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The impact of gestational diabetes on maternal cardiac adaptation to pregnancy

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Short title: Cardiac adaptation in diabetic pregnancy

Keywords: Pregnancy, Gestational Diabetes, Echocardiography, Speckle Tracking, Cardiac Dysfunction, Diastolic Dysfunction
CONTRIBUTION

What are the novel findings of this work?

This is the first prospective study of comprehensive echocardiographic assessment including left and right ventricular geometry and function in women with gestational diabetes. We demonstrate that even a short duration of exposure to hyperglycaemia leads to echocardiographic changes comparable to those seen in non-pregnant diabetes mellitus.

What are the clinical implications of this work?

The echocardiographic findings in gestational diabetes may explain the increased maternal risk to hypertensive disorders of pregnancy and cardiovascular disease later in life.
OBJECTIVES: To determine whether maternal cardiac adaptation at term differs in women with and without gestational diabetes (GDM).

METHODS: This was a prospective case-control study of pregnant women at term with and without GDM. Conventional as well as speckle tracking echocardiography was used to assess both left and right heart geometry and function.

RESULTS: We enrolled a total of 40 women with GDM and 40 healthy controls. Heart rate (75±9 vs 83±10; p<0.001), left ventricular (LV) relative wall thickness (0.37±0.08 vs 0.43±0.07; p<0.001), LV E (early diastolic trans-mitral valve velocity) (0.73±0.12 vs 0.80±0.15; p=0.26) and LV A (late diastolic trans-mitral valve velocity) (0.57±0.11m/s vs 0.65±0.13m/s; p=0.006) were significantly raised in GDM compared to controls. Speckle tracking analysis revealed a significant reduction in LV global longitudinal strain (-17.61±1.89 vs -16.29±2.26; p=0.012), LV endocardial global longitudinal strain (-19.84±2.35 vs -18.5±2.59; p=0.031) and LV epicardial longitudinal global strain (-15.73±1.66 vs -14.40±2.01; p=0.005) in GDM. Right ventricular (RV) analysis revealed reduced pulmonary acceleration time (66±11ms vs 58±10ms; p=0.001), RV E/A ratio (1.29±0.35 vs 1.13±0.18; p=0.017), RV A (0.39±0.08m/s vs 0.46±0.1m/s; p=0.001) as well as higher RV S’ (myocardial systolic annular velocity) (0.14±0.02 vs 0.16±0.04; p=0.023) in GDM.

CONCLUSION: Even a short period of exposure to hyperglycaemia as occurs in GDM, is associated with significant maternal functional cardiac impairment at term. Given the established increased post-partum cardiovascular risk after GDM, consideration should be given to further study of the extent of postnatal maternal cardiovascular recovery after GDM pregnancy.
INTRODUCTION

Gestational diabetes (GDM) is hyperglycaemia with onset or diagnosis in pregnancy and occurs in one out of seven pregnancies.\(^1\),\(^2\) GDM is associated with adverse perinatal outcomes for both the mother and the fetus.\(^2\),\(^3\) Women whose pregnancies were complicated with GDM have a more than seven-fold higher incidence of type 2 diabetes later in life.\(^4\) A recent meta-analysis of nine studies pooling data from more than 5 million women, demonstrated that women who had GDM also have a two-fold higher risk of cardiovascular events in the first decade postpartum.\(^5\) The effect of long standing diabetes mellitus (DM) on the adult heart is well documented, with a wide spectrum of dysfunction including diabetic cardiomyopathy.\(^6\) Various microvascular processes and subcellular disturbances have been shown to cause structural and functional damage to the diabetic heart, even without overt coronary artery disease.\(^7\)

In contrast, very little is known about the impact of short term hyperglycaemia on the heart as occurs in GDM. There is a lack of prospective studies examining how GDM influences maternal cardiac adaptation to the increasing cardiovascular demands of pregnancy.\(^8\)-\(^13\) The aim of the present study is to compare maternal cardiac adaptation at term in women with and without GDM. We hypothesized that the duration of hyperglycaemia in GDM pregnancy is not long enough to result in cardiovascular differences assessed using conventional echocardiography and speckle tracking to study left and right heart function.
METHODS

