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IMPACT OF MATERNAL DIABETES ON THE PREVALENCE AND PATTERN OF CONGENITAL HEART DISEASES IN INFANTS

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Abstract

Background: Gestational diabetes mellitus (GDM) has already been recognized as an important risk factor for congenital heart disease (CHD). However, local studies have reported variable frequency for CHD among GDM. Learning the burden of diseases will be crucial in reducing preventable neonatal mortality by devising screening strategies for neonates born to diabetic mothers.

Objective: To assess the frequency of congenital heart diseases (CHD) in infants of diabetic mothers.

Methods: This cross-sectional study was conducted in the Department of Pediatrics at Fatima Memorial Hospital, Lahore, from January to December 2021. A total of 100 mothers who met the inclusion criteria were enrolled. In our study, the exposure of interest was mothers diagnosed with Gestational diabetes mellitus by a qualified physician, and the outcome of the interest was the Pattern of Congenital Heart Diseases in Infants, such as Ventricular Septal Defect, Patent Ductus Arteriosus, Atrial Septal Defect, etc. The neonates were enrolled using non-probability Consecutive sampling. Neonates were evaluated using a stethoscope to detect heart murmurs, and those with murmurs underwent echocardiography for CHD confirmation. Data were recorded on a standard questionnaire adopted from a previous study. Data was entered and analyzed using SPSS version 25.

Results: Congenital heart disease was diagnosed in 71% of neonates. The most frequent types were Ventricular Septal Defect (32.39%), Patent Ductus Arteriosus (35.21%), and Atrial Septal Defect (19.72%). The frequency of CHD was higher among older mothers and those with gestational ages

of 37-40 weeks. Male infants had a higher frequency of CHD (Male: 62%, Female: 38%, p-value=0.344). Neonates with weights <2.75 kg also had a higher frequency of CHD. These findings are consistent with national and international studies.

Conclusion: A high frequency of congenital heart disease was observed in infants of diabetic mothers. Effective screening for GDM mothers is crucial for early CHD diagnosis through echocardiography, which may help us with proper counseling and early intervention.

Keywords: Congenital Heart Diseases, Infants, Gestational Diabetes, Pregnancy

INTRODUCTION

Congenital heart diseases (CHDs) are a significant concern in infants born to diabetic mothers, with maternal diabetes mellitus (DM) being a well-established risk factor. The pathophysiology underlying this association is multifaceted, involving genetic predispositions, metabolic disturbances, and environmental influences during critical periods of fetal development.

Maternal diabetes significantly increases the risk of CHDs in offspring. This risk is exacerbated by poor glycemic control during pregnancy [1]. Hyperglycemia during early gestation is particularly teratogenic, leading to various cardiac malformations such as transposition of the great arteries, tetralogy of Fallot, and ventricular septal defects [2]. Studies have shown that maternal pregestational diabetes is associated with a fivefold increase in the risk of CHDs compared to non-diabetic pregnancies [3].

The mechanisms by which maternal hyperglycemia induces CHDs involve oxidative stress and inflammation pathways that disrupt normal cardiac morphogenesis. Elevated glucose levels increase the production of reactive oxygen species (ROS), damaging cellular structures and interfering with signaling pathways essential for heart development [4]. Also, hyperglycemia can alter gene expression patterns through epigenetic modifications, contributing to congenital anomalies [5].

Epidemiological data underscore the importance of preconception care in mitigating these risks. Preconception folic acid supplementation has been shown to reduce the incidence of neural tube defects and may also have protective effects against CHDs [6]. Moreover, achieving optimal glycemic control before conception and throughout pregnancy significantly decreases the likelihood of adverse outcomes [7].

The role of maternal obesity as a co-factor cannot be overlooked. Obesity exacerbates insulin resistance and hyperglycemia, compounding the risk for CHDs. A study highlighted that maternal obesity combined with diabetes increases the odds ratio for CHDs more than either condition alone [8]. This synergistic effect underscores the need for comprehensive management strategies addressing both weight control and glucose regulation.

