Original Research Article

The Association of Maternal Glycemic Control with Hypertrophic Cardiomyopathy in Infants of Diabetic Mothers

ABSTRACT

Background: Infants of Diabetic Mothers (IDMs) are at known risk for the development of hypertrophic cardiomyopathy (HCM). Echocardiography is essential for the diagnosis of HCM, to assess the left ventricular function, and the degree of left ventricle obstruction, and to rule out structural cardiac malformations.
Objective: To study the association and correlation of maternal third-trimester glycemic level with HCM in IDMs.
Study design: Observational cross-sectional study.
Participants: 108 diabetic mothers and IDMs.
Intervention: Third-trimester Glycosylated hemoglobin (HbA1c) levels were measured and Echocardiography was done for IDMs in their first week of life. Data were analyzed for correlations and associations between various parameters.
Outcomes: HCM was diagnosed when the absolute value of Inter Ventricular Septum (IVS) was ≥ 2SD from the mean (5mm) and Asymmetrical Septal Hypertrophy (ASH) was diagnosed when the IVS: LVPW ratio was ≥ 1.3.
Results: 85% of the study population had gestational diabetes, and 55.6% of them were on diet control only. The mean HbA1c was 6.69%. The mean birth weight was 3.1 kg. The most common complication observed was hypoglycemia (19.4%). Asymptomatic HCM was seen in 52% and ASH in 25.9% of the study population. HCM was found to be significantly associated with maternal HbA1c levels, birth weight and hypoglycemia.
Conclusion: HCM is a frequent finding in IDMs when routinely screened by echocardiography. A significant positive association of HCM with maternal glycemic control was seen in our study and hence strict glycemic control during pregnancy is of paramount significance.

Keywords: Atrial Septal Hypertrophy, Gestational Diabetes Mellitus, Glycaemic Control Hypertrophic Cardiomyopathy, Infants of Diabetic Mothers

1. INTRODUCTION

Maternal diabetes mellitus significantly affects the fetal heart and fetal–placental circulation in both structure and function. Pre-conceptional diabetes can alter cardiac morphogenesis in the first trimester itself.[1] HCM in IDMs has been recognized since the mid-1940s.[2,3] Fetal hyperinsulinemia and increased affinity of insulin receptors lead to the proliferation and hypertrophy of cardiac myocytes, which cause HCM.[4] Gutgesell et al. (1976) first described a transient type of hypertrophic subaortic stenosis in IDMs.[3] Halliday H.L (1981) studied 12

newborn infants of poorly controlled diabetic mothers out of which ten infants were macrosomic and had echocardiographic evidence of myocardial hypertrophy, reduced ejection time, and systolic anterior movement of the mitral valve.[5] Pedersen's hypothesis states that maternal hyperglycemia results in fetal hyperglycemia because glucose readily traverses the placenta.[6] After 20 weeks gestation, the fetus has a functioning pancreas and fetal hyperglycemia results in hypertrophy of fetal pancreatic islets and hyperinsulinemia. This raised insulin then acts as a growth factor for cardiac myocytes leading to HCM.

The investigation of choice for HCM is Echocardiography. This shows a hypercontractile, thickened myocardium with septal hypertrophy. Small ventricles and anterior systolic motion of the mitral valve often cause Left Ventricular Outflow Tract (LVOT) obstruction.

The spectrum of presentation of HCM can vary from asymptomatic to congestive cardiac failure. HCM is diagnosed as absolute septal thickness exceeding 2SD i.e. ≥ 5mm.[7,8] Asymmetric septal hypertrophy (ASH) is diagnosed as a ratio of Inter Ventricular Septum (IVS) to Left Ventricle (LV) free wall exceeding 1.3.

The detection of HCM has several implications regarding the therapy of IDMs. Firstly, HCM may produce respiratory distress which may be mistaken for hyaline membrane disease. Secondly, the large cardiac shadow on the chest roentgenogram in HCM should not be confused with a dilated, poorly contracting heart. And finally, the use of positive inotropic agents is contraindicated in HCM as they increase LVOT obstruction.

