Impact of gestational diabetes mellitus on fetal cardiac morphology and function: cohort comparison of second- and third-trimester fetuses

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Contribution

What are the novel findings of this work

1. In fetuses of GDM mothers, compared to controls, there is reduction in right ventricular function and this response is not aggravated with increasing gestational age.
2. In fetuses of GDM mothers, compared to controls, the heart is more globular but this difference is significant only >32 weeks' gestation.

What are the clinical implications of this work

Fetuses of mothers with GDM, compared to controls, have reduced right ventricular systolic function, but the findings are subtle and the long term clinical consequences remain unclear.

ABSTRACT

Objective: To assess differences in morphology and cardiac function in fetuses of mothers with gestational diabetes mellitus (GDM) compared to controls and to assess whether in women with GDM fetal cardiac changes are accentuated with advancing gestational age.

Methods: We studied 112 women with GDM and 224 women with uncomplicated pregnancy at 24-40 weeks' gestation. In all fetuses, a standard four chamber oblique view was obtained and offline speckle tracking analysis was performed to measure right and left global endocardial longitudinal strain and tricuspid and mitral annular plane systolic excursion. Global sphericity index was also calculated. Analysis between GDM fetuses and controls was compared between two gestational age time periods of 24^{+0} - 32^{+0} and 32^{+1}- 40^{+1} weeks.

Results: At 24^{+0}-32^{+0} weeks, we phenotyped 43 fetuses from mothers with GDM and 71 from uncomplicated pregnancy and at 32^{+1}- 40^{+1} weeks 69 fetuses from mothers with GDM and 153 from women with uncomplicated pregnancy. In fetuses of mothers with GDM, compared to controls, right ventricular functional indices were consistently lower both at 24^{+0}-32^{+0} weeks (mean adjusted reduction in right ventricular deformation 0.7, 95% CI 0.3, 1.1) and at 32^{+1}-40^{+1} weeks (mean adjusted reduction in deformation 0.9, 95% CI 0.6, 1.1). Fetal left ventricular global ventricular function was similar in GDM and controls with the exception of the contractility of the left ventricular basal segment which was reduced. Global sphericity index was reduced in GDM only at 32^{+1}-40^{+1} weeks (mean adjusted reduction 0.4, 95% CI -0.7, -0.1).

Conclusion: The offspring of women with GDM are at high risk for development of cardiovascular disease in childhood and early adulthood. Our study demonstrates that GDM is associated with reduction mainly in fetal right ventricular function compared to controls and this response is not exaggerated with increasing gestational age. Further studies are needed to determine whether the fetuses with the observed alterations in cardiac function are the ones at highest risk for subsequent development cardiovascular disease.

INTRODUCTION

Animal studies have demonstrated that exposure to a hyperglycemic environment during pregnancy is associated with fetal myocardial remodeling; increased glucose can induce cardiomyocyte hyperplasia and alterations in myocardial architecture and metabolism[1]. Consistent with these observations, our group and others have shown that fetuses of mothers with gestational diabetes mellitus (GDM) have more globular hearts with increase in right and left ventricular sphericity indices and deformation analysis revealed subclinical systolic cardiac dysfunction which is more pronounced in the right ventricle[2,3]. However, these studies were carried out mainly in the third trimester of pregnancy and it is uncertain if the fetal cardiac changes are observed earlier in pregnancy and if they are progressive with advancing gestational age.

The objective of this cross-sectional study is to assess differences in morphology and cardiac function in fetuses of mothers with GDM compared to controls and to determine whether in GDM fetal cardiac changes are accentuated with advancing gestational age.

METHODS

Study population

This was a cross sectional study of singleton pregnancies at 24-40 weeks' gestation examined in the Fetal Medicine Units of Kings' College Hospital, London, UK and Hospital Clínico Universitario Virgen de la Arrixaca Murcia, Spain, between November 2018 and September 2019. We examined women attending for routine antenatal care and during the study period we invited women with GDM to participate in the research study. We excluded women with major fetal abnormalities and maternal chronic diseases, such as chronic hypertension. In about 7% of cases there was suboptimal four chamber view of the fetal heart for speckle tracking analysis and these cases were also excluded from the study; reasons for suboptimal imaging included fetal movements, inability to obtain the four chamber view in the appropriate angle of insonation or poor acoustic windows due to maternal habitus and suboptimal fetal lie. For every woman with GDM we recruited two controls as follows: in both centres there is a routine scan at 20-22 weeks' gestation and at this visit we invited volunteers to return for a scan at 24-30 weeks, second, at Kings' College Hospital there is a routine scan at 35-37 weeks and at Hospital Clínico Universitario Virgen de la Arrixaca Murcia there are two routine third trimester scans one at 30-35 weeks and another at 39-40 weeks.

