Maternal Cardiac Changes in Women With Obesity and Gestational Diabetes Mellitus

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OBJECTIVE

We investigated if women with gestational diabetes mellitus (GDM) in the third trimester of pregnancy exhibit adverse cardiac alterations in myocardial energetics, function, or tissue characteristics.

RESEARCH DESIGN AND METHODS

Thirty-eight healthy, pregnant women and 30 women with GDM were recruited. Participants underwent phosphorus MRS and cardiovascular magnetic resonance for assessment of myocardial energetics (phosphocreatine [PCr] to ATP ratio), tissue characteristics, biventricular volumes and ejection fractions, left ventricular (LV) mass, global longitudinal shortening (GLS), and mitral in-flow E-wave to A-wave ratio.

RESULTS

Participants were matched for age, gestational age, and ethnicity. The following data are reported as mean ± SD. The women with GDM had higher BMI (27 ± 4 vs. 33 ± 5 kg/m^2; $P = 0.0001$) and systolic (115 ± 11 vs. 121 ± 13 mmHg; $P = 0.04$) and diastolic (72 ± 7 vs. 76 ± 9 mmHg; $P = 0.04$) blood pressures. There was no difference in N-terminal pro-brain natriuretic peptide concentrations between the groups. The women with GDM had lower myocardial PCr to ATP ratio (2.2 ± 0.3 vs. 1.9 ± 0.4; $P < 0.0001$), accompanied by lower LV end-diastolic volumes (76 ± 12 vs. 67 ± 11 mL/m^2; $P = 0.002$) and higher LV mass (90 ± 13 vs. 103 ± 18 g; $P = 0.001$). Although ventricular ejection fractions were similar, the GLS was reduced in women with GDM (−20% ± 3% vs. −18% ± 3%; $P = 0.008$).

CONCLUSIONS

Despite no prior diagnosis of diabetes, women with obesity and GDM manifest impaired myocardial contractility and higher LV mass, associated with reductions in myocardial energetics in late pregnancy compared with lean women with healthy pregnancy. These findings may aid our understanding of the long-term cardiovascular risks associated with GDM.

Gestational diabetes mellitus (GDM), defined as hyperglycemia with onset or first recognition during pregnancy that is below diagnostic thresholds for type 2 diabetes (T2D) (1), is increasing in prevalence, affecting 5% to 18% of all pregnancies worldwide, driven by the increasing burden of obesity among women of reproductive age (2,3). The diagnosis of GDM has long-term implications for maternal cardiovascular health, with up to a twofold higher cardiovascular disease (CVD) risk postpartum, including a greater risk of heart failure (hazard ratio [HR] 2.8 [95% CI

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2.25–3.48]), stroke (HR 1.77 [95% CI 1.53–2.04]), and ischemic heart disease (HR 2.61 [95% CI 2.25–3.48]) in later life compared with women without a history of GDM (4–7). Moreover, women with a history of GDM have an up to sevenfold increased risk of developing T2D later in life (8). A recent meta-analysis suggested that women with a history of GDM have double the risk of major cardiovascular events compared with women with uncomplicated pregnancies, irrespective of a T2D diagnosis later in life (4). In a population-based study of parous women, the estimated proportion of CVD risk attributable to subsequent T2D in women with GDM was 23% (7).

The metabolic abnormalities underlying GDM include insulin resistance and pancreatic β-cell defects (9). Normal pregnancy requires maternal hemodynamic and metabolic adaptations to meet the increasing demands of the developing fetus (10). The hemodynamic changes include hyperdynamic circulation, systemic vasodilatation, increased filling capacity of the vasculature, and volume expansion (10). However, a recent study has shown maternal hemodynamic maladaptation to pregnancy in women with GDM, including lower cardiac output and stroke volume, and higher total vascular resistance (11).

To meet the energy needs of pregnancy, hepatic glucose production increases by 30% in healthy pregnant (HP) women by the end of gestation, and peripheral insulin sensitivity decreases by ∼50% (12). Although there is a twofold to threefold increase in insulin secretion in women with normal glucose tolerance in response to the decreased insulin sensitivity, in women who were normoglycemic before pregnancy but went to develop GDM in late gestation, the β-cell insulin secretion was unable to compensate for pregnancy-induced insulin resistance, resulting in hyperglycemia (12).

Maternal inability to adapt to these metabolic and hemodynamic changes can expose underlying, previously silent pathology, leading to appreciation of pregnancy as "nature's stress test" (13). Despite being the most prevalent metabolic disorder during pregnancy, the impact of GDM on maternal myocardial energetics has not been assessed previously, to our knowledge. Myocardial energy depletion is a common feature of metabolic disorders and compromised cardiac energy production is an important contributor to most forms of heart disease (14).

