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FETUSES OF MOTHERS WITH HYPERGLYCEMIA FIRST DETECTED IN PREGNANCY HAVE SIGNIFICANT CARDIAC CHANGES

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ABSTRACT

Fetal cardiomyopathy is one of the complications of diabetic pregnancy. World Health Organization (WHO) classified hyperglycemia first detected during pregnancy in to gestational diabetes mellitus (GDM) and diabetes in pregnancy (DIP) based on the severity of hyperglycemia as revealed by the fasting blood sugar. This study aimed at characterizing and comparing the fetal cardiac changes in mothers with GDM and DIP. One hundred and fifty consenting mothers at 32-35 weeks gestation were enrolled in this study and grouped in to GDM, DIP, pre-gestational DM (PDM) and control groups. The basic obstetric and fetal echocardiographic scans were performed on all the participants. The fetuses of mothers with GDM, DIP and PDM groups had significantly thickened end diastolic interventricular septal thickness and end systolic interventricular septal thickness compared to fetuses of mothers in the control group. The mitral and tricuspid E/A were also significantly reduced in the fetuses of mothers in the hyperglycemic group compared to fetuses of mothers in the control group. This study has shown that the higher the level of maternal hyperglycemia the more the severity of fetal cardiac complications. It also showed that hyperglycemia in pregnancy whether symptomatic or not, is associated with significant fetal cardiac changes. Hence, blood glycemic level should be kept within normal range during pregnancy.

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INTRODUCTION:

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[1] DM is a common medical condition that may complicate pregnancy, in which case, it is known as gestational DM (GDM).[2] However, according to WHO classification, women with hyperglycemia first detected in pregnancy, could be grouped as having gestational DM (GDM), fasting plasma glucose between 5.1-6.9 mmol/l (92 -125 mg/dl), 1-h post 75g oral glucose load ≥10.0 mmol/l (180 mg/dl) or 2-h post 75g oral glucose load 8.5 – 11.0 mmol/l (153-199 mg/dl) and diabetes in pregnancy(DIP) fasting plasma glucose ≥ 7.0 mmol/l (126 mg/ dl), 2-h plasma glucose ≥ 11.1 mmol/l (200 mg/dl) following a 75g oral glucose load or random plasma glucose ≥ 11.1 mmol/l (200 mg/ dl).[3]

When there is maternal hyperglycemia, blood glucose from mother readily traverses the placenta and causes fetal hyperglycemia. The fetal hyperglycemia induces excess insulin secretion in the fetus as a feedback response.[2] Insulin, produced by the β-cells of the pancreatic islet of Langerhans, is an anabolic hormone that plays an essential role in carbohydrate, fat and protein metabolism.[4] Fetal hyperinsulinemia leads to the proliferation and hypertrophy of cardiac muscles as well as the interventricular septum.[5] The interventricular septal hypertrophy can result in hypertrophic subaortic stenosis and compromised cardiac contractility. This may present with symptoms of left ventricular outflow obstruction leading to cardiomyopathy.[6] The degree of cardiac impairment varies considerably, therefore therapeutic interventions vary from close monitoring to full cardiovascular and ventilatory support for congestive heart failure.

The degree of fetal cardiac structural and functional anomalies in hyperglycemic mothers can be reliably assessed by fetal echocardiography, the technique used in this study.[7] This study aimed at characterizing

and comparing the fetal cardiac changes in mothers with GDM, DIP, PDM and control.

MATERIAL AND METHODS

One hundred and fifty consenting pregnant women at fetal gestational ages between 32 to 35 weeks were enrolled during their antenatal clinic visit at LAUTECH Teaching Hospital Osogbo, south west Nigeria.

According to WHO classification, women with hyperglycemia first detected in pregnancy, were grouped as gestational DM (GDM), fasting plasma glucose between 5.1-6.9 mmol/l (92 -125 mg/dl), 1-h post 75g oral glucose load ≥10.0 mmol/l (180 mg/dl) or 2-h post 75g oral glucose load 8.5 – 11.0 mmol/l (153-199 mg/dl) and diabetes in pregnancy (DIP) fasting plasma glucose ≥ 7.0 mmol/l (126 mg/ dl), 2-hplasma glucose ≥ 11.1 mmol/l (200 mg/dl) following a 75g oral glucose load or random plasma glucose ≥ 11.1 mmol/l (200 mg/ dl)based.[3]

These women were grouped as follows: 27 GDM, 45 DIP, and 3 PDM and 75 controls. This study was approved by the Institution´s Research and Ethics Committee.

