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Cardiac function in gestational diabetes mellitus: A longitudinal study from fetal life to infancy

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Objective To determine whether cardiac functional and structural changes in fetuses of mothers with gestational diabetes mellitus (GDM) persist in the offspring beyond the neonatal period.

Design Longitudinal study.

Setting Fetal Medicine Unit in a UK teaching hospital.

Methods 73 women with GDM and 73 women with uncomplicated pregnancy were recruited and fetal cardiac scans were performed at 35–36 weeks' gestation. Repeat echocardiogram was performed in their offspring during infancy.

Main outcome measures Fetal and infant cardiac functional and structural changes.

Results Fetuses of mothers with GDM, compared with controls, had more globular right ventricles (sphericity index 0.7, interquartile range [IQR] 0.6/0.7 versus 0.6, IQR 0.5/0.6, $P < 0.001$) and reduced right global longitudinal systolic strain (−16.4, IQR −18.9/−15.3 versus −18.5, IQR −20.6/−16.8, $P = 0.001$) and left global longitudinal systolic strain (−20.1, IQR −22.5/−16.9 versus −21.3, IQR −23.5/−19.5), $P = 0.021$). In the GDM group, compared with controls, in infancy there was higher left ventricular E/e' (8.7, IQR 7.3/9.7 versus 7.9 IQR, 6.8/8.9 $P = 0.011$) and lower left ventricular global longitudinal systolic strain (−21.0, IQR −22.5/−19.4 versus −22.3, IQR −23.5/−20.7, $P = 0.001$) and tricuspid annular plane systolic excursion (13.8, IQR 12.7/16.1 versus 15.2, IQR 13.8/16.8, $P = 0.003$). These differences remained following multivariable analysis.

Conclusion Gestational diabetes mellitus is associated with alterations in fetal cardiac function and structure compared with controls and persistent cardiac changes in infancy.

Keywords Cardiac, diabetes, fetal, offspring.

Tweetable abstract Gestational diabetes mellitus, even when well controlled, is associated with fetal cardiac changes and these persist in infancy.

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Introduction

Epidemiological studies have shown that children of women with gestational diabetes mellitus (GDM) have increased risk of developing early cardiovascular disease in childhood and young adulthood.[1,2] Such a finding would be consistent with the developmental origin of cardiovascular disease according to which exposure to adverse maternal influences in utero may have long-term implications for the cardiovascular health of the offspring.[3] However the mechanisms responsible for this association remain speculative.

We and others have shown that GDM is associated with fetal cardiac morphological and functional changes which are mostly noted in the right ventricle, which is consistent with the dominance of the right heart late in gestation.[4–6] However, it remains unknown whether these cardiac changes in response to a relative mild and transient maternal disease persist in postnatal life and whether they identify the subgroup of children who are at increased long-term cardiovascular risk. To date, only a few studies have carried out postnatal assessment in offspring of mothers with GDM and these studies were confined to the neonatal period.[6,7]

The objective of this study is to determine whether cardiac functional and structural changes in fetuses of mothers with GDM persist in the offspring beyond the neonatal period.

Methods

Study population – study design

This is a prospective longitudinal study in which women with singleton pregnancies with GDM and an equal number of control women with uncomplicated pregnancies

were recruited at the time of their routine fetal ultrasound scan at 35–36 weeks' gestation. Details about the recruitment have been reported previously and the prenatal data from this study constitute part of data included in a previous publication from our group.[4] Mothers were asked to bring their children for a repeat cardiovascular assessment at around 6 months after delivery. Women provided written informed consent to participate in the Advanced Cardiovascular Imaging Study which received ethical approval (REC No 18/NI/0013, 2018, IRAS ID:237936). Patients had no involvement in the design of this study.