The diagnosis of GDM was made at 24-28 weeks' gestation. At King's College Hospital the diagnosis was based on the results from the 75 grams oral glucose tolerance test which 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[4]. At Hospital Clínico Universitario Virgen de la Arrixaca Murcia diagnosis of GDM was made by the use of two-step screening; first, the 50 grams glucose test was carried out and if this was positive (1-hour glucose level ≥7.8 mmol/L), the 100 grams oral glucose test was carried out and this was considered to be positive if two or more glucose concentrations were increased (fasting glucose ≥5.8 mmol/L, 1-hour ≥10.6 mmol/L, 2-hour ≥9.2 mmol/L, 3-hour ≥8.1 mmol/L). Two fasting plasma glucose levels ≥7.0 mmol/L on different days or a random glycemia ≥11.1 mmol/L would also be sufficient to confirm the diagnosis of GDM without the need for an oral glucose tolerance test.

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. All participants signed informed consent for the study which was approved by REC in each centre (REC No 18/NI/0013, IRAS ID:237936 and in Murcia (CI:2018-11-5-HCUVA)

Maternal characteristics

We recorded information on maternal age, racial origin (White, Black, Asian and mixed), method of conception (natural or assisted by *in-vitro* fertilization or ovulation induction drugs), cigarette smoking during pregnancy, and parity (parous and nulliparous if there was no previous pregnancy with delivery at ≥24 weeks´ gestation). At the clinic visit we measured weight, height and calculated body mass index.

Fetal cardiac functional analysis

Prenatal ultrasonographic examination was performed to estimate fetal weight from measurements of fetal head circumference, abdominal circumference and femur length (EPIQ ELITE Philips, Bothell, WA, USA),[5] and the values were converted to z scores based on the Fetal Medicine Foundation fetal weight chart.[6]

Fetal cardiac functional measurements were performed at an “apex oblique” projection with an angulation of at least 30° (EPIQ ELITE-Philips C5-1 or C9- transducers, Philips, Bothell, WA, USA). A clip of 3-5 seconds with a minimum of 100 frames per second was obtained for each case as per recent guidelines[7]. To achieve high frames per rate, the field of view was

optimized by reducing sector width and depth and appropriate use of zoom. The clips were exported in the original frame per rates in an external hard drive and then transferred for offline analysis using fetal 2D Cardiac Performance Analysis 1.4, TomTec Imaging Systems, Gmbh, Munich, Germany.

The results of the speckle tracking analysis included the values for global right and left longitudinal peak endocardial systolic strain (Figure 1). The software provides a semi-automated contour detection for the end-systolic contour, which is triggered by placing three reference markers at the septal annulus, the lateral annulus and the apex. Starting from the initial end-systolic contour, the software uses an established speckle tracking algorithm to automatically detect the endocardial borders on all frames of the selected cardiac cycle. For the analysis of individual segments, the left and right ventricle were divided into 24 segments[8]: 8 basal segments, 8 middle segments and 8 apical segments; using a calculator developed for this purpose. When comparing two strain values in this analysis, we refer to the more negative number as higher strain as it represents increased deformation and to the less negative values as lower strain. To calculate transverse shortening fraction, we used the information derived from the raw data to measure distances of a specific point at end diastole and end systole, based on pixels information, obtaining the 24-Segments described previously by Devore[7]. A conversion factor, obtained from the software, was applied to get the measurements in millimetres. For each of these 24 segments we computed Transverse Shortening Fraction using the following formula: [(ED distance - ES distance)/ED distance] * 100. Finally, by computing the Shortening Fraction for each of the 24 segments, we calculated the mean value for the segments 1-8, 9-16 and 17-24, which represent the base, medial and apical portion, respectively.

