

ASSESSMENT OF CONGENITAL HEART DISEASE AND RELATED VARIOUS FACTORS IN THE NEONATES OF MOTHERS WITH DIABETES

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ABSTRACT

Objective: To assess the frequency of congenital heart disease and its association with various factors in neonates of mothers with diabetes.

Study Design: Cross-sectional study.

Study Place and Duration of Study: Department of Pediatrics, Combined Military Hospital (CMH) Lahore and Army Cardiac Centre Lahore, from Feb 2018 to Aug 2018.

Methodology: A total of 92 neonates born to mothers with diabetes of aged up to 28 days of either gender were included. Preterm, post term and other multiple congenital anomalies were excluded. Patient was diagnosed as having congenital heart disease based on the results of 2-D Echocardiography done by consultant pediatric cardiologist. Findings of the 2-D Echo along with other information like name, age, gender, weight and HbA1c were recorded. Data was collected using proforma and analysis was done with statistical package for social sciences version 23.

Results: Total neonates born to mothers with diabetes included in study were 92. Age of neonates ranged from 0 to 28 days with mean of 13.36 ± 4.49 days. Mostly patients 64 (69.57%) ranged between 4-15 days. Mean weight of baby was 3.24 ± 0.49 kg. Out of the 92 patients, males were 53 (57.61%) and females were 39 (42.39%) with ratio of 1.5: 1 respectively. In this study, the frequency of congenital heart disease in neonates of mothers with diabetes was 71 (77.17%) while 21 (22.83%) new born did not have congenital heart disease. Patent Ductus Arteriosus was the most common congenital heart defect in 25 (27.17%) neonates. Congenital heart defects in neonates were significantly ($p=0.039$) associated with weight of neonates >3 kg. Moreover neonates born to the mothers with poorly controlled diabetes had significantly more chances of developing CHD ($p=0.0001$).

Conclusion: This study has shown that the congenital heart disease is quiet frequent in neonates born to mothers with diabetes and particularly common in neonates expectant mothers with poorly controlled diabetes.

Keywords: Atrial septal defect, Congenital heart defects, Gestational diabetes mellitus, Tetralogy of fallot, Ventricular septal defect.

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INTRODUCTION

Diabetes mellitus with increasing prevalence worldwide is considered a pandemic disease affecting both genders and all ethnic groups and it has posed a great threat to human health. According to the International Diabetes Federation (IDF), there are 371 million people with diabetes worldwide, out of which, 7 million people reside in Pakistan¹. Gestational Diabetes mellitus (GDM) is prevalent in approximately 3-15% pregnant women, and on the rise with lifestyle changes like decrease in physical activity, increase in body

mass index (BMI) and other associated risk factors². In Pakistan, there is an increased incidence of gestational diabetes, from 3.45% in 1996 to 22.58% in 2013². Studies have shown that children have increased risk of congenital abnormality in women with pre-gestational and gestational diabetes mellitus compared to mothers with no diabetes; this include congenital heart defect (CHD), both structural and functional, with an incidence of 15-18.7% in some middle-eastern populations³.

CHD include a various defects of structural components of the heart or different blood vessels arising from it, present at the time of birth. It is the most common congenital defect followed by spina bifida⁴. Frequency of CHD is different in

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different studies as well as different in different ethnic regions of the world. Prevalence of CHD is found to be around 20.0 per 1,000 live births^{5,6}. The incidence of CHD varies in different studies. Incidence in Spain is reported to be 13.6 %⁷. In Pakistan a study done by Hussain *et al*, the incidence of congenital heart disease was found to be 15/1000 live births⁸. Moreover babies with syndromes have much more chance of having CHD particularly babies with Down syndrome.

Although the correlation of CHD in infants of mothers with diabetes is well established in the literature, there is inadequacy of local data. Due to limited resources large scale population studies cannot be carried out⁸. A study conducted in Pakistan on this topic was at Lady Reading Hospital Peshawar which manifested that 52.5% neonates born to mothers with diabetes had CHD⁹. Because of lack of local data, routine echocardiography is not done in neonates of mothers with diabetes. Echocardiography can help in establishing an early diagnosis of CHD, so that timely treatment for such children can be carried out. While the research on whether fetal echocardiography for CHD with early postnatal treatment improves overall outcomes is conflicting¹⁰. some papers suggest a significant improvement in morbidity and mortality for specific abnormalities such as Transposition of the Great Arteries (TGA).

The rationale was to evaluate the incidence of CHD in neonates born to mothers with diabetes in Pakistani population, in relation to type of diabetes and level of diabetic control, to formulate a set of guidelines for pregnant women with diabetes and the new-borns. Most importantly, providing evidence to make a standard operating procedure (SOP) to perform an echocardiography of all neonates born to mothers with diabetes to facilitate early diagnosis and prompt treatment.

METHODOLOGY

This cross-sectional study was carried out in the department of Pediatrics, Combined Military Hospital, Lahore, and Army Cardiac Centre, Lahore spanning over duration of six months

from February 2018 to August 2018. Approval from the "Hospital's Ethics Committee" was obtained (Ref No: 65/ERC/CMH LMC Dated 14-11-2017). All neonates born to mothers with diabetes and compatible with the inclusion criteria of this study were included. Informed consent from parents of neonates was taken before any procedure or test. Mothers were diagnosed with diabetes if fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl). Maternal blood level of HbA1c ≤ 6.5 was considered good control of maternal diabetes and >6.5 was considered poor control.