After consent was taken from the patients, they filled the questionnaires. The questionnaire had sections such as patient´s biodata, clinical and obstetric history, which included history of associated medical disorders and drug intake. Fetal echocardiography was performed on each of the participant using Mindray® DC3 ultrasound machine with a 3.5 -5.0 MHz curvilinear prob.

The ultrasound examination was carried out with the mother in a supine position, gel was applied to the skin of the abdomen of the patient and a basic obstetric scan was done followed by a fetal heart scan. The measurements for fetal biometry, ultrasound estimated gestational age and the fetal weight were taken. The 4-chamber view of the fetal heart was demonstrated by doing a transverse scan at the level of the thorax, with some rotation done either to the left or right side to facilitate the evaluation. Cine images were used to overcome the random fetal movements that posed challenges to imaging.

Interventricular septal thickness

The structural parameters were taken by placing the M mode cursor perpendicular to the interventricular septum just below the atrioventricular valve according to the standard recommended by the American society of echocardiography. The interventricular septal thickness was measured using the electronic calipers on the biventricular activity tracing. The interventricular septal thickness at diastole and

systole were taken and measured in centimetres (cm). Three measurements were taken on each fetus and the average was determined to minimize the intra observer error. All subjects were scanned by a researcher and the same machine was used to scan all the participants. In addition, magnified images were taken to minimize the error obtained from the caliper system. Fetal heart rate was determined on M mode tracing to ensure the interventricular septal thickness was taken at the normal circadian rhythm.

Diastolic function E/A ratio

The diastolic function parameters were taken on the pulsed wave Doppler, the insonation angle was kept at <20 degree from the direction of blood flow across the atrioventricular valves. The E/A ratio (ratio of the velocity during early ventricular filling E and the velocity during atrial contraction A) of mitral and tricuspid valves were determined by placing the sample volume cursor within the ventricle along the course of the apex of mitral and tricuspid valves sequentially. The Doppler wave was automatically created by the ultrasound machine after the pulse Doppler knob was pressed. The E and A waves produced corresponds to the passive ventricular filling and the filling by the atrial contraction respectively. The peak velocities at the E and A waves were measured on the Doppler wave and the ratio was calculated by the ultrasound machine.

The end systolic and end diastolic thicknesses of interventricular septum [IVS] and diastolic function parameters: E and A wave velocities across the atrioventricular valves using pulsed Doppler pattern are shown in figure 1.

Statistical Analysis

Data analysis was performed using statistical package for social sciences (SPSS) version 17. Continuous variables were presented as means and standard deviation. Independent t test was used to compare the mean EDIVST and ESIVST between the hyperglycemic groups and controls. Likewise, the E/A ratio across the mitral and tricuspid valves between the hyperglycemic groups and the controls was also compared using the independent t test. One–way analysis of variance (ANOVA) was used to compare EDIVST, ESIVST, E/A ratio across mitral and tricuspid valves within the diabetic subgroups (GDM, DIP and PDM) and control group as well as individual group with the controls. The fasting blood glucose was correlated with the fetal cardiac parameters using Spearman´s correlation analysis. Results were expressed in graphs and tables and considered statistically significant if $p < 0.05$.

RESULTS

Demographic parameter of participants

This study comprised of 150 consenting pregnant women. Based on WHO classification of hyperglycemia first detected in pregnancy, the participants were group as follows. [3] 27 GDM, 45 DIP, 3 PDM; and 75 matched controls. There was no statistically significant difference in the mean maternal age (30.3±5.10 years versus 30.1±5.22 years, $p>0.05$), mean estimated gestational age (33.60±1.22 versus 33.80±1.20, $p>0.05$) and parity (1.4 versus 1.3, $p>0.05$) of the control and the hyperglycemic groups. The mean estimated fetal weight (EFW) was observed to be significantly higher in the hyperglycemic group than controls (2236g versus 2425g, $p<0.05$).

Fetal cardiac parameters

The fetal cardiac parameters taken were End Diastolic Interventricular Septal Thickness (EDIVST), End Systolic Interventricular Septal Thickness (ESIVST), E/A ratio (ratio of the velocity during early the ventricular filling E and velocity during the atrial contraction A) of mitral valve (MVE/A), and tricuspid valves (TVE/A).