Advanced maternal age (AMA) also contributes to an elevated risk profile for congenital anomalies, including CHDs. AMA often correlates with higher incidences of gestational diabetes mellitus (GDM), further complicating pregnancy outcomes [9]. Women over 35 years old with GDM are at a heightened risk for delivering infants with cardiac malformations due to compounded metabolic stresses on fetal development.

Recent advances in prenatal screening techniques have improved early detection rates of CHDs in high-risk pregnancies. Fetal echocardiography is particularly valuable for assessing cardiac structure and function in utero. Early diagnosis allows for timely interventions to improve neonatal outcomes [10].

Despite advancements in perinatal care, infants born to diabetic mothers remain at high risk for several complications beyond structural heart defects. These include hypertrophic cardiomyopathy (HCM), which has been identified as a significant contributor to neonatal morbidity and mortality among this population [11]. HCM results from hyperinsulinemia-induced myocardial hypertrophy secondary to maternal hyperglycemia.

Preventive strategies should focus on stringent glycemic control, starting preconceptionally through postpartum periods. Lifestyle modifications, including diet adjustments adhering to Mediterranean

dietary patterns, have shown promise in reducing GDM incidence and improving overall pregnancy outcomes [12]. Additionally, continuous monitoring using advanced diagnostic tools like fetal electrocardiography can help detect early signs of cardiac dysfunctions, allowing prompt medical interventions.

In conclusion, congenital heart diseases represent a major concern among infants born to diabetic mothers due to complex interactions between genetic susceptibilities and metabolic derangements induced by maternal hyperglycemia. Effective management requires multidisciplinary approaches encompassing preconception counseling, rigorous glycemic control throughout pregnancy, early diagnostic screenings, and targeted therapeutic interventions aimed at minimizing both immediate neonatal risks and long-term cardiovascular sequelae.

METHODOLOGY

Study Design and Sample Size

A cross-sectional study was conducted using non-probability, Conclusive sampling. The participants were selected from the Department of Pediatrics, Fatima Memorial Tertiary Care Teaching Hospital, and Postgraduate Institute Lahore. The study was conducted for a period of six months. All the neonates of either gender delivered to diabetic mothers referred from the Department of Obstetrics & Gynecology were considered our relevant population. Neonates with major central nervous system, pulmonary anomalies, severe hypoxia, or neonatal sepsis (on clinical examination) were excluded from the study. In our study, the exposure of interest was mothers diagnosed with Gestational diabetes mellitus by a qualified physician, and the outcome of the interest was the Pattern of Congenital Heart Diseases in Infants, such as Ventricular Septal Defect, Patent Ductus Arteriosus, Atrial Septal Defect, etc.

Open Epi statistical software was used to calculate the sample size. The sample size for our study was calculated at 95% CI, at a 5% margin of error, while considering previous study prevalence, taking an expected percentage of CHD as 52.5% born to diabetic mothers [13]. We used the standard sample size calculation formula n = [DEFF*Np (1- p)]/ [(d2/Z21-a/2*(N-1)+p*(1-p)]. The estimated sample size was 110. However, the response rate was n=100.

Study Variables.

In our study, the exposure of interest was mothers diagnosed with Gestational diabetes mellitus by a qualified physician, and the outcome of the interest was the Pattern of Congenital Heart Diseases in Infants, such as Ventricular Septal Defect, Patent Ductus Arteriosus, Atrial Septal Defect, etc.

Further, the study also includes independent variables such as demographic variables, such as the mother's age, gestational age at birth, age of neonate (in hours), gender of the neonate, birth weight, etc. The sociodemographic variables (independent) were correlated with the pattern of congenital anomalies (dependent variables).

Ethical Approval

The Fatima Memorial Medical College’s Institutional Ethical Review Board, Lahore, Pakistan, approved the study. Formal written permission was sought from every guardian (mother) before documenting further information. We confirm that the study project followed all the local and international ethical guidelines and standards.