Phosphorus MRS (^{31}P-MRS) reveals the biochemistry of ATP, ADP, and phosphocreatine (PCr), which are critical to the supply of energy for contractile work in the myocardium (15). The relative concentration of PCr to ATP (PCr/ATP) is a marker of the myocardium's ability to convert substrate into ATP for active processes and is a sensitive index of the energetic state of the myocardium (Supplementary Fig. 1). Myocardial energetic compromise, indicated by decreased PCr/ATP, is a predictor of mortality (16) and linked to contractile dysfunction (16,17). The effects of gestational metabolic and hemodynamic alterations on the myocardial energetic state can be assessed noninvasively by ^{31}P-MRS without the need for ionizing radiation or contrast exposure.

Moreover, cardiovascular magnetic resonance (CMR) allows comprehensive evaluation of myocardial structure, function, strain, and tissue characteristics, with excellent reproducibility. CMR parametric mapping methods (such as T1 and T2 mapping) are quantitative techniques that provide a pixel-by-pixel representation of numeric T1 or T2 properties. These techniques provide information on myocardial tissue type and composition without the need for contrast agents (18).

CMR, therefore, provides insight into cardiovascular physiology, and noncontrast CMR studies can be safely performed during pregnancy (19–22). Using CMR and ^{31}P-MRS in the third trimester, we investigated the effect of pregnancy-associated cardiometabolic stresses on maternal myocardial energetics, structure, function, or tissue characteristics in women with pregnancies complicated by GDM.

RESEARCH DESIGN AND METHODS

This single-center, observational, case-control study complied with the Declaration of Helsinki. It was approved by the National Research Ethics Committee (no. REC20/NE/0117), and informed written consent was obtained from each participant.

Participants

A total of 68 participants (n = 38 pregnant women with an uncomplicated pregnancy and n = 30 pregnant women with a diagnosis of GDM) were recruited in the study (Fig. 1). The pregnant participants were recruited via the Leeds Teaching Hospitals National Health Service Trust antenatal clinics attendance register and GDM clinics.

Inclusion and Exclusion Criteria

Participants with ongoing pregnancy at 26–38 weeks' gestation and who were >18 years old were recruited. Recruitment for both groups was restricted to singleton first pregnancies. Women with a diagnosis of preeclampsia, antenatally small-for-gestational-age babies at week 33 transabdominal ultrasound (<10th percentile for estimated fetal weight) or any other adverse pregnancy outcomes; known cardiovascular problems (congenital or acquired heart disease); contraindications to CMR (e.g., pacemaker, cranial aneurysm clips, metallic ocular foreign bodies, severe claustrophobia); medical conditions that could affect cardiac function, including severe anemia, maternal diabetes (type 1 or type 2), chronic renal disease, chronic hypertension, liver disease, and former or current smokers were excluded. Ethnicity group was self-reported by participants.

The presence of preexisting diabetes was checked on electronic health care records at the prescreening stage. The absence of preexisting diabetes was then confirmed with the participants during the research visit.

Oral Glucose Tolerance Test

Diagnosis of GDM was confirmed by a 75 g oral glucose tolerance test (OGTT) in all participants in the GDM group at the antenatal clinics using the U.K. National Institute for Health and Care Excellence guideline criteria for GDM of fasting glucose ≥5.6 mmol/L (≥100.8 mg/dL) and/or 2 h glucose ≥7.8 mmol/L (≥140.4 mg/dL) after intake of 75 g of oral glucose at ∼26 weeks' gestation (23).

Anthropometric Measurements

All women had height and weight recorded and BMI calculated at the booking visit performed at ∼8th gestational week in antenatal clinics. Brachial artery blood pressure (BP) was recorded after an initial 5 min rest as an average of three sitting measurements taken over

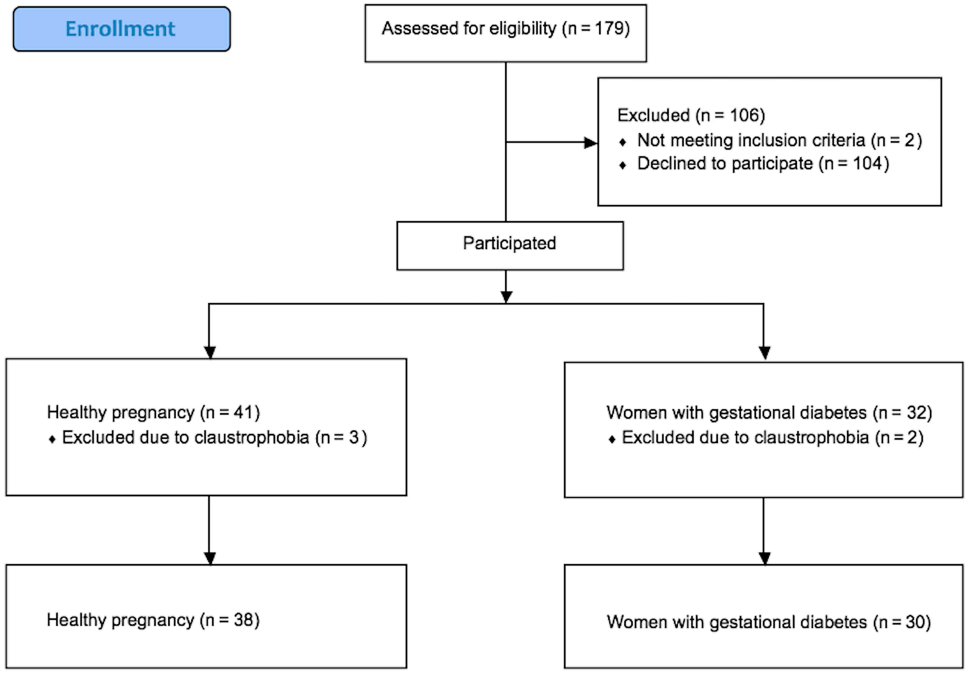

Figure 1—Consolidated Standards of Reporting Trials flow diagram of the recruitment pathway for study participants with HP and those with GDM.