The mean EDIVST and mean ESIVST in the hyperglycemic group were significantly higher compared to the control group (6.50±0.90mm versus 4.60±0.43mm, $p=0.001$) and (7.70±1.30mm vs. 5.60±0.47mm, $p=0.001$) respectively.

The mean EDIVST and ESIVST were higher in DM, DIP, and PDM than the control group, ($p=0.0001$ for each *post hoc* test) (Table 1). Similarly, the mean E/A ratio across the tricuspid valve (TVE/A) and mitral valve (MVE/A) was lower in hyperglycemic group than the control group. In addition, the mean E/A ratio across the tricuspid valve (TVE/A) and mitral valve (MVE/A) was lower in GDM, DIP, and PDM when compared with control group (Table 2).

Correlation of fasting plasma glucose and interventricular septal thickness in the hyperglycemic group.

The fasting blood glucose positively correlated with EDIVST and ESIVST in hyperglycemic group ($p= 0.0024$ and $p< 0.0001$ respectively), (figure 2).

The fasting blood glucose negatively correlated with the TVE/A and MVE/A in hyperglycemic group ($p < 0.0003$ and $p < 0.0001$ respectively), (figure 3).

TABLE 1: The mean EDIVST and ESIVST are higher in DM, DIP, and PDM than control:

	CONTROL a n=75	**GDM b n= 45**	**DIP c n= 27**	**PDM d n= 3**	***P value***	**R^2**
EDIVST (mm)	4.6±0.44	6.2±0.51	6.7±0.82	8.0±2.56	a vs b=0.0001 a vs c=0.0001 a vs d=0.0001	0.677
ESIVST (mm)	5.6±0.47	6.9±0.59	8.1±1.13	9.5±3.7	a vs b=0.0001 a vs c=0.0001 a vs d=0.0001	0.647

EDIVST end diastolic interventricular septal thickness; ESIVST end systolic interventricular septal thickness; GDM gestational diabetes mellitus; DIP diabetes mellitus in pregnancy; PDM pre gestational diabetes mellitus.

TABLE 2: The mean E/A ratio across the tricuspid valve (TVE/A) and mitral valve (MVE/A) is lower in GDM, DIP, and PDM than controls:

	CONTROL a	GDM b	DIP c	PDM d	*P value*	**R^2**
Tricuspid E/A	0.77±0.06	0.70±0.07	0.65±0.05	0.6±0.1	a vs b=0.0001 a vs c=0.0001 a vs d=0.0001	0.495
Mitral E/A	0.77+/-0.05	0.68±0.05	0.65±0.05	0.6±0.1	a vs b=0.0001 a vs c=0.0001 a vs d=0.0001	0.557

E/A passive ventricular filling/ventricular filling via atrial systole; GDM gestational diabetes mellitus; DIP diabetes mellitus in pregnancy; PDM pre gestational diabetes mellitus.