Maternal characteristics

We recorded information on maternal age, racial origin (white, black, Asian and mixed), medical history, parity (parous and nulliparous if there was no previous pregnancy with delivery at ≥24 weeks´ gestation). Weight and height were measured and body mass index calculated at their clinical visit. The diagnosis of GDM was made by performing the two-step approach at 24–28 weeks' gestation as recommended by NICE guidelines; a result from the 75-mg oral glucose tolerance test (OGTT) was considered to be positive if the fasting plasma glucose was ≥5.6 mmol/l or the 2-hour plasma glucose level was ≥7.8 mmol/l.[8] Management of GDM was based on target glucose ranges and insulin or metformin was used when dietary management failed. Glycaemic control was assessed by home self-monitoring and use of a glycometer for daily measurement of the fasting and 1-hour post-prandial capillary blood glucose level; the normal values for fasting blood glucose are 3.9–5.3 mmol/l and for 1-hour post-prandial blood glucose 5.0–7.8 mmol/l. The records of each patient were reviewed by an endocrinologist at the time of the clinical visit; based on the results, the method and dose of treatment were adjusted appropriately to ensure good glycaemic control. Postnatally, all patients with GDM were offered a fasting plasma glucose test 6–13 weeks after birth to exclude the presence of diabetes mellitus. Data on pregnancy outcome were collected from hospital delivery records or the general medical practitioners. Birthweight for gestational age was converted to a Z-score based on the Fetal Medicine Foundation fetal and neonatal weight chart.[9]

Fetal cardiac assessment

The methodology has been described in detail previously.[4] Essentially, fetal heart was assessed using Canon Aplio i900 machines equipped with a convex transducer (10C3 and i8CX1). Left and right ventricular sphericity indices were measured on images from an apical 4-chamber view at end-diastole. Left myocardial performance index was obtained using pulsed wave Doppler. Systolic functional assessment included tricuspid annular plane systolic excursion (TAPSE) using M-Mode, isovolumic contraction (IVCT) from Doppler waveforms of blood flow. Diastolic function was assessed with Doppler waveforms of blood flow and tissue Doppler. The E/A ratio, E/e' and isovolumic relaxation time (IVRT) were measured. Myocardial deformation of the left and right ventricle was measured in the apical 4-chamber view. All images were acquired at 100–160 frames/second and analysed using special speckle tracking software (Vitrea, Canon, Canon Medical Systems Europe BV, ZOETERMEER, The Netherlands) as previously described.[4] Global longitudinal strain (GLS) and diastolic peak strain rate (E and A), from the right and left ventricle, were measured.

Childhood cardiovascular assessment

Echocardiography was performed using a Canon Aplio i900 machine (PST-50BT neonatal transducer) according to the guidelines of the American Society of Echocardiography.[10] Measures which were assessed were indices of systolic and diastolic left ventricular function, including peak systolic mitral annular tissue velocity and midwall fractional shortening and peak mitral annular velocities in early diastole (e'), a measure of diastolic relaxation. The ratio of early diastolic transmitral flow velocity, E/e', was calculated. Left ventricular mass (LVM) measurements were normalised to body surface area as indexed LVM (LVMI). Speckle tracking analysis was also performed to calculate the left ventricular global longitudinal systolic function. Right ventricular systolic function was also assessed by tricuspid annular plane systolic excursion.

Statistical analysis

Data were assessed for normality. Cardiac measurements were compared between GDM and controls with the independent samples Student's *t*-test or the Mann–Whitney *U*-test and the Chi-square test for continuous and categorical variables, respectively. General linear regression models were used to assess the association between GDM and a range of echocardiographic parameters.

We used linear mixed models with two random effects (random intercept and random slope) and an unstructured variance-covariance matrix to compare changes in echocardiographic parameters before and after pregnancy for the GDM and control group. Cardiac parameters which were used as outcome variables included E/A, E/E', global longitudinal strain, and myocardial performance index. An interaction term (GDM yes/no*time interval between prenatal and postnatal assessment) was introduced in linear mixed models to evaluate the potential differential effect of GDM on changes in cardiac measurements before and after delivery. Analysis was further adjusted for a pre-specified set of confounders, including maternal age, race, time elapsed from delivery to postnatal visit and change in infant weight from birthweight. Statistical analysis was conducted with STATA package, version 13.1 (StataCorp,

College Station, TX, USA). We deemed statistical significance to be at $P < 0.05$. All tests were two-tailed.

