Fetal Echocardiography: A Screening Tool for Congenital Heart Disease in Maternal Diabetes

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Authors’ contributions
This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

ABSTRACT

Background: The imbalance of the adipoinsular axis has been shown recently to predispose to cardio renal syndromes. Epigenetics, which deals with the metabolic influences on genetic signaling, is a new concept. Diabetes during gestation can also cause an inflammatory response in placenta. The levels of leptin/adiponectin in the neonate of a mother with diabetes can affect post insulin signaling leading to fuel mediated teratogenicity. The reactive oxidative species generated at the maternal-fetal interface can alter inhibitory or permissive gene expression resulting in chromatin epigenetic remodeling of genes in multiple organs dysfunction, including the pancreas, kidney, heart, and the muscle. The fetal cardiac malformations can be mediated by these modifications of the transcriptome.

Objectives: The primary objective of the study was to explore the relationship between maternal type II diabetes mellitus and gestational diabetes with congenital heart disease in new-borns. The secondary outcome of the study was to do pre-conception counseling and emphasize the importance of peri-conceptional sugar control.

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Materials and Methods: This prospective study involved cardiovascular system examination of 229 single pregnancies with pre-gestational and gestational diabetes (19 pregnant women were lost for follow up in control group). Two hundred twenty nine non-diabetic women were taken as matched controls. The case and control group were comparable with no significant differences in maternal age, ethnicity and parity. Diabetic pregnant women were also offered fetal echocardiography at 24-28 weeks of gestation in second trimester.

Results: In this study, 1 out of 78 gestational diabetes and 7 out 132 pregnancies with type 2 diabetes mellitus resulted in Congenital Heart Defects. Overt diabetes mellitus (p value significant) as compared to gestational diabetes was found to be a more likely risk factor associated with CHD. There were two cases of Ventral Septal Defect (VSD) in non-diabetic pregnant women diagnosed postnatally.

Conclusion: Community education programmes should be initiated in high-risk population to promote better fetal surveillance in diabetic mothers for early in utero detection of cardiac defects. Maternal counseling for peri-conceptional control of blood glucose, adequate weight maintenance, intake of Insulin and exercise is needed to prevent CHD. Fetal echocardiography is a useful tool to screen high-risk fetus that require tertiary neonatal set up and emergency cardiac surgical interventions.

Keywords: Congenital heart defects; maternal risk; gestational diabetes; fetal echocardiography.

1. BACKGROUND

Gestational Diabetes Mellitus (GDM) is defined as glucose intolerance of first onset or recognition during pregnancy. According to recent survey the incidence of GDM in south India is 16.2% [1,2]. The prevalence of gestational diabetes in other states of India is also high and reported as 3.8% in Kashmir, [3] 6.2% in Mysore, [4] 9.5% in Western India [5]. In more recent studies, using a different criteria, prevalence rates as high as 35% in Punjab [6] and 41% in Lucknow have been reported [7]. Maternal metabolic state affects cardio genesis at a very early stage of embryogenesis, before 7 weeks of gestation. Though the effects of diabetes in pregnant women is well known, a little is known about the effects of type II DM and gestational diabetes mellitus (GDM) and their role in the etiology of congenital heart diseases (CHD).

About 10% cases of infant mortality in India are caused by CHDs [8]. Diabetes during pregnancy is associated with various structural defects such as left to right shunts, valvular or obstructive defects and defects with dominant right to left shunt. The genetic factors of cardiovascular anomalies are non modifiable though CHD can be prevented by identifying diabetes during pregnancy and maintaining a good peri-conceptional glycemic control.

This study was conducted to emphasize universal screening for fetal cardiac anomalies in gestational diabetes and pregnancy with overt diabetes mellitus. Treating overt diabetes with pre-conception insulin can reduce the burden of CHD.