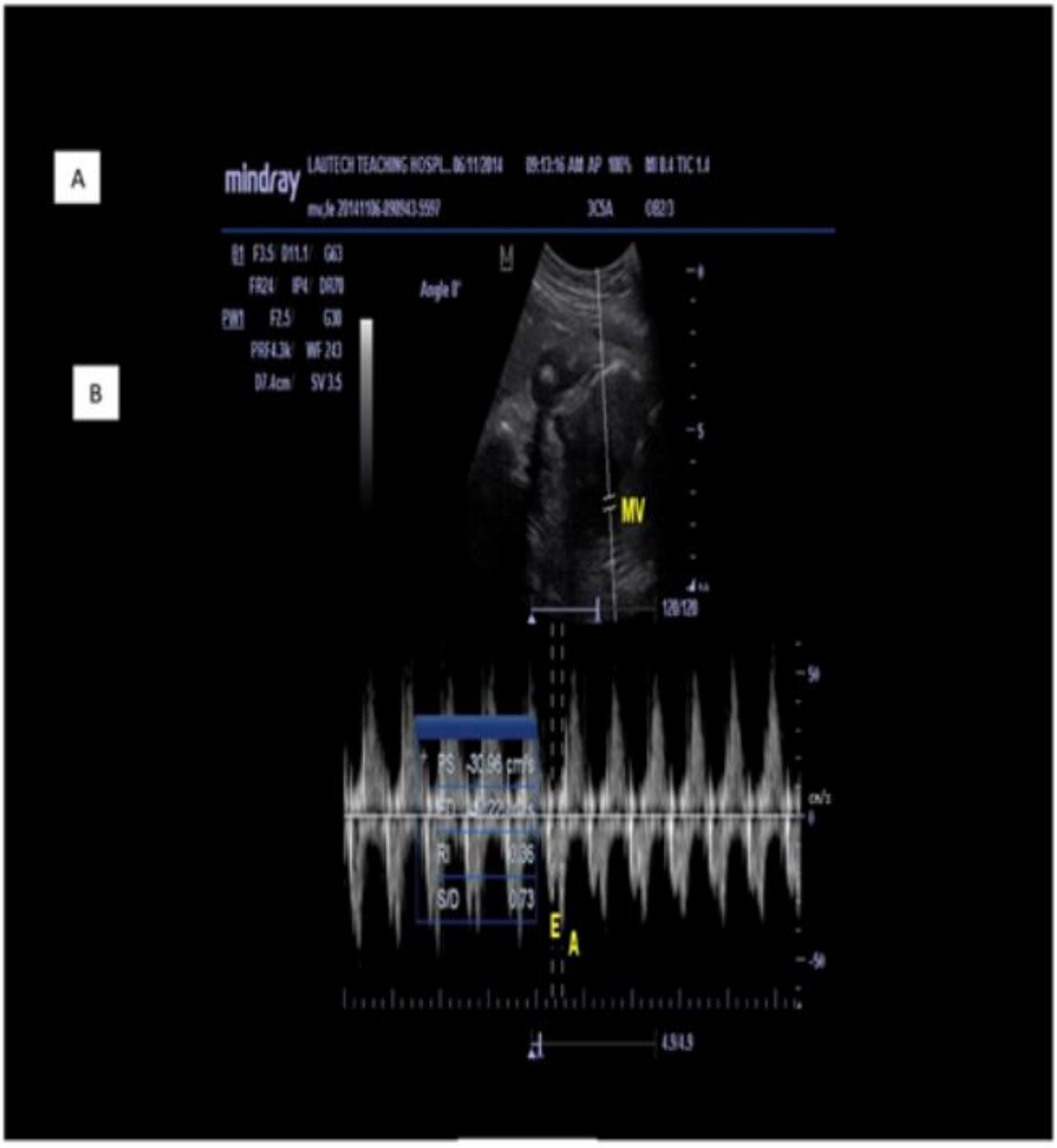

Figure 1: B-mode sonogram of the fetal heart (A); a pulse Doppler ultrasound (B) image showing the E/A ratio of the mitral valve in a control subject.

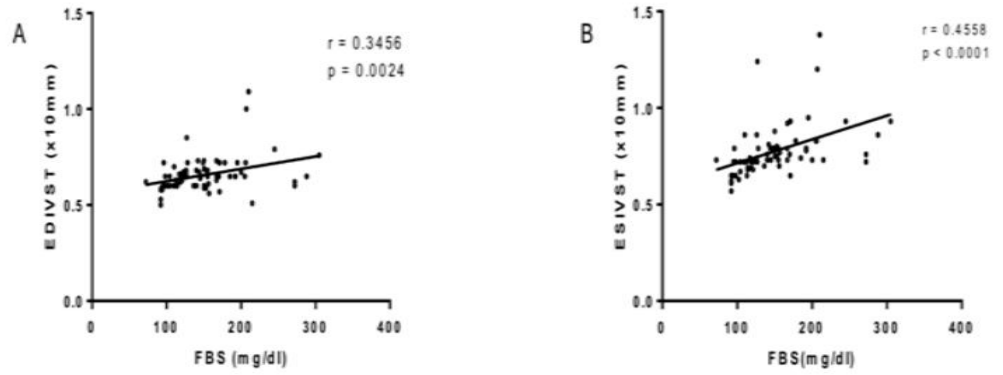

Figure 2: Correlation between fasting blood glucose and the EDIVST and ESIVST: Using Spearman correlation analysis, the fasting blood glucose positively correlates with the EDIVST (A) and ESIVST (B). FBS fasting blood glucose. EDIVST end diastolic interventricular septal thickness; ESIVST end systolic interventricular septal thickness

