Myocardial hypertrophy in fetuses of women with gestational diabetes

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ABSTRACT
Fetuses of diabetic mothers are known to have structural and functional cardiac changes. There are minuscule data on fetal cardiac changes from the Indian subcontinent. Hence, this study aimed to detect myocardial hypertrophy using 2D and M-mode fetal echocardiography (ECHO) in South Indian women with gestational diabetes mellitus (GDM) in their late phase of pregnancy. We have compared ECHO findings among nondiabetic controls and well-controlled and poorly controlled GDM through a cross-sectional observational study. Myocardial and interventricular septum (IVS) thicknesses were measured at the end of systole and diastole. The study included a total of 247 pregnant women; among them, 152 were diabetics [(well-controlled (n = 74) and poorly controlled (n = 78)], and 95 were nondiabetic controls. Myocardial hypertrophy is evident only beyond 29 weeks of gestation. During 29–34 weeks, myocardial hypertrophy is less severe among those with glycemic control. The fetuses beyond 35 weeks have a consistent and significant progressive thickening of fetal myocardium in all dimensions (p-value < 0.05). The overall thickness of ventricular walls and IVS increases with the diabetic status from nondiabetic controls to poorly controlled GDM women. There is a clear need to explore the perinatal implications of structural changes, considering the huge burden of diabetes in the Indian population.

INTRODUCTION
Diabetes in pregnancy or gestational diabetes mellitus (GDM) is one of the most typical risk factors for adverse perinatal outcomes. The prevalence has noted up to 17% in the South Indian population (Rajput et al., 2013). Fetal cardiac structural abnormality is frequently seen in the fetuses of diabetic mothers. This developmental abnormality broadly ranges from structural heart disease to subclinical myocardial dysfunction (Gandhi et al., 1995; Turan et al., 2011). Although early fetal cardiac development is unpretentious, throughout pregnancy, hyperinsulinemic state interferes with fetal metabolism that increases the expression and affinity of insulin receptors and leads to the proliferation and hypertrophy of cardiac myocytes. Physiologically myocardial hypertrophy unveils the mechanism of fetal adaptation to hyperinsulinemia (Garcia-Flores et al., 2011).

The studies on fetal cardiac hypertrophy among GDM pregnancy and its correlation with somatic overgrowth and metabolic control have shown heterogeneous results across the literature. It is not clear whether cardiac hypertrophy is the only reflection of metabolic control in the fetuses. There is a lack of robust literature on fetal cardiac changes among pregnant women with GDM in their late phase of pregnancy. Hence, this study was carried out to assess the structural changes in the fetal heart using echocardiography (ECHO). The study also compares fetal ECHO findings among nondiabetic healthy pregnant women and well-controlled and poorly controlled pregnant diabetics.

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METHODS AND MATERIALS

Study design and participant

A cross-sectional study was performed in the South Indian adult population at a tertiary care center between December 2015 and June 2017. The study included pregnant women beyond 24 weeks of gestation with GDM. Women with pre-eclampsia, hypertension, renal insufficiencies, liver cirrhosis, blood diathesis, severe anemia (<9 g/dl), maternal cardiac disease, evidence of congenital fetal anomaly of any organ including heart, hypoxic-ischemic encephalopathy, intra-uterine growth retardation, chromosomal abnormalities, twin pregnancy, and fetal arrhythmia were excluded from the study. Nondiabetic healthy pregnant women with the same inclusion criteria were involved as controls.

Ethical consideration

Ethical approval was obtained from the Institutional Ethics Committee (IEC) on December 9, 2015 (No. IEC 858/2015). The written informed consent was taken from all the participants before examinations. There was no risk to fetus and mother as this was an observational study.

Diagnostic criteria

GDM was diagnosed using the International Association of Diabetes in Pregnancy Study Group criteria for oral glucose tolerance test (GTT) (Cutoffs being 92/180/153 mg/dl following 75 g of oral glucose) between 24 and 28 weeks. Cases were categorized into controlled GDM and poorly controlled GDM based on the American Diabetes Association guidelines 2016 criteria for glycemic targets in pregnancy, of which repeat test results in fasting plasma glucose (FPG) level of ≤95 mg/dl (5.3 mmol/l) or 2-hours postprandial value of ≤120 mg/dl (6.7 mmol/l) among GDM were considered. The fasting blood glucose level of ≤90 mg/dl (5.0 mmol/L) or 2-hours postprandial value of ≤120 mg/dl (6.7 mmol/l) was taken as the cutoff for the well-controlled group. All fetuses across three gestational age groups were further classified into macrosomic and non-macrosomic groups taking either abdominal circumferences (AC) or expected fetal weight (EFW) at or above 90th centile.