2. MATERIALS AND METHODS

The prospective study case control matched study was conducted in the outpatient department of Obstetrics and Gynecology at Saveetha Medical College and Hospital, Chennai. Study was carried out by consecutive enumerative sampling between 1 April 2014 and 31 October 2018 after getting written informed consent from participants in local language. Inclusion criteria were pregnant women age between 20-34 years with GDM or Overt Diabetes at the first antenatal visit.

Sample size was calculated $N = \frac{Z^2 \times p \times (1-p)}{d^2} = \frac{1.96 \times 1.96 \times 16.2 \times 83.8/5 \times 5}{5} = 208.60$ [9]. The sample size was adjusted for the attrition rate of 10%. The final sample size (208.60+20.8) was 229. The pregnant women were recruited in first trimester for study. Inclusion criteria were single pregnancy with gestational or overt diabetes mellitus. Diabetes of first onset or recognition during pregnancy was considered as gestational diabetes. Nineteen women in case group were lost for follow up and results were analyzed in 210 diabetic women. Diagnostic criteria for diabetes has been made according to WHO criteria and diagnosis of GDM were based on the recommendations of the HAPO study and International study group on Diabetes in pregnancy [10,11]. Two hundred and twenty nine non-diabetic pregnant women were taken as controls.
Multiple Pregnancies, consanguineous marriage, non-intake of folic acid and pregnancy with previous congenital heart disease in newborns were excluded to eliminate selection bias and confounding factors with other well-established causes of CHD. In multiple pregnancies the likely cause of CHD is not maternal but abnormal placentation [12]. The CHD in twin pregnancy may be attributed to ischemic organ damage caused by placental vascular anastomoses leading to feto-fetal transfusion. Consanguineous marriages are a known etiology of congenital cardiovascular malformations. This may be explained fetal genetic and chromosomal aberration, which are common in first and second-degree consanguineous marriages [13,14]. Folic acid deficiency is also postulated to be the cause of CHD [15].

All pregnant women were asked to fill a questionnaire in local language about age, consanguineous marriage, and previous history of any congenital malformations and intake of folic acid in first trimester (yes/no type of questions). Prepregnancy weight and height was also recorded. A first trimester scan was done to measure Crown Rump Length (CRL) to date the pregnancy in all cases. In the second trimester at 24-28 weeks fetal echo was performed in the department of cardiology for all antenatal mothers with gestational and overt diabetes mellitus. A 5-step study of visceral situs, base-apex axis, and cardiac segmental anatomy was made in all diabetic Mothers (Fig. 1(a)-1(e)).

In the newborn, gestational age as calculated by Naegle’s formula was confirmed according to the Ballard’s modification of Dubowitz et al. [16]. The detailed account of postpartum events like Apgar score and resuscitation were recorded. The pulse oximeter used was GT 700 (with sensors for infants). A saturation of value of < 95% or a difference in measurement of >3% in 48 hours of birth in the hospital, the presence of murmurs, apnea, duration of oxygen therapy and ventilator support were noted. Neonatal echocardiogram was done using P7-3e Phased array neonatal cardiac probe by Mindray (North America) to confirm the diagnosis by trained pediatric cardiologist in the Department of Neonatology [Table 1]. The cardiac vascular imaging involved performing cross-sectional echocardiography, and Doppler and color flow imaging in various views. Data was entered in Microsoft excel sheet in password protected computer. The research team obstetrician explained the need for fetal ECHO, fetal condition and prognosis to the patient party and got a written informed consent in local language for Medical Termination of Pregnancy (MTP) if indicated according the concurrently enforced MTP act.

The diagnosis was reconfirmed after birth in the Department of Cardiothoracic surgery by IE-33 Philips Echocardiography Equipment, Bothell, WA, USA. Statistical analysis was done by first comparing the data with \( \chi^2 \) test Odd’s ratio and p value were calculated by MEDCALC (Belgium). Confidence level was kept at 95% Interval. The Institutional Ethical Committee of Saveetha Medical College and Hospital approved this study.

