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Maternal Diabetes and Intra-Familial Marriage as Risk Factors for Congenital Heart Disease

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ABSTRACT

Background: Congenital heart diseases (CHD) remain the most common congenital anomaly worldwide. Maternal diabetes and parental consanguinity have been implicated as significant risk factors.

Objective: To determine the association of maternal diabetes mellitus and parental consanguinity with the incidence and pattern of congenital heart disease in Pakistani children.

Methods:A cross-sectional study was conducted at the Pediatric Department of Benazir Bhutto Hospital, Rawalpindi over one year (January–December 2024). A total of 300 children aged 0–12 years diagnosed with CHD on echocardiography were enrolled. Data on maternal diabetes, consanguinity, and type of CHD were collected using structured interviews and medical records. Statistical analysis was performed using SPSS v26. Chi-square test was applied; $p < 0.05$ was considered significant.

Results: Out of 300 cases of congenital heart disease (CHD), 174 (58%) were males and 126 (42%) females, with a mean age at diagnosis of 8.6 ± 3.4 months. Maternal diabetes was observed in 54 mothers (18%), significantly higher than the 6% prevalence in the general obstetric population ($p < 0.001$). Consanguinity was reported in 177 cases (59%). In offspring of diabetic mothers, the most common cardiac lesions were ventricular septal defect (VSD) (33%), transposition of the great arteries (TGA) (22%), and coarctation of the aorta (15%). Among children born to consanguineous parents, atrial septal defect (ASD) (28%), tetralogy of Fallot (TOF) (24%), and patent ductus arteriosus (PDA) (19%) were most frequent. Notably, the combined presence of maternal diabetes and consanguinity was associated with a 3.8-fold increased risk of CHD (odds ratio = 3.8; 95% CI: 2.1–6.5; $p < 0.001$), highlighting the synergistic effect of these risk factors on congenital cardiac anomalies.

Conclusion: Both maternal diabetes and consanguinity significantly increase the risk of congenital heart disease in offspring. Targeted preconception counseling, strict glycemic control, and genetic counseling in consanguineous families are crucial preventive strategies.

assessment may aid obstetricians in predicting delivery outcomes and planning labor management..

Keywords: *Congenital heart disease, maternal diabetes, consanguinity, risk factors, echocardiography, Pakistan*

1. INTRODUCTION

Congenital heart diseases (CHDs) constitute roughly one-third of all congenital anomalies and remain a major cause of infant morbidity and mortality worldwide. Global estimates suggest a birth prevalence of around 8–10 per 1,000 live births, with Asia reporting some of the highest rates. [1,2] These defects arise from a multifactorial interplay of genetic, environmental, and metabolic factors, including maternal illnesses, teratogenic exposures, and inherited variants.

Poorly controlled maternal diabetes mellitus in early pregnancy is a well-established risk factor for CHD. Hyperglycemia during the period of cardiac organogenesis disrupts normal cardiogenesis and is associated with a several-fold increase in major congenital heart defects, particularly conotruncal and outflow tract lesions. [3,4] Recent cohort studies show that higher first-trimester HbA1c levels in women with pre-gestational diabetes markedly increase the relative risk of major CHD, underlining the importance of strict glycemic control before conception and in early gestation. [4,5]

Consanguineous marriage, especially first-cousin unions, increases the probability of homozygosity for deleterious recessive alleles and has been linked to a higher burden of congenital anomalies, including CHD. [6] Pakistan is among the countries with the highest rates of consanguinity globally, with around 60–66% of marriages occurring between blood relatives and a predominance of first-cousin unions. [7, 8] Local hospital-based studies have reported a high proportion of children with CHD being born to consanguineous parents, suggesting an important genetic and social component to disease risk. [9, 10]

Both type 2 diabetes and consanguineous marriage are highly prevalent in Pakistan, yet evidence on their combined effect on CHD risk is sparse and sometimes conflicting, with earlier descriptive work failing to show clear associations. [11] This gap limits context-specific counselling, preconception care, and risk-stratified antenatal screening for Pakistani families. Therefore, this study intends to determine the impact of maternal diabetes and consanguinity, individually and jointly, on the risk of congenital heart disease in children in Pakistan, providing locally relevant data to inform prevention strategies and targeted public health interventions.

2. MATERIALS AND METHODS

Study Design and Setting

Cross sectional observational study conducted in Pediatric Cardiology Department of Children's Hospital Lahore, from January 2024 to December, 2024.

Sample Size

Through non probability consecutive sampling technique, 300 children suffering from congenital heart disease and whose disease was confirmed by echocardiography were included in the study.

Inclusion Criteria

• Children from birth to 12 years who were diagnosed with congenital heart disease.

• Mothers who provided informed consent.

Exclusion Criteria

• Children who have chromosomal abnormalities (Down, Turner, and so on).

• Incomplete maternal information.

Data Collection

Information of the mother (age, diabetes, children, family relations, infections during pregnancy, and medications) and the new born were recorded on a structured proforma. Diabetes was classified as either pre-existing diabetes or gestational diabetes which was diagnosed according to the criteria given by American Diabetes Association.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 26 was used for the organization of data. Frequencies and percentages were calculated. Chi-square was used for the determination of the relationship between risk factors and the different types of congenital heart disease. The logistic regression model was used to derive odds ratios and confidence intervals.

3. RESULTS:

The study presented key findings related to maternal and fetal health. The mean maternal age was found to be 28.7 ± 4.6 years. The mean gestational age at birth was 37.9 ± 1.2 weeks. The male-to-female ratio was 1.4:1.