Echocardiography

The 2D and M-mode fetal ECHO wa performed by a trained and certified fetal medicine specialist using a transducer of Vivid 7, GE health-care system ECHO machine with the convex transducer of frequency 1.7–2.4 MHz A standard lateral four-chamber view was obtained after adequate magnification in 2D ECHO followed by the application of M Mode. The thickness of left ventricular (LV) and right ventricular (RV) walls and interventricular septum (IVS) were measured at the end of systole and diastole.

Statistical analysis

Depending on the distribution, continuous variables were expressed as mean ± SD, and categorical variables were reported as proportions. Proportions were compared using the Chi-square test, and continuous variables were compared by Student t-test and ANOVA for normally distributed data. M-mode findings among the three groups were compared using the analysis of variance test with Bonferroni correction. The statistical analyses were performed with the Statistical Package for the Social Sciences software version 20.0, and a significant p-value was considered to be <0.05.

RESULTS

Clinical characters

The study included a total of 247 pregnant women. Among them, 152 were diabetics [(well-controlled (n = 74) and poorly controlled (n = 78)], and 95 were nondiabetic controls.

The tendency of increasing AC centile and increasing EFW centile was seen from healthy controls to poorly controlled diabetics. However, it is observable that there is no significant difference in fetal biometry between the groups (Table 1). The correlation coefficient of 0.42 showed a clinically significant (p = 0.03) linear relationship between fasting blood sugar (FBS) value and LV and IVS myocardial thicknesses at term.

Echocardiographic results

The overall thickness of ventricular walls and IVS increases with the diabetic status, from nondiabetic controls to well-controlled GDM and poorly controlled GDM women. The trend was statistically significant for all the thickness between groups. Intergroup differences remain significant when poorly controlled diabetics were compared to healthy controls. Yet, it was not substantial between poorly controlled and well-controlled GDM groups except for LV end-systolic thickness (EST) and end-diastolic thickness (EDT) (Table 2).

<table>
<thead>
<tr>
<th>Variable (mean ± SD)</th>
<th>Non-diabetics (control) (n = 95)</th>
<th>Well-controlled GDM (n = 74)</th>
<th>Poorly controlled GDM (n =78)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>29 ± 4</td>
<td>30 ± 4</td>
<td>29 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Gestational age at examination (weeks)</td>
<td>31 ± 4</td>
<td>32 ± 3</td>
<td>32 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>80 ± 5</td>
<td>86 ± 5</td>
<td>108 ± 18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PPBS (mg/dl)</td>
<td>–</td>
<td>112 ± 12</td>
<td>152 ± 32</td>
<td>0.01</td>
</tr>
<tr>
<td>USG AC-Centile</td>
<td>52.22 ± 26.9</td>
<td>61.23 ± 3.42</td>
<td>65.23 ± 30.6</td>
<td>0.03</td>
</tr>
<tr>
<td>USG EFW-Centile</td>
<td>42.90 ± 24.54</td>
<td>55.5 ± 26.17</td>
<td>56.62 ± 28.32</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

FPG = fasting plasma glucose; PPBS = postprandial blood sugar; AC = abdominal circumference; EFW = expected fetal weight; USG = ultrasound; GDM = gestational diabetes mellitus.

NS: it represents the statistically non-significant difference between the group where p-value was more than 0.05.

*p < 0.05 for poorly controlled vs control.

