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Three-dimensional echocardiography and cardiac strain imaging in women with gestational diabetes mellitus

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KEYWORDS: deformation; ejection fraction; three-dimensional echocardiography

CONTRIBUTION

What are the novel findings of this work?
Left and right ventricular systolic function is marginally reduced in mothers with gestational diabetes mellitus. These early cardiac changes can be detected by strain imaging. Volumetric assessment using three-dimensional echocardiography is not a sensitive modality to identify early cardiac functional changes in women with gestational diabetes mellitus.

What are the clinical implications of this work?
Longitudinal cardiac strain imaging is a sensitive echocardiographic modality to assess early subclinical cardiac dysfunction in women with a history of gestational diabetes mellitus.

ABSTRACT

Objectives *Gestational diabetes mellitus (GDM) is associated with premature cardiovascular disease and adverse cardiovascular outcome in the mother. Subclinical cardiac functional changes in the left ventricle have been reported during pregnancy in women with GDM using conventional echocardiography, but results are inconsistent. The aims of the current study were to assess whether GDM is associated with biventricular systolic dysfunction in the mother and whether these cardiac changes can be detected using the novel echocardiographic modalities of strain imaging and three-dimensional (3D) echocardiography.*

Methods *This was a cross-sectional study in women with GDM and controls examined at 26–40 weeks of gestation. All women underwent echocardiography, and 3D volumes of the left and right ventricles and left atrium were collected. Ejection fraction and left ventricular mass were measured using 3D echocardiography. Left ventricular mass was indexed to body surface area. Speckle-tracking echocardiography was used to assess global longitudinal strain of the left and right ventricles and strain of the left atrium.*

Results *The study population included 123 women with GDM and 246 controls. Women with GDM, compared to controls, were older (35.1 ± 5.2 vs 32.4 ± 5.5 years; P < 0.001), had higher body mass index (30.6 (interquartile range (IQR), 26.2–35.2) vs 27.5 (IQR, 24.7–30.7) kg/m^2; P < 0.001) and had higher systolic blood pressure (119.9 ± 11.2 vs 116.4 ± 12.0 mmHg; P = 0.007). In all women with GDM, there was good glycemic control. In women with GDM, compared to controls, there was lower global longitudinal strain of the left ventricle (−19.3% (IQR, −21.4 to −17.6%) vs −20.1% (IQR, −22.1 to −18.7%); P = 0.002) and right ventricle (−22.2% (IQR, −26.1 to −19.8%) vs −24.1% (IQR, −27.0 to −21.9%); P < 0.001). There was no significant difference between the groups in ejection fraction, left ventricular mass, diastolic function assessed by left atrial strain, or 3D functional indices.*

Conclusions *Women with GDM, compared to women with uncomplicated pregnancy, have lower left and right ventricular myocardial deformation. Volumetric assessment using 3D echocardiography does not provide additional information about maternal cardiac function. Strain imaging is a sensitive echocardiographic modality to detect early cardiac functional changes in women with GDM. Further studies are needed to assess the pattern of deterioration of cardiac function with advancing age in women with a history of GDM. © 2021 International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Gestational diabetes mellitus (GDM), which affects 5–10% of pregnant women, is associated with short-

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and long-term risks for the health of the mother[1–6]. There is general recognition that identification and treatment of GDM can improve pregnancy outcome[4–6] but it is uncertain whether such treatment can alter the reported long-term cardiovascular risk of these women[7,8]. Considering that glycemia is known to affect myocardial function[9,10], accurate assessment of myocardial contractility in pregnancy is necessary to allow detection of early myocardial changes.

