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Frequency and Spectrum of Congenital Heart Disease in Neonates Born to Diabetic Mothers, and its Association with Maternal Glycemic Control

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Author`s Contribution

[1,2,6]Substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work, [3]Drafting the work or revising it critically for important intellectual content, [4]Acquisition of data that is performing echocardiogram on neonates, critically review, [5]Final approval of the study to be published,

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ABSTRACT

Objective: To determine the frequency and spectrum of cardiac abnormalities classified as congenital heart disease (CHD) in term neonates born to diabetic mothers and assess their association with maternal glycemic control.

Methodology: This prospective descriptive study was conducted at the Department of Pediatrics, Federal Government Polyclinic (FGPC), Islamabad, Pakistan, from November 2023 to April 2024. A total of 130 term neonates born to diabetic mothers were enrolled through consecutive sampling. Maternal diabetes type and first-trimester HbA1c values documented in antenatal records were recorded; the study did not involve follow-up of mothers from the first trimester. Glycemic control was categorized as well controlled (HbA1c ≤ 6.5%), moderately controlled (6.6–8.0%), and poorly controlled (>8.0%). All neonates underwent echocardiography within 24–48 hours of birth. Data were analyzed using SPSS version 23. Chi-square or Fisher's exact test was applied, with $p < 0.05$ considered significant.

Results: Cardiac abnormalities classified as CHD were detected in 33 neonates (25.4%). Hypertrophic cardiomyopathy/septal hypertrophy was the most frequent finding, 18 (54.5%), followed by ventricular septal defect, 6 (18.2%), atrial septal defect, 5 (15.2%), hypoplastic left heart syndrome, 2 (6.1%), pulmonary stenosis, 1 (3.0%), and transposition of the great arteries, 1 (3.0%). Isolated PDA, 4 (3.1%), pulmonary hypertension, 3 (2.3%), and mitral regurgitation, 2 (1.5%), were recorded separately and excluded from final CHD frequency. Maternal glycemic control was significantly associated with CHD occurrence ($p = 0.013$).

Conclusion: Cardiac abnormalities classified as CHD were detected in one-fourth of term neonates born to diabetic mothers and were significantly associated with poor first-trimester glycemic control.

Keywords: Congenital heart disease, diabetes mellitus, echocardiography, glycemic control, neonates, prevalence.

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Introduction

Congenital heart disease (CHD) is one of the most common congenital anomalies across the globe, occurring in approximately 1 in every 100 live births. It remains a significant contributor to neonatal morbidity and early infant mortality.[1] Maternal diabetes is a recognized risk factor for fetal cardiac abnormalities. This includes pre-existing type 1 or type 2 diabetes mellitus (DM) and gestational diabetes mellitus (GDM).[2] The risk of CHD is higher in pregnancies of diabetic mothers compared with the non-diabetic ones.[3] A recent

meta-analysis reported odds ratios of 3.48 for pregestational diabetes and 1.55 for GDM.[4]

Fetal heart development starts early in embryogenesis and major morphological development of heart takes place during the first trimester.[5] Therefore, maternal hyperglycemia during early pregnancy may interfere with normal cardiac morphogenesis. Oxidative stress, mitochondrial dysfunction, altered biochemical signaling pathways, and disruption of septation and outflow tract development are the most likely mechanisms.[6] Reduced incidence of major CHD subtypes have been found associated with improved maternal glycemic management prior to and during early pregnancy.[7] Ventricular septal defects (VSD), followed by patent ductus arteriosus (PDA) and atrial septal abnormalities, are frequently seen in infants of diabetic mothers.[8] Tetralogy of Fallot and double-outlet right ventricle are two conotruncal abnormalities that are more likely to occur when endocardial cushion formation and neural crest cell migration are disrupted.[6] Echocardiographic investigations also report myocardial hypertrophy and altered chamber geometry in the infants born to diabetic mothers even when their glycemic control appears adequate.[9]

Different screening practices, timing of echocardiography, diagnostic criteria, and healthcare setting may account for variation in the reported frequency and spectrum of cardiac abnormalities among neonates of diabetic mothers. Several Pakistani studies have already examined this association, but their reported frequencies and lesion profiles differ, partly because of differences in study populations and the timing and criteria used for echocardiographic assessment. Data specifically describing term neonates who undergo standardized echocardiography within the first [24–48] hours of life, together with assessment of documented first-trimester HbA1c, remain comparatively limited. The present study was therefore undertaken to characterize early neonatal cardiac findings among term neonates born to diabetic mothers at a tertiary-care hospital in Islamabad, Pakistan, and to assess their association with maternal diabetes type and first-trimester HbA1c-based glycemic control.