*p < 0.05 for poorly controlled vs well-controlled GDM.
For subgroup analysis, we have categorized the women based on the period of gestation; 82 pregnant women were between 24 and 28 weeks, 80 between 29 and 34 weeks, and 85 were beyond the 35 weeks. The subgroup analysis showed that there was no significant difference in myocardial hypertrophy between all three groups of gestational age between 24 and 28 weeks. Ventricular walls and IVS thickness were almost the same in three groups. EST- has increased progressively for IVS, LV, and RV and EDT for RV from control to poorly controlled group in 29–34 weeks old fetuses. The same three measurements showed significant intergroup differences when poorly controlled diabetics were compared to controls. Similarly, we found a significant difference in IVS-EST, LVEST, and RV-EDT between well-controlled and poorly controlled diabetics that reflects worse fetal myocardial hypertrophy among fetuses of the poorly controlled mothers. The ECHO analysis of fetuses beyond 35 weeks showed that there was a consistent and significant progressive thickening of fetal myocardium from healthy controls to well-controlled diabetics and reaching maximum thickness among the poorly controlled diabetics. There were no intergroup differences between well-controlled versus poorly controlled diabetics. Therefore, a strict control of maternal sugars could not reduce the severity of myocardial hypertrophy. Comparing healthy controls and well-controlled diabetics, the IVS-EST, LV-EST, RV-EDT, and IVS-EDT were significantly thicker among well-controlled diabetics, reflecting significant myocardial hypertrophy even after strict control of sugars (Table 3).

The prevalence of macrosomia was almost the same (10.52% vs. 12.16%) among control and well-controlled groups; 25.64% of fetuses were macrosomic among the poorly controlled group. This difference was statistically significant, with an overall $p$-value of 0.003. Analysis with an independent $t$-test showed no significant difference in myocardial wall thickness among fetuses with and without macrosomia (Table 4). Thus, cardiac structural changes among diabetic groups were not a direct reflection of somatic overgrowth in this study.

**DISCUSSION**

This study presented the comparison of fetal cardiac structural changes among diabetic pregnancy and nondiabetic controls that showed significant myocardial hypertrophy among fetuses of diabetic mothers compared to nondiabetic controls. We also found that the myocardial hypertrophy increases proportionally with the gestational age. There was no significant difference between macrosomic and non-macrosomic fetuses.

Myocardial hypertrophy is known to result in diastolic dysfunction and reduced global myocardial performance. However, this usually does not result in cardiovascular compromise before birth (Wong et al., 2003).

**Gestational age and myocardial hypertrophy**

In this study, myocardial hypertrophy in GDM was evident only beyond 29 weeks of gestation. A prospective study on Indian fetuses concluded that there is a fetal myocardial hypertrophy in diabetic pregnancy, and these changes are observed only during late pregnancy (Garg et al., 2014). The prevalence of hypertrophic cardiomyopathy in the fetuses of pregnant women with GDM before the initiation of treatment was 54% (95% CI: 41.3%–65.1%) in another cross-sectional study. The mean gestational age at the diagnosis of GDM was 30.59 weeks in their study (Palmieri et al., 2017). Thus, some cardiac changes would have already occurred in these fetuses at the time of diagnosis.

**Glycemic control and myocardial hypertrophy**

This study revealed that between 29 and 34 weeks of gestational age, myocardial hypertrophy was less severe among those with strict glycemic control. However, beyond 35 weeks, this intergroup difference was disappeared. Garcia-Flores et al. (2011) showed similar results where myocardial structural changes were evident in the well-controlled GDM group, with delayed manifestation compared to a suboptimal glycemic control group. A study is aimed to compare cardiac structure and function in fetuses of well- and poorly controlled pre-gestational diabetic pregnancy in the third trimester. There was no difference between the two groups in cardiac size, IVS wall thickness, and ejection fraction (Wong et al., 2003). Another study on GDM pregnancies performed in China leads to similar conclusions, in which good glycemic control delayed fetal cardiac structural/functional changes but could not reduce the severity (Chen et al., 2012). A large prospective study on 300 gestational diabetes mothers and controls from India showed that there is a significant myocardial hypertrophy among GDM fetuses and was irrespective of maternal glycemic control status (Garg et al., 2014). The other studies are concluding that strict glycemic control does not prevent fetal cardiac changes (Ren et al., 2011; Wang et al., 2015).