Data Collection Procedure

A total of 100 mothers who met the inclusion criteria were included in the study from the emergency department of the Pediatrics Department at Fatima Memorial Hospital, Lahore. After obtaining informed consent from the parents, demographic variables were collected, including the mother's name, age, gestational age at birth, and the neonate's age (in hours), gender, and birth weight. The neonates were then evaluated using a stethoscope to detect any heart murmurs. If murmurs were

present, the neonates underwent echocardiography to confirm congenital heart disease (CHD) as per the operational definition. All data were recorded using a structured and validated questionnaire.

Data Analysis

The data were entered and analyzed using SPSS version 25. Quantitative variables such as maternal age, gestational age, neonatal age, and birth weight were presented as means and standard deviations (SD). Qualitative variables, including gender and the presence of congenital heart disease (CHD), were presented as frequencies and percentages.

To explore potential associations, data were stratified by maternal age, gestational age, neonatal age, gender, and birth weight. The stratified groups were then compared for the presence of CHD using the chi-square test. A p-value of ≤0.05 was considered statistically significant. This approach allowed for a detailed examination of how different demographic and clinical factors might be related to the occurrence of CHD in the study population.

Results

The study population consisted of 100 mothers with a mean age of 32.58 years (SD = 3.08), ranging from 24 to 39 years. The gestational age of the patients averaged 37.49 weeks (SD = 1.83), with a minimum of 28 weeks and a maximum of 40 weeks. Among the neonates, 59% were male (n=59), and 41% were female (n=41), making a total of 100 neonates. The birth weights of the neonates had a mean of 2.71 kg (SD = 0.36), ranging from 2.24 kg to 3.36 kg, as shown in table 1.

Table 1: General characters of the study population (n=100)

Characteristic	Value
Age of Patients	
N	119
Mean	32.58
Standard Deviation	3.08
Minimum	24
Maximum	39
Gestational Age of Patients	
N	119
Mean	37.49
Standard Deviation	1.83
Minimum	28
Maximum	40
Gender of Patients	
Male	59 (59%)
Female	41 (41%)
Total	100 (100%)
Birth Weight of Neonates	
N	119
Mean	2.71
Standard Deviation	0.36
Minimum	2.24
Maximum	3.36

These results indicate a relatively mature maternal population with pregnancies generally reaching full term. The gender distribution shows a higher proportion of male neonates. The birth weights suggest that, despite the presence of gestational diabetes mellitus (GDM) in mothers, the neonates' birth weights were within a normal range. This data provides a baseline understanding of the study

population, essential for interpreting the primary outcomes related to the frequency of congenital heart diseases (CHD) in infants of diabetic mothers, as shown in Table 1.