Various studies have been conducted to evaluate the association of maternal glycemic control and the development of HCM in IDMs, and the correlation of maternal HbA1c levels with HCM. These studies have produced conflicting results. Hence, our study aims to establish these associations and correlations for a better understanding and management of HCM in IDM.

2. MATERIAL AND METHODS

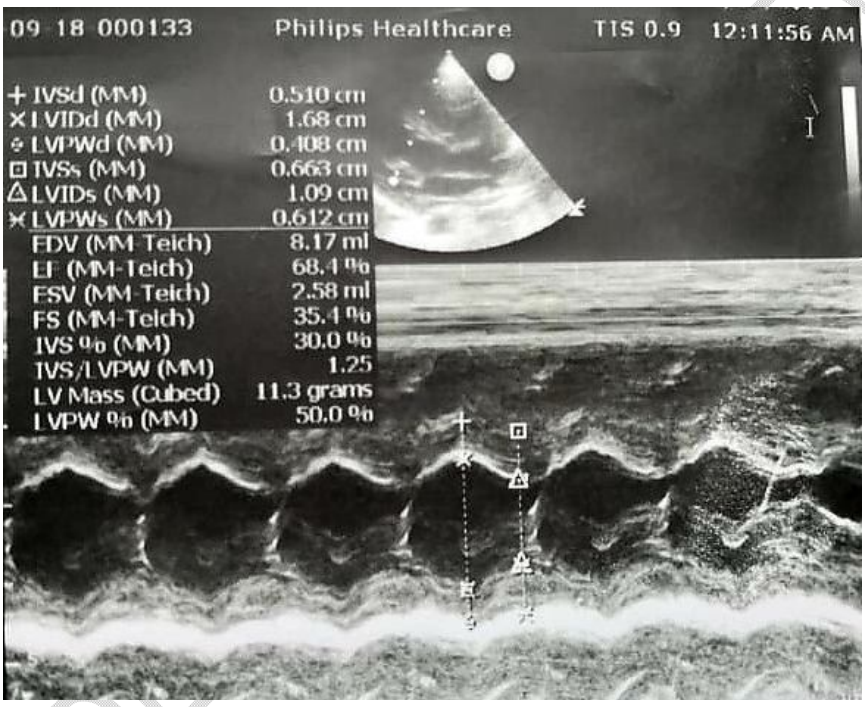
An observational cross-sectional study was conducted in the perinatal unit of a hospital from April 2018 to December 2019, to study the association and correlation of maternal glycemic control with HCM in IDM. Live-born IDMs during the study period (with either type 1 or type 2 overt diabetes mellitus or gestational diabetes mellitus) were included. Patients with a history of familial cardiomyopathy, gross congenital anomalies and non-consenting mothers were excluded from the study. Maternal factors affecting HbA1c levels such as hemoglobinopathies, severe anemia (Hb < 7 g/dl) or a history of recent transfusion were also excluded. After obtaining consent, detailed antenatal and birth history was taken followed by a clinical examination.
Glycemic control was estimated by glycosylated hemoglobin (HbA1c) levels during the third trimester. HbA1c testing was done by High-Performance Liquid Chromatography (HPLC) as recommended by the International Federation of Clinical Chemistry (IFCC).

The following echocardiographic parameters were evaluated during the first week of life.
(Figure 1)

1. Left Ventricular Internal Dimension (mm):
    a. At the end of systole – LVID(s)
    b. At the end of diastole – LVID(d)
2. Thickness of Inter Ventricular Septum (mm):
    a. At the end of systole – IVS(s)
    b. At the end of diastole – IVS(d)

3. Thickness of Left Ventricular Posterior Wall (mm):
    a. At the end of systole – LVPW(s)
    b. At the end of diastole – LVPW(d)
4. Diameter of aorta (mm)
5. Width of Left Atrium (mm)
6. Width of Right Ventricular Outflow Tract (mm) - RVOT
7. Inter Ventricular Septum: left ventricular posterior wall ratio – IVS: LVPW
8. Ejection fraction (%)
9. Left ventricular mass (g)
10. The percentage shortening of internal dimension

