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

Marietta Charakida[1], Kypros Nicolaides[2], Janina Semmler[3], Jesica Aguilera[2], Huijing Zhang[1], and Santiago Anzoatgui[1]

[1]King's College London Faculty of Life Sciences and Medicine
[2]Fetal Medicine Institute
[3]King's College Hospital

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Abstract

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 Population: 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 to controls, had more globular right ventricles (sphericity index 0.7, IQR 0.6/0.7 vs 0.6, IQR 0.5/ 0.6, p<0.001) and reduced right global longitudinal systolic strain (-16.4, IQR -18.9/-15.3 vs -18.5, IQR -20.6/-16.8, p=0.001) and left global longitudinal systolic strain (-20.1, IQR -22.5/-16.9 vs -21.3, IQR -23.5/-19.5), p=0.021). In the GDM group, compared to controls, in infancy there was higher left ventricular E/e' (8.7, IQR 7.3/9.7 vs 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 vs -22.3, IQR -23.5/-20.7, p=0.001) and tricuspid annular plane systolic excursion (13.8, IQR 12.7/16.1 vs 15.2, IQR 13.8/16.8, p=0.003). These differences remained following multivariable analysis. Conclusion: GDM is associated with alterations in fetal cardiac function and structure compared to controls and persistent cardiac changes in infancy.

INTRODUCTION

Epidemiological studies have shown that children of women with gestational diabetes mellitus (GDM) have increased risk to develop early cardiovascular disease in childhood and young adulthood (1, 2). 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 (3-5). However, it remains unknown whether these cardiac changes persist in postnatal life and they identify the subgroup of children who are at increased long-term cardiovascular risk. To date only few studies have carried out postnatal assessment in offspring of mothers with GDM but these studies were confined to the neonatal period (5, 6).

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. Women with prior known cardiovascular disease, pregestational diabetes, gestational or pre-existing hypertensive disorder, fetal structural defects or chromosomal abnormalities were not eligible to participate in this study. Mothers were asked to bring their children for a repeat cardiovascular assessment at around six 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, IRAS ID:237936). The prenatal data from this study constitute part of data included in a previous publication from our group (3).

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 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/ (7). Management of GDM was based on target glucose ranges and insulin or metformin were used when dietary management failed. Glycemic 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 are 5.0-7.8 mmol/L. The records of each patient were reviewed by an endocrinologist at the time of the clinical visit and based on the results the method and dose of treatment were adjusted appropriately to ensure good glycemic 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. Birth weight for gestational age was converted to a Z-score based on the Fetal Medicine Foundation fetal and neonatal weight chart (8).

Fetal cardiac assessment

The methodology was described in detail previously (2, 3). 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. Measurements included E/A ratio, E/e', isovolumic relaxation time (IVRT). Myocardial deformation of the left and right ventricle was measured in the apical 4-chamber view. All images were acquired at 100-160 frames per second as per recent guidelines (14) and analysed using special speckle tracking software (Vitrea, Canon) as previously described (3). Global longitudinal strain (GLS) and diastolic peak strain rate (E and A), from the right and left ventricle, were measured.

Childhood cardiovascular assessment

Conventional and tissue Doppler echocardiography was performed using a Canon Aplio i900 machine (PST-50BT neonatal transducer) according to the guidelines of the American Society of Echocardiography (9). 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 normalized to body surface area as indexed LVM (LVMI). Speckle tracking analysis was also performed to calculated left ventricular global longitudinal systolic function. Right ventricular systolic function was also assessed by tricuspid annular plane systolic excursion.

Statistical analysis

Normally distributed continuous variables are presented as mean (+- standard deviation) and variables not following normal distribution as median (25^{th} - 75^{th} percentile). Nominal variables are summarized as counts and absolute percentages. Distribution of continuous variables was graphically assessed by histograms and quantile-quantile plots. 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-squared 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.

To facilitate the comparison of changes in echocardiographic parameters before and after pregnancy for the two groups of interest, we used linear mixed models with two random effects (random intercept and random slope) and an unstructured variance-covariance matrix. 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, Texas USA). We deemed statistical significance at $p < 0.05$. All tests were 2-tailed.

RESULTS

Participant characteristics

We studied 73 women with GDM and 73 women with uncomplicated pregnancy. Women with GDM, compared to controls, were older and were more of Black racial origin but there was no difference in weight and body mass index between the groups (Table 1). In the GDM group, 23 women were on diet, 24 on metformin and 26 were on insulin alone or insulin and metformin. Women with GDM delivered approximately one week earlier compared to controls. There was no difference in birthweight z score between the two groups.