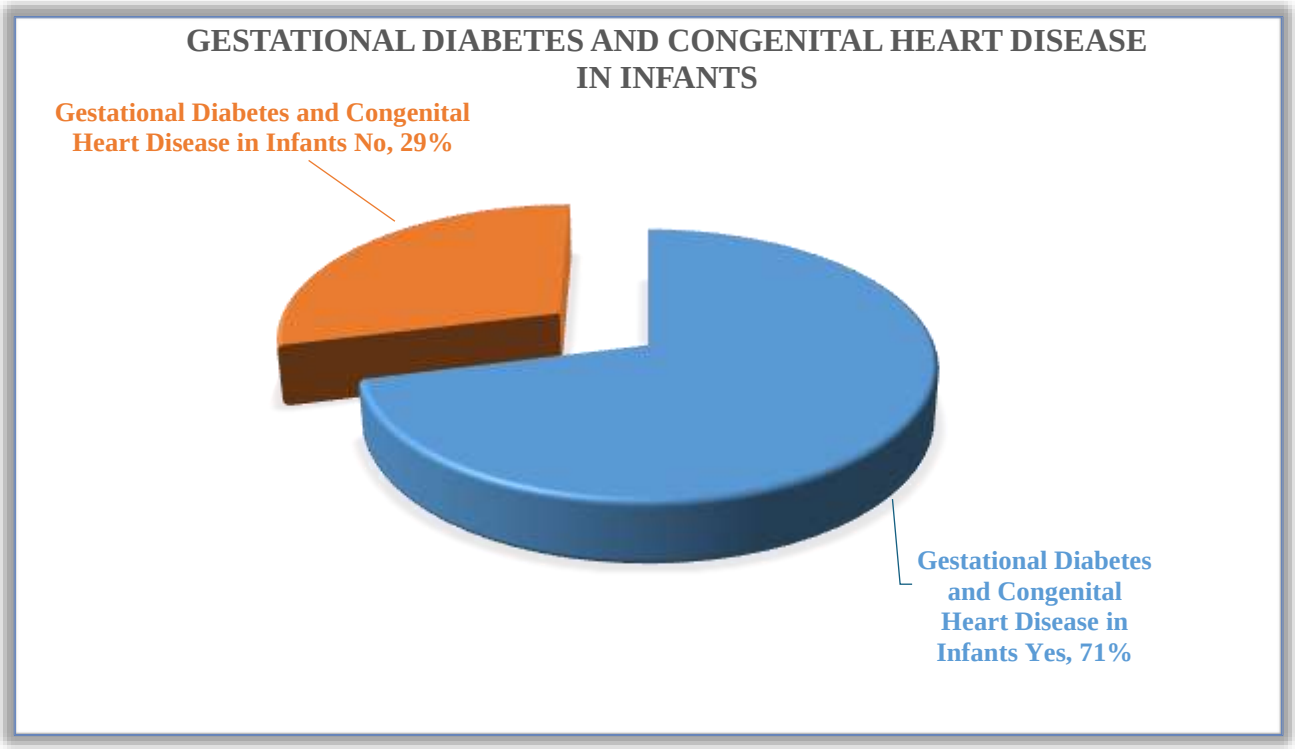

Figure 1: Prevalence of Congenital Heart Disease among infants born to mothers presented with Gestational diabetes mellitus.

Regarding the prevalence of congenital heart diseases in newborns of diabetic mothers presented in tertiary care hospitals of Pakistan. The results indicated that out of 100 newborns, 71 had some form of CHD, suggesting a high prevalence of 71%. The most common types of CHD identified were Patent Ductus Arteriosus (PDA) and Ventricular Septal Defect (VSD). PDA was the most frequently observed, affecting 25 newborns, accounting for 35.21% of the cases. This defect is characterized by the persistence of the ductus arteriosus, a vessel that normally closes after birth. VSD, involving an opening in the ventricular septum, was found in 23 newborns, making up 32.39% of the cases, as shown in Table 2.

Table 2: Types of Congenital Heart Disease in Newborns

Congenital Heart Disease	Frequency (n=100)	Percent (%)
Ventricular Septal Defect (VSD)	23	32.39%
Atrial Septal Defect (ASD)	14	19.72%
Patent Ductus Arteriosus (PDA)	25	35.21%
Tetralogy of Fallot	0	0.00%
Transposition of Great Arteries	5	7.04%
Septal Hypertrophy	2	2.82%
Promoter	1	1.41%
Unspecified Defect (USD)	1	1.41%
Total	**71**	**100.00%**

Atrial Septal Defect (ASD) was the third most common CHD, present in 14 newborns, which is 19.72% of the sample. ASD involves a hole in the wall separating the heart's two upper chambers. Transposition of the Great Arteries, a severe condition where the main arteries are switched, was

observed in 5 newborns (7.04%). Less common CHDs included Septal Hypertrophy, seen in 2 newborns (2.82%), and rare defects such as Promoter? and Unspecified Defect (USD), each affecting one newborn (1.41%). This study did not observe tetralogy of Fallot, a complex condition involving four heart defects.