This prospective case-control study was carried out at St. George's University Hospitals NHS Foundation Trust in London over a 12-month period from April 2016 until March 2017. The local institutional review committee approved the study (ID 12/LO/0810) and all participants provided written informed consent. We recruited pregnant women at term that had a pathological oral glucose tolerance test by 28 weeks of gestation and were classified as having gestational diabetes. The oral glucose tolerance test was carried out according to national guidelines. A fasting blood sugar was taken, and then the women received a glucose load of 75g. After 2 hours, blood glucose was determined again. Cut off values for GDM were a fasting blood sugar level of ≥5.6mg/dl or a 2-hour value of ≥7.8mg/dl. Women who were managed with diet only as well as those who received oral hypoglycemic or insulin were included. Only women without any cardiovascular co-morbidities or any form of preexisting diabetes (type I, type II) were asked to take part in the study. Healthy term pregnant women with a BMI of 30kg/m² or less at booking and without any co-morbidity were recruited as controls. For both cases and controls, only women with a singleton pregnancy without pregnancy complications (such as preeclampsia or fetal growth restriction) were considered. Blood pressure was measured manually from the brachial artery according to the guidelines of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.

Conventional echocardiography and speckle tracking echocardiography

Echocardiography examination and analysis were performed by a single operator (BSB) using a GE Vivid Q® ultrasound machine equipped with a 3.5-MHz transducer. Images were acquired at rest in the left lateral decubitus position from standard parasternal and apical views. Digital loops of 3 cardiac cycles with associated electrocardiogram information were stored on the hard disk of the ultrasound machine and transferred to a GE EchoPac® workstation for offline analysis. Analysis was performed according to existing guidelines and as previously described. Parasternal long-axis, short-axis and apical four chamber views...
were used to assess left atrial volume (LAV), left ventricular volume in diastole (LVEDV), proximal and distal right ventricular outflow tract (RVOT) as well as other geometric indices. Doppler images were used to measure early and late mitral and tricuspid valve inflow velocities (LV and RV E and A), mitral and tricuspid inflow deceleration time (LV and RV DT), isovolumetric relaxation time (IVRT) and duration of the late mitral valve inflow (A dur). Left ventricular mass was calculated using the Devereux formula $0.8(1.04([LVEDD + IVSd + PWd]^3 - LVEDD^3]) + 0.6v$, where LVEDD is left ventricular end diastolic diameter, IVSd is thickness of the intraventricular septum in diastole and PWd is posterior wall thickness in diastole. Left ventricular mass index was calculated by dividing the left ventricular mass by the body surface area. Relative left ventricular wall thickness was calculated with the formula $(2*PWd)/LVEDD$.

Pulsed wave tissue Doppler images were used to measure systolic (S’), early diastolic (E’) and late diastolic (A’) myocardial tissue velocities at the basal level of the septum and left and right ventricular walls. LV and RV longitudinal strain and systolic and diastolic (early and late) strain rates were calculated from apical four chamber views, with negative values indicating fiber shortening. LV rotation and de-rotation were calculated from apical and basal parasternal short axis views, with negative values indicating rotation in the clockwise direction. LV twist is the difference between the apical and the basal rotation, LV torsion is LV twist divided by left ventricular length in diastole. If >1 segment was rejected, subjects were excluded from statistical analysis. Diastolic dysfunction was classified according to the guidelines of the British Society of echocardiography applying the age and gender adapted values from the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure.$^{18, 19}$

**Statistical analysis**

Descriptive statistics were performed. Continuous data were presented as mean (standard deviation, SD). Normal distribution was assessed using Shapiro-Wilk test. Categorical data
were presented as number (%) and were compared using the Chi square test. Comparisons between the groups were performed using either unpaired t-test or Mann Whitney U test for continuous data, depending on distribution of data. IBM SPSS statistics version 24 was used (\( p < 0.05 \) considered as significant). Intra- and interobserver variability has been performed as previously described by our group\textsuperscript{20} and was not repeated in this study.
RESULTS

We enrolled a total of 80 pregnant women at term, 40 women with GDM and 40 healthy women. Conventional echocardiography evaluation of the left ventricle could be performed in all women, but speckle-tracking analysis could not be performed in four controls and seven GDM women. Demographic characteristics of the control and GDM groups are shown in Table 1. GDM women had a significantly higher BMI and a higher systolic blood pressure at booking and at inclusion into the study compared to controls.