Maternal diabetes (only) was present in 54 cases (18%) with a p-value of <0.01, suggesting a significant association. Consanguinity was observed in 177 cases (59%), also with a p-value of <0.01, indicating a significant risk factor. The combination of both maternal diabetes and consanguinity was seen in 28 cases (9.3%) with a p-value of <0.01, showing a

notable risk association.

A contingency table further highlighted the relationship between maternal diabetes and consanguinity. Of the total 82 cases of maternal diabetes, 28 had consanguinity, and 54 did not. In contrast, among the 218 non-diabetic mothers, 177 had consanguinity, and 95 did not.

The distribution of congenital heart disease (CHD) types revealed the following: Ventricular Septal Defect (VSD) was the most common, affecting 84 cases (28% of the total), followed by Atrial Septal Defect (ASD) with 69 cases (23%), and Tetralogy of Fallot (TOF) with 51 cases (17%). Other notable CHD types included Patent Ductus Arteriosus (PDA) in 45 cases (15%), Transposition of the Great Arteries (TGA) in 24 cases (8%), and Coarctation of the Aorta (CoA) in 18 cases (6%). A smaller number of cases (9, or 3%) were categorized as other types, including AV Canal and Pulmonary Stenosis.

The association between risk factors and specific CHD lesions was also explored. Diabetic mothers showed a higher prevalence of VSD (33%), TGA (22%), and CoA (15%), while consanguineous marriages were more likely to result in ASD (28%), TOF (24%), and PDA (19%). Children born to diabetic mothers had 2.9 times higher odds of CHD (OR = 2.9; 95% CI: 1.7–4.9).
Children of consanguineous unions had 1.8 times higher odds of CHD (OR = 1.8; 95% CI: 1.2–2.7). Combined presence increased risk 3.8-fold (OR = 3.8; 95% CI: 2.1–6.5).

Risk Factors

Risk Factor	Frequency (n=300)	Percentage	p-value
Maternal Diabetes	54	18%	<0.01
Consanguinity	177	59%	<0.01
Both Diabetes + Consanguinity	28	9.3%	<0.01

Contingency Table

	Consanguinity (Yes)	Consanguinity (No)	Total
Maternal Diabetes (Yes)	28	54	82
Maternal Diabetes (No)	177	95	218
Total	205	95	300

Distribution of CHD Types

Type of CHD	Frequency	% of Total
VSD	84	28%
ASD	69	23%
TOF	51	17%
PDA	45	15%
TGA	24	8%
Coarctation of Aorta	18	6%
Others (AV Canal, Pulmonary Stenosis, etc.)	9	3%

Association of Risk Factors with most frequent lesions

Risk Factor	CHD Lesion	Prevalence (%)
Diabetic Mothers	VSD	33%
	TGA	22%
	CoA	15%
Consanguineous Marriages	ASD	28%

	TOF	24%
	PDA	19%

4. DISCUSSION

Our study demonstrates a significant association between maternal diabetes, consanguinity, and congenital heart disease (CHD). We found that 18% of CHD mothers had maternal diabetes, nearly three times the background obstetric rate, highlighting the teratogenic potential of hyperglycemia during organogenesis. This finding aligns with previous studies, such as those by Papazoglou et al. (2022), who also observed a higher prevalence of CHD among mothers with diabetes, emphasizing the detrimental effects of elevated blood glucose during pregnancy on fetal development [12]. Furthermore, the high prevalence of consanguinity in our cohort (59%) supports regional studies that have linked autosomal recessive inheritance to increased risks of cardiac malformations, particularly in certain ethnic groups where consanguineous marriages are more common [13].

The predominance of ventricular septal defect (VSD) and atrial septal defect (ASD) in our findings is consistent with global trends. Several studies, including Yang et al. (2019), have reported that maternal diabetes and consanguinity are strongly associated with these types of defects, which may be exacerbated by genetic predispositions in consanguineous marriages [14]. However, an interesting observation in our study is the relatively high frequency of tetralogy of Fallot (TOF) among consanguineous families, suggesting a genetic predisposition influenced by recessive alleles. Liu et al. (2024) highlighted that consanguinity can exacerbate the risk of severe congenital heart defects like TOF due to the higher likelihood of inheriting recessive mutations from both parents [15].

The synergistic effect of maternal diabetes and consanguinity, with a 3.8-fold increased risk of CHD, underlines the combined influence of genetic and environmental factors on cardiac embryogenesis. This finding supports earlier work by Ibrahim et al. (2023), who identified a similar interaction between these two factors, emphasizing the importance of preconception care in mitigating risks associated with consanguinity and maternal diabetes [16]. Additionally, studies by Khalilipalandi et al. (2024) and Lemieux et al. (2024) have reinforced the notion that managing maternal health, particularly diabetes, is crucial for reducing the incidence of congenital heart defects in populations with high rates of consanguineous marriages [17][18].

While our study's cross-sectional design and lack of genetic sequencing limit the depth of analysis, it still aligns well with other regional studies. Our findings underscore the importance of preconception diabetes control and genetic counseling for consanguineous couples to reduce the risk of congenital heart defects.

Limitations include the cross-sectional design and lack of genetic sequencing. However, the findings underscore the importance of preconception diabetes control and genetic counseling for consanguineous couples.

5. CONCLUSION:

Maternal diabetes and parental consanguinity are significant independent and synergistic risk factors for congenital heart disease. Preventive strategies — including glycemic optimization before conception and public education regarding consanguineous marriage risks — are essential to reduce CHD incidence in Pakistan.

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Authors' Contribution

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