10 min (DINAMAP-1846-SX, Critikon Corp.) using the appropriate cuff size based on the mid-arm circumference. These assessments were then repeated during the research CMR scan visit performed during the third trimester. A standard 12 lead electrocardiogram (ECG) was performed in all participants on the same day as the CMR. A venous blood sample was taken for assessments of full blood cell count, estimated glomerular filtration rate (eGFR), liver function, glycated hemoglobin (HbA_{1c}), lipid profile (concentrations of triglycerides and HDL, LDL, and total cholesterol concentrations) and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) also on the same day as the CMR. Given the pregnant status of the participants, a flexible approach to blood tests were used, and participants were requested to fast for 4 h prior to research visits per the recommendations of the local patient and public involvement group at the stage of study design.

^{31}P-MRS

^{31}P-MRS was performed to obtain the PCr/ATP ratio from a voxel placed in the midventricular septum, with the participants lying supine, and in the isocenter of the magnet of a 3.0 Tesla MR system (Prisma; Siemens, Erlangen, Germany), a ^{31}P transmitter/receiver cardiac coil (Rapid Biomedical GmbH, Rimpar, Germany) was placed over the participant's heart. ^{31}P-MRS data were acquired with a nongated, three-dimensional, acquisition-weighted chemical shift imaging sequence, as previously described (24).

Cardiovascular MRI

All scans were performed on a 3.0 Tesla MR system (Prisma; Siemens) and all participants underwent cardiac MRI scans. The CMR protocol (Fig. 2) consisted of cine imaging, velocity-encoded mitral inflow imaging, native T1 mapping, and T2 mapping.

To capture cross-sectional mitral valve (MV) flow, velocity-encoded mitral inflow imaging was planned from an acquisition plane placed at the position of the MV at end systole. Velocity sensitivity was set at 200 cm/s. The phase-contrast images were acquired using retrospective ECG gating, using established methods (25).

Native T1 maps were acquired in three short-axis slices using a breath-held, modified look-locker inversion recovery acquisition, as previously described (24). T2 maps were acquired from the matching three short-axis positions to native T1 mapping using a T2-prepared true fast imaging with steady-state precession pulse sequence to produce single-shot T2-prepared images, each with different T2 preparation times, as previously described (26).

Quantitative Imaging Data Analysis

All ^{31}P-MRS analyses were performed off-line by one author (S.T.) using the OXSA toolbox as previously described (27). CMR postprocessing analysis using cvi42 software (Circle Cardiovascular Imaging, Calgary, Canada) was performed by one author (S.T.) offline and blinded to all participant details after completion of the study, and scan contours were subsequently reviewed another author (E.L.) who was also blinded to participant details.

Global longitudinal shortening (GLS) data were derived from horizontal and vertical long-axis images, and image reconstruction and processing were implemented using the Gadgetron software framework with the previously developed convolutional neural network for labeling landmarks on CMR images (28).

Diastolic function was measured from mitral in-flow velocity-encoded images (25). Regions of interest were manually drawn on one frame to encircle the entire cross-section of MV leaflets and propagated using a semiautomated contouring mode in cvi42 software (Circle Cardiovascular Imaging), yielding velocity versus time graphs characterizing diastolic E and A waves. The mean of

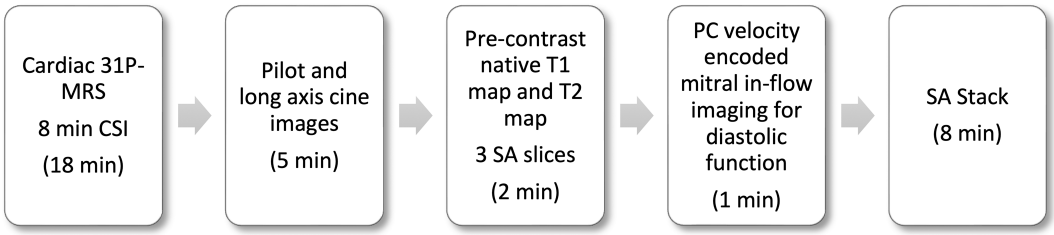

Figure 2—^{31}P-MRS and CMR protocol used (3 T, cine imaging, velocity-encoded mitral in-flow imaging, T1 and T2 mapping). CSI, chemical shift imaging; PC, phase contrast; SA, short axis.After the acquisition of cardiac ^{31}P-MRS, using the same scanner after a coil change, the CMR imaging was performed. The CMR protocol included balanced steady-state free precession (bSSFP) localizers in three orthogonal planes, anatomic imaging with half-Fourier acquisition single-shot turbo spin-echo in different orthogonal planes, long- and short-axis, bSSFP, retrospectively gated breath-held cines for the assessment of ventricular function. Phase-contrast velocity-encoded mapping for the mitral in-flow imaging was performed for diastolic assessments of mitral-inflow E/A ratio and DT. Native T1 mapping and T2 mapping images were acquired for myocardial tissue characterization.