On the contrary, a few studies are concluding that strict glycemic control prevents diabetic cardiomyopathy (Gardiner
The fetal cardiac changes are significant only among overt diabetics with high glycated hemoglobin, whereas well-controlled GDM fetuses hardly show structural/functional changes (Fouda et al., 2013). It is interesting to note that some cardiac hypertrophy is seen even among women with very mild glucose intolerance in pregnancy, as shown by abnormal Glucose Challenge Test but normal GTT (Koşüş et al., 2011). These inconsistent results disclose that myocardial hypertrophy is not a simple reflection of basal glycemic control. It is, in fact, due to fetal hyperinsulinemia and increased activity of insulin receptors, which leads to the proliferation and hypertrophy of cardiac myocytes (Breitweser et al., 1980; Buchanan and Kitzmiller, 1994). It has been postulated that subtle fluctuations in glucose values correlate with fetal cardiac and general somatic growth in maternal diabetes (Greco et al., 2003). Thus, the literature is inconclusive on the correlation of diabetic fetal cardiomyopathy versus the degree of glycemic alterations. In this study, we found a correlation between increasing FBS and myocardial thickness at term. This may reflect a possible association between metabolic control and cardiac changes.

Table 3. Myocardial thicknesses of fetuses in different gestational age.

<table>
<thead>
<tr>
<th>Variable (mean±SD)</th>
<th>Non-diabetic controls (n = 33)</th>
<th>Well-controlled GDM (n = 23)</th>
<th>Poorly controlled GDM (n = 26)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age of &lt;28 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV EST (mm)</td>
<td>4.00 ± 1.46</td>
<td>3.96 ± 0.98</td>
<td>4.01 ± 0.94</td>
<td>*NS</td>
</tr>
<tr>
<td>IVS EST (mm)</td>
<td>4.18 ± 1.13</td>
<td>4.04 ± 0.87</td>
<td>4.31 ± 1.19</td>
<td>NS</td>
</tr>
<tr>
<td>LV EST (mm)</td>
<td>4.08 ± 1.26</td>
<td>4.23 ± 1.06</td>
<td>4.53 ± 0.88</td>
<td>NS</td>
</tr>
<tr>
<td>RV EDT (mm)</td>
<td>3.33 ± 1.06</td>
<td>2.93 ± 0.64</td>
<td>3.64 ± 0.63</td>
<td>NS</td>
</tr>
<tr>
<td>IVS EDT (mm)</td>
<td>3.59 ± 1.11</td>
<td>3.43 ± 0.78</td>
<td>3.78 ± 1.13</td>
<td>NS</td>
</tr>
<tr>
<td>LV EDT (mm)</td>
<td>3.37 ± 1.07</td>
<td>3.56 ± 1.03</td>
<td>3.61 ± 0.71</td>
<td>NS</td>
</tr>
<tr>
<td>Gestational age of 29–34 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV EST (mm)</td>
<td>4.61 ± 0.96</td>
<td>4.71 ± 1.12</td>
<td>5.57 ± 1.43*</td>
<td>0.04</td>
</tr>
<tr>
<td>IVS EST (mm)</td>
<td>5.67 ± 1.39</td>
<td>5.81 ± 1.24</td>
<td>6.98 ± 1.61**</td>
<td>0.05</td>
</tr>
<tr>
<td>LV EST (mm)</td>
<td>4.91 ± 0.98</td>
<td>4.76 ± 1.16</td>
<td>5.91 ± 1.12**</td>
<td>0.04</td>
</tr>
<tr>
<td>RV EDT (mm)</td>
<td>4.10 ± 0.98</td>
<td>3.92 ± 0.92</td>
<td>5.12 ± 1.09**</td>
<td>0.03</td>
</tr>
<tr>
<td>IVS EDT (mm)</td>
<td>5.09 ± 1.28</td>
<td>5.21 ± 1.13</td>
<td>5.32 ± 1.61</td>
<td>NS</td>
</tr>
<tr>
<td>LV EDT (mm)</td>
<td>4.17 ± 1.39</td>
<td>4.04 ± 0.83</td>
<td>4.12 ± 1.53</td>
<td>NS</td>
</tr>
<tr>
<td>Gestational age of &gt;35 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV EST (mm)</td>
<td>5.16 ± 1.70</td>
<td>5.92 ± 1.76</td>
<td>6.43 ± 1.52*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IVS EST (mm)</td>
<td>5.93 ± 1.38</td>
<td>6.67 ± 1.51*</td>
<td>7.12 ± 1.45*</td>
<td>0.04</td>
</tr>
<tr>
<td>LV EST (mm)</td>
<td>5.17 ± 1.29</td>
<td>6.23 ± 2.43*</td>
<td>6.43 ± 1.67*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RV EDT (mm)</td>
<td>4.17 ± 0.98</td>
<td>5.28 ± 1.34*</td>
<td>5.41 ± 0.98*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IVS EDT (mm)</td>
<td>4.70 ± 1.26</td>
<td>5.62 ± 0.71*</td>
<td>6.18 ± 1.84*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV EDT (mm)</td>
<td>4.30 ± 1.05</td>
<td>4.67 ± 1.31</td>
<td>5.76 ± 1.32*</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

