OBSTETRICS

Paired maternal and fetal cardiac functional measurements in women with gestational diabetes mellitus at 35–36 weeks' gestation

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BACKGROUND: Gestational diabetes mellitus is associated with early-onset cardiovascular disease and increased incidence of adverse cardiovascular outcomes in mothers and their offspring. Few studies with a limited number of patients have reported subclinical cardiac changes in association with gestational diabetes mellitus; however, it remains unclear whether the mother and the fetus respond in a similar fashion to gestational diabetes mellitus; thus, by assessing the heart of one, we can estimate or predict changes in the other.

OBJECTIVE: This study aimed to compare maternal and fetal cardiovascular functions in the third trimester between women with gestational diabetes mellitus and women with uncomplicated pregnancy and to explore whether gestational diabetes mellitus affects to the same extent the maternal and fetal heart.

STUDY DESIGN: This was a cross-sectional study of maternal and fetal echocardiography for assessment of cardiovascular function in the third trimester in women with singleton pregnancies who received a diagnosis of gestational diabetes mellitus and the control group with uncomplicated pregnancies.

RESULTS: In this study, we included 161 women with gestational diabetes mellitus and 483 women with uncomplicated pregnancies. Compared with women in the control group, women with gestational diabetes mellitus were older (34.5, standard deviation, 5.3 years] vs 32.5, standard deviation, 4.8 years]; $P<.001$), had higher body mass index (31.3 kg/m^2 [standard deviation, 5.8] vs 28.6 kg/m^2 [standard deviation, 4.4]; $P<.001$), had lower weight gain during pregnancy (8.3 [interquartile range, 4.8–11 kg] vs 10.8 [interquartile range, 8.2–13.5 kg]; $P<.001$), and delivered babies with lower birthweight ($P<.001$). After multivariable analysis, accounting for differences in maternal characteristics and fetal weight, mothers with gestational diabetes mellitus had lower left ventricular diastolic and systolic (tissue Doppler systolic [s'] wave) functional indices ($P<.01$ for both) compared with those of mothers in the control group. The noted cardiac changes did not fulfill the adult criteria for clinical cardiac dysfunction. No differences in hemodynamic indices (cardiac output and peripheral vascular resistance) and left ventricular mass were noted between the groups. Fetuses of mothers with gestational diabetes mellitus had more globular-shaped hearts with increased right and left ventricular sphericity indices ($P<.001$ for both) and reduced global longitudinal right and left ventricular systolic functional indices ($P<.001$ for both). The effect of gestational diabetes mellitus on maternal and fetal hearts was different, and there was no clear association between the two.

CONCLUSION: In the third trimester, in pregnancies with gestational diabetes mellitus, there were subclinical cardiac changes in both the mother and the fetus, but there was no significant difference in any of the fetal cardiac parameters between women with and women without unfavorable cardiac profile. This suggests that the stimulus for cardiovascular responses in the mother and fetus may not be the same in pregnancies with gestational diabetes mellitus.

Key words: deformation, diastolic cardiac function, systolic cardiac function

Introduction

Gestational diabetes mellitus (GDM) is the most common pregnancy complication among all ethnic groups[1] and is associated with short- and long-term risks for the health of the mother and her fetus and/or child.[2–6] Compared with women with uncomplicated pregnancies, women with GDM are at an increased risk of developing type 2 diabetes mellitus and cardiovascular (CV) events within the first decade after delivery.[7,8] In addition, offspring of mothers with GDM have a higher incidence of early-onset CV disease from childhood to adulthood compared with offspring who have not been exposed prenatally to a hyperglycemic environment.[9,10] Despite these observations, the link between GDM and CV disease remains largely unexplored, and there are no studies reporting that the increased susceptibility to CV events affects the mother and baby pairs. Few studies with small numbers of women reported that GDM is associated with subclinical cardiac changes in both the mother[11–13] and the fetus[14–17] such as evidence of diastolic and systolic biventricular function abnormalities and fetal cardiac morphologic changes. However, none of these studies examined maternal and fetal pairs; therefore, it is uncertain whether there is a common stimulus for CV responses in the mother and fetus.

To better understand the impact of GDM on the maternal and fetal CV system, we analyzed cardiac data that were collected as part of an extensive prospective CV phenotype study of women who developed GDM at 35–36 weeks' gestation and compared them with healthy pregnant women of the same gestational age. Our study aimed to assess the differences in maternal and fetal CV functional parameters close to term between pregnancies exposed to GDM and uncomplicated pregnancies

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AJOG at a Glance

Why was this study conducted?

This study aimed to compare maternal and fetal cardiovascular function in the third trimester between women with gestational diabetes and women with uncomplicated pregnancies and to explore whether gestational diabetes affects to the same extent the maternal and fetal heart.

Key findings

Compared with women in the control group, women with gestational diabetes had lower left ventricular diastolic and systolic functional indices. Furthermore, compared with fetuses in the control group, fetuses of mothers with gestational diabetes had more globular-shaped hearts with increased right and left ventricular sphericity indices and subclinical biventricular systolic cardiac dysfunction. There was no significant difference in any of the fetal cardiac parameters between women with and women without unfavorable cardiac profile.

What does this add to what is known?

In pregnancies with gestational diabetes, there were subclinical cardiac changes in both the mother and the fetus, but there was no significant difference in any of the fetal cardiac parameters between women with and women without unfavorable cardiac profile.

after controlling for differences in CV risk factor profile and to assess whether fetal and maternal cardiac functional changes are influenced in the GDM population, in that mothers with worse CV function have fetuses with impaired cardiac function as well.

Methods

Study design and participants

Our study population included women who attended the Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, United Kingdom, for routine growth scan at 35−36 weeks' gestation[18,19] and participated in the Advanced Cardiovascular Imaging Study (Research Ethics Committee no. 18/NI/0013; Integrated Research Application System ID: 237936). In the previous substudy, we analyzed women with singleton pregnancy who received a diagnosis of GDM, and for each GDM case, we included, as controls, 3 pregnant women who had uncomplicated pregnancy and were assessed with the GDM participants. From the study, we excluded women with previous known CV disease, gestational or preexisting hypertensive disorder, thyroid disease without treatment, fetal structural defects, or chromosomal abnormalities. Women with breast implants were also excluded as implants commonly compromise the echocardiographic acoustic windows.[20] All women provided written informed consent to participate in the study. Data on pregnancy outcomes were collected from hospital delivery records or from general medical practitioners.