maximum velocity obtained for MV was recorded. The deceleration time (DT) was calculated as previously described from the same images (25).

Native T1 and T2 maps were analyzed using cvi42 software (Circle Cardiovascular Imaging) and were measured for each of the 16 segments using the American Heart Association classification.

Statistical Analysis

Statistical analysis was performed using SPSS statistics, version 26.0 (IBM). Categorical data were compared with the Pearson χ^2 test. Continuous variables are presented as mean ± SD and were checked for normality using the Shapiro-Wilk test. Comparisons of all CMR and biochemistry data were performed with two-tailed paired *t* test or Mann Whitney *U* test, as appropriate. $P \leq 0.05$ was considered statistically significant. Bivariate correlations were performed using the Pearson or Spearman method, as appropriate.

A priori sample-size calculations were performed before the study; these showed that to detect a 20% difference in the mean myocardial PCr/ATP ratio between the two groups, a minimum of 26 participants per group would be needed (with 80% power at $\alpha = 0.05$). These recruitment goals were exceeded in the study.

In this study, prespecified hypotheses were tested on three variables: myocardial PCr/ATP ratio, left ventricular (LV) mass, and GLS. Linear regression models were used to test for associations among these three variables and systolic and diastolic BPs, BMI, plasma triglyceride concentrations, and HbA_{1c}.

RESULTS

Study Population

Demographic, clinical, and biochemical data of the two study groups are shown in Table 1. A total of 38 HP women and 30 participants with GDM were prospectively recruited. Maternal age, gestational age, and ethnicity distribution were similar between the groups. Ethnicity distribution (*n* = 33 of 38 participants in the HP arm were Caucasian, *n* = 3 Pakistani, *n* = 1 Chinese, and *n* = 1 Black; in the GDM group, *n* = 26 of 30 participants were Caucasian, *n* = 1 Indian, *n* = 2 Chinese, and *n* = 1 Black) was broadly in line with the local population demographics. Both groups included similar numbers of participants classified as at advanced maternal age (>35 years old) (HP versus GDM: 6 vs. 4; *P* = 0.8). None of the participants in either group had a family history of T2D.

Diagnosis of GDM was confirmed by OGTT in all participants with GDM, per clinical guidelines (29). On the day of OGTT, the mean fasting glucose in the GDM group was 5.1 ± 0.7 mmol/L and the mean 2-h plasma glucose was 9.0 ± 1.4 mmol/L. Of the participants with GDM, 12 (40%) were receiving metformin treatment and 4 (13%) were receiving additional insulin treatment for glycemic control. The remaining 18 women with GDM received dietary advice alone.

The women with GDM had higher BMI than those in the HP arm, both at the booking antenatal clinic visit and at the third trimester CMR-scan visit. However, both groups had similar gestational weight gain (Table 1). There was no significant difference in resting heart rate between the two groups, but the GDM group had higher resting systolic and diastolic BP measurements both at the booking antenatal clinic visit and at the third trimester CMR scan visit (Table 1). The plasma triglyceride, free fatty acid, ketone (β-hydroxybutyrate), and HbA_{1c} levels were all significantly higher in the GDM group (Table 1). There was no significant difference in NT-proBNP levels between the two groups.

Myocardial Energetics, Structure, and Function Comparisons

^{31}P-MRS results for myocardial energetics and CMR results for biventricular volumes, systolic function, LV mass, diastolic function, and GLS are summarized in Table 2.

The women with GDM had significant reduction in myocardial PCr/ATP ratio (mean [95% CI], HP: 2.2 [2.1–2.4] vs. GDM: 1.9 [1.7–2.0]; $P \leq 0.0001$) (Fig. 3). This was accompanied by important structural and functional differences. The women with GDM had lower LV end-diastolic volumes (EDVs) indexed for body surface area (mean [95% CI], HP: 76 [72–80] mL/m^2 vs. GDM: 67 [63–71] mL/m^2; *P* = 0.002) but greater LV mass (mean [95% CI], HP: 90 [85–94] g vs. GDM: 103 [96–112] g; *P* = 0.001) and greater LV mass over LV to EDV ratio, suggestive of increased concentricity of the LV (mean [95% CI], HP: 0.6 [0.6–0.7] g/mL vs. GDM: 0.8 [0.7–0.8] g/mL; *P* = 0.0001) (Fig. 4). LV end-diastolic wall thickness was also greater in women with GDM (mean [95% CI], HP: 7.6 [7.2–8.0] mm vs. GDM: 9.5 [9.3–10.0] mm; *P* = 0.0001). When adjusted for booking BMI and for gestational weight gain, the comparisons of myocardial