Figure 1 - M-mode echocardiography in IDM with HCM



3. RESULTS AND DISCUSSION

3A. RESULTS

A total of 108 diabetic mothers and their infants were included in our study. The mothers were aged between 24 and 40 yrs with a mean of 31.13 yrs. 59.3% (N=64) of the participants were primigravida and 40.7% (N=44) were multigravida. 42.6% (N=46) of the participants had complications antenatally while 57.4% (N=62) of the participants had an uneventful antenatal period. The majority of antenatal complications noted in our study were

gestational hypertension (16.7%) and hypothyroidism (16.7%). Others included genital tuberculosis (N=2), intrahepatic cholestasis of pregnancy (N=5), and the carrier of the Halleroverden–Spatz mutation (N=1). **(Table 1)**

14.8% (N=16) of the participants had abnormalities on antenatal USG, which included polyhydramnios (N=4, 3.7%), oligohydramnios (N=8, 7.4%), altered Doppler studies (N=3, 2.7%) and cord around the neck of baby (N=1, 0.9%). 85.2% (N=92) of the participants had Gestational Diabetes while 14.8% of the participants were overt diabetics. 55.6% (N=60) of the participants were on diet control, 13% (N=14) were on oral hypoglycemic agents, 29.6% (N=32) were on insulin and 1.9% (N=2) were not on any treatment. These two patients were unbooked cases with incomplete antenatal check-ups. The HbA1c levels ranged from 5.1 to 13.4% with a mean of 6.69%. **(Table 1)**

51.9% (N=56) of newborns were males and 48.1% (N=52) were females. The birth weight varied from 2.08 to 4.30 kg with a mean of 3.09 kg. 9.3% (N=10) of the neonates were low birth weight babies (< 2.5 kg). 7.4% (N=8) neonates were Small for Gestational Age (SGA – less than 10^{th} centile), 79.6% (N=86) were Appropriate for Gestational Age (AGA – between 10^{th} and 90^{th} centile) and 13.0% (N=14) macrosomic or Large for Gestational Age (LGA – more than 90^{th} centile) based on standard weight charts.[9] **(Table 2)**

Postnatal complications were seen in 46.3% (N=50) of the newborns which included hypoglycemia (N=21, 19.4%), NNH - Neonatal Hyperbilirubinemia (N=11, 10.2%), PPHN - Persistent Pulmonary Hypertension (N=2, 1.9%), TTNB - Transient Tachypnoea of Newborn (N=14, 13.0%), culture positive septicemia (N=4, 3.7%), MAS - Meconium Aspiration Syndrome (N=4, 3.7%) and RDS - Respiratory Distress Syndrome (N=2, 1.9%). Cardiac examination was abnormal in 2 babies, one had supraventricular tachycardia and the other had a systolic murmur that was confirmed to be VSD on echocardiography.

The IVS(s) ranged from 2.3 to 6.74 mm with a mean of 4.61 mm. The LVPW(s) ranged from 1.53 to 6.54 mm with a mean of 4.28 mm. IVS(s): LVPW(s) ratio ranged from 0.54 to 1.94 with a mean of 1.08. The LV Mass ranged from 4.0 to 11.3 g with a mean of 6.68 g. 51.9% (N=56) of the participants had echocardiographic features of HCM, whereas 25.9% (N=28) had ASH.

Non-parametric Wilcoxon test was used to find the association of HbA1c levels with HCM since the values were not normally distributed. A statistically significant difference was seen in HbA1c levels in patients with HCM (7.23%) and without HCM (6.35), depicting a positive association between the two variables ($W = 894.000$, $p = 0.002$). **(Figure 2)** There was a statistically significant moderate positive correlation between IVS(s) and HbA1c ($rho = 0.30$, $p = 0.001$). **(Table 3)**

Table 1: Summary of Maternal Parameters

Maternal Parameters	Mean ± SD/N (%)
Maternal Age (Years)	31.13 ± 3.29
Parity	
Primigravida	64 (59.3%)
Multigravida	44 (40.7%)
Antenatal History	