Evaluation of myocardial contractility using echocardiography has traditionally been performed by volume-based assessment of ejection fraction and estimation of myocardial thickening[11]. These methods, however, are sensitive to loading conditions and prone to variability due to assumptions regarding geometric modeling and errors with foreshortened echocardiographic views. In the last decade, advances in cardiac imaging led to the introduction of novel echocardiographic techniques, such as two-dimensional (2D) speckle-tracking and three-dimensional (3D) echocardiography, which allow accurate quantification of ventricular function[11,12]. Two-dimensional speckle-tracking echocardiography measures myocardial velocities and deformation parameters and has evolved to be the imaging modality of choice for the detection of subclinical cardiac dysfunction[12]. With the use of this technique, early left ventricular myocardial dysfunction has been reported in young patients with diabetes mellitus and few studies have shown that similar changes present in women with GDM even after short exposure to glycemia in the third trimester of pregnancy[13–16]. As far as 3D echocardiography is concerned, the technique has evolved from a slow and labor-intensive offline reconstruction modality to real-time volumetric imaging which allows accurate assessment of cardiac chamber volume. Using 3D echocardiography, accurate and reproducible quantification of ventricular size, function and left ventricular mass can be performed; however, data on use of this technique in pregnancy are scarce[17]. Adverse cardiac effects in relation to diabetes mellitus have been demonstrated more commonly for the left ventricle, although data suggest that deterioration of right ventricular function can also be present and may affect both the course and prognosis of these patients[18]. However, there is limited information about right ventricular function in women with GDM.

The objectives of this study were to define accurately left and right ventricular function using novel echocardiographic techniques, such as 2D speckle-tracking and 3D echocardiography, in women with GDM and to compare these data to those obtained from women with uncomplicated pregnancy.

METHODS

Study design and participants

This was a cross-sectional study performed in the Maternal-Fetal Medicine Unit of Hospital Clinical Universitario 'Virgen de la Arrixaca', Murcia, Spain, between November 2019 and September 2020. We recruited women with GDM at 26–40 weeks of gestation (median of 35 (interquartile range (IQR), 31–37) weeks), and for every woman with GDM we recruited two women with uncomplicated pregnancy at a similar gestational age. As assessment in the third trimester is not part of routine screening for women with uncomplicated pregnancy in Spain, women who were recruited as controls were invited for additional scan at the same gestational age as women with GDM. Exclusion criteria for the study were the presence of fetal abnormalities and pre-existing diabetes mellitus.

The diagnosis of GDM was made by the use of two-step screening; first, the 50-g glucose test was carried out and, if this was positive (1-h glucose level ≥ 7.8 mmol/L), then the 100-g oral glucose test was carried out, which was considered to be positive if two or more glucose concentrations were increased (fasting glucose ≥ 5.8 mmol/L, 1-h glucose ≥ 10.6 mmol/L, 2-h glucose ≥ 9.2 mmol/L, 3-h glucose ≥ 8.1 mmol/L). Two fasting plasma glucose levels ≥ 7.0 mmol/L on different days or a random glycemia ≥ 11.1 mmol/L was also 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 was used when dietary management failed; oral therapy is not included in the current protocol. Glycemic control was assessed by home self-monitoring with the use of a glycometer for daily measurement of the fasting and 1-h postprandial capillary blood glucose levels. Normal values for these measurements were 3.9–5.3 mmol/L for fasting and 5.0–7.8 mmol/L for 1-h postprandial blood glucose. The clinical records of the patients were reviewed by an endocrinologist at the time of the clinical visit, and diabetic treatment was 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. The study was approved by the research ethics committee in Murcia (CI:2018-11-5-HCUVA) and all participants gave signed informed consent.

Maternal characteristics

We recorded information on maternal age, racial origin (white, black, Asian or mixed), method of conception (spontaneous or assisted by *in-vitro* fertilization or ovulation induction drugs), cigarette smoking and parity (parous or nulliparous if there was no previous pregnancy with delivery at ≥ 24 weeks of gestation). At the clinic visit, weight and height were measured and body mass index was calculated. For all pregnancies, birth weight was recorded and the *Z*-score was calculated[19].

Maternal cardiac functional analysis

Maternal echocardiography was performed using the X5-1 transducer with an EPIQ 7G or EPIQ Elite ultrasound machine (Philips, Bothell, WA, USA), according to the European Association of Cardiovascular Imaging/American Society of Echocardiography guidelines[20]. Measurements of the left ventricle and atrium were obtained in the standard four-chamber apical view, whereas measurements of the right ventricle were performed at a 45° angle. The clips were exported in the original frame rate to an external hard drive and transferred for offline analysis using the QLAB Advanced Quantification software (Philips). Using 3D echocardiography, the ejection fractions of the left and right ventricles were calculated, as well as left ventricular mass (Figure 1). Left ventricular mass was indexed to body surface area. Longitudinal right ventricular functional assessment was also performed by calculating tricuspid annular plane systolic excursion (TAPSE) and fractional area change.