The diagnosis of GDM was made by performing the 2-step approach recommended by the National Institute for Health and Care Excellence guidelines.[21] The screening test that was performed at 24−28 weeks' gestation was a 50-g oral glucose tolerance test; if plasma glucose after 1 hour was >6.7 mmol/L, a second oral glucose tolerance test was performed as a diagnostic test. GDM was diagnosed if 2 or more plasma glucose measurements met or exceeded the following thresholds: fasting glucose level >5.6 mmol/L or 2-hour plasma glucose level >7.8 mmol/L. After 28 weeks' gestation, if there was polyhydramnios and/or estimated fetal weight for gestation >95th centile, an oral glucose tolerance test was performed.[21] Management of GDM was based on target glucose ranges. Insulin and metformin were used when dietary management failed. To exclude the presence of type 2 diabetes mellitus, all patients with GDM were offered a fasting plasma glucose test 6−13 weeks after birth.

Maternal characteristics and cardiovascular assessment

We recorded information on maternal age, racial origin (white, black, Asian, and mixed), method of conception (natural or assisted by in vitro fertilization), cigarette smoking during pregnancy, medical history, medications, and parity (nulliparous if there was no previous pregnancy with delivery at ≥24 weeks' gestation). Weight and height were measured in all women.

Using validated devices, mean arterial pressure was measured during pregnancy and after delivery.[22] No information on maternal lipid profile was available. Maternal echocardiography was performed using a Canon Aplio i900 scanner (Canon Medical Systems Europe BV, Zoetermeer, the Netherlands). As per guidelines by the European Association of Cardiovascular Imaging-American Society of Echocardiography (EACVI/ASE), the protocol included standard parasternal and apical views.[23] Hemodynamic and detailed systolic and diastolic left ventricular (LV) functional assessment was performed.[24] Cardiac output was calculated from stroke volume (derived from the LV outflow tract velocity−time integral) multiplied by heart rate. Left atrial area was calculated in end-systole from the 4-chamber view. The LV mass was calculated with the Devereux formula using measurements of the anatomic M-mode applied in the parasternal long axis.[23] Tricuspid annular plane systolic excursion (TAPSE) was measured using M-mode in the right ventricular (RV) lateral wall. The mitral peak early (E) and late (A) diastolic flow velocities were measured from Doppler waveforms of blood flow, and the E/A ratio was calculated. Pulsed tissue Doppler images were obtained at the septal and lateral aspects of basal left ventricle at the junction with the mitral valve annulus in the apical 4-chamber view. The ratio

TABLE 1
Characteristics of the study population

Variable	Controls (n=483)	Gestational diabetes (n=161)	*P* value
Age, y	32.4 (4.8)	34.5 (5.3)	<.001
Race			
White	347 (71.8)	88 (54.7)	—
Black	83 (17.2)	38 (23.6)	—
Asian	34 (7.0)	26 (16.2)	—
Mixed	19 (3.9)	9 (5.6)	<.001
Weight, kg	76.5 (70.0–85.9)	82 (72–96)	<.001
Height, cm	166 (161–170)	164 (159–168)	.002
Body mass index, kg/m^2	28.6 (4.3)	31.3 (5.8)	<.001
Parous	239 (49.5)	93 (57.8)	.069
Conception by in vitro fertilization	23 (4.8)	14 (8.7)	.063
Cholestasis	1 (0.0)	1 (0.62)	.427
Smoking	4 (0.8)	2 (1.24)	.636
Systolic blood pressure, mm Hg	118 (9.0)	119 (10.6)	.048
Diastolic blood pressure, mm Hg	72.7 (6.6)	74.4 (7.5)	.007
Mean arterial pressure, mm Hg	87.6 (6.5)	89.1 (8.0)	.022
Heart rate, beats/min	81 (72–89)	82 (73–92)	.094
Weight gain, kg	10.8 (8.2–13.5)	8.3 (4.8–11)	<.001
Gestational week at study, wk	36.0 (35.8–36.2)	36.0 (35.8–36.2)	.317
Estimated fetal weight, kg	2900 (2728–3048)	2900 (2741–3112)	.164
Estimated fetal weight z-score	0.47 (0.88)	0.64 (1.09)	.047
Small for gestational age, n (%)	47 (9.7)	17 (10.6)	.761
HbA1c	—	5.6 (5.3–5.9)	—
Delivery (cesarean delivery)	97.0 (20.1)	61 (37.9)	.983
Gestational week at delivery, wk	40.1 (39.29–41.0)	39.3 (38.7–40.0)	<.001
Birthweight, kg	3500 (3222/3745)	3,300 (3055/3645)	<.001
Birthweight z-score	0.086 (0.896)	0.057 (1.22)	.750

Measurements are presented as median (interquartile range), mean (standard deviation), or n (%). *P* values are derived from the parametric independent *t*-test, nonparametric Mann-Whitney *U* test, or Pearson's chi-square test.

Small for gestational age, estimated fetal weight <10th centile for gestation.

HbA1c, glycosylated hemoglobin.

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between early mitral inflow velocity and mitral annular early diastolic velocity (E/e') was calculated using the mean value between septal and lateral peak e' waves. Timing intervals (isovolumic contraction time [IVCT] and isovolumic relaxation time [IVRT]) were calculated from tissue Doppler measurements. Speckle tracking echocardiography (STE) was used to assess global longitudinal strain (GLS) of the left ventricle.