Results

Participant characteristics

We studied 73 women with GDM and 73 women with uncomplicated pregnancy. Women with GDM, compared with controls, were older and were more of black racial origin, but there was no difference in weight or body mass index between the groups (Table 1). In the GDM group, 23 women were on a diet, 24 on metformin and 26 on insulin alone or insulin and metformin. Women with GDM delivered approximately 1 week earlier compared with controls. There was no difference in birthweight Z-score between the two groups. Eight children from the GDM group and nine from the controls had birthweights ≥90th centile. Six children had birthweights ≤10th centile (two from the control group and four from the GDM group).

Table 1. Characteristics of the study population

Characteristic	Controls *n* = 73	GDM *n* = 73	*P*-value
Age (years)	32.8 (4.5)	35.1 (5.5)	0.008
Gestational age at scan (weeks)	36.2 (0.4)	36.0 (0.5)	0.065
Gestational age at delivery (weeks)	40.1 (1.0)	39.2 (1.0)	<0.001
Weight (kg)	82.2 (12.7)	84.7 (14.6)	0.285
Height (cm)	165.5 (7.2)	164.6 (6.2)	0.423
Body mass index (kg/m^2)	30.1 (4.8)	31.2 (5.1)	0.163
Mean arterial pressure (MOM)	0.98 (0.1)	1.0 (0.1)	0.072
Racial origin			
White	57 (78)	37 (51)	0.007
Black	9 (12)	21 (29)	
Asian	5 (7)	12 (16)	
Mixed	2 (3)	3 (4)	
Parity (% multiparous)	49.3	60	0.244
Diabetic treatment			
Diet		23	
Metformin		24	
Insulin		10	
Combination		16	
HB1Ac		5.5 (0.4)	
Birthweight (g)	3580 (476)	3396.5 (424)	0.015
Birthweight (Z-score)	0.4 (−0.3/0.7)	0.01 (−0.4/0.7)	0.357

Values given as mean (standard deviation) or median (interquartile range) and *n* (%).
GDM, gestational diabetes mellitus.

Comparison of fetal cardiac parameters in GDM and controls

Fetal heart rate was similar in GDM and controls. Fetuses of mothers with GDM, compared with controls, had more globular right ventricles (sphericity index 0.7, interquartile range [IQR] 0.6–0.7 versus 0.6, IQR 0.5–0.6, $P < 0.001$) and reduced right and left ventricular systolic function (Table S1) but there was no significant difference in diastolic functional indices (Table 2).

Comparison of postnatal cardiac indices in GDM and controls

Postnatal assessment was carried out at 7 ± 2.3 months in the offspring of women with GDM and at 11 ± 2.7 months in the controls. Infant weight and height were lower in women with GDM than in controls. In the GDM group, compared with controls, there was higher left ventricular E/e' (8.7, IQR 7.3/9.7 versus 7.9, IQR, 6.8/8.9, $P = 0.011$) and left ventricular global longitudinal systolic strain (−21.0, IQR −22.5/−19.4 versus −22.3, IQR −23.5/−20.7, $P = 0.001$) and lower tricuspid annular plane systolic excursion (13.8, IQR 12.7/16.1 versus 15.2, IQR 13.8/16.8, $P = 0.003$) (Table 3, Figure 1a,b). These differences remained following multivariable analysis (Table 2). There was no significant interaction between GDM and time interval from fetal cardiac assessment. There was no difference in postnatal cardiac functional and structural indices within the GDM group according to diabetic treatment in pregnancy (Table S2).