Longitudinal right and left ventricular function were also assessed by calculating tricuspid and mitral annular plane systolic excursion with Speckle Tracking and the results were automatically calculated by the software. All the fetal speckle tracking analysis was performed by one fellow (LY) who worked consecutively in the two participating centers and was blinded to maternal characteristics and GDM status.

Global Sphericity Index was calculated as the ratio of basal-apical length/transverse distance[3]. The difference from end diastolic and end systolic area of the left and right ventricle was calculated to measure fractional area change (FAC).

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. Maternal and fetal characteristics as well as fetal 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.

To facilitate the comparison of changes in echocardiographic parameters with advancing gestation, we divided the 16 weeks of study period into two 8-week intervals, 24^{+0} - 32^{+0} and 32^{+1} - 40^{+1} weeks' gestation. Thus, we classified our study population into four discrete groups: GDM at 24^{+0} - 32^{+0} weeks, GDM at 32^{+1}- 40^{+1} weeks, normoglycemic at 24^{+0} - 32^{+0} weeks and normoglycemic at 32^{+1}- 40 weeks. Subsequently, we used linear regression models to assess the association between a range of fetal echocardiographic parameters and the combination of GDM and gestational age. An interaction term [GDM yes/no*gestational age] was introduced in the regression models to evaluate the potential differential effect of GDM on changes in fetal cardiac measurements across advancing gestation. In addition, we examined pairwise linear contrasts from respective fitted regression models to estimate differences in fetal cardiac markers between GDM status (GDM versus control pregnancies separately at 24^{+0} - 32^{+0} and at 32^{+1} - 40^{+1}) and between early and late gestation within the GDM or control group. Given that pairwise comparisons for each cardiac fetal parameter were based on a single fitted regression model, we did not perform adjustment for multiple comparisons. To ensure normality assumptions in regression analyses, we employed the inverse ranking normalization for all continuous variables used as dependent variables in respective models[9]. Analysis was further adjusted for a pre-specified set of confounders, including maternal

characteristics (age, weight, height, race, parity and gestational age), study centre and estimated fetal weight[2].

Reproducibility of speckle tracking analysis was assessed on 25 participants who were analyzed twice by the same operator (LY) using the intraclass correlation coefficient (ICC) alongside 95% confidence intervals for intra-operator reproducibility of fetal strain and cardiac indices on two different heart cycles as previously described[10]. Agreement in repeated measurements of the same operator were evaluated by a two-way random-effects model. ICC values >0.75 were suggestive of good reliability and >0.9 of excellent reliability.

Statistical analysis was conducted with STATA package, version 13.1 (StataCorp, College Station, Texas USA). We deemed statistical significance at p =<0.05

RESULTS

Study population

The number of participants who consented for this study was 360. Among them 244 were from the London site and 116 from Murcia. A total of 24 patients were excluded; in 17 fetal cardiac imaging was suboptimal due to fetal movements and poor acoustic windows and in 7 the angle of insonation (apex oblique view) could not be obtained due to fetal lie. The study population comprised of 112 women with GDM and 224 women with uncomplicated pregnancy; each woman was seen only once and did not participate in any other cardiovascular study[2]. There was no significant difference between the groups in mean gestational age at investigation (GDM: mean 33.5, SD 3.1 weeks vs. controls: mean 33.7, SD 2.9 weeks, p=0.45). However, women with GDM, compared to controls, were older (34.1, SD 5.2 years vs. 32.0, SD 5.8, p=0.001), had higher body mass index (30.6, SD 5.5 kg/m^2 vs. 27.8, SD 4.7, p<0.001), and were more likely to be parous (n=76, 67.9% vs. n=122, 54.5%, p=0.019) and less likely to be of White racial origin (n=81, 72.4% vs. n=187, 83.5%, p=0.02). In women with GDM, 27 were treated with insulin and/or metformin while the remaining were on diet; in all cases there was optimal diabetes control as per ADA and ACOG recommendations[11, 12].