Fetal ultrasound examination and echocardiography

To assess fetal growth and to estimate fetal weight, prenatal ultrasonographic examination was performed using a Canon Aplio i900 scanner.[25] Values were converted to z-scores based on the Fetal Medicine Foundation fetal weight chart.[26]

The fetal heart was assessed in all cases and controls using Canon Aplio i900 machines equipped with a convex transducer (10C3 and i8CX1). The LV and RV sphericity indices were measured by dividing transverse diameter at the

TABLE 2
Comparison of maternal cardiac parameters between gestational diabetes mellitus and controls

Variable	Controls (n=483)	Gestational diabetes (n=161)	*P* value
Systemic vascular resistance (mm Hg×min×L^{-1})	1396.7 (1220.4–1641.8)	1384.7 (1169.2–1628.9)	.035
Cardiac output (L/min)	5.0 (4.3–5.7)	5.1 (4.4–5.9)	.141
Diastolic indices			
Isovolumic relaxation time (ms)	68 (56–83)	75 (58–89)	.009
E/A	1.38 (1.18–1.67)	1.3 (1.1–1.59)	.02
E/e'	5.8 (4.9–6.9)	6.5 (5.2–7.6)	<.001
e' (cm/s)	8.0 (7.1–8.9)	8.3 (7.1–9.5)	.021
a' (cm/s)	12.9 (11.3–14.8)	11.7 (10.4–13.4)	<.001
Left atrium volume indexed to body surface area (cm^3)	17.6 (14.1–21.2)	18.8 (14.6–23.6)	.036
Systolic indices and left ventricular mass			
s' average, median (cm/s)	9.9 (8.8–11.0)	9.5 (8.4–10.6)	.013
Myocardial performance index	0.5 (0.4–0.6)	0.5 (0.4–0.6)	.117
Ejection fraction (%)	58.5 (54.9–62.9)	59.0 (3.7–63.4)	.958
Global longitudinal strain (%)	−21.4 (−23.2 to −19.8)	−21.1 (−22.6 to −19.6)	.052
Left ventricular mass indexed to body surface area (g/m^2)	114 (100–131)	122 (103–143)	<.001

Measurements are presented as median (interquartile range) or n (%). *P* values are derived from the parametric independent *t*-test, nonparametric Mann-Whitney *U* test, or Pearson's chi-square test.
a', peak late diastolic mitral annular velocity; *A*, peak late diastolic flow velocities; *e'*, peak early diastolic mitral annular velocity; *E*, early mitral inflow velocity; *s'*, peak systolic mitral annular velocity.
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base by the base-to-apex length for each ventricle on 2-dimensional images from an apical 4-chamber view at end-diastole. Cardiac function was assessed using conventional and tissue Doppler imaging (TDI) and STE.[27] Fetal heart rate was calculated using spectral Doppler imaging of the aortic flow. Left myocardial performance index was obtained using pulsed wave Doppler in a cross-section of the fetal thorax at the 5-chamber view with sample volume including aortic and mitral flows; valvular clicks in the Doppler wave were used as landmarks to calculate each time period.[28] Systolic functional assessment included TAPSE using M-mode, systolic annular peak velocities (S'), and IVCT from Doppler waveforms of blood flow.[27]

Diastolic function was evaluated by peak early (E) and late (A) transmitral filling and IVRT using Doppler waveforms of blood flow, and the E/A ratio was then calculated. TDI was applied in the mitral lateral and septal annuli from an apical or basal 4-chamber view to calculate early (e') and late (a') myocardial Doppler velocities, and the E/e' ratio was calculated.[27] Myocardial deformation of the left and right ventricles was measured in the apical 4-chamber view. All images were acquired at 100 to 160 frames/s.[29] The raw data of the generated 4-chamber clips were exported from the ultrasound machine so that the original frame rate was available for offline analysis using proprietary special speckle tracking software (Vitrea, Canon). Each clip had a duration of 3.5 seconds so that a cardiac cycle could be selected for analysis, with the endocardium being most clearly delineated and with the least fetal movements. The results of the speckle tracking analysis included the values for endocardial GLS from the right and left ventricles, diastolic peak strain rate (E and A), and heart rate. When comparing 2 strain values in this analysis, we refer to the more negative number as the higher strain as it represents increased deformation and refer to the less negative values as the lower strain. Analysis was performed by 2 trained operators.

Statistical analysis

In this study, distributed continuous variables were presented as mean (± standard deviation) and variables not following normal distribution as median (25th to 75th percentile). Nominal variables were summarized as counts and absolute percentages. Distribution of continuous variables was graphically assessed by histograms and quantile-quantile plots. Differences among subgroups of GDM treatment (diet, metformin, insulin, and combination of treatment) were assessed by one-way analysis of variance or Kruskal-Wallis test for continuous parameters and chi-square test for nominal variables. We used the nonparametric Mann-Whitney test to compare maternal and fetal

TABLE 3
Regression analysis of maternal cardiac parameters in gestational diabetes mellitus vs controls

	Unadjusted		Adjusted for maternal characteristics[a]		Adjusted for maternal characteristics[a] and estimated fetal weight	
Variable	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value
E/A	−0.22 (−0.40 to −0.043)	.015	−0.09 (−0.27 to 0.08)	.292	−0.09 (−0.26 to 0.08)	.299
E/e'	0.36 (0.18−0.53)	<.001	0.22 (0.03−0.41)	.0211	0.22 (0.034−0.41)	.019
s'	−0.23 (−0.40 to −0.05)	.014	−0.22 (−0.40 to −0.04)	.02	−0.22 (−0.41 to −0.04)	.019
Isovolumic relaxation time	0.23 (0.05−0.406)	.013	0.19 (0.01−0.38)	.047	0.19 (0.01−0.38)	.049
Myocardial performance index	0.14 (0.04−0.32)	.119	0.10 (−0.09 to 0.29)	.29	0.10 (−0.09 to 0.28)	.298
Left atrium volume indexed for body surface area	0.19 (0.02−0.37)	.037	0.12 (−0.07 to 0.30)	.214	0.11 (−0.07 to 0.230)	.238
LV mass indexed for body surface area	0.29 (0.12−0.47)	.001	0.09 (0.08−0.26)	0.274	0.09 (−0.08 to 0.26)	.302
Global longitudinal LV systolic function	0.22 (0.04−0.41)	.019	0.11 (0.07−0.29)	.243	0.11 (−0.07 to 0.29)	.244
Cardiac output	0.201 (0.03−0.39)	.022	−0.02 (−0.18 to 0.14)	.796	−0.02 (−0.18 to 0.13)	.772
Peripheral vascular resistance	0.16 (−0.02 to 0.34)	.084	−0.02 (−0.19 to 0.16)	.857	−0.02 (−0.19 to 0.15)	.834

A, peak late diastolic flow velocities; *CI*, confidence interval; *e'*, peak early diastolic mitral annular velocity; *E*, early mitral inflow velocity; *LV*, left ventricular; *s'*, peak systolic mitral annular velocity.