3. RESULTS

Data was analyzed for 210 diabetic pregnancies and 229 non-diabetic pregnancies. Nineteen pregnant women were lost for follow up. During the study period, 8 (3.80%) pregnancies resulted in CHD out of total 210 pregnancies. Out of 8 CHD newborns, Table 1 shows the various cardiac defects diagnosed in newborns. Seven CHD fetuses were associated with other congenital malformations (syndromic) and 1 CHD fetus had isolated cardiac defects (nonsyndromic) not associated with any other congenital malformation. 2 cases of Ventral septal defect were found postnatal in newborns of non-diabetic women.

It was found that maternal overt diabetes in 7/132 cases had an Odd’s ratio association of 3.91 with CHD (p value =0.0911). Gestational diabetes 1/78 was also associated with an increased risk of CHD even though the p value was non significant (Odd’s ratio 1.47, p value=0.7528) (Table 2).

All of the 3 newborns that had congenital heart disease antenatal in the study underwent echocardiography after birth. The average time interval for the performance of echocardiography on these infants was overall 2 ± 1 days after birth.

All three newborns had neonatal echocardiography, confirming the fetal cardiac anomaly.

In the group of 210 diabetic mothers, 132 (62.86%) suffered from overt diabetes, and the other 78 (37.14%) had gestational diabetes. Seven out of 132 infants born to mothers with overt diabetes (5.3%) had cardiovascular anomalies. While among the 78 infants born to mothers with gestational diabetes, 1 new born (1.28%) had cardiovascular anomalies (Fig. 2).
Table 1. Types of congenital heart defects diagnosed (n=8). (VSD=Ventricular Septal Defect, ASD= Atrial Septal Defect, TAPVC=Total Anomalous Pulmonary Venous Connection, TR= Tricuspid Regurgitation)

<table>
<thead>
<tr>
<th>S. no</th>
<th>Age</th>
<th>Parity</th>
<th>Previous obstetric history</th>
<th>Fetal echocardiogram</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>G3P2L1</td>
<td>G1-full term NVD G2-NVD, Preterm Died on Day 5</td>
<td>Total Anomalous Pulmonary Venous Drainage</td>
<td>Referred to neonatal ICU and cardiothoracic unit</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>G2P1L1</td>
<td>G1-full term NVD</td>
<td>Heterotaxy syndrome with complex cardiac defect-TAPVC, ASD, Common atria, levocardia, situs ambiguous, bilateral SVC</td>
<td>Intrauterine Death and medical termination</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td></td>
<td>Primi</td>
<td>Hydrops fetalis, Tricuspid Regurgitation, generalized Lymphedema</td>
<td>Intrauterine Death and medical termination</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>G2P1L1</td>
<td>G1-Previous Newborn with imperforate anus</td>
<td>Right Chamber Hypoplasia with no pulmonary stenosis, small tricuspid valve, small infundibular VSD, large fossa ovalis</td>
<td>Referred to neonatal ICU and cardiothoracic unit</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>Primi</td>
<td></td>
<td>Tetralogy of Fallot</td>
<td>Referred to neonatal ICU and cardiothoracic unit</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>Primi</td>
<td></td>
<td>Situs solitus, levocardia, Atrioventricular concordance, sub aortic VSD with aortic overriding, Aorta committed more to right ventricle, pulmonary atresia with duct dependent pulmonary circulation</td>
<td>Medical Termination of Pregnancy</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>G2P1L1</td>
<td>G1 Full term NVD</td>
<td>Common Atria/ Levocardia / TAPVC/ASD/TR</td>
<td>Medical Termination of Pregnancy</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>Primi</td>
<td></td>
<td>Asymmetry of Cardiac chambers, outflow tract and arches (right&gt;left), hypo plastic aortic arch with intermittent flow reversal</td>
<td>Medical Termination of Pregnancy</td>
</tr>
</tbody>
</table>