The exclusion criteria were strictly followed to control bias and confounders in the study results and included; preterm babies (born before 37 weeks of gestation) or post term babies (born after 42 weeks of gestation); Babies born with other multiple congenital anomalies/syndromic babies; Patients not consenting, and Mother on treatment for multiple other diseases. All the neonates included in the study were examined by registrar in pediatrics under supervision of a consultant pediatrician. Patient was diagnosed as having congenital heart disease based on the results of 2-D Echocardiography done by consultant pediatric cardiologist and sub-divided into anyone of these¹. Hypertrophic Cardiomyopathy (HOCM)². Ventricular Septal Defect (VSD)³. Atrial Septal Defect (ASD)⁴. Tetralogy of Fallot (TOF)⁵. Transposition of The Great Arteries (TGA)⁶. Patent Ductus Arteriosus (PDA):

Findings of the 2-D Echo along with other information like name, age, gender, weight and HbA1c were recorded in a predesigned proforma, by registrar in pediatrics. A sample size of 92 was calculated using WHO calculator by taking 95% confidence level, 8% margin of error and taking expected percentage of congenital heart disease as 18.7%³. Non-probability, consecutive sampling technique was used to select patients.

The data were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 23. Qualitative variables like gender, type of diabetes and congenital heart disease were measured in the form of percentages and

frequencies. Means and Standard deviations were calculated for data like age and birth weight. Post stratification of the data, chi-square test was used, *p*-value ≤0.05 was regarded statistically significant.

RESULTS

Total neonates born to mothers with diabetes included in study were 92. Age of neonates ranged from 0 to 28 days with mean of 13.36 ± 4.49 days. Mostly patients 64 (69.57%) ranged between 4-15 days. Mean weight of baby was 3.24 ± 0.49 kg. Out of the 92 patients, males were 53 (57.61%) and females were 39 (42.39%) with ratio of 1.5:1 respectively. Eighty two (89.13%) pregnant mothers had gestational diabetes, 07 (7.61%) had type 2 diabetes mellitus while only 03 (3.26%) pregnant mothers had type 1 diabetes mellitus.

In this study, congenital heart disease was present in 71 (77.17%) neonates of mothers with diabetes, however, 21 (22.83%) neonates did not have congenital heart defects. PDA was the most common CHD in 25 (27.17%) neonates followed by the ASD in 22 (23.9%) neonates (table-I).

Relation of age, gender and birth weight of neonates and type of maternal diabetes and control of maternal diabetes with congenital heart defects is shown in table-II. Congenital heart defects in neonates were significantly (*p*=0.039) associated with birthweight of neonates >3kg. Moreover neonates born to the mothers with poorly controlled diabetes had significantly more chances of developing CHD (*p*=0.0001).

DISCUSSION

Although various factors play role in development of congenital defects like congenital heart disease¹¹, but it has been reported to be particularly associated with abnormally increased intrauterine blood glucose levels particularly at the time of embryogenesis of fetus in expectant ladies with uncontrolled diabetes mellitus^{12,13}. Even a minor increment in the blood levels of the glucose can be very harmful for the growing fetus¹³. The incidence of complications like still-birth or preterm delivery is decreased when blood glucose level is controlled more strictly.

Diabetic embryopathy is the process playing role in development of congenital malformations

Table-I: Frequency and percentages of different congenital heart defects in neonates of mothers with diabetes: (n=92).

Congenital Heart Defects	n	%
Patent Ductus Arteriosus (PDA)	25	27.1
Atrial Septal Defect (ASD)	22	23.9
Ventricular Septal Defect (VSD)	16	17.3
Tetralogy of Fallot (TOF)	5	5.4
Transposition of The Great Arteries (TGA)	2	2.1
Hypertrophic Cardiomyopathy (HOCM)	1	1.1
No Congenital Heart Defect	21	22.8

Table-II: Association of congenital heart defects with various neonatal and maternal characteristic.

Characteristics	Neonates With Congenital Heart Defects n (%)	Neonates Without Congenital Heart Defects n (%)	<i>p</i> -value
Total	71 (77.1)	21 (22.8)	
Age (Days)			
≤15	53 (74.6)	11 (52.3)	0.051
>15	18 (25.3)	10 (47.6)	
Gender			
Male	44 (61.9)	09 (42.8)	0.119
Female	27 (38.1)	12 (57.1)	
Birth Weight (Kg)			
≤3	26 (36.6)	13 (61.9)	0.039
>3	45 (63.3)	08 (38.1)	
Type of Maternal Diabetes Mellitus			
Type 1 Diabetes Mellitus	03 (4.2)	-	0.190
Type 2 Diabetes Mellitus	07 (9.8)	-	
Gestational Diabetes Mellitus	61 (85.9)	21 (100)	
Control of Maternal Diabetes Mellitus			
Good control	05 (7.0)	11 (52.3)	0.0001
Poor control	66 (92.9)	10 (47.6)	

occurring in pregnant females. Serum hyperglycaemia very strongly effect this process. Environmental factors and various genetic characteristics of fetus¹⁴, and mother, may play major role in embryopathy, which is considered to be a

complicated process involving altered signalling mechanisms, being shown in the various studies done in animals.