[a] Maternal characteristics in the analysis adjusted for age, weight, height, mean arterial pressure, heart rate, race, parity, and gestational age.

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cardiac measurements between the GDM group and the control group. To avoid inflation of type I error, the Sidak correction for multiple pairwise comparisons with the prespecified reference category was used.

General linear regression models were used to assess the association between GDM and a range of echocardiographic parameters. To ensure normality assumptions in regression analyses, we used the inverse ranking normalization for all continuous variables used in respective models[30] (see Statistical section). Maternal cardiac parameters that were used as outcome variables included structural markers (LV mass indexed for body surface area) and functional parameters (E/A, E/e', GLS) that have been shown to be altered during pregnancy as part of the maternal CV adaptation.[31,32] The analysis was further adjusted for a range of maternal characteristics that have been found to affect cardiac functional indices (ie, age, weight, height, heart rate, mean arterial pressure, race, parity, and gestational age) and fetal weight.[1]

Statistical analysis was conducted with Stata package, version 13.1 (StataCorp, College Station, TX). The packages "dunntest" and "pwcompare" were implemented for correction of multiple comparisons, whereas the commands "rank" and "invnormal" were sequentially used for inverse ranking normalization of continuous dependent variables. The module "regress" was used in all regression analyses. Statistical significance was at $P<.05$.

Results

Study population

The study included 161 women with GDM and 483 women with uncomplicated pregnancies. According to the GDM status, demographic characteristics are shown in Table 1. Compared with women in the control group, women with GDM were older, had higher body mass index (BMI), had lower weight gain during pregnancy, and delivered babies with lower birthweight. Systolic, diastolic, and mean arterial pressures were also increased in patients with GDM compared with patients in the control group.

Maternal cardiac functional indices

Compared with women in the control group, women with GDM had higher LV mass (122 [interquartile range, IQR, 103−143 g/m^2] vs 114 [IQR, 100−131 g/m^2]; $P<.001$) and lower tissue Doppler systolic (s') wave and GLS. Furthermore, a higher E/e', left atrial area and prolonged IVRT (75 [IQR, 58−89 ms] vs 68 [IQR, 56−83 ms]) were observed in women with GDM ($P<.009$) compared with women in the control group (Table 2). Following multivariable analysis, accounting for maternal characteristics and fetal weight, only LV diastolic functional indices remained significant, and for systolic parameters, tissue Doppler LV systolic wave remained lower in patients with GDM compared with patients in the control group (Table 3). There was no significant difference in cardiac output and peripheral vascular resistance between the groups.

Among the 161 women in the GDM group, 54 (33.5%) were treated by diet alone, 52 (32.3%) were given metformin, 17 (10.6%) took insulin, and 38 (23.6%) were given both metformin and insulin. Only 15 women (9.1%) had

TABLE 4
Comparison of fetal cardiac parameters in gestational diabetes mellitus and controls

Variable	Controls	Gestational diabetes	*P* value
Heart rate (beats/min)	140 (134–147)	139 (133–148)	.944
Diastolic indices			
E/A	0.82 (0.72–0.93)	0.83 (0.75–0.94)	.296
E/e'	9.35 (7.93–11.01)	9.26 (7.64–11.10)	.753
Isovolumic relaxation time (s)	0.05 (0.05–0.06)	0.05 (0.05–0.06)	.579
Diastolic peak left ventricular strain rate E	−2.06 (−2.55 to −1.78)	−2.06 (−2.50 to −1.74)	.750
Diastolic peak left ventricular strain rate A	−1.68 (−2.01 to −1.40)	−1.7 (−2.03 to −1.47)	.335
Diastolic peak right ventricular strain rate E	−1.96 (−2.43 to −1.57)	−1.76 (−2.33 to −1.52)	.053
Diastolic peak right ventricular strain rate A	−1.52 (−1.81 to −1.3)	−1.42 (−1.72 to −1.26)	.160
Systolic indices			
Left ventricular tissue Doppler s' (cm/s)	4.15 (3.74–4.95)	4.2 (3.65–4.75)	.279
Isovolumic contraction time (s)	0.04 (0.03–0.05)	0.04 (0.04–0.05)	.522
Myocardial performance index	0.58 (0.5–0.68)	0.60 (0.52–0.67)	.404
Left ventricular ejection fraction (%)	0.62 (0.55–0.69)	0.58 (0.53–0.65)	<.001
Left ventricular endocardial global longitudinal strain (%)	−20.7 (−22.8 to −18.3)	−19.7 (−21.9 to −17.1)	.001
Tricuspid annular plane systolic excursion (mm)	7.6 (6.6–8.5)	7.6 (6.6–8.4)	.818
Right ventricular endocardial global longitudinal strain (%)	−19.1 (−20.9 to −17.4)	−16.6 (−18.8 to −15.2)	<.001
Morphometry			
Right ventricular sphericity index	0.58 (0.53–0.63)	0.62 (0.57–0.69)	<.001
Left ventricular sphericity index	0.51 (0.47–0.56)	0.53 (0.48–0.61)	.035

Measurements are presented as median (interquartile range). *P* values are derived from the parametric independent *t*-test, nonparametric Mann-Whitney *U* test, or Pearson's chi-square test.

A, peak late diastolic flow velocities; *e'*, peak early diastolic mitral annular velocity; E, early mitral inflow velocity; *s'*, peak systolic mitral annular velocity.

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glycosylated hemoglobin measurements higher than 6% during pregnancy. Differences between maternal characteristics and cardiac functional indices between the GDM treatment group and control group are listed in Supplemental Table 1.

Fetal cardiac functional indices

Compared with fetuses in the control group, fetuses of mothers with GDM had more globular-shaped hearts with higher RV and LV sphericity indices ($P<.001$ for both). Lower peak RV systolic GLS (−16.6% [IQR, −18.8 to −15.2] vs −19% [IQR, −20.9 to −17.4]; $P<.001$) and peak LV systolic GLS (19.7% [IQR, −21.9 to −17.1] vs −20.7% [IQR, −22.8 to −18.3]; $P=.001$) were observed in the GDM group compared with the control group (Table 4). LV ejection fraction was also lower in the GDM group compared with the control group. Following multivariable analysis, adjusting for maternal characteristics, estimated fetal weight, and fetal heart rate, the noted associations remained significant (Table 5).