Table 1—Clinical characteristics and the biochemistry

Variable	HP (n = 38)	GDM (n = 30)	P value
Age, years	31 ± 4	31 ± 5	1
Ethnicity, White, %	87	87	1
Gestational date at CMR, wk	30 ± 2	31 ± 2	0.2
Booking BMI, kg/m^2	25 ± 5	31 ± 5	0.0001
BMI at scan visit, kg/m^2	27 ± 4	33 ± 5	0.0001
Heart rate, bpm	88 ± 12	91 ± 14	0.3
Hip circumference, cm	104 ± 13	117 ± 16	0.004
Waist circumference, cm	100 ± 11	110 ± 14	0.002
Booking systolic BP, mmHg	113 ± 10	120 ± 9	0.004
Systolic BP, mmHg	115 ± 11	121 ± 13	0.04
Booking diastolic BP, mmHg	69 ± 8	74 ± 8	0.01
Diastolic BP, mmHg	72 ± 7	76 ± 9	0.04
Biochemistry			
Hemoglobin, g/L	121 ± 9	122 ± 9	0.7
HDL, mmol/L	2.2 ± 0.4	1.9 ± 0.4	0.003
LDL, mmol/L	3.6 ± 1.3	3.3 ± 1.2	0.3
TG, mmol/L	2.5 ± 1.0	3.1 ± 0.8	0.009
Creatinine, μmol/L	47 ± 7	46 ± 10	0.6
eGFR, ml/min/1.73 m^2	90 ± 0	89 ± 3	0.04
Urine alb to creatinine ratio	1.3 ± 1.3	1.9 ± 3.2	0.3
HbA_{1c}, mmol/mol	31 ± 3	33 ± 3	0.008
Glucose, mmol/L	5.2 ± 1.1	6.6 ± 7.1	0.2
NT-proBNP, ng/L	55 ± 32	46 ± 17	0.2
FFA, mmol/L	0.3 ± 0.1	0.4 ± 0.2	0.009
β-hydroxybutyrate, mmol/L	0.1 ± 0.07	0.2 ± 0.2	0.006
Pregnancy-specific parameters			
Gestational weight gain, kg	8.9 ± 4.9	7.9 ± 4.4	0.38
Birth weight, g	3,429 ± 1,166	3,196 ± 667	0.04
Birth weight for gestational age, %	42 ± 25	41 ± 26	0.8
Female sex, %	29	47	0.1

Values are means (SD) or median (interquartile range) for continuous variables and n (%) for categorical variables. Alb, albumin; FFA, free fatty acid; TG, triglyceride.

energetics, GLS, and cardiac concentricity between the two groups remained statistically significant (Fig. 4).

Although the LV ejection fraction was similar between the two groups, the LV GLS was significantly lower in the GDM group (mean [95% CI], HP: −20% [18–21%] vs. GDM: −18% [17–19%]; P = 0.008) (Fig. 5). Both pregnancy groups exhibited similar mitral inflow E-wave to A-wave (E/A) ratio and DT measured from mitral in-flow velocity-encoded images. Similar to LV EDV differences, the right ventricular (RV) EDV was smaller in the GDM group (mean [95% CI], HP: 85 [79–88] mL vs. GDM: 77 [67–80] mL; P = 0.04). There were no significant differences in RV ejection fraction between the two groups. There were no significant differences in left atrial volumes or function between the groups.

Myocardial Tissue Characteristics

Although, numerically, the HP group had higher myocardial native T1 measurements than the GDM group, this difference did not reach statistical significance (HP: 1,325 ± 34 ms vs. GDM: 1,308 ± 38 ms; P = 0.05). There was no significant difference between the groups on T2 mapping measurements (HP: 40 ± 3 ms vs. GDM: 39 ± 3 ms; P = 0.2).

Birth Weight, Birth Weight for Gestational Age, and Sex Comparisons

A subtle difference in birth weight was detected between the babies born to women in the HP and the GDM groups, with a higher birth weight in the HP group. Birth weight for gestational age was slightly lower in the GDM group (HP: 42 ± 25 vs. GDM: 41 ± 26; P = 0.8). There were no differences in sex distribution of the babies.

Correlations

There was significant correlation between the PCr/ATP ratio and LV mass (r = −0.37; P = 0.005). Multilinear regression showed that LV mass was independently associated with systolic BP and BMI (Table 3). There were no other significant bivariate correlations.

CONCLUSIONS

In this prospective study, diagnosis of GDM was associated with subclinical alterations in cardiac energetics, structure, and function. Compared with age, gestational age– and ethnicity-matched women with an uncomplicated HP, young women with GDM displayed enhanced LV concentricity with greater LV wall thickness and mass, and smaller LV chamber size. These structural alterations were accompanied by significant reductions in myocardial energetics and in LV GLS in the GDM group. These findings may aid our understanding of the long-term cardiovascular risks posed by GDM.