Speckle-tracking echocardiography was used to assess global longitudinal strain (GLS) of the left and right ventricles, as described previously[21]. Starting from the initial end-systolic contour, the software used an established speckle-tracking algorithm to detect automatically the endocardial borders in all frames of the selected cardiac cycle (Figure 2). Measurements were performed at 60–70 frames per second. Left atrial area and volume were calculated manually in end systole from the four-chamber apical view in 2D, as described previously[21]. Left atrial strain measurements were performed according to the European Association of Cardiovascular Imaging guidelines[22].

Statistical analysis

The distribution of continuous variables was assessed using histograms and quantile–quantile plots. Normally distributed continuous variables are presented as mean ± SD, and variables not following a normal distribution are presented as median (IQR). Nominal variables are summarized as *n* (%). We employed the Student's *t*-test and Mann–Whitney *U*-test to compare maternal cardiac measurements between women with GDM and controls. General linear regression models were used to assess the association between GDM and a range of echocardiographic parameters which were shown to differ between the groups. Analyses were adjusted for maternal age, body mass index, medical history and birth-weight *Z*-score as a proxy for fetal size. The effect of GDM treatment (dietary management or insulin) on maternal cardiac indices was assessed using the Mann–Whitney *U*-test. Inter- and intrarater variability in the analysis of strain and 3D measurements was assessed in 30 participants on previously acquired clips. Operators were blinded to the previous analysis and to the diagnosis of GDM. Agreement and reproducibility were assessed using the intraclass correlation coefficient; values > 0.7 were considered to indicate good reproducibility and those > 0.9 were considered to indicate excellent reproducibility.

Statistical analyses were performed using Stata package version 16.0 (StataCorp, College Station, TX, USA).

RESULTS

Maternal and pregnancy characteristics

The study population included 123 women with GDM and 246 controls. Women with GDM, compared to controls, were older, had higher body mass index and higher systolic blood pressure, delivered earlier and had