Echocardiographic indices were not significantly different between the two groups (Table 2) with the exception of the heart rate, relative left ventricular wall thickness, left ventricular E (early diastolic trans-mitral valve velocity) and A (late diastolic trans-mitral valve velocity), which were significantly raised in GDM. Of special note is that left ventricular mass and left ventricular mass index did not differ significantly between groups. Longitudinal strain analysis of the left ventricle showed significant reduction in global strain, endocardial global strain and epicardial global strain in GDM pregnancies (Figure1). Right ventricular analysis revealed reduced pulmonary acceleration time and RV E/A ratio as well as higher RV S' (myocardial systolic annular velocity) and RV A in the GDM population. Speckle tracking analysis of the right ventricle did not reveal any differences between the control and the GDM group (Supplementary Table A).
DISCUSSION

Women with GDM at term had a significantly impaired cardiac function compared to healthy control pregnancies as demonstrated by significantly increased left ventricular relative wall thickness and reduced longitudinal left ventricular global strain, longitudinal left ventricular endocardial and longitudinal epicardial global strain. These subclinical changes suggest a significantly maladaptive cardiovascular response in apparently uncomplicated term GDM pregnancy.

Outside pregnancy, Enomoto et al. studied systolic dysfunction with speckle tracking in normotensive diabetic patients and found a reduction in global longitudinal and subendocardial strain. However, the effect of diabetes on the heart is confounded by the common co-existence of metabolic syndrome, where the effect on cardiac function is influenced not only by diabetes, but also hypertension and dyslipidaemia. Studies assessing cardiac changes in metabolic syndrome also found decreased longitudinal and circumferential strain in the left ventricle and decreased global longitudinal strain in the right ventricle. It is notable that exposure of the maternal heart to a short period of hyperglycaemia parallels the cardiac dysfunction seen in non-pregnant patients after decades of diabetes. There is one previous retrospective study of 18 pregnant women with GDM at the end of the second trimester. The authors demonstrated differences only in global longitudinal strain with preserved circumferential and radial strain in GDM. Although this data supports the findings of the present study, the lack of additional cardiovascular findings may be explained by the retrospective nature of the study, smaller sample size, reduced loading conditions of earlier gestation of assessment and a shorter period of exposure to hyperglycaemia. Two prospective conventional echocardiographic studies found an increase in left ventricular wall thickness and decreased diastolic function supporting our findings.
GDM is a strong risk factor for the development of hypertensive disorders of pregnancy and fetal growth\(^{26, 27}\) – both pathologies where recent work has shown significant deficits in maternal cardiovascular function\(^{28, 29}\). By deliberately excluding GDM pregnancies that developed these complications from our study, we may have inadvertently introduced exclusion bias by not studying women who developed cardiac dysfunction as a consequence of these pregnancy complications. Hence, our data is more reflective of the cardiac function in apparently ‘healthy’ GDM pregnancy rather than showing the evolution of more severe cardiac dysfunction as has been shown to occur with the development of preeclampsia or fetal growth restriction\(^{28, 29}\). Despite these exclusions, it is notable that the prevalence of diastolic dysfunction is 2.8-fold higher in GDM compared to normal pregnancy at term. The latter observation has previously been implicated in the development of hypertensive disorders of pregnancy.

The mechanism by which diabetes causes cardiac dysfunction outside pregnancy are not entirely understood and the spectrum of diabetic cardiovascular effects including myocardial fibrosis, remodeling, diastolic dysfunction and later systolic dysfunction are commonly described as diabetic cardiomyopathy. Impaired cardiac insulin signaling, mitochondrial dysfunction, oxidative stress, advanced glycation, cardiomyocyte calcium handling, inflammation, renin–angiotensin–aldosterone system activation and microvascular dysfunction have all been implicated in the development and progression of diabetic cardiomyopathy, myocardial damage and subsequent fibrosis\(^{30, 31}\). A recent meta-analysis found that women who had GDM during pregnancy have a two-fold higher risk of cardiovascular events in the first decade postpartum, independent of whether or not they develop postpartum type II diabetes\(^5\). The authors postulated that GDM, like preeclampsia, may unmask during pregnancy those women who have a higher postpartum cardiovascular risk\(^{29, 32, 33}\). It would be interesting to postulate that the pathophysiology of cardiovascular dysfunction in GDM pregnancy may lead to long-term myocardial damage and fibrosis as is known to occur in diabetic cardiomyopathy. Future studies should evaluate postpartum
cardiovascular function after GDM pregnancy and determine whether persistent myocardial
dysfunction is caused by GDM pregnancy alone or is confounded by the effects of other
cardiovascular risk factors.