Table 3: Association of Congenital Heart Disease by Participants Characteristics

Mother's Age (Years)	Congenital Heart Disease	No Congenital Heart Disease	*P*-Value
24-28	5 (7.0%)	3 (10.3%)	0.768
29-32	33 (46.5%)	9 (31.0%)	0.060
33-39	33 (46.5%)	17 (58.6%)	0.021
Gestational age (Weeks)	Congenital Heart Disease	No Congenital Heart Disease	P-Value
28-32 Weeks	2(2.8%)	0(0%)	0.787
33-36 Weeks	11(15.5%)	4(13.8%)	0.053
37-40 Weeks	58(81.7%)	25(86.2%)	0.031
Gender	Congenital Heart Disease	No Congenital Heart Disease	P-Value
Male	44(62%)	15(51.7%)	0.671
Female	27(38%)	14(48.3%)	0.712
Birth weight	Congenital Heart Disease	No Congenital Heart Disease	P-Value
2.24-2.75	38(53.5%)	18(62.1%)	0.811
2.76-3.36	33(46.5%)	11(37.9%)	0.796

As illustrated in Table 3, the association between maternal age and the occurrence of congenital heart disease (CHD) in infants is within the context of a study on the impact of maternal diabetes on CHD prevalence and patterns. For mothers aged 24-28 years, 7.0% of the infants had CHD, compared to 10.3% without CHD. The p-value of 0.768 indicates that there is no significant association between maternal age in this group and the occurrence of CHD.
In the age group of 29-32 years, a higher percentage (46.5%) of infants had CHD compared to 31.0% of those without CHD. The p-value of 0.060 suggests a trend toward significance, indicating that maternal age in this range might be associated with a higher occurrence of CHD. However, the result is not statistically significant at the conventional threshold. However, for mothers aged 33-39 years, the occurrence of CHD in infants was again 46.5%, whereas 58.6% of infants without CHD fell into this age group. The p-value of 0.021 demonstrates a statistically significant association, suggesting that maternal age in this range is significantly associated with CHD in infants. Overall, the data suggests that maternal age, particularly in the range of 33-39 years, maybe an important factor in the prevalence of CHD in infants born to diabetic mothers. The significant p-value in this group indicates a noteworthy correlation that warrants further investigation and could have implications for prenatal care and monitoring strategies.

We further explored the association between gestational age and the occurrence of congenital heart disease (CHD) in infants. For mothers with gestational ages between 28-32 weeks, there is no significant association between gestational age in this range and the occurrence of CHD.
In the 33-36 weeks gestational age group, the p-value (0.053) indicates a trend towards significance, suggesting that gestational age in this range might be associated with a higher occurrence of CHD. However, it is not statistically significant at the conventional threshold.

For mothers with gestational ages between 37-40 weeks, the majority of infants (81.7%) with CHD were born in this gestational range, compared to 86.2% without CHD. The p-value (P<0.05) shows a statistically significant association, suggesting that infants born at term (37-40 weeks) to diabetic

mothers are more likely to have CHD compared to preterm infants. These findings highlight the importance of monitoring and managing maternal diabetes closely, especially as pregnancy approaches full term, to mitigate the risk of CHD in newborns. Surprisingly, gender and infant weight at birth did not reflect any significant association with the prevalence of CHD among infants, as highlighted in table 3.

Table 4: Maternal History of Drug consumption and disease during pregnancy

Variable	Gestational History of drug and disease	Total Mothers
Drug history during pregnancy	No H/O drug ingestion	61 (61%)
	Anti-pyrectics	15 (15%)
	Anti-emetics	14 (14%)
	Vitamin-A	5 (5%)
	Anti-epileptics	3 (3%)
	Hormone	2 (2%)
History of disease during pregnancy	No Disease	82 (82%)
	Diabetes Mellitus	8 (8%)
	Maternal Infection	7 (7%)
	Hypertension	3 (3%)

The findings from this table highlight the diverse range of drug use and diseases experienced by mothers during pregnancy. The high percentage of mothers with no drug history or disease suggests that the majority of the pregnancies were relatively uncomplicated in these aspects. However, the presence of diabetes mellitus in 8% of the mothers is particularly relevant to the study, as it directly relates to the research focus on the prevalence and patterns of congenital heart diseases in infants born to diabetic mothers. The data underscores the importance of monitoring and managing maternal health conditions and medication use during pregnancy to ensure better outcomes for both mothers and their infants, as illustrated in Table 4.