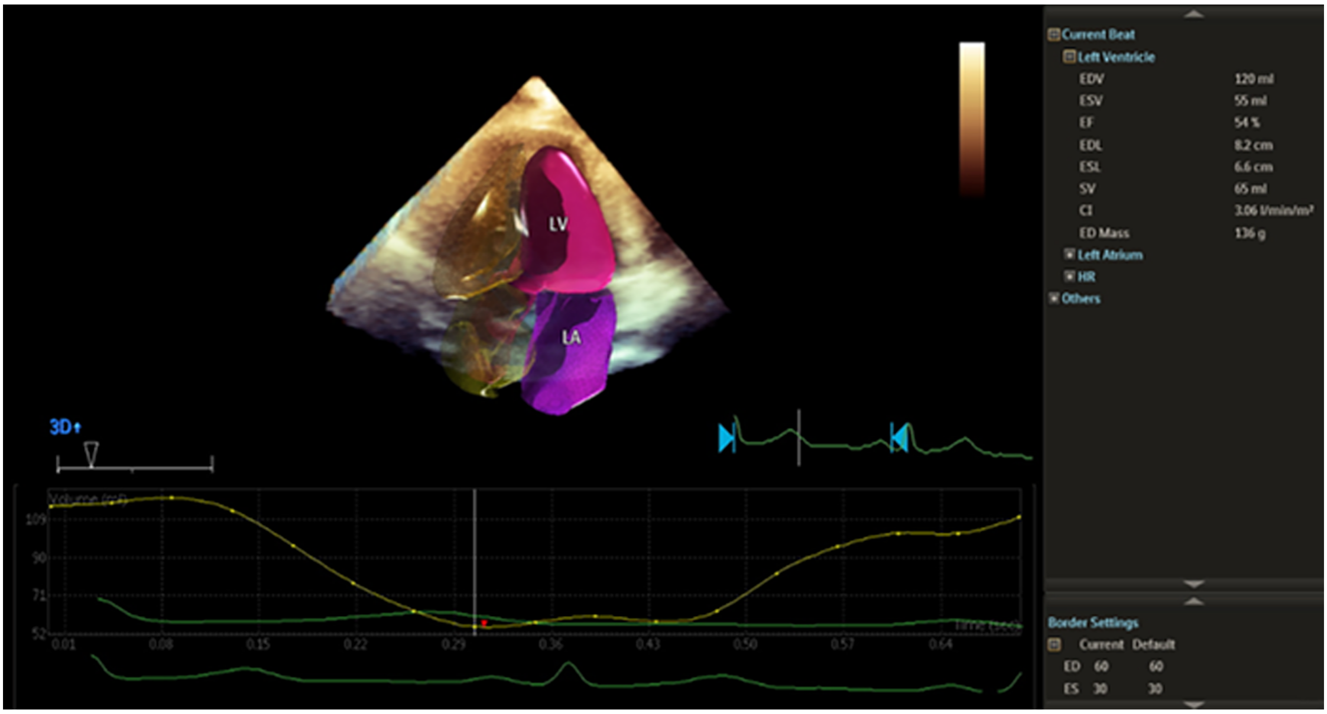

Figure 1 Demonstration of automatic volumetric assessment of the left ventricle (LV) and left atrium (LA) using three-dimensional echocardiography.

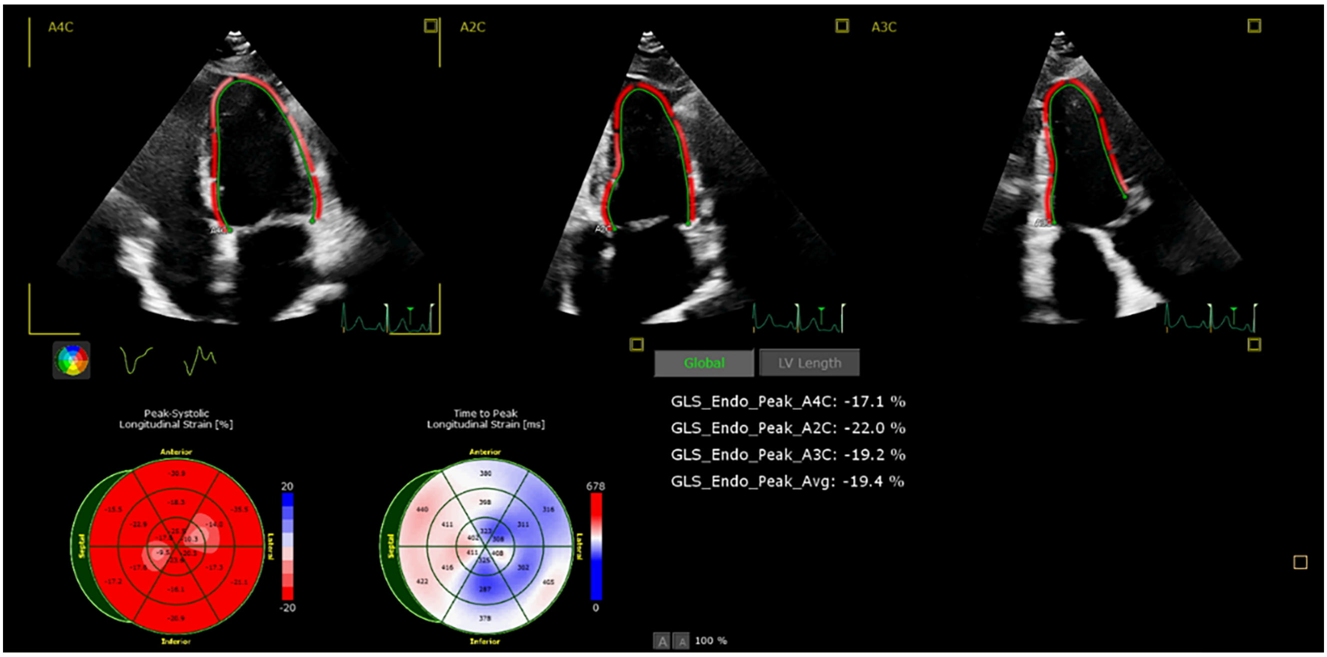

Figure 2 Two-dimensional strain imaging of the left ventricle. Demonstration of endocardial tracing in the four-chamber, two-chamber and three-chamber views, allowing calculation of the global longitudinal strain in the left ventricle.

higher birth-weight *Z*-score (Table 1). Among the GDM participants, 33 were on insulin and the remaining were on dietary management. The median interval between the time of diagnosis of GDM and echocardiographic assessment was 9.4 (IQR, 5.0–15.3) weeks.