Table 2. Association of congenital heart defects with overt diabetes and gestational diabetes. (GDM=Gestational Diabetes Mellitus)

<table>
<thead>
<tr>
<th>S. no</th>
<th>Maternal characteristics</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>Z statistic</th>
<th>Significance Level (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Maternal Overt Diabetes</td>
<td>3.9138</td>
<td>0.8038-19.0557</td>
<td>1.69</td>
<td>0.0911</td>
</tr>
<tr>
<td>2</td>
<td>GDM</td>
<td>1.4740</td>
<td>0.1318-16.4837</td>
<td>0.31</td>
<td>0.7528</td>
</tr>
</tbody>
</table>
Fig. 1(a). Apical Four Chamber view and four-chamber view: The stomach and apex are on the same side of the fetus. The correct relationship of the aorta and inferior vena cava in the abdomen is noted. The four-chamber view is seen in a lateral projection in which the fetus lies with the right anterior chest closest to the transducer. The ultrasound beam is perpendicular to the ventricular septum (four-chamber view is slightly different from the apical projection).

Fig. 1(b). Left and right outflow tracts and transverse arch sequentially. The size and crossover of the pulmonary artery over the aorta is checked.
Fig. 1(c). The ductal and aortic arches are seen in the long axis of the fetus in slightly different planes.

Fig. 1(d). Flow across the two atrioventricular valves (with pressure gradient) and two arterial valves within their respective outflow tracts are visualized to rule out valvular and aortic stenosis.
Fig. 1(e). The Aorta, inferior vena cava and superior vena cava and carotids are also visualized

Fig. 1. Fetal echocardiography in a pregnancy with gestational diabetes on insulin

Fig. 2. Distribution of congenital heart disease in diabetic pregnant women

4. DISCUSSION

Developments in neonatal and pediatric cardiovascular surgery and anesthesia have improved the prognosis of CHD. Current challenges in the primary prevention of CHD include accurate identification of modifiable maternal risk factors. The frequency of CHD in newborns of diabetic mothers in this study was 3.80%; the reported incidence varies from 2.5 to
12% [17]. This increased incidence of CHD in this study as compared to reported incidence could be explained, as our center is a tertiary referral hospital receiving cases from peripheral villages surrounding Chennai where the prevalence of diabetes is high.

Vascular disruption and oxidative stress associated with increased blood sugar levels may lead to increased risk of CHD in diabetes mellitus [18]. GDM, on the contrary is associated with hyperglycemia and worsening glucose control as the gestation progresses, and may not be a significant contributor during the developmental period. In recent literature, the imbalance of the adipoinsular axis has been shown to predispose to cardio renal syndromes [19]. Epigenetics, which deals with the metabolic influences on genetic signaling is a new concept. The levels of leptin/adiponectin in the neonate of a mother with diabetes can affect post insulin signaling leading to fuel mediated teratogenises [20]. Diabetes during gestation can also cause an inflammatory response in placenta. The Reactive oxidative species generated at the maternal-fetal interface can alter inhibitory or permissive gene expression resulting in chromatin epigenetic remodeling of genes in multiple organs dysfunction, including the pancreas, kidney, heart, and muscle [21]. The fetal cardiac malformations can be mediated by these modifications of the transcriptome.

Other congenital malformations linked to maternal diabetes include neural tube defects that have been found 16 times more frequently seen in maternal Insulin Dependent Diabetes Mellitus (IDDM) or type I diabetes mellitus. In particular, the risk of anencephaly is 13 times higher, whereas the risk of spina bifida is 20 times higher. The risk of caudal dysplasia is specifically very high up to 600 times higher in newborns of diabetic mothers [22]. Other congenital malformations are renal defects like hydronephrosis, renal agenesis, ureteral duplication, ear abnormalities, gastrointestinal defects like duodenal or anorectal atresia and small left colon syndrome. Other complications are respiratory distress syndrome, growth abnormalities such as macrosomia (large for gestational age) and microsomia (small for gestational age), hyper viscosity syndrome secondary to polycythemia, hypoglycemic episodes due to unstable glucose compensating regulation, hypocalcaemia, hypomagnesaemia, and iron deficiency anemia [23].