Methodology

This prospective descriptive study was conducted at the Department of Pediatrics, Federal Government Polyclinic (FGPC) Hospital, Islamabad, Pakistan, over a six-month period (November 2023 to April 2024). The study recruited eligible neonates prospectively at birth; maternal first-trimester HbA1c values were obtained from existing antenatal or hospital records and therefore did not require follow-up from the first trimester. The sample size was calculated using the WHO sample size calculator for descriptive studies, taking a CHD incidence of [9.0]% in neonates of diabetic mothers, [3] with a [95]% confidence level and absolute precision of [5]%. The estimated sample size was n=126, which was rounded to 130 neonates. Ethical approval for the study was obtained from the Institutional Review Board (IRB) of the hospital (Approval No. FGPC.1/12/2023/Ethical Committee, dated 13/10/23). The study was conducted in accordance with the principles of the Declaration of Helsinki.

All term neonates, defined as neonates born at ≥37 weeks of gestation, were eligible for inclusion if they were born to mothers with documented diabetes mellitus during pregnancy. Maternal diabetes was classified as gestational diabetes mellitus (GDM) or pregestational diabetes mellitus (PGDM) according to antenatal, obstetric, endocrine, or hospital records. For the purpose of this study, GDM was defined as diabetes first recognized during pregnancy in mothers without previously known diabetes, and PGDM was defined as known type 1 or type 2 diabetes diagnosed before pregnancy or documented as pre-existing diabetes in early pregnancy. As this was a neonatology-based observational study, maternal diabetes classification was based on the diagnosis documented in antenatal, obstetric, endocrine, or hospital records. Maternal glycemic control was assessed using the documented first-trimester HbA1c value and categorized into well-controlled (HbA1c ≤6.5%), moderately controlled (HbA1c 6.6-8.0%), and poorly controlled (HbA1c >8.0%) groups according to the predefined study cutoffs. The study population was recruited through consecutive sampling from the maternity ward of FGPC. Neonates were included only after written informed consent was obtained from their parents/guardians. Neonates who were preterm (<37 weeks of gestation), those with known syndromic features, chromosomal abnormalities, or genetic disorders associated with congenital anomalies were excluded from the study. Neonates born to mothers with comorbid conditions other than diabetes, such as hypertension or autoimmune disorders, that may independently affect fetal development were also excluded. Neonates whose parents/guardians did not provide written informed consent were excluded.

Maternal and neonatal data were recorded on a predesigned case record form. Maternal variables included maternal age, type of diabetes, first-trimester HbA1c level, glycemic-control category, and mode of delivery. Neonatal variables included birth weight, gestational age, Apgar score, and echocardiographic findings. All enrolled neonates underwent transthoracic echocardiography within 24–48 hours of birth. Echocardiography was performed by experienced pediatric cardiologists using a high-resolution ultrasound system, Philips Affiniti 50, Philips Medical Systems, Bothell, WA, USA. The examination included two-dimensional, M-mode, color Doppler, and spectral Doppler assessment. The echocardiographic evaluation included assessment of cardiac anatomy, septal defects, valvular abnormalities, outflow tract abnormalities, ductus arteriosus, ventricular function, and myocardial hypertrophy, including interventricular septal thickness where applicable. For the purpose of this study, cardiac abnormalities classified as CHD included ventricular septal defect, atrial septal defect, hypoplastic left heart syndrome, pulmonary stenosis, transposition of the great arteries, and hypertrophic cardiomyopathy/septal hypertrophy. Isolated patent ductus arteriosus (PDA) detected within the first 24–48 hours of life, pulmonary hypertension, and mitral regurgitation were recorded separately as transitional or functional echocardiographic findings and were not included in the final CHD frequency.

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 23. Continuous variables, including maternal age, first-trimester HbA1c level, neonatal gestational age, birth weight, and Apgar score, were summarized as mean ± standard deviation. Categorical variables, including maternal diabetes type, mode of delivery, HbA1c-based glycemic-control category, echocardiographic findings, and frequency of CHD, were presented as frequency and percentage. The Chi-square test was used to assess the association of CHD with maternal diabetes type and mode of delivery, while Fisher's exact test was used for glycemic-control category where expected cell counts were less than five. A p-value of < 0.05 was considered statistically significant.

Results

The study included 130 term neonates of diabetic mothers. Most mothers had gestational diabetes, and nearly half had poor first-trimester HbA1c-based glycemic control. Neonates were predominantly delivered vaginally and had overall stable birth characteristics (Table I).