DISCUSSION

This study, titled "Impact of Maternal Diabetes on the Prevalence and Pattern of Congenital Heart Diseases in Infants," provides significant insights into the relationship between maternal diabetes and the incidence of congenital heart diseases (CHD) in newborns. The study population comprised 100 mothers with an average age of 32.58 years, indicating a relatively mature maternal age group. The gestational age of the pregnancies averaged 37.49 weeks, suggesting that most pregnancies reached full term. The gender distribution of the neonates showed a higher proportion of males (59%) compared to females (41%). Despite maternal diabetes, the birth weights of the neonates were within a normal range, with an average of 2.71 kg. This data establishes a baseline understanding of the study population, which is crucial for interpreting the primary outcomes related to CHD prevalence in infants of diabetic mothers.

A key finding of this study is the high prevalence of CHD in newborns of diabetic mothers, with 71% of the infants diagnosed with some form of CHD. This prevalence is notably higher compared to the general population, where the prevalence of CHD is estimated to be around 0.8% to 1.2%, according to various studies [14-17]. The most common types of CHD identified in this study were Patent Ductus Arteriosus (PDA) and Ventricular Septal Defect (VSD), affecting 35.21% and 32.39% of the cases, respectively. Previous studies have also identified these defects as common in infants of diabetic mothers, although the reported prevalence rates vary [13,18]. For instance, a study by Wren et al. (2003) reported a prevalence of PDA in 12.7% and VSD in 20.5% of CHD cases among infants of diabetic mothers. This discrepancy may be due to differences in study populations, diagnostic criteria, and healthcare settings.

Atrial Septal Defect (ASD) was our study's third most common CHD, present in 19.72% of the sample. In comparison, the prevalence of ASD in the general population is reported to be around 10% of all CHD cases. Transposition of the Great Arteries, a severe condition, was observed in 7.04% of our cases, higher than the general incidence rate of approximately 5% in CHD populations. Less

common CHDs in our study included Septal Hypertrophy (2.82%), and rare defects such as Promoter and Unspecified Defect (USD), each affecting 1.41% of the newborns. Interestingly, Tetralogy of Fallot, a complex condition involving four heart defects, was not observed in this study, contrasting with its general prevalence of about 10% among CHD cases [4,13,19].

The analysis of maternal age revealed important associations with the occurrence of CHD in infants. For mothers aged 24-28 years, there was no significant association with CHD occurrence, as indicated by a p-value of 0.768. However, there was a trend towards significance in the 29-32 years age group (p-value of 0.060), suggesting a possible association between maternal age and higher CHD occurrence. Notably, a statistically significant association was found for mothers aged 33-39 years (p-value of 0.021), indicating that maternal age in this range is a significant factor in the prevalence of CHD in infants. This finding highlights the importance of targeted prenatal care and monitoring for older pregnant women with diabetes. These findings align with previous research indicating that advanced maternal age is associated with an increased risk of congenital anomalies, including CHD [3,11,17,20].

The study also examined the association between gestational age and CHD occurrence. For gestational ages between 28-32 weeks, there was no significant association with CHD. In the 33-36 weeks group, there was a trend towards significance (p-value of 0.053), suggesting a possible association. However, the most significant finding was for the 37-40 weeks gestational age group, with a statistically significant association (p-value < 0.05). This indicates that infants born at term to diabetic mothers are more likely to have CHD compared to preterm infants. These results underscore the importance of closely monitoring maternal diabetes as pregnancy approaches full term to reduce the risk of CHD in newborns. This finding is consistent with previous studies that have shown an increased risk of CHD in full-term infants of diabetic mothers compared to preterm infants [6,21].