Fetal cardiac changes in GDM and controls

In fetuses of women with GDM, compared to controls, right ventricular functional indices were consistently lower both at 24^{+0} - 32^{+0} weeks and at 32^{+1} - 40^{+1} weeks (Table 1 and 2). Right ventricular global longitudinal strain was reduced in the GDM group at 24^{+0} - 32^{+0} week's gestation (mean reduction 0.7, 95% CI 0.3, 0.05; p<0.001) and at 32^{+1} - 40^{+1} weeks (0.9, 95% CI 0.7, 10.2; p<0.001). Tricuspid annular systolic excursion was also reduced at 24^{+0} - 32^{+0} weeks (-0.7, 95% CI -1.1, -0.4; p<0.001) and at 32^{+1}- 40^{+1} weeks (-0.8, 95% CI -1.04,-0.5; p<0.001). Segmental analysis revealed that all segments (basal, mid and apical) of the right ventricle had lower systolic function in the GDM group compared to controls (Supplementary Table 1). There was no significant difference in the frame rate image acquisition between GDM and controls (108.6, SD 8.3 vs 109.1, SD 7.0; p=0.607)

Fetal left ventricular global longitudinal function was similar between the GDM group and controls, with the exception of the contractility of the left ventricular basal segment which was reduced in GDM (Table 2 and Supplementary Table 1). Global sphericity index was reduced in the GDM group only at 32^{+1} - 40^{+1} weeks (Table 2). There was no interaction between diabetes status and gestational age on cardiac indices.

Good to excellent reliability was noted for all outcome measures (Supplementary Table 2). To assess whether women on insulin treatment were the ones who accounted for the noted differences with controls, sensitivity analysis was performed by excluding these patients and results remained similar (Supplementary Table 3).

DISCUSSION

Main findings of the study

This cross-sectional study demonstrates that fetuses exposed to GDM, compared to those who are not, first, have lower right ventricular function both at 24^{+0} - 32^{+0} and at 32^{+1} - 40^{+1} weeks' gestation and this decrease is observed in all segments of the right ventricle, second, have lower global sphericity index but this difference is apparent only at 32^{+1} - 40^{+1} weeks, and third, left ventricular fetal cardiac function is mostly preserved with the only exception of reduced contractility of the basal segment.

Comparison with results of previous studies

In this study, we elected to perform detailed fetal cardiac assessment using speckle tracking. The reason for this choice is that we and others have previously shown that in GDM fetal cardiac changes are subtle and are not detectable by conventional Doppler techniques[2,3]. Speckle tracking is non-invasive, reproducible when the quality of imaging is optimal and can be performed from early in gestation as it involves post-processing analysis of the easily obtainable four chamber view of the fetal heart[7]. Specific features of our study are: first, selection of a homogeneous group of women with GDM excluding women with pregestational diabetes who might have different pathophysiology; second, we assessed two separate gestational windows to identify the association between GDM earlier and later in pregnancy; and third, we followed strict protocol in image acquisition (at an "apex oblique" projection and obtained clips >100 frames per second) and analysis to minimize the variability of results[10]. Although different methods of screening for GDM were used in the two centres, it has been previously shown that this does not modify the incidence of GDM diagnosis [13].

We found that in fetuses of women with GDM, compared to controls, there was reduced right but not left ventricular systolic function as measured by global longitudinal systolic strain. Previous studies also reported right ventricular systolic dysfunction in GDM fetuses[2,3,14]. However, studies reported contradictory results concerning left ventricular systolic function. In our study decrease in left ventricular function in fetuses of mothers with GDM compared to controls was noted only at 24^{+0} - 32^{+0} weeks by measuring ejection fraction, fraction area change and mitral valve annular excursion and no difference was noted after 32 weeks

gestation. Miranda *et al*, who examined 76 fetuses of women with GDM at 31 weeks' gestation found normal left ventricular systolic function[3]. In contrast, Patey *et al*[14], examined 21 fetuses of women with pregestational diabetes or GDM after 35 weeks' gestation and reported reduced left ventricular systolic function; similar findings were reported by Kulkarni *et al*[15], in a combined group of 31 women with GDM and 51 with pregestational diabetes at 20-30 weeks' gestation. Wang *et al*[16] in 35 fetuses of women with GDM at 28-38 weeks' gestation reported segmental left ventricular systolic functional changes in GDM fetuses. Such differences between studies might be due to inclusion of pregestational diabetes in some and variation between studies in maternal characteristics, diabetes control, protocol for optimal image acquisition and software used for fetal speckle tracking analysis[17].