Hypertrophic cardiomyopathy is a defect more characteristic in infants of IDDM mothers, characterized by thickening of the interventricular septum and ventricular walls, and by systolic and diastolic dysfunction of the neonatal heart. This condition is usually asymptomatic in utero and may only result in congestive heart failure in the immediate postnatal period, though this is rare and transient [24]. The closure of ductus arteriosus and postnatal decrease in pulmonary artery pressure are also delayed in newborns of diabetic mothers when compared with control infants during the first few days of life [25,26].

First trimester diabetic embryopathy is a complicated process mediated by maternal and fetal genes, metabolic cell signaling and local milieu factors like hyperglyceremia. Hyperglyceremia affects the fetal metabolic and circulatory homeostasis resulting in a hypoxic environment [27,28]. This can explain the increased odds of CHD in diabetic women in this study.

Even in non-diabetic pregnancies, maternal insulin resistance rises due to release of human placental lactogen (somatomammotropin) from growing syncytiotrophoblast, increased cortisol and estrogen and progesterone and growth hormone levels during pregnancy [29,30]. But there is an increased insulin secretion from beta cells of pancreas and glycemic control is established. Thus no association of congenital heart disease was found in nondiabetic pregnant women in this study.

The occurrence of CHD in pregnancies complicated by GDM may reflect a combination of hyper glycemia, insulin resistance, an elevated BMI and undiagnosed pre gestational diabetes [31]. Although, conotruncal abnormalities are more frequent in diabetes with pregnancy nearly all types of CHD has been seen in newborns of diabetic mothers [32]. This study also shows an association with complex and syndromic cardiac diseases.

Environmental and lifestyle factors are important contributors where the staple food is rice [33]. Two cultural changes in food habits have been recognized in recent times in South India that could have resulted in increased prevalence of type 2 diabetes. One is the use of cane sugars over the traditional used palm sugars and the other is the use of polished milled rice over brown rice. Palm sugar has low glycemic index than cane sugar [34]. Brown rice has higher
amounts of phytic acid, polyphenols, dietary fiber and oil as compared to milled rice. Further more there are differences in some physiochemical properties such as minimum cooking time and degree of gelatinization [35]. Another intervention could be fortification of diet with soybean phenolic rich extracts that inhibit key enzymes linked to type 2 diabetes such as alpha amylase and alpha glycosidase inhibitors [36].

5. CONCLUSION
The results of this study suggest that in reducing the incidence of CHD, public health strategy needs to focus on universal fetal surveillance by fetal echocardiography in diabetic mothers. Prepregnancy maternal BMI, insulin intake, diet and exercise have to be emphasized to correct the peri-conceptional blood sugars in the first trimester at the time of organogenesis. Maternal overt diabetes and hyperglycemia during pregnancy needs to be screened and managed timely in the first trimester to reduce the incidence of CHD. Gestational diabetes mellitus and overt diabetes with pregnancy increase the risk of a variety of severe complex or common CHD by 3 times as compared to nondiabetic pregnancies. Pregnanacies complicated by type II DM and GDM should be offered detailed fetal echo cardiac evaluation in second trimester. This approach can help to plan delivery at an equipped tertiary neonatal care center with facilities of emergency pediatric cardiac surgery.

CONSENT
Study was carried out by consecutive enumerative sampling between 1 April 2014 and 31 October 2018 after getting written informed consent from participants in local language.

ETHICAL APPROVAL
The Institutional Ethical Committee of Saveetha Medical College and Hospital approved this study.

ACKNOWLEDGEMENT
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COMPETING INTERESTS
Authors have declared that no competing interests exist.

REFERENCES


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