Discussion

Main findings

In this longitudinal study we demonstrated that fetuses of mothers with GDM, compared with controls, had more globular hearts and reduced biventricular systolic function. Second, diastolic and systolic ventricular function remained reduced beyond the neonatal period. Third, these associations were not modified by maternal diabetic treatment. These findings suggest that maternal GDM may have a prolonged adverse influence on the cardiovascular health of the offspring.

Strengths and limitations

Strengths of our study include longitudinal cardiovascular assessment in pregnancies affected only by GDM without the confounding effect of pregestational diabetes, which could potentially affect early embryonic development and alter cardiac morphogenesis and placental development. Secondly, by performing detailed cardiac functional evaluation from fetal to postnatal life, we were able to detect subtle fetal cardiac functional changes and track these through

Table 2. Differences in fetal–postnatal cardiac indices in gestational diabetes mellitus and controls

Variable	Difference between GDM and Controls Fetal		Difference between GDM and Controls Postnatal		Difference between fetal–postnatal Controls		Difference between fetal-postnatal GDM		Interaction [group*time]	
	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value
Diastolic indices										
E/e'	−1.1 (−2.1/−0.2)	0.0182	0.2 (−0.5/0.8)	0.603	−2.1 (−2.8/−1.3)	<0.001	−0.8 (−1.5/0.01)	0.052	1.3 (0.3/2.4)	0.0144
Mitral valve early diastolic Doppler velocity (E)	−2.0 (−5.5/1.5)	0.268	−1.2 (−6.3/3.8)	0.637	49.4 (45/53.7)	<0.001	50.1 (45.9/54.4)	<0.001	0.8 (−5.2/6.7)	0.799
Mitral valve late diastolic Doppler velocity (A)	−0.5 (−4.8/3.9)	0.839	7.2 (0.8/13.5)	0.027	13.3 (7.9/18.7)	<0.001	20.9 (15.6/26.2)	<0.001	7.6 (0.2/15)	0.045
E/A	−0.01 (−.0.1/0.1)	0.693	−0.2 (−0.3/0.01)	0.068	0.6 (0.5/0.7)	<0.001	0.5 (0.4/0.6)	<0.001	−0.1 (−0.3/0.03)	0.099
Isovolumic relaxation time (msec)	0.6 (−3.3/4.5)	0.767	7.6 (3.6/11.7)	<0.001	−14 (−17.6/−10.4)	<0.001	−7.0 (−10.6/−3.3)	0.00016	7.0 (2.0/12)	0.006
Systolic indices										
Isovolumic contraction time (msec)	−0.3 (−3.9/3.4)	0.886	−5.3 (−10.5/−0.1)	0.047	5.7 (1.5/9.9)	0.00787	0.7 (−3.5/4.9)	0.743	−5.01 (−10.8/0.8)	0.089
Myocardial performance index	0.02 (−0.03/0.1)	0.415	0.04 (0.0/0.1)	0.055	−0.2 (−0.2/−0.1)	<0.001	−0.2 (−0.2/−0.1)	<0.001	0.02 (−0.04/0.07)	0.491
Tricuspid annular plane systolic excursion (mm)	0.00 (−0.6/0.6)	0.988	−1.2 (−2.0/−0.3)	0.008	7.5 (6.8/8.2)	<0.001	6.3 (5.6/7.0)	<0.001	−1.2 (−2.2/−0.2)	0.021
Left ventricular global longitudinal systolic function (%)	1.6 (0.3/2.9)	0.018	1.3 (0.4/2.2)	0.006	−1.0 (−2.1/0.2)	0.089	−1.3 (−2.5/−0.2)	0.021	−0.4 (−1.9/1.2)	0.659
Left ventricular ejection fraction (%)	−3.9 (−8.0/0.2)	0.059	2.5 (0.5/4.5)	0.013	−7.0 (−9.9/−4.1)	<0.001	−0.6 (−3.6/2.3)	0.673	6.4 (2.3/10.5)	0.002

Values are adjusted for maternal age, race, gestational age, difference in child's weight from birth, postnatal height, time elapsed from birth to postnatal visit and changes in heart rate.
Analysis was performed using linear mixed models.
GDM, gestational diabetes mellitus.