Fetuses whose mothers were treated with insulin had lower global longitudinal RV systolic function compared with that of fetuses in the control group; furthermore, no significant differences in other morphologic or functional fetal cardiac indices were noted between treatment groups (Supplemental Table 2).

Paired analysis of maternal and fetal cardiovascular responses

Considering significant adjusted differences between pregnancies exposed to GDM and controls with respect to tissue Doppler imaging s' wave, IVRT, and E/e', we further divided women with GDM into 2 subgroups: women with an unfavorable cardiac profile (group 1), characterized by at least 2 parameters (including 1 systolic and 1 diastolic) with abnormal distribution (ie, lowest tertile of tissue Doppler imaging s' wave, lowest tertile of IVRT, and highest tertile of E/e'), and women with a normal cardiac profile (none or maximum 1 systolic or diastolic parameter with abnormal distribution; group 2). There was no significant difference between group 1 and group 2 in any fetal cardiac parameters (Table 6).

Comment

Main findings of the study

This study of contemporaneous third-trimester detailed maternal and fetal cardiac functional assessment has

TABLE 5
Regression analysis of fetal cardiac parameters between gestational diabetes mellitus and controls

Variable	Unadjusted		Adjusted values[a]	
	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value
Diastolic indices				
E/A	0.09 (−0.09 to 0.27)	.353	0.12 (−0.07 to 0.31)	.219
E/e'	−0.02 (−0.21 to 0.17)	.835	−0.0016 (−0.205 to 0.202)	.988
Isovolumic relaxation time (s)	−0.042 (−0.22 to 0.14)	.651	−0.042 (−0.235 to 0.151)	.670
Systolic indices				
Tricuspid annular plane systolic excursion (mm)	0.00011 (−0.180 to 0.183)	.999	−0.0209 (−0.21 to 0.17)	.831
Right ventricular endocardial GLS (%)	0.48 (0.28−0.69)	<.001	0.55 (0.33−0.76)	<.001
Left ventricular myocardial performance index	0.09 (−0.09 to 0.27)	.344	0.057 (−0.14 to 0.25)	.561
Left ventricular ejection fraction (%)	−0.39 (−0.59 to −0.18)	.00022	−0.38 (−0.60 to −0.16)	.00062
Left ventricular endocardial GLS (%)	0.40 (0.19−0.60)	.00013	0.42 (0.20−0.64)	.00017
Morphometry				
Right ventricular sphericity index	0.63 (0.43−0.83)	<.001	0.58 (0.37−0.79)	<.001
Left ventricular sphericity index	0.27 (0.06−0.48)	.0106	0.24 (0.02−0.46)	.0356

Measurements are presented as median (interquartile range).

A, peak late diastolic flow velocities; *CI*, confidence interval; *e'*, peak early diastolic mitral annular velocity; *E*, early mitral inflow velocity; *GLS*, global longitudinal strain.

[a] Values were adjusted for maternal age, height, race, parity, weight gain, gestational age, fetal heart rate, and estimated fetal weight.

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demonstrated the following: first, women with GDM had worse cardiac function with lower LV diastolic and systolic functional indices compared with women in the control group, and LV mass was comparable between groups after accounting for differences in maternal characteristics; second, fetuses of mothers with GDM had more globular-shaped hearts with higher RV and LV sphericity indices and reduced deformation compared with those of fetuses in the control group, indicating subclinical biventricular systolic cardiac dysfunction; and third, in pregnancies exposed to GDM, there was no significant difference in any of the fetal cardiac parameters between women with and without unfavorable cardiac profile, suggesting that the stimulus for CV responses in the mother and fetus may not be the same.

Interpretation of results and comparison with existing literature

By definition, gestational diabetes is a transient condition; however, there are data to suggest that women with GDM continue to be at an increased risk for adverse health outcomes in the postpartum period and long after. For instance, an increased risk for type 2 diabetes and CV disease has been reported within the first decade for mothers with GDM. Although the association between GDM and CV risk was thought to be mediated by the development of type 2 diabetes,[33] a number of research studies and a previous meta-analysis suggest that this association is present even in the absence of type 2 diabetes.[34] However, most of the reported data are derived from cohort studies with incomplete information on risk factor profile.[35−37] Thus, it is difficult to assess whether the reported association between GDM and CV risk is the result of an acute and possibly sustained insult on the CV system because of the transient exposure to GDM or is the result of a prolonged exposure to an adverse CV risk factor profile.

We found that women with GDM had reduced myocardial relaxation compared with that of women with uncomplicated pregnancies. From the different cardiac indices, tissue Doppler parameters were more sensitive to identify subclinical cardiac functional alterations in women with GDM compared with women in the control group. Our findings complement results of 2 previously reported studies in 13 and 18 women with GDM, respectively, where a mild degree of diastolic abnormality was reported both during pregnancy and after delivery[11,12]; as per European or American guidelines, the diastolic changes were subtle and did not fulfill the criteria for adult clinical diastolic dysfunction.[38,39] In contrast, another study involving 40 women with GDM reported increased LV wall thickness and decrease LV GLS; however, in that study, no adjustments were made for maternal characteristics despite the fact that the BMI and blood pressure in the GDM group were higher than in the control group.[13] In our study, global longitudinal LV functional changes and LV mass in women with GDM were not significantly different from women in

TABLE 6
Comparison of fetal cardiac function according to the upper and lower tertiles of cardiac function in mothers with gestational diabetes mellitus

Variable	Abnormal cardiac profile[a] (group 1)	Normal cardiac profile (group 2)	*P* value
Fetal diastolic cardiac indices			
E/A	0.85 (0.78–0.95)	0.82 (0.73–0.92)	.11
E/e'	8.46 (7.42–10.60)	9.57 (7.71–11.5)	.13
Isovolumic relaxation time (s)	0.05 (0.05–0.06)	0.05 (0.05–0.06)	.64
Fetal systolic cardiac indices			
Tricuspid annular plane systolic excursion (mm)	7.5 (6.50–8.40)	7.6 (6.70–8.45)	.47
Right ventricular endocardial GLS (%)	−16.7 (−18.9 to −15.5)	−16.4 (−18.5 to −15.1)	.40
Left ventricular myocardial performance index	0.59 (0.49–0.65)	0.60 (0.52–0.68)	.30
Left ventricular ejection fraction (%)	0.60 (0.48–0.63)	0.57 (0.53–0.65)	.75
Left ventricular endocardial GLS (%)	−19.1 (−20.7 to −16.9)	−19.8 (−22.3 to −17.3)	.44
Fetal cardiac morphometry			
Right ventricular sphericity index	0.62 (0.59–0.68)	0.61 (0.56–0.71)	.70
Left ventricular sphericity index	0.54 (0.48–0.62)	0.52 (0.48–0.59)	.49

Measurements are presented as median (interquartile range). *P* values are derived from the parametric independent *t*-test, nonparametric Mann-Whitney *U* test, or Pearson's chi-square test.