Reductions in Myocardial Energetics in GDM

During HP, the maternal physiology adapts to compensate for many changes in energy demands. In our study, using ^{31}P-MRS, we show that despite their young age, women with obesity and GDM display significant reductions in myocardial energetics, whereas in women with HP, these were maintained at normal levels. This finding suggests insufficient adaptation of the maternal myocardial metabolic machinery to cope with the challenging metabolic and hemodynamic demands of the pregnancy in the GDM group.

The heart has a very high energy demand while having minimal energy-storing capacity (30). Efficient matching of energy supply to demand in the heart, therefore, is essential for maintaining cardiac function. Compromised cardiac energy production is an important contributor to most forms of heart disease (14,31–33), and myocardial metabolic insult of a pregnancy with GDM may be a potential driver of the enhanced CVD risk. Manipulating myocardial energy metabolism, therefore, may be a

Table 2—CMR and ^{31}P-MRS findings

Variable	HP (n = 38)	GDM (n = 30)	P value	Adjusted P value for BMI	Adjusted P value for gestational weight gain
LV structural parameters					
EDV, mL	143 ± 23	136 ± 24	0.2	0.2	0.2
EDV index, mL/m^2	76 ± 12	67 ± 11	0.002	0.003	0.03
End systolic volume, mL	59 ± 12	59 ± 14	1	1	1
End systolic volume index, mL/m^2	31 ± 6	29 ± 7	0.2	0.2	0.2
Stroke volume, mL	84 ± 15	77 ± 13	0.04	0.02	0.1
Stroke volume index, mL/m^2	49 ± 12	46 ± 8	0.2	0.2	0.2
Ejection fraction, %	59 ± 4	57 ± 6	0.05	0.05	0.05
Mass, g	90 ± 13	103 ± 18	0.001	0.009	<0.001
Mass index, g/m^2	46 ± 8	50 ± 7	0.3	0.3	0.03
LV mass/LV EDV, g/mL	0.6 ± 0.1	0.8 ± 0.2	0.0007	<0.001	0.004
Wall thickness, mm	7.6 ± 1.2	9.5 ± 1.2	0.0001	<0.001	<0.001
Myocardial energetics					
PCr/ATP ratio	2.2 ± 0.3	1.9 ± 0.4	<0.0001	0.001	0.003
Functional parameters					
LV ejection fraction, %	59 ± 4	57 ± 6	0.05	0.05	0.05
RV ejection fraction, %	55 ± 6	54 ± 7	0.5	0.5	0.5
GLS, %	−20 ± 3	−18 ± 3	0.008	<0.001	0.002
MAPSE, mm	14 ± 3	14 ± 2	1	1	1
E/A ratio	1.7 ± 0.4	1.7 ± 0.4	1	1	1
DT, ms	152 ± 38	179 ± 75	0.06	0.06	0.06

Values are means (SD) or median (interquartile range) for continuous variables and n (%) for categorical variables. LA, left atrium; MAPSE, mitral annular plane systolic excursion.

promising strategy to improve cardiovascular outcomes in women with GDM.

The metabolic and hemodynamic challenges of pregnancy were augmented in the GDM group, with higher plasma HbA_{1c}, triglyceride, ketone body, and free fatty acid levels; lower HDL levels; and higher resting BP measurements in the GDM group compared with the HP cohort. Given the multitude of metabolic and hemodynamic alterations in the GDM group, the driving factor for this energetic impairment is likely to be multifactorial.

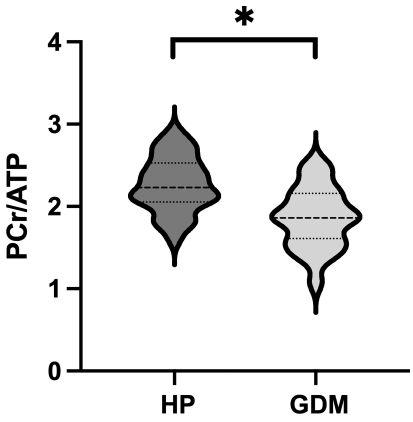

Figure 3—Violin plots demonstrating the differences in PCr/ATP ratio between the participants with GDM and participants with HP.

Consistent with previous reports (34), in our study, women with GDM had higher booking BMI, which is a close estimate of prepregnancy weight, but the gestational weight gain was similar between the groups in this study. Being overweight or obese before pregnancy is considered the most important GDM risk factor (34). Our results add more evidence for increased body weight as an integrating determinant of maternal myocardial alterations in women with GDM. In our study, BMI was associated with myocardial PCr/ATP ratio, whereas diabetes-specific parameters such as HbA_{1c} and plasma glucose concentrations did not correlate with cardiac parameters. In a similar pattern as in this study, in previous studies of established T2D cohorts, we have not detected correlations of HbA_{1c} or plasma glucose with cardiac parameters, including energetics, cardiac structural changes, or cardiac contractile function measured by GLS (33,35). These findings are in keeping with the long-standing existing evidence that despite the strict glycemic control in patients with T2D, the excess risk of heart failure persists (36).