Cardiovascular indices

There was good-to-excellent inter- and intrarater agreement for all key cardiac measures (Table 2).

In women with GDM, compared to controls, there was lower GLS of the left ventricle (Table 3). There was no significant difference between the groups in left ventricular or atrial ejection fraction, left ventricular mass, diastolic function assessed by left atrial strain, or 3D functional indices. Cardiac output was also similar in the two groups. On multivariable analysis, women with GDM, compared to controls, had evidence of reduced left ventricular myocardial deformation (adjusted mean difference (MD) in left ventricular GLS, 0.6% (95% CI, 0.01–1.2%); $P = 0.047$), after controlling for maternal characteristics and birth-weight *Z*-score.

3D volumes of the right ventricle could not be analyzed in 17.1% (63/369) of cases due to technical failures, including inappropriate angle of insonation or suboptimal 3D quality. In women with GDM, compared to controls, TAPSE and right ventricular GLS were reduced, but there was no significant difference in right ventricular ejection fraction or fractional area change. On multivariable analysis, women with GDM, compared to controls, had lower right ventricular myocardial deformation (adjusted MD in right ventricular GLS, 1.7% (95% CI, 0.8–2.7%); $P < 0.001$).

Left atrial volume was similar in the two groups. From the different left atrial functional indices, left atrial contraction was higher in women with GDM compared to controls; however, on multivariable analysis, there was no evidence of a significant difference between the groups (adjusted MD in left atrial contraction strain, 0.04% (95% CI, −0.9 to 0.9%); $P = 0.750$).

Within the GDM group, women on insulin, compared to those on dietary management, had higher body mass index (32.8 ± 5.4 kg/m^2 *vs* 29.9 ± 5.5 kg/m^2; $P = 0.012$), but there were no significant differences in risk-factor profile or cardiac functional or structural indices.

DISCUSSION

Principal findings

In this study, we demonstrated that women with GDM, compared to those with uncomplicated pregnancy, have evidence of subclinical reduction in biventricular systolic function. There were no significant differences between the groups in diastolic function assessed by 2D strain or ejection fraction assessed by 3D echocardiography. These data suggest that cardiac volumes and left ventricular mass are not affected within the first few weeks of development of GDM and that 2D strain imaging is a sensitive echocardiographic modality to assess early cardiac functional changes in women with GDM.

Comparison with findings of previous studies and interpretation of results

The realization that women with GDM are at increased cardiovascular risk[7,8] has stimulated the undertaking of studies involving cardiovascular functional assessment during pregnancy to identify risk factors, which, if modified, can alter the cardiovascular risk for these women. Some, but not all of the studies reported a small reduction in left ventricular GLS[13–16], and there is contradictory evidence of an increase in left ventricular mass[13,14,16,23]. In our study, using 2D strain imaging, a small reduction in left ventricular myocardial deformation was noted after adjusting for differences in maternal characteristics and birth weight, but, using 3D echocardiography, there were no significant differences in ejection fraction or left ventricular mass. Our data suggest that left ventricular ejection fraction is preserved in GDM. It is thus possible that either ejection fraction is a late marker of ventricular dysfunction or women with GDM may be at risk of diastolic heart failure with preserved left ventricular ejection fraction and that early functional changes can be identified only by myocardial strain imaging[24]. Myocardial strain imaging can allow early identification of changes in myocardial mechanics, and its measurements provide prognostic information about major cardiac events in patients with different cardiovascular diseases[11].