Table 3. Postnatal comparison of cardiac parameters in controls and gestational diabetes mellitus

Variable	Controls	GDM	*P*-value
Weight (kg)	9.2 (1.1)	7.9 (1.4)	<0.001
Height (cm)	72.4 (3.1)	67.4 (4.8)	<0.001
Interval for postnatal examination (months)	11 (10/12.5)	7 (5/9)	<0.001
Heart rate (beats/min)	131 (18)	131 (20)	0.918
Diastolic indices			
Mitral valve early diastolic Doppler velocity (E)	46.6 (39.2/52.7)	44.4 (38.1)	0.794
Mitral valve late diastolic Doppler velocity (A)	55.8 (47.6/63.7)	54.2 (47.1/60.2)	0.067
E/A	1.4 (1.2/1.8)	1.3 (1.1/1.4)	0.056
E/e'	7.9 (6.8/8.9)	8.7 (7.3/9.7)	0.011
Isovolumic relaxation time (msec)	38 (35/47)	45 (38/55)	0.001
Systolic indices			
Isovolumic contraction time (msec)	45 (35/53)	38 (31/48)	0.015
Myocardial performance index	0.4 (0.3/0.5)	0.4 (0.3/0.5)	0.083
Left ventricular ejection fraction (%)	69.4 (64.3/72.9)	67.2 (56.6/72.2)	0.082
Left ventricular endocardial global longitudinal strain (%)	−22.3 (−23.5/−20.7)	−21.0 (−22.5/−19.4)	0.001
Tricuspid annular plane systolic excursion (mm)	15.2 (13.8/16.8)	13.8 (12.7/16.1)	0.003
Structural cardiac markers			
Left ventricular mass indexed to body surface area	150.3 (129.3/163.1)	153.1 (124.9/176.5)	0.227
Left ventricular interventricular septal thickness (mm)	4.8 (4.2/5.2)	4.2 (3.7/4.8)	0.039
Left ventricular posterior wall thickness (mm)	4.3 (3.9/4.8)	4.5 (4.0/5.0)	0.282

Measurements are presented as mean (standard deviation) or median (interquartile range). *P*-values are derived from the parametric independent *t*-test, non-parametric Mann–Whitney *U*-test.
GDM, gestational diabetes mellitus.

the first year of life. Cardiac measurements were performed using advanced echocardiographic modalities and following strict imaging protocols. Thirdly, trained Fellows blinded to maternal characteristics performed the analysis to avoid any bias in the results. The main limitation of the study is that fetal speckle tracking analysis was performed using one analysis platform and as such the measurements may not be generalisable to those generated by other software.[11] Another limitation was that postnatal cardiac assessment was performed 4 months earlier for the GDM than for the control group; however, we took this discrepancy into account in the multivariable analysis. Finally, no fasting maternal glucose levels were available, thus the relation between glucose and fetal or postnatal offspring cardiac function could not be established.