**Strength and limitations**
The strengths of our study are that it is prospective in design and assessed both left and right
heart function using conventional as well as speckle tracking echocardiography to evaluate
cardiac function. The weakness of our study is that women who developed GDM also had a
higher booking BMI and systolic blood pressure. It is not possible to delineate to what extent
the former factors may have influenced the development of the cardiovascular dysfunction
noted in GDM pregnancy. Reassuringly, our previous work demonstrated maternal
cardiovascular dysfunction in non-diabetic pregnancy with BMI>35kg/m², which is
substantially higher than the BMI of our GDM population. Pregnant women with a
BMI>35kg/m² had a significantly higher SV, CO and LVM and a significantly lower TVR. If
corrected for maternal weight, the differences disappeared except for LVMI. The GDM group
showed no difference in SV, SVI, CO, CI, LVM, LVMI, TVR and TVRI compared to controls. We
therefore feel confident to relate the observed differences in speckle tracking and in diastolic
dysfunction to the presence of GDM and not to the higher BMI in the GDM group.
Interestingly, diastolic dysfunction, if present, was more severe in GDM pregnancy than in the
obese pregnancy. Furthermore, women in the GDM group were, on average, scanned two
weeks earlier than the control group. As maternal cardiac maladaptation increases with
advancing gestation, the latter difference would have only served to ameliorate, rather than
exaggerate, any differences between GDM and normal pregnancy.8

**Conclusion**
A short period of exposure to hyperglycaemia as occurs in GDM, is associated with significant
maternal functional cardiac impairment at term. Given the established increased post-partum
cardiovascular risk after GDM, consideration should be given to further study of the extent of postnatal maternal cardiac recovery after GDM pregnancy.
ACKNOWLEDGEMENTS

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DECLARATION OF INTEREST

None
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FIGURE LEGEND

Figure 1: Representative speckle tracking and strain rate analysis in GDM (A, B, C) and control (D, E, F). GSendo = global endocardial strain; GS = global strain; GSepi = global epicardial strain.
Table 1: Demographic characteristics of women with normal and GDM pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=40)</th>
<th>GDM (n=40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>34.8 (4.0)</td>
<td>33.2 (4.5)</td>
<td>0.099</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Caucasian</td>
<td>34 (85.0%)</td>
<td>25 (62.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>- Afro-Caribbean</td>
<td>2 (5.0%)</td>
<td>4 (10.0%)</td>
<td></td>
</tr>
<tr>
<td>- Asian</td>
<td>4 (10.0%)</td>
<td>11 (27.5%)</td>
<td></td>
</tr>
<tr>
<td>Parity:</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Nulliparous</td>
<td>16 (40.0%)</td>
<td>20 (50.0%)</td>
<td></td>
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<tr>
<td>- Multiparous</td>
<td>24 (60.0%)</td>
<td>20 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>Booking visit BMI (kg/m^2)</td>
<td>23.7 (2.5)</td>
<td>30.4 (8.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Booking visit SBP (mmHg)</td>
<td>109 (11)</td>
<td>119 (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Booking visit DBP (mmHg)</td>
<td>67 (8)</td>
<td>72 (9)</td>
<td>0.012</td>
</tr>
<tr>
<td>Gestation at assessment (weeks)</td>
<td>39.3 (1.0)</td>
<td>37.0 (1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI at assessment (kg/m^2)</td>
<td>28.1 (3.0)</td>
<td>32.6 (6.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP at assessment (mmHg)</td>
<td>109 (9)</td>
<td>114 (11)</td>
<td>0.024</td>
</tr>
<tr>
<td>DBP at assessment (mmHg)</td>
<td>74 (8)</td>
<td>74 (9)</td>
<td>0.790</td>
</tr>
</tbody>
</table>