A decline in diastolic function often precedes systolic dysfunction. The findings of recent studies suggest that left atrial functional measures assessed by speckle-tracking echocardiography are sensitive early markers of left ventricular diastolic dysfunction. In patients with normal left atrial size, it has been shown that a reduction of reservoir strain is a predictor of developing New York Heart Association Class-II and -IV symptoms[25,26]. Regardless of etiology, atrial dysfunction develops with a decrease in reservoir and conduit function and a compensatory increase in contractile function. In our study, atrial contraction was higher in women with GDM and no other alterations in functional left atrial parameters could be detected. Considering that the noted association was attenuated and lost after controlling for maternal characteristics, this would suggest that the change in left atrial contraction is unlikely to be the result of the glycemic insult and our data would not support the presence of early diastolic dysfunction in women with GDM. Previous studies using mitral inflow Doppler indices and tissue Doppler reported only small reductions in myocardial relaxation in women with GDM compared to those with uncomplicated pregnancy, and none fulfilled the clinical criteria for diastolic dysfunction[13,14,23,27].

Apart from left ventricular function, right ventricular function has a key role in the overall myocardial contractility. However, most of the previous studies regarding diabetes-induced changes in myocardial contractility have focused on the left ventricle, ignoring the role of the right heart[13,14,23,27]. This is partly due to the fact that assessment of right ventricular function remains challenging because of its complex geometry. A number of studies, however, have demonstrated that speckle-tracking echocardiography, as well as 3D echocardiography, can overcome these issues and provide accurate right ventricular functional assessment[28–30]. In our study, right ventricular GLS was lower in women with GDM compared to controls, whereas other functional indices were similar between the two groups. Although there is a lack of data on right ventricular function in the context of

Table 1 Maternal and pregnancy characteristics of the study population of 369 pregnancies, according to diagnosis of gestational diabetes mellitus (GDM)

Characteristic	*GDM (n = 123)*	*Controls (n = 246)*	P
Age (years)	35.1 ± 5.2	32.4 ± 5.5	< 0.001
Weight (kg)	79 (70–93)	75 (69–84)	0.003
Height (cm)	163 ± 6.4	163 ± 6.1	0.740
BMI (kg/m²)	30.6 (26.2–35.2)	27.5 (24.7–30.7)	< 0.001
GA at scan (weeks)	34.7 (30.9–37.3)	35.0 (31.3–37.4)	0.554
Racial origin			0.112
White	121 (98.4)	242 (98.4)	
Black	0 (0)	3 (1.2)	
Asian	2 (1.6)	0 (0)	
Mixed	0 (0)	1 (0.4)	
Medical history			
Chronic hypertension	3 (2.4)	0 (0)	0.036
SLE/APS	1 (0.8)	1 (0.4)	1.0
Smoker	13 (10.6)	26 (10.6)	0.999
Method of conception			0.086
Natural	106 (86.2)	226 (91.9)	
In-vitro fertilization	17 (13.8)	20 (8.1)	
Nulliparous	49 (39.8)	116 (47.2)	0.183
Pre-eclampsia	4 (3.3)	2 (0.8)	0.083
PIH	3 (2.4)	2 (0.8)	0.207
Diabetes treatment			
Diet	90 (73.2)	—	
Insulin	33 (26.8)	—	
Systolic BP (mmHg)	119.9 ± 11.2	116.4 ± 12.0	0.007
Diastolic BP (mmHg)	71.5 ± 8.4	71.4 ± 8.8	0.963
Heart rate (bpm)	82 ± 12.0	80 ± 11.4	0.313
GA at delivery (weeks)	39.2 (38.7–40.4)	40.1 (39.0–40.9)	0.001
Birth weight (g)	3455 (3160–3660)	3355 (3047–3650)	0.082
Birth-weight *Z*-score	0.1 ± 0.1	−0.2 ± 0.1	0.008

Data are given as mean ± SD, median (interquartile range) or *n* (%). Comparisons between groups were made by chi-square or Fisher's exact test for categorical variables and Student's *t*-test or Mann–Whitney *U*-test for continuous variables. APS, antiphospholipid syndrome; BMI, body mass index; BP, blood pressure; GA, gestational age; PIH, pregnancy-induced hypertension; SLE, systemic lupus erythematosus.

Table 2 Inter- and intraobserver variability of key cardiac measures

	Intraclass correlation coefficient	
Cardiac index	*Intraobserver*	*Interobserver*
LV GLS (in %)	0.964	0.926
RV GLS (in %)	0.938	0.772
LV EF (in %)	0.966	0.912
TAPSE (in mm)	0.919	0.872

EF, ejection fraction; GLS, global longitudinal strain; LV, left ventricular; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion.