Reductions in myocardial PCr/ATP ratio have been demonstrated in chronic obesity (37) and in overt T2D (33). Numerous previous studies have reported an increased risk of GDM among women who are overweight or obese compared with women with normal body weight (34). Therefore, it is clear the GDM risk is, in a big part, driven by the obesity epidemic, and maintaining a healthy body weight throughout the reproductive life would likely confer great benefits in reducing the risk of GDM. In this study, although the comparisons of principal findings between the two groups remained statistically significant even when adjusted for booking BMI and for gestational weight gain, the potential impact of prior overweight status on the findings cannot be ruled out by our study design.

However, it is not possible to draw conclusions from comparison with existing literature on cardiac studies in overweight cohorts, because of their significant methodological differences from this study (38,39). The existing reports of cardiac assessments in overweight cohorts included older adults, with a significant proportion of male participants and significantly higher BMI in the obesity cohort and a lower BMI in the control group than in our study—all of which are likely to have a significant impact on the cardiac findings. Despite

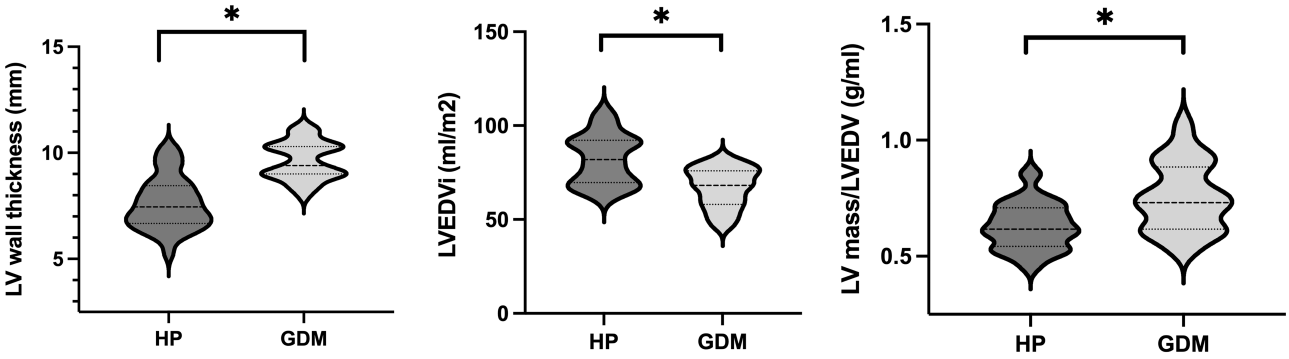

Figure 4—Violin plots demonstrating the differences in LV end diastolic wall thickness, LV end diastolic volumes indexed for the body surface area (LVEDVi), and LV mass over LV end diastolic volume as a measure of LV concentricity between the participants with GDM and participants with HP.

the significantly younger age and lower BMI of our participants, we have detected significant reductions in energetics and cardiac contractile function in the GDM cohort, which likely suggest at least an additive impact of GDM and overweight status on the cardiac findings.

With regard to the long-term cardiovascular outcomes, a higher incidence of CVD was found in women with both a history of GDM and obesity (HR 1.76 [95% CI 1.59–1.95]) compared with women with a history of GDM alone (HR 1.43 [95% CI 1.38–1.49]), with a multiplicative interaction between GDM and obesity (7).

Cardiac Structural and Functional Changes in GDM

The enhanced cardiac concentricity revealed in our study may be an important component of the worsened cardiovascular outcomes in women with GDM in the longer term. Although initially an adaptive response for maintaining cardiac output, sustained hypertrophic growth of the myocardium induced by pathological stimuli is a leading predictor for the development of heart failure and for cardiovascular death (40).

To our knowledge, our study is the only study of women with GDM to use CMR and ^{31}P-MRS. Consistent with our findings, using echocardiography, two prospective studies reported increased LV mass and abnormalities in GLS in women with GDM (41,42). Moreover, in a multicenter, longitudinal, observational CARDIA (Coronary Artery Risk Development in Young Adults) study, 609 women (n = 64 with GDM) were followed with echocardiograms over 20 years (43). After adjusting for potential confounders, including BMI, BP, lipid levels, and incident T2D, women with prior GDM had higher LV mass index as well as systolic dysfunction at the end of the study.

Although these observational clinical studies, including our own study, cannot prove causality, using a GDM model of female rats (HIP rats), Verma et al. (44) reported supportive evidence of a causal relationship between pathological cardiac hypertrophy and GDM. Their results implicated altered calcium handling as the central mechanism that underlies the maternal myocardial hypertrophic response in GDM, leading to activation of the calcineurin-dependent transcriptional pathway for cardiac hypertrophy (nuclear factor of activated T-cell signaling), as well as calcium/calmodulin-

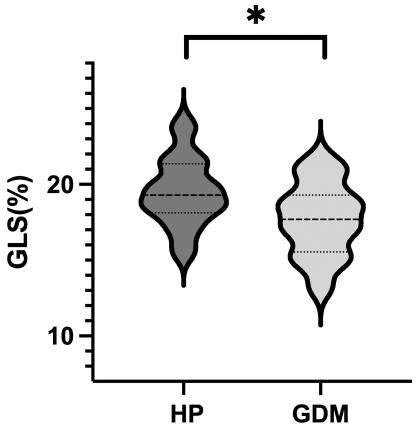

Figure 5—Violin plots demonstrating the differences in LV GLS between participants with GDM and participants with HP.