Maternal Parameters	Mean ± SD/N (%)
Complication Present	46 (42.6%)
Uneventful	62 (57.4%)
Gestational Hypertension (Present)	18 (16.7%)
Hypothyroidism (Present)	18 (16.7%)
Antenatal USG	
Abnormal	16 (14.8%)
Normal	92 (85.2%)
Polyhydramnios (Present)	4 (3.7%)
Oligohydramnios (Present)	8 (7.4%)
Diabetic History	
Gestational Diabetes	92 (85.2%)
Overt Diabetes	16 (14.8%)
Treatment	
None	2 (1.9%)
Diet Control	60 (55.6%)
OHA	14 (13.0%)
Insulin	32 (29.6%)
HbA1c (%)	6.69 ± 1.31

Table 2: Summary of Baby Parameters

Baby Parameters	Mean ± SD/N (%)
Birth Weight (Kg)	3.09 ± 0.48
Birth Weight	
<2.5 Kg	10 (9.3%)
>2.5 Kg	98 (90.7%)
Weight for Gestational Age	
SGA	8 (7.4%)
AGA	86 (79.6%)
LGA	14 (13.0%)
Baby Gender	
Male	56 (51.9%)
Female	52 (48.1%)
Postnatal Complications (Present)	50 (46.3%)
Cardiac Examination	
Abnormal	2 (1.8%)
Normal	106 (98.1%)

Table 3: Association between HCM and Parameters

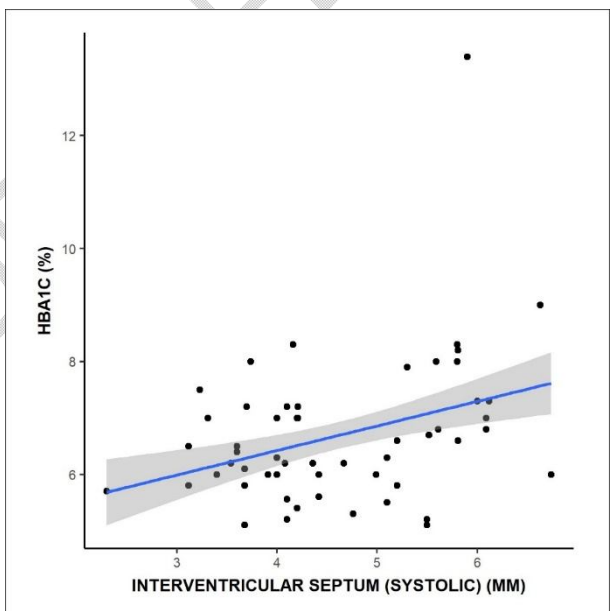
Parameters	HCM: Present (n = 56)	HCM: Absent (n = 52)	p-value
Maternal Age (Years)	31.00 ± 3.62	31.27 ± 2.92	0.513[1]
Diabetic History			0.356[2]
Gestational Diabetes	46 (82.1%)	46 (88.5%)	

Parameters	HCM: Present (n = 56)	HCM: Absent (n = 52)	p-value
Overt Diabetes	10 (17.9%)	6 (11.5%)	
Treatment			0.225[3]
None	2 (3.6%)	0 (0.0%)	
Diet Control	28 (50.0%)	32 (61.5%)	
Oral Hypoglycemic Agents	6 (10.7%)	8 (15.4%)	
Insulin	20 (35.7%)	12 (23.1%)	
HbA1c (%)	6.35± 0.78	7.23± 1.75	0.002[1]
Birth Weight (Kg)* **	3.28 ± 0.44	2.89 ± 0.44	<0.001[4]
Birth Weight* **			0.047[3]
<2.5 Kg	2 (3.6%)	8 (15.4%)	
>2.5 Kg	54 (96.4%)	44 (84.6%)	
Weight for Gestational Age* **			0.012[3]
SGA	2 (3.6%)	6 (11.5%)	
AGA	42 (75.0%)	44 (84.6%)	
LGA	12 (21.4%)	2 (3.8%)	
Hypoglycemia (Present)* **	16 (28.6%)	5 (9.6%)	0.013[2]

*****Significant at p<0.05, 1: Wilcoxon Test, 2: Chi-Squared Test, 3: Fisher's Exact Test, 4: t-test*

The following variables were significantly associated (p<0.05) with the variable 'Hypertrophic Cardiomyopathy': Birth Weight (Kg), Weight for Gestational Age, Hypoglycemia, and HbA1c.