Table I: Baseline maternal and neonatal characteristics of term neonates born to diabetic mothers. (n=130)

Characteristic		n (%)	Mean ± SD
Maternal Characteristics			
Maternal Age (years)		—	30.5 ± 5.2
HbA1c Level (%)		—	7.8 ± 1.4
Diabetes Type	Gestational	99 (76.2%)	—
	Pregestational	31 (23.8%)	—
Type of Delivery	Cesarean Section	54 (41.5%)	—
	Vaginal Delivery	76 (58.5%)	—
Glycaemic control	Well-Controlled	34 (26.2%)	—
	Moderately-Controlled	34 (26.2%)	—
	Poorly-Controlled	62 (47.7%)	
Neonatal Characteristics			
Birth Weight (kg)		—	3.2 ± 0.5
Gestational Age (weeks)		—	38.5 ± 1.2
Apgar Score		—	8.3 ± 0.7

Table II shows echocardiography was unremarkable in 97 neonates (74.6%), while cardiac abnormalities classified under the study definition of CHD were detected in 33 neonates (25.4%). Isolated PDA 4 (3.1%), pulmonary hypertension 3 (2.3%), and mitral regurgitation 2 (1.5%) were not included in the final CHD frequency and were recorded separately as transitional or functional echocardiographic findings. Among the 33 neonates with CHD, hypertrophic cardiomyopathy/septal hypertrophy was the most frequent finding, observed in 18 neonates (54.5%), followed by ventricular septal defect in 6 neonates (18.2%), atrial septal defect in 5 neonates (15.2%), hypoplastic left heart syndrome in 2 neonates (6.1%), pulmonary stenosis in 1 neonate (3.0%), and transposition of the great arteries in 1 neonate (3.0%).

Table III shows that CHD was more frequent among neonates of mothers with pregestational diabetes than gestational diabetes, but this difference was not statistically significant. Mode of delivery was also not significantly associated with CHD. However, maternal glycemic control showed a significant association with CHD ($p = 0.013$), with CHD detected in 8.8% of neonates of well-controlled mothers, 23.5% of moderately controlled mothers, and 35.5% of poorly controlled mothers.

Table II: Overall echocardiographic outcome (normal vs congenital heart disease) and lesion-wise spectrum of CHD in the study cohort of children born to diabetic mothers. Overall echo findings use n = 130; CHD subcategories are presented with n = 33 where applicable.

Variable	Category	n (%)
Echo findings included in final analysis	Unremarkable	97 (74.6%)
	CHD	33 (25.4%)
	Total	130 (100%)
Categories of CHD	HCM	18 (54.5%)
	VSD	6 (18.2%)
	ASD	5 (15.2%)
	HLHS	2 (6.1%)
	PS	1 (3.0%)
	TGA	1 (3.0%)
	Total	33 (100.0%)

HCM = hypertrophic cardiomyopathy; VSD = ventricular septal defect; ASD = atrial septal defect; HLHS = hypoplastic left heart syndrome; PS = pulmonary stenosis; TGA = transposition of the great arteries. Isolated PDA detected within 24–48 hours of life, pulmonary hypertension, and mitral regurgitation were excluded from the final CHD frequency and recorded separately as transitional or functional echocardiographic findings.

Table III: Association of CHD with maternal diabetes type, mode of delivery, and glycemic control among neonates born to diabetic mothers (n=130).

Variables	Category	CHD Absent n (%)	CHD Present n (%)	p-value
Diabetes Type	Gestational Diabetes	77 (79.4%)	22 (66.7%)	0.159
	Pregestational Diabetes	20 (20.6%)	11 (33.3%)	
Mode of Delivery	Cesarean Section	37 (38.1%)	17 (51.5%)	0.221
	Vaginal Delivery	60 (61.9%)	16 (48.5%)	
Maternal Glycaemic Control	Well Controlled	31 (32.0%)	3 (9.1%)	0.013
	Moderately Controlled	26 (26.8%)	8 (24.2%)	
	Poorly Controlled	40 (41.2%)	22 (66.7%)	

p-value for maternal glycemic control was calculated using Fisher's exact test because Chi-square assumptions were not met, as one cell had an expected count <5. All percentages are column-wise.

Discussion

In our study cohort, the observed predominance of septal hypertrophy is clinically relevant. Maternal hyperglycemia and prenatal hyperinsulinemia have been closely associated with neonatal hypertrophic cardiomyopathy, which typically manifests as asymmetric septal thickening.[11] Fetal hyperinsulinism may cause excessive glycogen and lipid deposition in the heart, leading to disproportionate septal thickness.[12] About 20–40% of infants of diabetic mothers had septal hypertrophy or hypertrophic cardiomyopathy, according to reports from high-income nations,[13] which closely parallels the 54.5% frequency recorded in the present study. Although many of these lesions regress spontaneously during infancy, they may contribute to significant morbidity during this time typically due to diastolic dysfunction, outflow tract obstruction, or low cardiac output. This emphasizes the significance of early detection and monitoring because temporary but clinically significant lesions might otherwise go undetected.[14]