The mechanisms by which GDM affects the fetal heart remains unclear. It is possible that fetal hypoxemia in response to GDM induces myocardial cell damage, myocyte death and impaired ventricular function[18]. Hyperglycemia can also attenuate angiogenic capability of surviving in endothelial cells and this can modify cardiac function and morphology by controlling total cardiomyocyte number[19,20]. Animal studies have also shown that intrauterine exposure to hyperglycemia can induce fetal myocardial hyperplasia and myocardial remodeling which can explain differences in morphology and endocardial deformation between fetuses of GDM mothers and controls[1].

Strengths and limitations

Strengths of our study include, first, detailed fetal speckle tracking analysis in a large number of pregnancies affected by GDM and healthy controls using unifying protocols and strict methodology in image acquisition in the two participating centres, and second, cardiac functional analysis by one fellow who was blinded to maternal characteristics thus minimizing the variability. The main limitation of the study is that this was a cross sectional rather than a longitudinal examination of the same patients at 24-32 and 32-40 weeks. Our women with GDM had optimal diabetes control and it is therefore uncertain whether our findings can be generalized to those with poor diabetes control. In addition, we present data on segmental analysis however we acknowledge that interpretation is challenging due to small distances between measured point strain and their clinical significance remains unknown.

Conclusion

The offspring of women with GDM are at high risk for development of cardiovascular disease in childhood and early adulthood[21]. Our study demonstrates that GDM is associated with reduction in fetal right ventricular function compared to controls irrespective of the method of screening for GDM and this response is not exaggerated with increasing gestational age. Further studies are needed to determine whether the fetuses with the observed alterations in cardiac function are the ones at highest risk for subsequent development cardiovascular disease.

Conflicts of interest: None

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Figure legends

Figure 1. Endocardial tracing of the right and left ventricle to calculate global longitudinal strain. The top left picture demonstrates the 4 chamber view in oblique projection for optimal tracking of the endocardial border. Strain measurements for the left and right ventricle are shown at the top right picture. Values generated by the software are depicted in the bottom left part of the picture.

Figure 2. Box and whisker plots of fetal right ventricular endocardial global longitudinal strain (left) and right ventricular fractional area change (right) in control (white boxes) and GDM (grey boxes) at 24^{+0}-32^{+0} and 32^{+1}-40^{+1} weeks' gestation**.**

Supplementary table legends

Supplementary Table 1: Fetal segmental left and right ventricular transverse shortening fraction.

Supplementary Table 2: Reproducibility of repeated analysis of fetal cardiac indices.

Supplementary Table 3: Sensitivity analysis excluding women with GDM treated with insulin

Table 1. Unadjusted comparison of fetal cardiac indices in gestational diabetes mellitus and controls at 24-32 and 32-40 weeks' gestation.

Variable	Difference between GDM and controls at 24^{+0}-32^{+0} w		Difference between GDM and controls at 32^{+1}-40^{+1} w		Difference in controls between 24^{+0}-32^{+0} and 32^{+1}-40^{+1} w		Difference in GDM between 24^{+0}-32^{+0} and 32^{+1}-40^{+1} w		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
Overall Sphericity Index	-0.3 (-0.7, 0.1)	0.145	-0.4 (-0.6 -0.1)	0.016	-0.2 (-0.5, 0.04)	0.087	-0.3 (-0.7, 0.1)	0.104	-0.1 (-0.5, 0.4)	0.771
LV endocardial global longitudinal strain	0.3 (-0.1, 0.7)	0.126	0.05 (-0.2, 0.3)	0.755	0.7 (-0.01, 0.6)	0.061	0.02 (-0.4, 0.4)	0.922	-0.3 (-0.7, 0.2)	0.321
LV fractional area change	-0.5 (-0.8, -0.1)	0.017	0.04 (-0.2, 0.3)	0.775	-0.3 (-0.53, 0.03)	0.081	0.3 (-0.1, 0.6)	0.192	0.5 (0.03, 1.0)	0.037
LV ejection fraction,	-0.5 (-0.9, -0.1)	0.008	-0.1 (-0.4, 0.2)	0.535	-0.1 (-0.4, 0.1)	0.335	0.3 (-0.1, 0.7)	0.145	0.4 (-0.1, 0.9)	0.081
Mitral annular systolic excursion	-0.4 (-0.8, -0.1)	0.033	-0.2 (-0.5, 0.1)	0.123	0.4 (0.1, 0.7)	0.007	0.6 (0.2, 0.9)	0.003	0.2 (-0.3, 0.6)	0.432
RV endocardial global longitudinal strain	0.6 (0.3, 0.9)	0.001	0.9 (0.7, 10.2)	<0.001	-0.1 (-0.3, 0.2)	0.669	0.3 (-0.1, 0.6)	0.105	0.4 (-0.1,0.8)	0.120
RV fractional area change	-0.8 (-1.1, -0.4)	<0.001	-0.9 (-0.2, -0.7)	<0.001	-0.03 (-0.3, 0.2)	0.808	-0.2 (-0.5, 0.2)	0.278	-0.2 (-0.6, 0.3)	0.466
Tricuspid annular systolic excursion	-0.7 (-1.1, -0.4)	<0.001	-0.8 (-0.04, -0.5)	<0.001	0.6 (0.3, 0.8)	<0.001	0.5 (0.2, 0.8)	0.004	-0.1 (-0.5, 0.4)	0.814
RV / LV end diastolic area	-0.4 (-0.7, 0.02)	0.065	-0.2 (-0.5, 0.1)	0.106	0.4 (0.1, 0.7)	0.003	0.5 (0.2, 0.9)	0.004	0.1 (-0.3, 0.5)	0.612