Table 3 Two-dimensional strain and three-dimensional echocardiography of the study population of 369 pregnancies, according to diagnosis of gestational diabetes mellitus (GDM)

Cardiac index	*GDM* (n = *123)*	*Controls* (n = *246)*	P
LV global longitudinal strain (%)	−19.3 (−21.4 to −17.6)	−20.1 (−22.1 to −18.7)	0.002
LV end-systolic volume (mL)	55 (49–67)	57 (49–67)	0.963
LV end-diastolic volume (mL)	132 (118–147)	133 (122–150)	0.256
LV ejection fraction (%)	57 (53–60)	58 (53–62)	0.167
LV mass indexed to BSA (g/m^2)	66.0 (60.0–74.7)	67.2 (61.1–73.8)	0.749
LV cardiac output (L/min)	3.9 (3.3–4.5)	4.2 (3.5–4.9)	0.072
LA volume indexed to BSA (mL/m^2)	24 (20–30)	24 (20–29)	0.921
LA ejection fraction (%)	66 (62–71)	68 (63–72)	0.257
LA reservoir strain (%)	6.3 (4.8–8.6)	6.4 (4.5–8.6)	0.558
LA conduit strain (%)	−4.1 (−5.5 to −2.9)	−4.2 (−5.8 to −3.0)	0.245
LA contraction strain (%)	−2.4 (−3.3 to −1.5)	−1.9 (−3.0 to −1.1)	0.022
Tricuspid annular plane systolic excursion (mm)	19.1 (17.2–22.1)	20.7 (17.4–23.8)	0.049
RV fractional area change (%)	45.1 (40.3–48.7)	43.9 (39.8–47.8)	0.297
RV end-diastolic volume indexed to BSA (mL/m^2)	50.5 (44.1–57.1)	56.3 (47.9–64.0)	< 0.001
RV end-systolic volume indexed to BSA (mL/m^2)	24.8 (22.1–27.7)	26.9 (23.4–31.7)	< 0.001
RV ejection fraction (%)	50.1 (48.2–53.3)	50.1 (48.3–53.6)	0.872
RV global longitudinal strain (%)	−22.2 (−26.1 to −19.8)	−24.1 (−27.0 to −21.9)	< 0.001

Data are given as median (interquartile range). Comparisons between groups were made using Mann–Whitney *U*-test. BSA, body surface area; LA, left atrial; LV, left ventricular; RV, right ventricular.

GDM, our findings would suggest the presence of subclinical right ventricular dysfunction in women with GDM, consistent with changes reported in Type-2 diabetes at a young age[18,31].

Implications for clinical practice

In the current study, we used novel echocardiographic techniques to quantify cardiac function and structure in women with GDM and in those with uncomplicated pregnancy. We showed that GDM is associated with subtle biventricular systolic functional changes which can be detected using speckle-tracking imaging. In addition, we demonstrated, using 3D echocardiography, that cardiac volumes and left ventricular mass are not modified shortly after GDM development.

Strengths and limitations

The main strengths of this study are, first, detailed cardiac functional assessment of the left and right ventricles using the novel and reproducible techniques of speckle-tracking and 3D echocardiography, and, second, using standardized methodology, we demonstrated that speckle tracking is a sensitive method to detect early right and left alterations in myocardial deformation. The main limitations of this study are that our population was primarily of white origin, thus our results might not be applicable to women of other racial origins. Similarly, women with GDM were either on dietary management or insulin therapy and, therefore, our results may not apply to women who receive oral hypoglycemic therapy. Previous studies have also shown that 2D myocardial strain measurements vary when equipment from different vendors is used for analysis and this should be considered when comparisons between studies are made[32].

Conclusions

In women with GDM who have good glycemic control, there are subtle biventricular functional changes and these can be detected using 2D speckle-tracking imaging. 3D echocardiography did not demonstrate any significant differences in left ventricular mass or ejection fraction. Considering that all functional measurements were within the appropriate normal range for gestational age, our data would not support the presence of an acute detrimental effect of GDM on maternal cardiac function. Further studies are needed to describe the pattern of deterioration of cardiac function with advancing age in women with a history of GDM and to quantify whether management and modification of conventional cardiovascular risk factors in the postpartum period can delay the development of cardiovascular disease in these women.

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