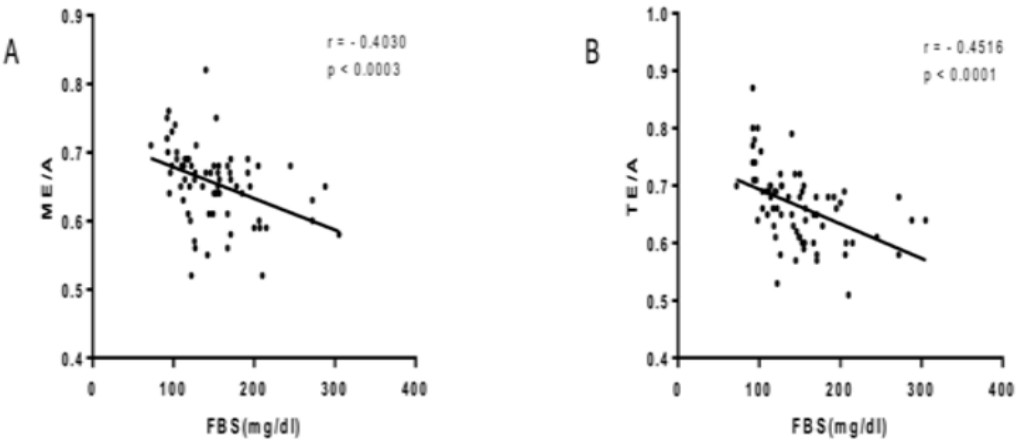

Figure 3: Correlation between fasting blood glucose and the E/A ratio across mitral and tricuspid valves: Using Spearman correlation, the fasting blood glucose was negatively correlated with the E/A ratio across mitral valve (A) and across the tricuspid valve (B). MEA mitral valve passive ventricular filling/ventricular filling via atrial systole; TEA tricuspid valve passive ventricular filling/ventricular filling via atrial systole; FBS fasting blood glucose.

DISCUSSION

The effects of maternal diabetes on fetal heart cannot be over emphasized because it is a known cause of fetal morbidity and mortality. Cardiovascular complications in the fetus is a major factor in intrauterine fetal death in diabetic mothers. This study has demonstrated significant fetal cardiac changes in mothers with hyperglycemia, based on WHO classification of hyperglycemia first detected in pregnancy. [4] Previous studies have reported the normal interventricular septum thickness at systole and diastole at different gestational ages and that it increases significantly in a linear fashion with advancing gestational ages from 18 weeks to term in uncomplicated pregnancies. [8,9]

Thickened interventricular septum as well as reduction in the tricuspid and mitral E/A ratio in diabetic mothers compared to the controls have also been documented in the literature.[10,11] This is similar to findings in this study. Some studies described similar reduction in the tricuspid and mitral E/A ratio in both ventricles while others stated that one ventricle is more affected than the other. Turan et al stated that reduction in ventricular relaxation was apparent for both ventricles, however, the effect on the ventricular filling was prominent for the left ventricle.[12] Hatem suggested that diabetic mellitus is associated with alterations in the fetal left ventricular diastolic function.[13] Rizzo et al demonstrated similar findings of lower E/A ratios related to hyperglycemia, suggesting an association between impaired diastolic function and ventricular filling.[14] Chu et al however found no significant changes in the left ventricular diastolic parameters of the diabetics compared to the controls but demonstrated changes in the right ventricular diastolic parameters.[15] This present study shows a similar effect on both ventricles.

However, to the best of our knowledge comparison of these fetal cardiac changes based on the WHO grouping of hyperglycemic first detected in pregnancy does not exist in literature. This study showed a significantly thickened EDIVST and ESIVST in the GDM, DIP and PDM when compared to the control. Similarly, there is an evidence of functional fetal cardiac changes in the groups of mothers with hyperglycaemia first detected in pregnancy when compared with the control as shown in reduction in the tricuspid and mitral E/A ratio

Furthermore, the severity of the fetal cardiac changes is determined by the level of

hyperglycemia as revealed in the groups of mothers with hyperglycemia. However, the fact that the GDM group with a less severe hyperglycemia had a significant fetal cardiac abnormality when compared with the control group suggests that mild hyperglycemia does lead to significant cardiac abnormality and this is further buttressed by the positive correlation between the level of hyperglycemia and structural fetal cardiac changes and negative correlation with tricuspid and mitral E/A ratio.

CONCLUSION

This study has shown that subtle or slight increase in the maternal glucose level even when not symptomatic is associated significant fetal changes.

We have also shown that the higher the level of maternal hyperglycemia the more the severity of fetal cardiac complication.

Conflict of interest statement:

Authors declare that there are no financial, personal or any other conflicts of interest that may affect the objectivity of this work.

Authors' contributions

All authors made contributions to the article

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