A, peak late diastolic flow velocities; *CI*, confidence interval; *e'*, peak early diastolic mitral annular velocity; *E*, early mitral inflow velocity; *GLS*, global longitudinal strain; *IVRT*, isovolumic relaxation time; *TDI*, tissue Doppler imaging.

[a] Abnormal cardiac profile was defined as lowest tertile of TDI S wave, lowest tertile of IVRT, and highest tertile of E/e'. Normal cardiac profile was defined as none or maximum 1 systolic or diastolic parameter with abnormal distribution.

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the control group after adjustment for maternal characteristics.

Gestational diabetes had an effect not only on the maternal CV system but also on the fetal heart. We used conventional and more advanced echocardiographic techniques to assess RV and LV functions. Consistent with previous reports, we showed the presence of early subclinical systolic functional impairment as assessed by STE in fetuses of mothers with GDM.[14] Functional changes were more pronounced in the right rather than the left ventricle. This was anticipated considering that there is RV dominance in the third trimester. Cardiac functional changes in fetuses of women with GDM can be a reaction to the effects of fetal hypoxemia[40] and may present initially with a compensatory period of increased LV contractility that is then followed by increased ventricular wall stress resulting in myocardial cell damage, myocyte death, and impaired ventricular function. These early systolic functional differences between fetuses exposed to GDM and fetuses in the control group remained after accounting for maternal characteristics and estimated fetal weight and fetal heart rate. Fetuses of mothers with GDM had more spherical hearts compared with those of fetuses in the control group, which is consistent with the data of Patey et al,[15] 21 fetuses of mothers with pregestational and gestational diabetes. In our study, both conventional and tissue Doppler diastolic fetal cardiac functional measurements were comparable between groups, and the finding was in agreement with a study by Miranda et al,[14] 76 fetuses of mothers with GDM at 31 weeks' gestation, but contradicts results by Balli et al,[17] 67 fetuses where measurements were performed at 24–36 weeks' gestation, and a study by Mohsin et al,[41] 50 fetuses of mothers with GDM at around 23 weeks' gestation. In the latter 2 studies, most of the abnormalities were noted in fetuses whose mother had poor diabetic control, and this together with differences in gestational age may account for the discrepancy in results from our study. However, in the study of Miranda et al,[14] subclinical diastolic abnormalities could be detected by speckle tracking analysis; both right and left early and late diastolic strain rate measurements were lower in fetuses of mothers with GDM compared with those of fetuses in the control group. Diastolic functional analysis by STE relies on measuring the rate of myocardial deformation (strain rate), which is often limited by temporal resolution, making values more variable, and this may account for the discrepancy in the reported findings. It is also possible that the noted differences between our study and that by Miranda et al[14] relate to the reported variability in measurements when fetal myocardial deformation is assessed by different ultrasound machines and software for analysis.[42]

In this study, the assessment of the mother and the fetus provided us with the opportunity to explore whether there is "pairing" in the degree of maternal and

fetal cardiac functional responses. Considering that none of the women with GDM fulfilled the criteria for clinical cardiac dysfunction, we elected to divide the population into tertiles. As a result, no relationship in fetal and maternal CV responses could be identified. These findings would possibly suggest that different pathways contribute to maternal and fetal cardiac functional changes in GDM and that assessment of both the mother and the fetus is needed to identify those who would benefit from postnatal CV assessment.

In the management of GDM, insulin therapy is often added when alterations in lifestyle and use of oral hypoglycemic agents fail to establish good glycemic control. Although insulin may have growth-stimulating effects on the myocardium, which may affect remodeling of the left ventricle,[43,44] in our study, there were no significant differences in maternal cardiac indices between treatment groups. Thus, our findings did not support an adverse effect of insulin on maternal cardiac function. Fetal cardiac functional indices were mostly unaffected by maternal diabetic treatment. From the different hypoglycemic treatments, it has been well described that metformin crosses the placenta, and concerns were raised regarding a potentially harmful effect of the medication to the fetal heart with sustained effects in childhood.[45] However, the results of this study would not support such a hypothesis.

The mechanisms by which GDM increases the woman's CV risk are not well explored. Although some pathways may be mediated through subsequent development of type 2 diabetes mellitus or increased exposure to CV risk factors, other mechanisms may also contribute.[46] Consistent with previous reports, compared with women in the control group, women with GDM in this study had an adverse risk factor prolife: they were older, had increased weight and blood pressure, and more were of African origin; however, in contrast to previous reports, weight gain and fetal weight were lower.[47] Although the mechanisms that link acute hyperglycemia with maternal cardiac dysfunction are not well explored, more information is available for the effect of hyperglycemia on the fetal heart. A number of experimental studies have shown that exposure to a hyperglycemic environment during pregnancy can be associated with myocardial remodeling; increased glucose can induce cardiomyocyte hyperplasia and alterations in myocardial architecture and metabolism.[48] These findings are consistent with the changes in myocardial shape and function noted in our study.

Strengths and limitations

The strengths of our study include paired maternal and fetal CV assessment in a large number of pregnancies affected by GDM and healthy controls within a narrow gestational age window in the third trimester, close monitoring of GDM to achieve good glycemic control, and CV assessments undertaken by operators who had received extensive training that demonstrated high reproducibility in measurements.[24]

Our study also has some limitations. The noted maternal and fetal cardiac functional changes were subtle, and it remained unclear whether these were associated with fasting blood glucose levels[49,50] and whether they persisted in the postpartum period. In our study, we used the 2-step approach for the diagnosis of GDM, and these results might not be applicable when the 1-step approach is implemented for the diagnosis of GDM. Another limitation was that we did not have maternal CV information before pregnancy or before GDM development; thus, it remained unknown whether GDM unmasked a women's preexisting CV subclinical abnormality or was a mediator of future CV pathogenesis.