Interpretation of results and comparison with existing literature

A number of studies have demonstrated that in utero exposure to hyperglycaemia can adversely affect the fetal heart.[4,5,6] Consistent with this, in our study, we showed that fetuses exposed to GDM have altered heart morphology with more globular right ventricles compared with that seen in controls. By using a variety of echocardiographic modalities we showed that right and left longitudinal myocardial deformation was reduced in fetuses exposed to GDM compared with controls but that diastolic indices were similar between the two groups when analysis was adjusted for differences in maternal characteristics, estimated fetal weight and heart rate. Similar results have been reported in some studies,[12,13,14] but not in all.[15] For example, in a combined group of 76 women with pregestational diabetes and GDM Miranda *et al.* demonstrated biventricular diastolic dysfunction in their fetuses.[5] Although measurements of diastolic function commonly precede systolic functional changes, these are more difficult to assess accurately in fetal life. In our study, we used speckle tracking analysis to assess the rate of change in the right and left myocardial deformation as well as conventional and tissue Doppler imaging. We followed a strict protocol for image acquisition using high frames per rate as per recent guidelines[16] and performed the analysis without compromising our temporal resolution. It is possible therefore that the noted discrepancies are due to differences in the study population, i.e. inclusion on pregestational diabetic women in Miranda et al.'s study as well as differences in the software used for speckle tracking analysis.[5]

The influence of GDM, however, might not be limited to fetal life, as observational data suggest that maternal diabetes before or during pregnancy is associated with an increased rate of early onset cardiovascular disease from childhood to adulthood.[2,3] To date, only a few studies have assessed

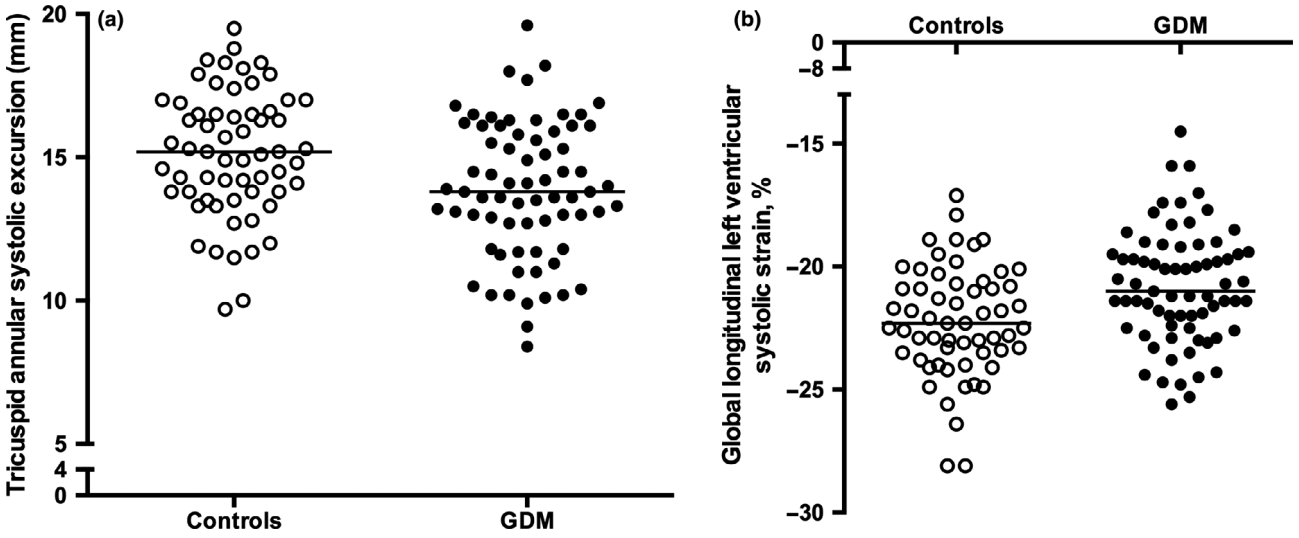

Figure 1. Comparison of cardiac function in offspring of mothers with uncomplicated pregnancy (controls) and those with gestational diabetes mellitus (GDM). (a) Tricuspid annular systolic excursion was lower in offspring of GDM mothers than controls ($P = 0.003$). Middle lines denote median value. (b) Global longitudinal left ventricular systolic strain was higher compared with controls ($P = 0.001$), denoting less myocardial deformation. Middle lines denote median value.