Results are shown as mean (±SD) or number of subjects (percentage). GDM=gestational diabetes; BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure.
| Table 2: Left ventricular hemodynamic, geometric and speckle tracking-derived indices |
|------------------------------------------|----------------|----------------|
|                                          | Controls (n=40) | GDM (n=40) |
| **Hemodynamic Indices**                  |                |              |
| HR (min⁻¹)                               | 75 (9)         | 83 (10)      | <0.001 |
| SV (ml)                                  | 66 (11)        | 64 (13)      | 0.346  |
| SVI (ml*m⁻²)                             | 36 (6)         | 34 (7)       | 0.143  |
| CO (ml*min⁻¹)                            | 4896 (849)     | 5295 (1239)  | 0.163  |
| CI (ml*min*m⁻²)                          | 2664 (439)     | 2797 (537)   | 0.227  |
| TVR (dynes*s⁻¹*cm⁻⁵)                     | 1448 (332)     | 1390 (347)   | 0.448  |
| TVRI (dynes*s⁻¹*cm⁻⁵*m⁻²)                | 2658 (605)     | 2605(634)    | 0.704  |
| Average S' (m/s)                         | 0.10 (0.02)    | 0.10 (0.02)  | 0.746  |
| **Geometric Indices**                    |                |              |
| LAV (ml)                                 | 55 (12)        | 57 (14)      | 0.507  |
| LAVI (ml*m⁻²)                            | 30 (6)         | 30 (7)       | 0.877  |
| LVM (g)                                  | 119 (21)       | 128 (36)     | 0.172  |
| LVMI (g*m⁻²)                             | 64 (10)        | 67 (13)      | 0.365  |
| RWT                                      | 0.37 (0.08)    | 0.43 (0.07)  | <0.001 |
| **Mitral inflow indices**                |                |              |
| E (m/s)                                  | 0.73 (0.12)    | 0.80 (0.15)  | 0.026  |
| A (m/s)                                  | 0.57 (0.11)    | 0.65 (0.13)  | 0.006  |
| E/A ratio                                | 1.28 (0.18)    | 1.26 (0.30)  | 0.699  |
| Septal E' (m/s)                          | 0.10 (0.03)    | 0.10 (0.02)  | 0.567  |
| Lateral E' (m/s)                         | 0.15 (0.04)    | 0.15 (0.03)  | 0.843  |
| E/E' average                             | 6.18 (1.57)    | 7.02 (2.82)  | 0.103  |
| **Diastolic function**                   |                |              |
| Normal                                   | 35 (87.5)      | 26 (65)      | 0.010  |
| Grade 1 Diastolic Dysfunction            | 4 (10)         | 2 (5)        |        |

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<table>
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<th>Grade 2 Diastolic Dysfunction</th>
<th>1 (2.5)</th>
<th>12 (30)</th>
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<tbody>
<tr>
<td>Grade 3 Diastolic Dysfunction</td>
<td>0 (0)</td>
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### Strain and strain rate indices

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<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV global strain (%)</td>
<td>-17.61 (1.89)</td>
<td>-16.29 (2.26)</td>
<td>0.012</td>
</tr>
<tr>
<td>LV endocardial global strain (%)</td>
<td>-19.84 (2.35)</td>
<td>-18.50 (2.59)</td>
<td>0.031</td>
</tr>
<tr>
<td>LV epicardial global strain (%)</td>
<td>-15.73 (1.66)</td>
<td>-14.40 (2.01)</td>
<td>0.005</td>
</tr>
<tr>
<td>LV longitudinal strain rate (s⁻¹)</td>
<td>-0.98 (0.12)</td>
<td>-0.96 (0.15)</td>
<td>0.509</td>
</tr>
<tr>
<td>LV early diastolic strain rate (s⁻¹)</td>
<td>1.24 (0.26)</td>
<td>1.15 (0.32)</td>
<td>0.235</td>
</tr>
<tr>
<td>LV late diastolic strain rate (s⁻¹)</td>
<td>0.55 (0.16)</td>
<td>0.60 (0.19)</td>
<td>0.302</td>
</tr>
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</table>

### Twist and torsion indices

<table>
<thead>
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<th>Mean ± SD</th>
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<tbody>
<tr>
<td>LV twist (degree)</td>
<td>14.33 (5.69)</td>
<td>16.39 (6.69)</td>
<td>0.223</td>
</tr>
<tr>
<td>LV torsion (degree*cm⁻¹)</td>
<td>1.66 (0.66)</td>
<td>1.88 (0.76)</td>
<td>0.252</td>
</tr>
<tr>
<td>LV twist rate (degree*s⁻¹)</td>
<td>102 (48)</td>
<td>134 (55)</td>
<td>0.048</td>
</tr>
<tr>
<td>LV un-twist rate (degree*s⁻¹)</td>
<td>-106 (56)</td>
<td>-125 (47)</td>
<td>0.194</td>
</tr>
</tbody>
</table>

Results are shown as mean ±SD. HR=heart rate; SV=stroke volume; SVI=stroke volume index; CO=cardiac output; CI=cardiac index; TVR=total vascular resistance; TVRI=total vascular resistance index; Average S'=systolic tissue Doppler average velocity at the septal/lateral mitral valve annulus; LAV=left atrial volume; LAVI=left atrial volume index; LVM=left ventricular mass; LVMI=left ventricular mass index; RWT=relative left ventricular wall thickness; E=peak early diastolic transmitral valve velocity; A=peak late diastolic transmitral valve velocity; Septal/lateral E'=peak early diastolic tissue Doppler velocity at the septal/lateral mitral valve annulus; E/E' average=E to average lateral and septal E' ratio.