Figure 2 - Scatter plot depicting the correlation between IVS and HbA1c



No significant association (W = 1276.000, p = 0.275) or correlation (rho = 0.18, p = 0.058) was seen between HbA1c levels and IVS: LVPW ratio and hence HbA1c levels were not found to be associated with ASH.

No significant association was seen between HCM and various types of treatment taken for diabetes (X^2 = 4.410, p = 0.225).

A statistically significant (t = 4.553, p = <0.001) difference in birth weight was seen in babies with HCM (3.28 kg) and without HCM (2.89 kg) depicting a positive association of HCM with birth weight. 12 out of 14 LGA neonates were found to have HCM, whereas only 2 out of 8 SGA neonates had HCM, indicating a significant difference between the various groups in terms of distribution of Weight for Gestational Age (X^2 = 9.054, p = 0.012). A significant association was seen between neonatal hypoglycemia and the presence of HCM (X^2 = 6.185, p = 0.013). 71.4% of neonatal hypoglycemia had HCM.

3B. DISCUSSION

The mean maternal age was 31 years. 85% of the mothers had gestational diabetes while 15% were overt diabetics. In the study by Vijayan et al, 96% of the mothers had GDM and 4% had overt diabetes[10], while in the study by Ullmo et al, 62% had GDM and 38% of the mothers had overt diabetes[11]. In our study, majority of the mothers were being managed by diet control alone (56%) while 13% were on oral hypoglycemic agents and 30% were on insulin. This is in contrast with the study of Vijayan et al, where majority of the mothers were on insulin (79%) and 21% were on diet control alone. Other significant antenatal history in the study population included gestational hypertension (16%) and hypothyroidism (16%).

The mean HbA1c was 6.69% indicating that majority of the mothers were well controlled diabetics. This was comparable to the studies by Vijayan et al.[10] (mean HbA1c-6.19%) and Ullmo et al.[11] (median HbA1c - 5.8%), whereas it was higher in studies by Sheehan et al.[8] (mean HbA1c-7.7%) and Reller et al.[12] (mean HbA1c- 8.8%).

The average birth weight of IDMs in our study was 3.1 kg, out of which 13% were macrosomic (LGA) and 7% were SGA. 91% of the infants weighed more than 2.5kg. This average birth weight is significantly higher than the average of non-diabetic mothers in our hospital. The mean birth weight in the study by Sheehan et al. was 3.85 kg and 60% infants were LGA. Our results are comparable to the study by Vijayan et al. where the mean birth weight was 3.2 kg, 20% IDMs were LGA and 5% were SGA.

Neonatal hypoglycemia is the most common complication in IDM (40%)[13]. It was seen in 19% of neonates in our study, comparable to the study by Deorari et al. (23%).

The mean LVID(d) was 15.09 mm, LVID(s) was 10.23 mm, aortic diameter was 6.15 mm, LA width was 10.96 mm, and RVOT width was 9.21 mm. In the study by Deorari et al, the mean LVID(d) was 15.1 mm, LVID(s) was 8.8 mm, aortic diameter was 9.2 mm, LA width was 11 mm, and RVOT width was 11 mm.

The mean IVS(d) was 3.49 mm, IVS(s) was 4.61 mm, LVPW(d) was 3.13 mm, LVPW(s) was 4.28 mm, IVS:LVPW ratio was 1.12 and the mean LV mass was 6.68 grams. These values are higher than the average observed in normal newborns[14]. Our results were comparable to the previous study done by Deorari et al, who found that the mean IVS(d) was 4.7 mm, IVS(s) was 6.1 mm, LVPW(d) was 2.7 mm, LVPW(s) was 3.9 mm, IVS:LVPW ratio was 1.79 and the mean LV mass was 8.41 grams. This increased myocardial thickness cannot be explained merely by the IDMs being large for gestational age because the myocardial thickness of large for gestation babies born to non-diabetic mothers rarely exceeds the upper limit of normal. Two of the eight SGA babies (3.6%) in our study also had thickened septum.