The overall prevalence of CHD in neonates of mothers with diabetes varies greatly. The study conducted in Pakistan on this topic was at Lady Reading Hospital Peshawar, which revealed that 52.5% of infants born to mothers with diabetes had CHD⁹ but our study has revealed prevalence of CHD 77.17% in neonates born to mothers with hyperglycemia. However the prevalence of cardiovascular anomalies was reported to be 42.8% in new born of mothers with diabetes in a study done by Akbariasbagh *et al*¹⁵. The prevalence of different types of cardiac malformations based on the echocardiography differ in various studies but Patent ductus arteriosus (PDA) is the most common CHD, followed by patent foramen ovale, atrial septal defect and ventricular septal defect¹⁶. Similarly in our study PDA was the commonest CHD present in 25 (27.1%) neonates followed by the ASD being diagnosed in 22 (23.9%) neonates.

What causes increased risk of congenital defects in mothers with diabetes, is not completely understood. It is postulated that during pregnancy for the purpose of fetal wellbeing, maternal circulatory and metabolic systems undergo various adaptations and physiological changes in order to increase insulin resistance in maternal body, even in normoglycaemic pregnant females¹⁷. These physiological changes may include altered response to anabolic hormones, changed glucose utilization in the body and altered glucose intolerance during gestation. The pregnant females with increased insulin resistance have higher chances of developing congenital malformations during gestation and this is evident with greatest risk of malformations in neonates of mothers with diabetes with poorly control glucose levels, particularly who used insulin at the time of conception^{1,18}.

The frequency of CHD in our study was highest in 66 neonates in the group of "poor control of maternal diabetes" compared to the 5

neonates with CHD in the group "good control of maternal diabetes" (table-II). Although increased insulin resistance has deleterious effect in pregnant females, at the same time limited physical activity during pregnancy along with increased caloric intake may also augment insulin resistance. Increased maternal weight and obesity before pregnancy is also related to bad outcome particularly the maternal weight gain in first 24 weeks of gestation is considered a risk factor for GDM¹⁹. The weight of neonates born to mothers with diabetes is generally higher than the neonates born to mothers without diabetes. The CHD is observed to be more prevalent in neonates born to mothers with diabetes with higher weights particularly more than 3Kg at birth in our study (table-II). This increased risk of CHD with increased weight of neonate is an independent risk factor or it is just the effect of hyperglycaemia in the mothers with diabetes, this need to be further studied and elaborated in future.

Another factor which may play a role in different risks of CHD in different types of the diabetes during pregnancy might be the different way of treating mothers with diabetes for better control of hyperglycaemia. However in the last few decades the treatment standard was use of metformin alone or its combination with insulin or alone insulin. But recent meta-analysis has shown that metformin is relatively safer compared to insulin in reference to the outcome of neonatal hypoglycaemia, macrosomia, NICU admission and maternal pre-eclampsia¹⁸.

The GDM was present in 89.13% of the pregnant mothers in our study. This percentage is higher than previously reported prevalence of 41.9% in pregnant ladies of low socioeconomic status in an Indian population study conducted in 2015²⁰. This difference might be because of different diagnostic criteria (oral glucose tolerance test instead of fasting glucose levels). The overall small no of cases in our study can be another factor for this difference.

When pre-gestational diabetes mellitus is compared with GDM in reference to perinatal

mortality and morbidity, the pre-gestational hyperglycaemia in the form of diabetes mellitus is more strongly related to the congenital anomalies of the fetus^{21,22}. Similar results were observed in a study carried out in 2015 by Hunter *et al*, which showed that in the GDM population the risk of CHD was 2.76% compared to CHD risk of 3.1% in the patients with pre-gestational diabetes particularly Insulin dependent diabetes mellitus in expectant females²³. This perhaps is partially, due to gestational diabetes mellitus occurring after 20 weeks of pregnancy compared to the pre-gestational DM having hyperglycaemia in critical embryogenesis period during early pregnancy.

The biggest limitation in our study is the small sample size of study, so the results may not be true projection of actual population. Secondly the study is conducted in a single centre. Moreover, the frequencies of individual CHD and other risk factors which may be associated with CHD has not been studied. In the future, multi-centre studies with higher sample size need to be carried with the evaluation of frequencies of individual congenital heart defects and their risk factors, which may reveal the better understanding of CHD in our population strata.

CONCLUSION

This study has shown that congenital heart disease is more frequent in neonates born to pregnant mothers with diabetes and particularly common in neonates of expectant mothers with poorly controlled diabetes. So, we recommend that clinicians should be encouraged to perform an echocardiography for all new born to mothers with diabetes to facilitate early diagnosis and prompt treatment. Moreover, proper management of mothers with diabetes should be taken in order to decrease the incidence of congenital heart defects.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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