Clinical perspective

This study, which undertook assessment of maternal and fetal cardiac function in the third trimester in pregnancies with GDM, has demonstrated deviations in both maternal and fetal cardiac adaptations, which were trending toward the dysfunctional phenotype. Specifically, in women with GDM, we found lower diastolic and systolic functional indices and their fetuses with more globular-shaped hearts with reduction in right and left myocardial deformation. There was discordance in "severity" of cardiac impairment in mothers and fetuses exposed to GDM. These findings possibly suggest that different pathways modulate maternal and fetal cardiac functional changes in response to glycemic stimulus during pregnancy. Further studies are needed to establish whether this pattern of cardiac changes persists and possibly deteriorates after delivery and renders women with GDM and their children at increased CV risk.

Conclusion

In conclusion, our study demonstrates that in third trimester pregnancies with GDM, women and their fetuses show distinct cardiac functional alterations. Although the observed cardiac changes were trending toward a dysfunctional cardiac phenotype, most of the measured parameters remained within the normal range for gestation. Long-term follow-up is needed to assess whether these women and their children are at risk for an accelerated decline in their cardiac function and, if so, whether this trend can be reversed or delayed by optimal CV risk factor modification. ■

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Appendix

Statistical section

Inverse ranking normalization: Inverse ranking normalization is a method of transformation that aims to render the sample distribution of a continuous variable more normally distributed. It belongs to a family of transformations collectively named inverse normal transformations (INTs) and in more detail in the rank-based INTs.[1]

The inverse ranking normalization is a 2-step transformation: (1) the sample measurements are first mapped to the probability scale by replacing the observed values with fractional ranks, and (2) ranks are then transformed into z-scores using the probit function. Furthermore, inverse ranking normalization transforms skewed continuous variables to z-scores, extending from −3.38 to 3.38. In cases of large sample sizes in which resampling or permutation techniques are computationally intensive, inverse ranking normalization is considered one of the most efficient and effective transformations[1] and is heavily used not only in genetic[2,3] but also in clinical studies.[4,5] After inverse rank normalization, the transformed variable is invariably normal and can be introduced more safely as a dependent variable in linear regression models. Of note, a normally distributed variable results in increased odds for normal distribution of the residuals of the model.

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SUPPLEMENTAL TABLE 1

Differences in maternal characteristics and cardiac parameters among various treatments for diabetes and controls

Variable	Controls	Diet	Metformin	Insulin	Metformin + insulin	*P* value[c]
N	483	54	52	17	38	
Age, y	32.4 (4.8)	34.3 (5.1)[a]	33.1 (5.6)	35.6 (5.6)[a]	35.9 (5.0)[a]	<.001
Weight, kg	76.5 (70.0–85.9)	78.3 (68.1–91.5)	83.8 (74.5–93.7)[a]	91.0 (81.0–104.0)[a]	82.6 (71.0–96.1)	<.001
Height, cm	166 (161–170)	164 (160–170)	164 (161–167)	165 (159–170)	163 (158–168)	.031
Weight gain, kg	10.8 (8.2–13.5)	9.9 (6.1–12.5)	7.1 (4.5–10.8)[a]	8.3 (5.3–13)	7.9 (3.5-10.4)[a]	<.001
Body mass index, kg/m^2	28.6 (4.3)	30.4 (6.5)[a]	31.6 (5.2)[a]	32.9 (5.0)[a]	31.4 (6.0)[a]	<.001
White racial origin	347 (71.8)	38 (70.4)	23 (44.2)[a]	6 (35.3)[a]	21 (55.3)	<.001
Parity	239 (49.5)	28 (51.9)	31 (59.6)	9 (52.9)	25 (65.79)	.26
Conception by in vitro fertilization	23 (4.8)	5 (9.3)	3 (5.8)	1 (5.9)	5 (13.2)	.203
Obstetric cholestasis	1 (50.0)	0	0	1 (50.0)	0	.717
Smoking	4 (0.8)	1 (1.9)	1 (1.9)	0	0	.805
Delivery (cesarean delivery)	97 (20.1)	18 (33.3)	20 (38.5)[a]	6 (35.3)	17 (44.7)[a]	<.001
Gestational age at delivery, wk	40.1 (39.3–41.0)	39.4 (39.0–40.1)	39.1 (38.6–39.9)	38.9 (38.3–39.1)	39.3 (38.6–39.7)	<.001
HbA1c, %	—	5.5 (5.0–5.7)	5.4 (5.2–5.9)	5.8 (5.6–6.4)[b]	5.65 (5.4–6.0)[b]	<.001
Hemodynamics						
Systolic blood pressure, mm Hg	118 (9.0)	119 (10.8)	119 (10.3)	121 (11.7)	119 (10.5)	.355
Diastolic blood pressure, mm Hg	72.7 (6.6)	75.3 (6.9)[a]	74.9 (7.5)	72.8 (10.7)	73.2 (6.7)	.031
Mean arterial pressure, mm Hg	87.6 (6.5)	89.6 (7.4)	89.2 (8.6)	88.5 (10.0)	88.5 (7.5)	.206
Heart rate, beats/min	81 (72–89)	77 (70–89)	86 (74–93)	83 (79–90)	84 (79–91)	.02
Peripheral vascular resistance (PRU)	3500 (2900–4100)	3600 (2900–4100)	3800 (3200–4400)	4000 (3300–5000)	3500 (3000–3900)	.064
Cardiac output, L/min	5.0 (4.3–5.7)	4.9 (4.4–5.7)	5.4 (4.5–6.1)	5.7 (4.7–7.1)	5.0 (4.3–5.6)	.138
Diastolic functional indices						
E/A	1.4 (1.1–1.7)	1.3 (1.1–1.6)	1.3 (1.1–1.5)	1.4 (1.1–1.6)	1.3 (1.2–1.5)	.184
E/e'	5.8 (4.9–6.9)	6.4 (5.6–7.4)[a]	6.6 (5.0–7.9)	6.3 (4.9–7.7)	6.5 (5.2–7.8)	<.001
A', cm/s	8.0 (7.1–8.9)	8.3 (7.2–9.4)	7.9 (7.0–9.2)	8.2 (7.5–9.4)	8.8 (8.0–9.6)[a]	.028
E', cm/s	12.9 (11.3–14.8)	11.9 (10.9–13.8)	11.6 (9.9–13.7)	11.8 (10.1–12.5)	12.1 (10.2–13.3)	<.001
Isovolumic relaxation time, ms	68 (56–83)	75 (58–89)	75 (58–89)	83 (75–89)	67 (50–86)	.05
Left atrium volume indexed for body surface area, mL/m^2	17.6 (14.1–21.2)	19.4 (14.6–23.4)	18.1 (14.1–23.7)	18.1 (12.1–22.4)	19.7 (15.7–24)	.265