offspring of diabetic mothers spanning from fetal to neonatal life and these have found conflicting results about the presence of persistent cardiac changes.[6,7,17] For instance, Patey *et al.*, in a group of 21 neonates of mothers with pregestational diabetes or GDM, compared with controls, demonstrated persistent alterations in left ventricular chamber geometry in the perinatal period[6] and Zablah *et al.*, in a retrospective study, reported that 75 neonates who were exposed to pregestational diabetes or GDM, compared with controls, had decreased left ventricular systolic and diastolic function in the first week of life.[18] In contrast, in 50 newborns of mothers with pregestational diabetes or GDM, Mehta *et al*. documented that early cardiac changes such as reduced diastolic ventricular function and myocardial hypertrophy are transient and resolve in the first month of life.[7] However, cardiac assessment in the neonatal period is also affected by changes in loading conditions, which relate to closure of cardiac shunts and the change from a parallel circulation to one in series as part of the physiological adaptation to postnatal life; this may obscure small differences from becoming apparent in offspring of women with GDM compared with controls. To minimise this confounding effect, we elected in our study to study children after the first few months of life. We showed that infants exposed prenatally to GDM have increased diastolic functional indices and reduced biventricular systolic function compared with controls, whereas no differences in left ventricular mass were noted. Cardiac changes were subtle and were seen in both ventricles; their clinical significance remains unknown. Thus, further studies are needed to establish whether the noted cardiac functional changes persist in childhood and contribute to the reported increased cardiovascular disease risk noted in offspring of diabetic mothers.

In the management of GDM, insulin therapy is often added when diet or oral pharmacological treatments fail to establish good glycaemic control. Although insulin may have growth-stimulating effects on the myocardium[19,20] it does not cross the placenta and is unlikely to have a direct effect on the fetal heart. However, from different hypoglycaemic treatments, it is well described that metformin crosses the placenta and concerns were raised regarding long-term programming effects on fetal metabolism as well as its impact on fetal heart with sustained effects in childhood.[21,22] In our study, there was no difference in cardiac indices either in fetal or in postnatal life between the treatment groups; thus our results would not support such a hypothesis.

The mechanisms that link GDM with changes in offspring cardiac function remain speculative. Glucose crosses the placenta and fetal hyperglycaemia leads to insulin production, increase in hepatic glucose uptake and glycogen synthesis in the fetus.[23] These metabolic changes are associated with glycogen uptake from myocardial cells and development of myocardial hypertrophy, which may vary in severity depending on glycaemic control during pregnancy. In animal studies, intrauterine exposure to hyperglycaemia can induce fetal myocardial hyperplasia and myocardial remodelling, which can account for differences in morphology and endocardial deformation noted between fetuses of mothers with GDM and controls. In addition, experimental studies have indicated that fetuses of mothers with GDM may experience hypoxaemia, which can lead to myocardial cell damage, myocyte death and impaired ventricular function.[24–26]

Finally, depending on the timing of in utero exposure to the hyperglycaemic stimulus, changes to critical developmental pathways can occur as a result of altered gene expression.[27]

Conclusion

This study demonstrates that GDM is associated with reduction in fetal cardiac function and that cardiac functional changes that persist in infancy. Further studies with longer follow up are needed to determine whether the fetuses and children of women with GDM that demonstrate such cardiac changes are the ones who will be at increased long-term cardiovascular risk.

Disclosure of interests

None declared. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

Jesica Aguilera, Janina Semmler, Santiago Anzoategui and Huijing Zhang were involved in patient recruitment data collection, data analysis and critical review of the manuscript. Kypros H. Nicolaides and Marietta Charakida were involved in study design, data analysis and writing of the manuscript.

Details of ethics approval

Advanced Cardiovascular Imaging Study (REC No 18/NI/0013, 2018, IRAS ID:237936).

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Comparison of fetal cardiac parameters in gestational diabetes mellitus and controls at 35–36 weeks' gestation.

Table S2. Infant cardiac functional indices according to diabetic treatment. ■

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