RV = right ventricle; LV = left ventricle; IVS = interventricular septum; EST = end-systolic thickness; EDT = end-diastolic thickness; GDM = gestational diabetes mellitus; NS = not significant.

*: it represents statistically non-significant difference between the group where p-value was more than 0.05.

*: p < 0.05 for poorly-controlled versus control.

*: p < 0.05 for poorly controlled versus well-controlled GDM.

Table 4. Fetal myocardial thickness of all macrosomic and non-macrosomic fetuses.

<table>
<thead>
<tr>
<th>Variable (mean±SD)</th>
<th>Nonmacrosomic fetus (n, 208)</th>
<th>Macrosomic fetus (n, 39)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV EST (mm)</td>
<td>4.84 ± 1.92</td>
<td>5.12 ± 2.23</td>
<td>0.21</td>
</tr>
<tr>
<td>IVS EST (mm)</td>
<td>5.62 ± 1.89</td>
<td>5.87 ± 2.15</td>
<td>0.23</td>
</tr>
<tr>
<td>LV EST (mm)</td>
<td>4.86 ± 1.12</td>
<td>5.12 ± 1.34</td>
<td>0.13</td>
</tr>
<tr>
<td>RV EDT (mm)</td>
<td>4.14 ± 1.17</td>
<td>4.34 ± 1.09</td>
<td>0.15</td>
</tr>
<tr>
<td>IVS EDT (mm)</td>
<td>4.86 ± 1.79</td>
<td>4.56 ± 1.36</td>
<td>0.11</td>
</tr>
<tr>
<td>LV EDT (mm)</td>
<td>4.91 ± 1.22</td>
<td>4.56 ± 1.65</td>
<td>0.10</td>
</tr>
</tbody>
</table>

RV = right ventricle; LV = left ventricle; IVS = interventricular septum; EST = end-systolic thickness; EDT = end-diastolic thickness; GDM = gestational diabetes mellitus.
Myocardial hypertrophy and macrosomia

A study postulated that the increase in myocardial thickness in the fetuses of diabetic pregnancy is secondary to accelerated growth and macrosomia (Gandhi et al., 1995). The macrosomic fetuses of mothers with uncontrolled diabetes showed higher mean IVS thickness in a study focused on the assessment of cardiomyopathies (Nashaat and Mansour, 2010). This correlation between somatic overgrowth and hypertrophic cardiomyopathy is also seen in other studies (Palmieri et al., 2017). However, this study did not show a significant difference in myocardial thickness among macrocosmic and adequate for gestational age fetuses. Fetal myocardial hypertrophy occurs due to various etiologies and found that the diabetic cardiomyopathy occurs more in second/third trimesters, independent of somatic overgrowth (Fontes-Pedra et al., 2002).

Limitations

The present study is a cross-sectional study recruiting different sets of pregnant women of different gestational groups. Rather, a longitudinal follow-up of the same fetuses through the gestation would give more meaningful results.

CONCLUSION

These data from a tertiary hospital in South India show a significant myocardial hypertrophy among the fetuses of diabetic mothers compared to nondiabetic controls, being worst among those with suboptimal glycemic control. Myocardial hypertrophy is evident only beyond 29 weeks of gestation. Between 29 and 34 weeks, myocardial hypertrophy is less severe among those with strict glycemic control. However, beyond 35 weeks, strict glycemic control could not lessen the severity of myocardial hypertrophy. Cardiac changes are not a simple reflection of somatic overgrowth. There was a small degree of correlation between FBS control status and myocardial hypertrophy. A fetal screening echo done at term diabetic pregnancy may help to identify fetuses with severe myocardial hypertrophy, which may help to identify fetuses at the risk of perinatal and neonatal morbidity.

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AUTHOR’S CONTRIBUTION

All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

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REFERENCES


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