In our study 52% of babies demonstrated echocardiographic evidence consistent with HCM, however all were asymptomatic. A similar incidence was also seen by El-Ganzoury et al. (43.5%)[15], Reller et al. (41%)[16], and Sheehan et al. (35%)[8]. The incidence of symptomatic disease has varied significantly among studies. Sheehan et al. and Reller et al. found none of the infants to be symptomatic, similar to the observation in our study. On the other hand, Mace et al. in their study of 34 IDMs found septal hypertrophy on echocardiography in 84% infants with 4 infants developing congestive heart failure with evidence of LVOT obstruction.[17]

The incidence of structural cardiac anomalies other than HCM observed was 2.7%, out of which two babies had atrial septal defect, one had ventricular septal defect and one had left sided superior vena cava draining into coronary sinus. This is similar to the incidence of congenital heart disease shown in studies by Narchi et al.[18] and Gladman et al.[19]

A statistically significant association was found in our study between the occurrence of HCM and HbA1c levels of mothers taken in the third trimester (p=0.002). The average HbA1c levels in neonates with HCM was 7.23% while in the neonates without HCM was 6.35%. In concordance with our findings, Reller et al.[16], El-Ganzoury et al.[15], Ullmo et al.[11], Narchi et al.[18], Czeszynska et al.[20] and Vijayan et al.[10] have also reported an association between poor maternal glycemic control and HCM.

Weber et al. reported that good maternal glycemic control during pregnancy assures a normal fetal cardiac growth. [21] On the contrary, Rizzo et al. found an increase in the cardiac size in fetuses of diabetic mothers, in spite of a careful metabolic control[22]. Sheehan et al.[8] found no association of HbA1c levels in the third trimester with the incidence of neonatal cardiomyopathy, macrosomia, or hypoglycemia.

The incidence of ASH in our study was 25.9% which is higher than Vijayan et al.[10] who reported 9.9% incidence. In our study, there was no significant association between HbA1c levels and ASH (p=0.275). In contrast, Vijayan et al. found that ASH was significantly associated with HbA1c levels.

In our study, 85% of infants with macrosomia had features of HCM, whereas only 48% of AGA and 3.6% of SGA infants showed signs of HCM. HCM was significantly associated with higher birth weight (p<0.001). Similar association has been found by El-Ganzoury et al, who found that increased birth weight was the best predictor of septal hypertrophy and Narchi et al. who reported the presence of cardiac septum hypertrophy in LGA. This could be explained by anabolic, hyperinsulinemic fetal state triggered by maternal hyperglycemia during the third trimester. Taylor et al. hypothesized that poorly controlled diabetes leads to hyperinsulinemia, which increases leptin and free fatty acids transfer leading to macrosomia[23,24]. However, Mehta et al. found no echocardiographic (systolic or diastolic) differences between LGA and AGA IDMs suggesting that the cardiac alterations in the IDMs are not due to the preponderance of macrosomia but rather the consequence of altered in-utero metabolic environment.

A statistically significant association of HCM was seen with presence of hypoglycemia (p=0.013). This was in accordance with Breitweser et al. who found that the most severe septal hypertrophy was noted in a subgroup with most profound neonatal hypoglycemia.[25] Hence, fetal hyperinsulinemia contributes directly to the septal hypertrophy and hypoglycemia. However, as the serum insulin level and number of insulin receptors decrease following birth, the septal hypertrophy also regresses.

4. CONCLUSION

HCM is frequently seen in IDMs when routinely screened with echocardiography. Even though the number of symptomatic cases presenting with features of congestive cardiac failure or LVOT obstruction due to diabetic HCM may be relatively small, the identification of this entity is important because the treatment course differs significantly from other causes of congestive cardiac failure seen in neonates. Strict maternal glycemic control can reduce the incidence and severity of HCM. The presence of HCM is associated with macrosomia and hypoglycemia, hence a higher index of suspicion is needed in such IDMs presenting with respiratory distress. Further studies can be done evaluating the role of pre-conceptional and first-trimester HbA1c levels.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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