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(continued)

SUPPLEMENTAL TABLE 1

Differences in maternal characteristics and cardiac parameters among various treatments for diabetes and controls *(continued)*

Variable	Controls	Diet	Metformin	Insulin	Metformin + insulin	*P* value[c]
Structural measures and systolic functional indices						
Left ventricular mass indexed for body surface area, g/m^2	114 (100–131)	115 (103–137)	129 (105–144)[a]	119 (114–144)	129 (103–143)	.009
Global longitudinal left ventricular systolic function, %	−21.4 (−23.2 to −19.8)	−20.9 (−22.6 to −19.7)	−20.8 (−22.2 to −19.5)	−22.4 (−23.1 to −20.0)	−21.4 (−22.5 to −18.6)	.247
Ejection fraction, %	58.5 (54.9–62.9)	57.8 (53.2–62.3)	60.5 (54.2–63.0)	62.5 (56.3–63.7)	58.8 (50.6–64.6)	.491
Myocardial performance index	0.5 (0.4–0.6)	0.5 (0.5–0.6)	0.5 (0.5–0.6)	0.5 (0.5–0.7)	0.5 (0.4–0.6)	.27
Tissue Doppler S', cm/s	9.9 (8.8–11.0)	9.5 (8.4–10.1)	9.2 (8.3–10.4)	9.5 (8.7–0.9)	9.9 (8.9–11.4)	.016

Measurements are presented as median (interquartile range), mean (standard deviation), or n (%).

a', early myocardial Doppler velocity; *A*, peak late diastolic flow velocities; *e'*, late myocardial Doppler velocity; *E*, early mitral inflow velocity; *HbA1c*, glycosylated hemoglobin; *PRU*, peripheral resistance unit.

[a] Indicating significant difference ($P<.05$) from controls after the Sidak correction for multiple comparisons.; [b] Denoting significant difference from the category of women with diabetes under treatment with diet.; [c] *P* values correspond to overall differences among compared categories and are derived from one-way analysis of variance or the nonparametric Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables.

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SUPPLEMENTAL TABLE 2
Differences in fetal weight and cardiac parameters among fetuses of mothers with GDM under different antidiabetic treatments and controls

Variable	Controls	Diet	Metformin	Insulin	Metformin + insulin	*P* value[b]
N	483	54	52	17	38	
Estimated fetal weight z-score	0.5 (0.9)	0.7 (1.0)	0.5 (1.2)	0.6 (0.8)	0.8 (1.2)	.089
Birthweight z-score	0.1 (0.9)	0.4 (1.4)	−0.2 (0.1)	−0.1 (0.5)	−0.01 (1.3)	.073
Heart rate, beats/min	140 (134–147)	141 (134–149)	138 (135–146)	139 (133–149)	139 (132–148)	.971
Diastolic functional indices						
E/A	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.8 (0.8–1.0)	0.9 (0.8–1.0)	0.8 (0.7–0.9)	.264
E/e'	9.4 (7.9–11.0)	9.2 (8.0–11.2)	9.8 (7.6–11.0)	8.2 (7.8–10.7)	9.4 (7.4–12.4)	.873
Isovolumic contraction time, s	0.04 (0.03–0.1)	0.04 (0.03–0.1)	0.03 (0.03–0.1)	0.04 (0.04–0.1)	0.04 (0.04–0.1)	.652
Isovolumic relaxation time, s	0.05 (0.05–0.1)	0.05 (0.05–0.1)	0.05 (0.04–0.1)	0.05 (0.05–0.1)	0.06 (0.05–0.1)	.437
Myocardial performance index	0.6 (0.5–0.7)	0.6 (0.5–0.7)	0.6 (0.5–0.6)	0.6 (0.5–0.6)	0.6 (0.6–0.7)	.244
Systolic functional indices and morphologic parameters						
TAPSE, mm	7.6 (6.6–8.5)	7.4 (6.8–8.3)	7.6 (6.7–8.5)	8.0 (6.6–8.8)	7.5 (6.3–8.4)	.626
Right ventricular endocardial GLS	−19.0 (−20.9 to −17.4)	−16.6 (−19.0 to −15.1)[a]	−16.5 (−18.7 to −15.9)[a]	−15.8 (−18.2 to −14.4)[a]	−16.9 (−19.3 to −15.3)	<.001
Left ventricular endocardial GLS	−20.7 (−22.8 to −18.3)	−18.9 (−22.6 to −17.3)	−18.8 (−21.8 to −16.8)	−20 (−21.2 to −16.7)	−20.4 (−21.1 to −17.8)	.028
Right ventricular sphericity index	0.6 (0.5–0.6)	0.6 (0.6–0.7)	0.6 (0.6–0.7)[a]	0.6 (0.6–0.7)	0.6 (0.6–0.7)	<.001
Left ventricular sphericity index	0.5 (0.5–0.6)	0.5 (0.5–0.6)	0.5 (0.5–0.6)	0.5 (0.5–0.5)	0.5 (0.5–0.6)	.067

Measurements are presented as median (interquartile range), mean (standard deviation), or n (%).

GSL, global longitudinal strain; *TAPSE*, tricuspid annular plane systolic excursion.

[a] Indicating significant difference ($P<.05$) from controls after the Sidak correction for multiple comparisons; [b] *P* value corresponds to overall differences among compared categories and are derived from one-way analysis of variance or the nonparametric Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables.

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