The study also considered maternal history of drug consumption and disease during pregnancy. A majority of the mothers (61%) reported no drug use during pregnancy. Among those who did, antipyretics and anti-emetics were the most commonly used drugs. The presence of diabetes mellitus in 8% of the mothers directly relates to the study's focus, emphasizing the need for effective management of maternal health conditions to ensure better outcomes for both mothers and infants. Additionally, maternal infections and hypertension, although less common, were also noted. The high percentage of mothers with no drug history or disease suggests that the majority of the pregnancies were relatively uncomplicated in these aspects. However, the presence of diabetes mellitus in 8% of the mothers is particularly relevant to the study, as it directly relates to the research focus on the prevalence and patterns of congenital heart diseases in infants born to diabetic mothers. The data underscores the importance of monitoring and managing maternal health conditions and medication use during pregnancy to ensure better outcomes for both mothers and their infants.

In conclusion, this study highlights the significant impact of maternal diabetes on the prevalence and patterns of CHD in infants. The findings suggest that maternal age, particularly in the range of 33-39 years, and gestational age at term are important factors associated with higher CHD prevalence. Effective management of maternal diabetes and close monitoring during pregnancy, especially as it approaches full term, are crucial in mitigating the risk of CHD in newborns. This research underscores the need for targeted prenatal care strategies to improve neonatal outcomes in diabetic pregnancies.

While this study provides valuable insights into the impact of maternal diabetes on the prevalence and pattern of congenital heart diseases (CHD) in infants, we acknowledge a few limitations: The study sample consisted of 100 mothers and their infants, while providing important data, may not be large enough to generalize the findings to the broader population. Future studies with larger sample sizes must validate these results and enhance their generalizability. The research was conducted in a single tertiary care hospital in Pakistan. Multi-center studies across different regions and countries would provide a more comprehensive understanding of the relationship between maternal diabetes and CHD. Secondly, the study relied on maternal self-reporting for drug use and disease history during pregnancy. This method can introduce recall bias, as participants might not accurately remember or report their medication usage and health conditions. More objective measures, such as medical records, could improve the accuracy of the data [9,13,21]. The study did not account for the

level of glycemic control in diabetic mothers, which is a critical factor influencing pregnancy outcomes. Detailed information on blood glucose levels and the management of diabetes during pregnancy could provide deeper insights into the relationship between maternal diabetes and CHD in infants. Although the study controlled for some variables, other confounding factors, such as genetic predispositions, lifestyle factors, and environmental influences, might not be accounted for. These factors could also impact the prevalence and types of CHD observed in infants. The cross-sectional nature of the study limits the ability to establish causality. Longitudinal studies tracking maternal health and infant outcomes over time would be more effective in understanding the causal relationships between maternal diabetes and CHD. Addressing these limitations could provide a more robust and comprehensive understanding of how maternal diabetes influences the prevalence and pattern of congenital heart diseases in infants. This would, in turn, inform better clinical practices and prenatal care strategies to mitigate the risks associated with maternal diabetes.

Conclusion:

Our findings reveal a high prevalence of CHD in infants born to diabetic mothers. The most common CHDs observed were Patent Ductus Arteriosus (PDA) and Ventricular Septal Defect (VSD). Maternal age and gestational age emerged as important factors associated with CHD prevalence, particularly in mothers aged 33-39 years and those delivering at term (37-40 weeks). Despite the presence of diabetes, the birth weights of the neonates were within normal ranges, suggesting effective diabetes management during pregnancy. These results underscore the need for early screening and intervention to improve neonatal outcomes.

Conflicts of Interest

The authors declare no conflict of interest.

Authorship:

ZS, AR: Wrote Research Project, Introduction, Method & Result Write-Up and Data Collection
MJ, SN: Contributed To Introduction Method and
Result and Discussion, Data Collection
MWA, ZN: Contributed to Introduction Method, Resultand Discussion
MU: Contributed to Data Collection, Revised Draft

Financial Disclosure

None

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