higher in FDM implying improved age related cardiac performance. Furthermore, FDM had increased amplitude of motion and myocardial velocities with coexisting hypertrophy, suggesting an adaptive response to hypertrophy rather than a cardiomyopathic process. This is in contrast to studies of ventricular hypertrophy in adults showing preservation of amplitude of motion but accompanying reduction in lengthening velocities.^{22–23} Moreover, in pathological ventricular hypertrophy in adults the lower early diastolic myocardial velocities are associated with augmented atrial systolic myocardial velocities. In this study atrial function was increased in diabetic pregnancies with higher absolute late lengthening myocardial velocities from early pregnancy with an increased gestational rise compared with controls. Both systolic and diastolic augmentation of myocardial velocities are seen in FDM suggesting that the hypertrophied ventricle shows adaptation which is not evident from isolated Doppler flow velocities and was interpreted as diastolic dysfunction in previous studies.^{24–30}

Although the mechanisms underlying improved cardiac performance in diabetic pregnancies are speculative, the cardiac hypertrophy observed is most likely due to fetal hyperinsulinaemia. Both improved myocardial velocities and hypertrophy are likely to be associated with the increased (but normal) gestational related flow velocities through the pulmonary valve rather than with true outflow tract obstruction, which is easily distinguished by Doppler velocities raised for gestational age and an abnormal wave-form.

Limitations

The diabetic mothers were not selected, as they were referred consecutively for fetal echocardiography. However, their good hospital attendance was a self selecting bias for those more motivated to attain optimal control during pregnancy. The practical issues of achieving an ideal fetal position from which to make long axis recordings were addressed in this study by allowing sufficient time for the examination (30 minutes) and by the experience of the operators. Fetal

Figure 2 (A) Comparison of gestational changes in systole showing left free wall myocardial shortening (TDI LS) velocities in N (circles) and FDM (triangles) cohorts. (B) Comparison of gestational changes in maximum long axis amplitude of motion of the left free wall and (C) in the septum in N (circles) and FDM (triangles) cohorts.

biometry, physiology, and outcome did not differ between the mothers with insulin dependent and with non-insulin dependent diabetes but, because of the relatively small numbers in each subanalysis, a type I error cannot be excluded. The infants did not undergo echocardiography after delivery, as they were all well and their assessment later in childhood will form the subject of a future publication. We did not assess maternal insulin concentrations at the time of

the study but relied on the fact that all patients were well and euglycaemic. Doppler and myocardial velocities are known to increase with fast heart rate but no significant differences in heart rate were found between our cohorts.

Conclusion

We have shown that periconceptual diabetic control appears to exert an influence on fetal cardiac performance and myocardial hypertrophy that is evident on measures of long axis function throughout gestation. Our results suggest that, unlike the pathophysiology observed in other types of ventricular hypertrophy, cardiac hypertrophy in FDM is accompanied by functional adaptation. We suggest the term "fetal diabetic cardiomyopathy" should be more accurately referred to as "adaptive hypertrophy" and that altered autonomic control may be a more likely explanation for the increased rate of stillbirth in diabetic pregnancies rather than primary cardiac dysfunction.

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IMAGES IN CARDIOLOGY

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Cardiogenic pulmonary oedema masquerading as a tumour mass

A 76-year-old man—past smoker with hypertension and history of anterior myocardial infarction treated 12 years ago by early balloon angioplasty of the left anterior descending coronary artery (LAD)—was referred to our attention for progressive exertional dyspnoea, cough and scanty mucosal expectoration. The previous angiographic examination performed three months ago for unstable angina revealed two moderate stenotic lesions of the LAD; the left ventricular ejection fraction was 52%. Soon after, asymptomatic new-onset atrial fibrillation was incidentally discovered by his physician prompting oral anticoagulation.

Physical examination disclosed abolished vesicular murmur with dullness to percussion over the right pulmonary base. There were no pulmonary crackles and no peripheral oedema. The patient was afebrile.

The chest radiograph demonstrated a dense round-shaped infiltrate in the right lower pulmonary lobe suggestive of a mass lesion (panel A). However, careful inspection of the

radiograph also revealed mild cardiomegaly, perihilar infiltrates and slurring of the costophrenic angles, all these elements pointing toward the possibility of a pulmonary oedema. Thus, the patient was initially started on oral diuretic treatment (furosemide 80 mg/day). Five days later, the symptoms resolved and the infiltrate on the chest radiograph disappeared (panel B).

Chest radiography has a prominent role in the diagnostic work-up for heart failure, but also possesses limitations. These images illustrate an atypical radiographic appearance of subacute cardiogenic pulmonary oedema masquerading as a pulmonary tumour and highlight the importance of minor details in the analysis of the chest radiograph.

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