The range of reported results seems to be significantly influenced by the time of echocardiography. Early neonatal evaluations tended to show temporary or functional abnormalities like septal hypertrophy, whereas studies that conducted echocardiography later in infancy frequently showed a higher frequency of structural defects like VSD and PDA.[6,11,12] All of the neonates in our study were assessed within 24 to 48 hours of delivery, which may have contributed to the predominance of septal hypertrophy and enhanced detection of early, potentially reversible abnormalities. This finding emphasizes the significance of diagnosis timing, which is a crucial factor to take into account when comparing prevalence statistics from various research. Additionally, the increased incidence of septal hypertrophy in our environment can be due to a lack of glycaemic surveillance throughout pregnancy, a delay in starting therapy, and the coexistence of other maternal risk factors such as systemic inflammation, obesity, and dyslipidemia.[11,14] These coexisting metabolic factors were not specifically stratified in our study.

Comparison with previous Pakistani reports shows that the frequency and distribution of cardiac findings are not uniform across studies. Earlier hospital-based studies, including those from Khyber Teaching Hospital and other Pakistani centers, reported higher overall frequencies of CHD, with VSD and PDA among the commonly reported lesions. [15], [6], [16] In contrast, more recent studies using early neonatal echocardiography have identified septal hypertrophy as a prominent finding. [11], [12], [17] Differences in the age at echocardiographic assessment, the populations studied, and the definitions used for cardiac abnormalities may therefore contribute to the variation between reported estimates. In our cohort, echocardiography was performed within [24–48] hours of birth, which may have favored detection of early myocardial hypertrophy associated with maternal diabetes. International population-based studies also support an increased risk of CHD with maternal diabetes, particularly presentational diabetes, and suggest that coexisting maternal metabolic factors may further increase this risk. [9], [18] Similar concerns have been reported from other low- and middle-income settings, highlighting the importance of appropriate maternal glycemic control and timely cardiac assessment in infants of diabetic mothers. [8], [10], [19-21]

In summary, this study shows that neonates born to diabetic mothers have a substantial burden of congenital heart disease (CHD), especially septal hypertrophy. The study findings support the objective that cardiac abnormalities in neonates of diabetic mothers are frequent and are associated with poor maternal glycemic control. Hence, strict metabolic control is essential before and throughout pregnancy, as evidenced by significant association between maternal hyperglycemia and the risk of CHD. Neonatal cardiac outcomes in such high-risk populations may facilitate timely detection by early echocardiography and appropriate prenatal diabetes control.

Limitations of the Study: This study has several limitations. First, it was a single-center study with a modest sample size; therefore, the findings may not be generalizable to other populations. Second, maternal glycemic control was assessed using a single documented first-trimester HbA1c value, while serial HbA1c measurements and detailed antenatal glucose records were not available for analysis. Although first-trimester HbA1c is relevant to early fetal cardiac development, variation in the exact timing of HbA1c measurement within the first trimester may have influenced assessment of glycemic exposure. Third, maternal medication details, diabetes duration, obesity/body mass index, lipid profile, inflammatory markers, dietary factors, level of prenatal care, and detailed sociodemographic variables were not recorded; therefore, their potential confounding effects could not be assessed. Fourth, echocardiography was performed within the first 24–48 hours of life, and there was no longitudinal follow-up to document persistence or regression of cardiac findings, including hypertrophic cardiomyopathy/septal hypertrophy. Isolated PDA, pulmonary hypertension, and mitral regurgitation were therefore interpreted cautiously, excluded from the final CHD frequency, and recorded separately. Fifth, although echocardiography was performed by experienced pediatric cardiologists using a standardized approach, interobserver variability cannot be completely ruled out. Finally, referral and selection bias may have occurred, and differences in methodology, echocardiography timing, and fetal cardiac screening protocols across studies may affect comparison with previously published data. Further large-scale, multicenter prospective studies with standardized fetal and postnatal cardiac assessment, detailed maternal metabolic profiling, and longitudinal follow-up are recommended.

Conclusion

This study demonstrated a high frequency of congenital heart disease in neonates of diabetic mothers, with septal hypertrophy as the most common lesion, followed by septal defects. The significant association between poor maternal glycemic control and CHD underlines the importance of optimizing blood glucose levels before conception and throughout pregnancy.

Early postnatal echocardiography may facilitate timely detection and monitoring of structural and functional cardiac abnormalities in this high-risk population. Improved preconception counselling and strict antenatal glycemic control are important measures to reduce the risk of CHD and improve neonatal outcomes among infants born to diabetic mothers.

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