LV = left ventricular, RV = right ventricular

Coefficients in inverse ranking scale

At 24^{+0} - 32^{+0} weeks: 43 cases of gestational diabetes and 71 controls

At 32^{+1} - 40^{+1} weeks: 69 cases of gestational diabetes and 153 controls

Table 2. Adjusted comparison of fetal cardiac indices in gestational diabetes mellitus and controls at 24-32 and 32-40 weeks' gestation.

Variable	Difference between GDM and controls at 24^{+0}-32^{+0} w		Difference between GDM and controls at 32^{+1}-40^{+1} w		Difference in controls between 24^{+0}-32^{+0} and 32^{+1}-40^{+1} w		Difference in GDM between 24-32^{+0} and 32^{+1}-40^{+1} w		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
Overall Sphericity Index	-0.2 (-0.6, 0.2)	0.299	-0.4 (-0.7, 0.1)	0.007	-0.03 (-0.5, 0.5)	0.903	-0.3 (-0.8, 0.3)	0.359	-0.2 (-0.7, 0.3)	0.366
LV endocardial global longitudinal strain	0.3 (-0.1, 0.7)	0.108	0.1 (-0.2, 0.4)	0.557	0.2 (-0.3, 0.7)	0.416	-0.02 (-0.6, 0.5)	0.925	-0.2 (-0.7, 0.3)	0.357
LV fractional area change	-0.5 (-0.9, -0.1)	0.018	-0.01 (-0.3, 0.3)	0.985	-0.2 (-0.7, 0.3)	0.453	0.3 (-0.3, 0.8)	0.302	0.4 (-0.01, 1.0)	0.057
LV ejection fraction	-0.5 (-0.9, -0.1)	0.010	-0.1 (-0.4, 0.2)	0.549	-0.1 (-0.5, 0.4)	0.835	0.4 (-0.2, 0.9)	0.184	0.4 (-0.1, 0.9)	0.098
Mitral annular systolic excursion	-0.5 (-0.9, -0.1)	0.007	-0.4 (-0.7, -0.1)	0.014	-0.3 (-0.7, 0.2)	0.270	-0.1 (-0.6, 0.4)	0.647	0.1 (-0.3, 0.6)	0.552
RV endocardial global longitudinal strain	0.7 (0.3, 0.05)	<0.001	0.9 (0.6, 0.17)	<0.001	0.1 (-0.3, 0.6)	0.593	0.3 (-0.2, 0.8)	0.221	0.1 (-0.3, 0.6)	0.404
RV fractional area change	-0.7 (-1.1, -0.4)	<0.001	-0.7 (-1.1, -0.5)	<0.001	-0.04 (-0.5, 0.4)	0.855	-0.05 (-0.6, 0.5)	0.84	-0.01 (-0.5, 0.4)	0.965
Tricuspid annular systolic excursion	-0.9 (-1.2, -0.5)	<0.001	-0.9 (-1.2, -0.7)	<0.001	-0.1 (-0.5, 0.3)	0.604	-0.2 (-0.7, 0.3)	0.464	-0.1 (-0.5, 0.4)	0.764
RV/LV end diastolic area	-0.4 (-0.8, -0.03)	0.033	-0.3 (-0.6, -0.03)	0.035	-0.4 (-0.8, 0.1)	0.116	-0.3 (-0.8, 0.2)	0.277	0.1 (-0.4, 0.6)	0.719

Adjustments made for maternal age, height, weight, race, parity, gestational age, participating centre and estimated fetal weight.