Table 3—Linear regression model for dependent variables PCr/ATP ratio, LV mass, and GLS

	β	SE	95% CI	*P* value
PCr/ATP ratio				
Constant	4.85	1.99	0.75–8.94	0.02
Systolic BP	−0.021	0.018	−0.060, 0.016	0.25
Diastolic BP	0.021	0.028	−0.037, 0.08	0.46
HbA_{1c}	−0.004	0.046	−0.1, 0.09	0.92
Triglyceride	−0.162	0.165	−0.5, 0.18	0.33
BMI	−0.368	0.026	−0.09, 0.02	0.17
LV mass				
Constant	37.60	54.36	−72.65, 147.8	0.49
Systolic BP	−0.89	0.41	−1.72, −0.07	0.03
Diastolic BP	1.33	0.67	−0.04, 2.70	0.05
HbA_{1c}	0.75	1.33	−1.95, 3.46	0.57
Triglyceride	−2.7	4.68	−12.19, 6.78	0.56
BMI	1.61	0.75	−0.09, 3.12	0.04
GLS				
Constant	32.81	7.24	18.10–47.53	<0.0001
Systolic BP	−0.014	0.053	−0.124, 0.095	0.7
Diastolic BP	−0.10	0.09	−0.29, 0.088	0.28
HbA_{1c}	−0.25	0.18	−0.61, 0.12	0.17
Triglyceride	1.08	0.64	−0.23, 2.39	0.1
BMI	−0.02	0.1	−0.22, 0.18	0.82

dependent kinase II/class IIa histone deacetylase (CaMKII/HDAC) signaling (the CaMKII/HDAC pathway), leading to expression of prohypertrophic genes (44,45).

Birth Weight for Gestational Age

Contrary to expectation, the birth weight for gestational age was slightly lower in the GDM group, which is likely due to careful monitoring and controlled GDM status of the participants. Larger population studies suggest an opposite finding, with higher birth weight observed in GDM (46).

Future Perspectives

Although much is known about GDM pathophysiology, molecular understanding of GDM has not yet been translated into efficacious therapies (9). The current treatment of GDM focuses on optimizing glycemic control. When this is not achieved despite lifestyle and dietary advice, treatment with antihyperglycemic medication is indicated.

However, because the cardiovascular risk associated with GDM does not diminish by attaining normoglycemia, there is a clear and pressing need for novel strategies specifically aiming to improve cardiovascular outcomes for women with GDM. If larger longitudinal studies confirm a consistent association between the cardiac alterations revealed in this study in women with GDM and higher rates of adverse maternal and fetal outcomes, the early detection of these adverse subclinical myocardial alterations might offer the opportunity of better stratifying women at risk for perinatal complications, as well as future CVD (13).

Although excessive gestational weight gain was shown to increase adverse pregnancy outcomes, prepregnancy maternal obesity might be a more important factor in driving these adverse outcomes (47). Supporting this notion, in this study, we did not detect significant differences in gestational weight gain between the two cohorts, although the booking BMI was significantly higher in the GDM group. Raising awareness with adequate prepregnancy counseling through public health initiatives to achieve ideal body weight in women who plan pregnancy might lead to improved maternal and offspring outcomes.

Limitations

This study is limited by a relatively small sample size, in line with its proof-of-principle nature. Although, to our knowledge, there are no prior studies evaluating nulliparous overweight or obese women of similar age to our study population, because the scans were performed during pregnancy, once a diagnosis of GDM was established, we cannot reliably rule out that these cardiac alterations were not present prepregnancy, reflecting underlying preexisting cardiometabolic risk factors in women with GDM. Moreover, longitudinal assessments are needed for the evaluation of reversibility after pregnancy of the maternal cardiac changes detected in this study.

Without an additional control group of women with obesity but without GDM, we cannot reliably exclude that the changes demonstrated in this study are driven by the GDM only or obesity only, or a combination of both conditions. Studies are needed to address this.

Although studies confirm that noncontrast MRI does not harm the fetus when performed at any stage of pregnancy (19), an increased risk of neonatal death or stillbirth with gadolinium-based contrast exposure has been reported (21). As a result, only noncontrast scans were performed in our study.

Conclusion

This study demonstrates that young primiparous women with obesity and GDM manifest impaired myocardial contractility and significantly greater LV mass associated with impaired myocardial energetics in late pregnancy compared with lean women with HP. These findings may aid our understanding of the long-term cardiovascular risks posed by GDM.

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