Comparison of fetal cardiac parameters in GDM and controls

Fetal heart rate was similar in GDM and controls. Fetuses of mothers with GDM, compared to controls, had more globular right ventricles (sphericity index 0.7, IQR 0.6 - 0.7 vs 0.6, IQR 0.5 - 0.6, $p<0.001$) and reduced right and left ventricular systolic function (Table 2), but, there was no significant difference in diastolic functional indices (Table 3).

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 GDM compared to controls. In the GDM group, compared to controls, there was higher left ventricular E/e' (8.7, IQR 7.3/9.7 vs 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 vs -22.3, IQR -23.5/-20.7, p=0.001) and tricuspid annular plane systolic excursion (13.8, IQR 12.7/16.1 vs 15.2, IQR 13.8/16.8, p=0.003) (Table 4). These differences remained following multivariable analysis (Table 3). 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 (Supplementary Table 1)

DISCUSSION

Main findings

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

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 (3, 4, 10). Consistent with this, in our study, we showed that fetuses exposed to GDM have altered heart morphology with more globular hearts compared to that seen in controls and the difference in shape were driven by changes in the right ventricle. By using a variety of echocardiographic modalities we also showed that fetuses of mothers with GDM, compared to controls, have subtle functional cardiac changes which can be identified only by using more advanced imaging modalities. Right and left longitudinal myocardial deformation were reduced in fetuses exposed to GDM compared to controls but 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 before, in some studies (11, 12) but not in all (13). For example, Miranda *et al* in a combined group of 76 women with pregestational diabetes and GDM demonstrated biventricular diastolic dysfunction in their fetuses (4). Although measurements of diastolic function commonly precede systolic functional changes, these are more difficult to accurately assess 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(14) 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 ie inclusion on pregestational diabetic women in Miranda's study as well as differences in the software used for speckle tracking analysis (15).

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 increased rate of early onset cardiovascular disease from childhood to adulthood (1,2). To date, only few studies have assessed offspring of diabetic mothers spanning from fetal to neonatal life and provided conflicting results about the presence of persistent cardiac changes (6, 16, 17). For instance, Patey*et al,* in a group of 21 neonates of mothers with pregestational diabetes or GDM, compared to controls, demonstrated persistent alterations in left ventricular chamber geometry in the perinatal period (5) and Zablah*et al,* in a retrospective study reported that 75 neonates who were exposed to pregestational diabetes or GDM, compared to controls, had decreased left ventricular systolic and diastolic function in the first week of life (17). In contrast, Mehta *et al,* documented in 50 newborns of mothers with pregestational diabetes or GDM, that early cardiac changes such as reduced diastolic ventricular function and myocardial hypertrophy are transient and resolve in the first month of life (6). 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 and this may obscure small differences to become apparent in offspring of women with GDM compared to controls. Therefore, to minimize this confounding effect, in our study we elected 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 to controls, whereas no differences in left ventricular mass was noted. Cardiac changes were seen in both ventricles but more apparent in the left ventricle and remained after accounting for differences in maternal characteristics, infant weight gain and interval of cardiac assessment since birth. However, it remains to be established 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 glycemic control. Although insulin may have growth stimulating effects on the myocardium (18) this does not cross the placenta and is unlikely to affect directly the fetal heart (19). 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 (20, 21). In our study, there was no difference in cardiac indices both in fetal or postnatal life between the treatment groups thus our results would not support such a hypothesis.

Possible pathophysiological mechanisms

Few studies have provided mechanistic insights about the link between maternal diabetes and increased cardiovascular disease in the offspring. It is well established that glucose crosses the placenta and fetal hyperglycaemia leads to insulin production, increase in hepatic glucose uptake and glycogen synthesis in the fetus (22). 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. Animal studies have also shown that 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 (23-25). 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 (26).

Strengths and limitations

Strengths of our study include, first, 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. Second, 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 the first year of life. Cardiac measurements were performed using advanced echocardiographic modalities and following strict imaging protocols. Third, trained fellows blinded to maternal characteristics performed 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 generalizable to those generated by other software(15). Another limitation was that although we aimed to have the same interval after delivery for postnatal cardiac assessment for the GDM and controls, this was not achieved and there was a mean difference of 4 months between the groups; however, we accounted for this discrepancy in the multivariable analysis.

Conclusion

The study demonstrates that GDM is associated with reduction in fetal cardiac function and that cardiac functional changes 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.

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