LV = left ventricular, RV = right ventricular

Coefficients in inverse ranking scale.

At 24^{+0} - 32^{+0} weeks: 43 cases of gestational diabetes and 71 controls

At 32^{+1} - 40^{+1} weeks: 69 cases of gestational diabetes and 153 controls

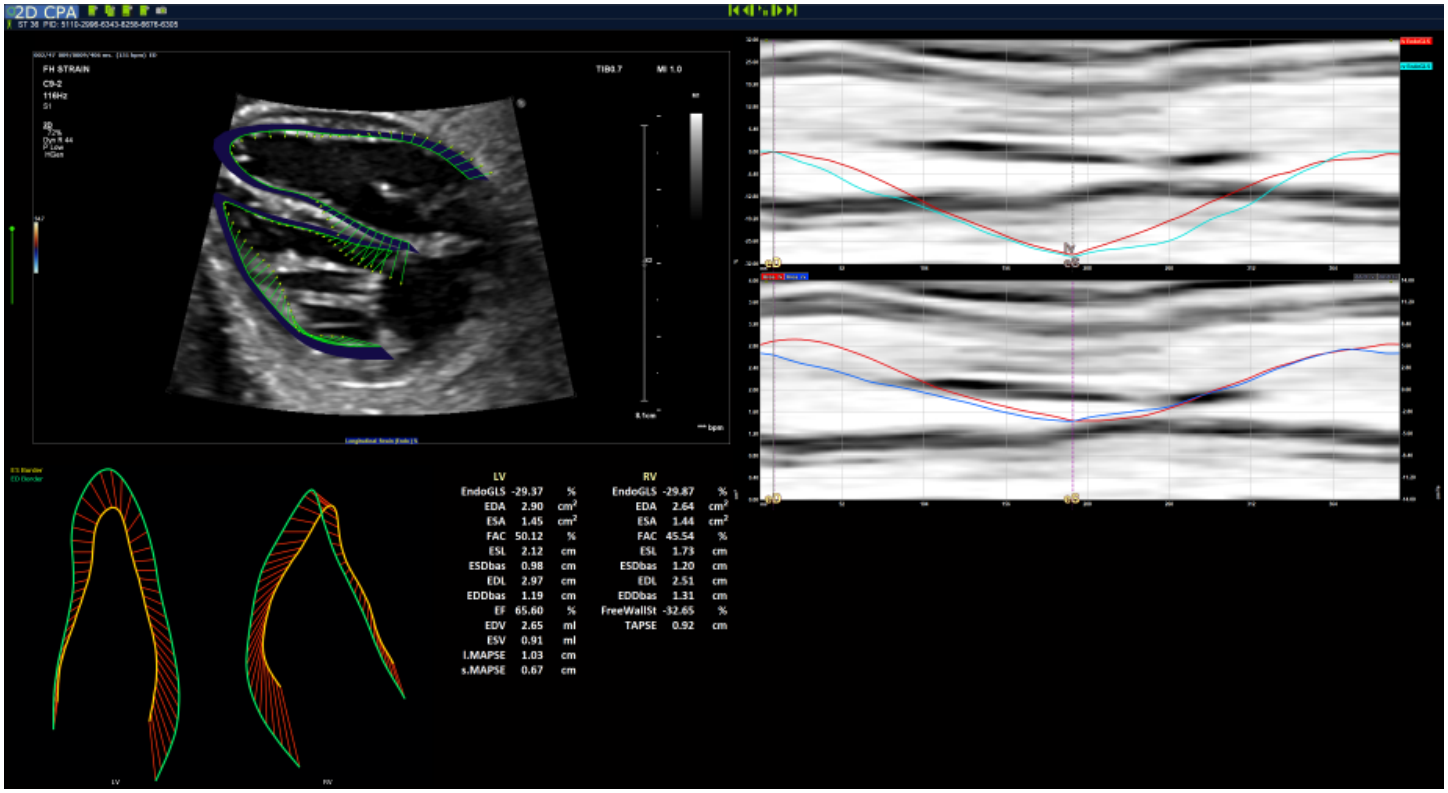

Figure 1

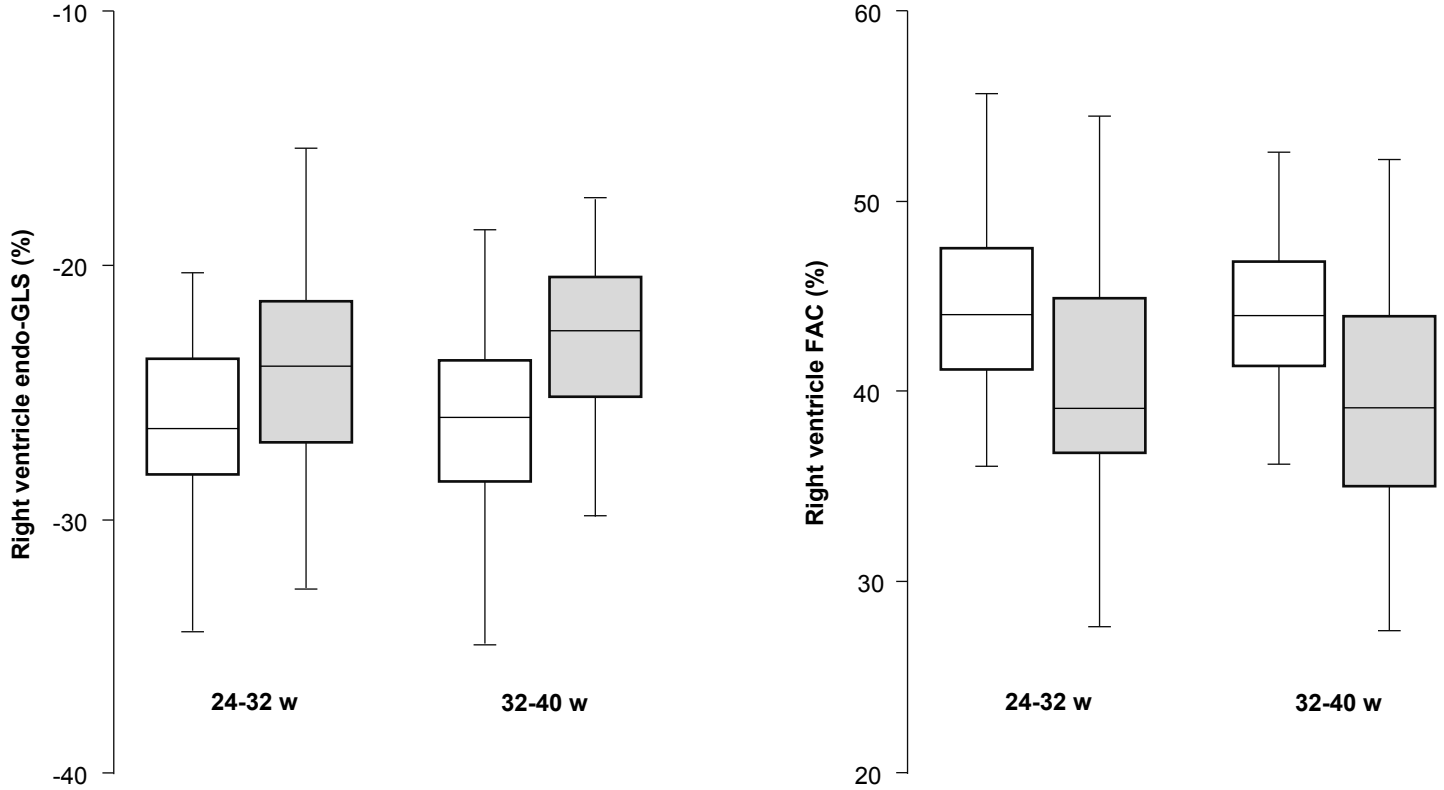

Figure 2