Original Article

Cardiac Defects in Neonates Born to Mothers with Gestational Diabetes Mellitus and their Association with Maternal Treatment Regime

Amna Siddique, Muhammad Umar Rasool, Riffat Naeem, Arooj Mirza, Salwa Naeem, Shahid Hamid

ABSTRACT

Objective: To determine the type of cardiac anomalies on echocardiography in neonates delivered to mothers diagnosed with gestational diabetes mellitus (GDM) and evaluate the association of neonatal cardiac defects with maternal treatment during pregnancy.

Methodology: This cross-sectional study was conducted at the Department of Pediatrics, Ittefaq Trust Hospital, Lahore from August 2024 to January 2025 after ethical approval. A total of 108 neonates delivered to mothers with gestational diabetes were included using non-probability consecutive sampling technique. After taking informed consent from parents, they were screened by using echocardiography and neonatal cardiac anomalies were noted, if present. All the neonates with cardiac anomalies were followed-up in outpatient department (OPD) for spontaneous closure of defect for 3 months. The data was analyzed by the Statistical Package for the Social Sciences (SPSS) version 25.

Results: The mean age of neonates at presentation was 2.00±0.72 days. Gestational diabetes was diagnosed in the second trimester in 72(66.7%) and the third trimester in 36(33.3%) mothers. Out of 108 females, 12(11.1%) were only on insulin, 76(70.4%) were prescribed metformin only, 16(14.8%) were taking combination of metformin with insulin and 4(3.7%) were on diet control. On echocardiography, patent ductus arteriosus (PDA) was detected in 56(70%) cases, ventricular septal defect (VSD) in 8(10%) neonates, septal hypertrophy with PDA in 8(10%) cases, VSD with PDA in 8(10%) cases while 28(25.9%) had normal cardiac functioning. At follow-up, spontaneous closure of defect occurred in 68(85%) neonates with congenital cardiac defects. On comparison, PDA was significantly more common in neonates of diabetic mothers on metformin ($p < 0.05$).

Conclusion: Neonates born to diabetic mothers had a high frequency of cardiac abnormalities (74%). The risk of cardiac anomalies was significantly high in neonates born to females with GDM who were treated with metformin alone.

Keywords: *Gestational diabetes. Echocardiography. Patent ductus arteriosus, Ventricular septal defect.*

INTRODUCTION

The World Health Organization defines gestational diabetes as the detection of blood glucose levels of more than 180 mg/dl at 2 hours post-prandial, after 20th week of gestation on oral glucose tolerance test (OGTT). Gestational diabetes affects around 14% of pregnancies worldwide. Its incidence varies depending on risk factors, screening and diagnosis methods. The prevalence of the disease is increasing in association with the growing rates of type 2 diabetes and obesity.[1,2] Consequently, the prevalence rate of GDM in Pakistani research ranged from 4.41% to 57.90%.[3]

During early pregnancy, sensitivity to insulin increases with higher uptake of glucose to cope up with the energy needs during pregnancy. During the second or third trimester, various hormones produced during pregnancy, for example, progesterone, placental growth hormone, lactogen, estrogen and cortisol cause resistance to insulin. This decreases the transport of glucose into the cells.[4] Developing novel diabetes treatments may depend on our ability to comprehend how placental signals improve beta cell (β-cell) secretion and insulin production.[5,6]

In GDM, β-cell dysfunction arises from reduced incretin hormones (glucose-dependent insulin tropic polypeptide, glucagon-like peptide-1), cytokine-induced insulin signaling disruption (via interleukin-6, tumor necrosis factor-α), and cellular stressors like endoplasmic reticulum stress, mitochondrial dysfunction, and decreased pancreatic duodenal homeobox-1 expression - leading to impaired insulin secretion and glucose uptake.[7] In addition to promoting hyperinsulinemia, reduced glucose uptake, glycogen synthesis, and a diminished ability of insulin to regulate hepatic gluconeogenesis, human placental growth hormone and pituitary growth hormone have diabetogenic actions.[8]

There are various predisposing factors of gestational diabetes such as increased age, obesity and family history or previous history of diabetes. Gestational diabetes is linked with poor maternal and perinatal outcomes such as cesarean sections, polyhydramnios, preeclampsia, premature rupture of membrane, preterm delivery, stillbirth, macrosomia and neonatal hyperbilirubinemia.[9]

Sharif Medical & Dental College, Sharif Medical City. Sharif Medical City Road, Off Raiwind Road, Jati Umra, Lahore 54000, Pakistan.

Correspondence: Dr. Muhammad Umar Rasool
Postgraduate Resident Department of Pediatrics
Ittefaq Hospital (Trust), Lahore
E-mail: m_umar_rasool@yahoo.com

Received: April 21, 2025; Accepted: May 24, 2025

Hyperglycemia is also a known contributing factor to the development of congenital defects, or structural or functional anomalies that occur during intrauterine life. This can be detected throughout pregnancy or at any point during 6 weeks of delivery.[10,11] Poor maternal glycemic management is linked to a high prevalence of congenital abnormalities. This also demonstrated a nearly universal lack of preconception care.[2]

Through literature, it has been observed that the risk of cardiac anomalies is high among neonates delivered to diabetic mothers and needs careful screening and management. However, in routine, neonates are not screened at the time of delivery and develop symptoms later, which leads to severe hazardous consequences. This study was planned to determine the frequency and type of cardiac anomalies on echocardiography in neonates delivered to mothers diagnosed with gestational diabetes mellitus and evaluate their association with treatment modalities among mothers. On the basis of findings, the early screening of neonates for cardiac anomalies, especially among diabetic mothers and those who were taking hypoglycemic medications can be recommended. The local data regarding association of cardiac defects with treatment modalities of mothers with GDM was sparse, so our results will also add knowledge in this regard as well.

METHODOLOGY

This cross-sectional study was conducted at the Department of Pediatrics, Ittefaq Trust Hospital, Lahore from August 2024 to January 2025 after approval from the institutional ethical review board (Letter No. IHT/Adm/30, 18-04-2024). A sample size of 108 neonates was estimated by keeping 95% confidence level, 7% absolute precision and the percentage of abnormal fetal echocardiographies in neonates delivered to mothers with gestational diabetes mellitus as 15.8%.[3] The parents gave written informed consent for inclusion in the study. A total of 108 neonates were enrolled by non-probability consecutive sampling technique from delivery wards and neonatal intensive care unit (NICU). The inclusion criteria were neonates of age 3-28 days of life, who were delivered at term (>37 weeks of gestation), and whose mothers had confirmed gestational diabetes. Gestational diabetes mellitus was confirmed after 20th weeks of gestation using 75-gram OGTT. According to the International Association of Diabetes and Pregnancy Study Groups, diagnosis of GDM was based on 1-hour postprandial glucose levels $\geq$153mg/dl, 2-hours postprandial glucose levels $\geq$180 mg/dL or fasting plasma glucose $\geq$92 mg/dL.[2] Neonates delivered to mothers with chronic diabetes, mothers with heart disease, family history of congenital heart disease, hypertensive disorder, and history of exposure to cardiac teratogens were excluded from the study. Demographic data like age of neonate at presentation, gravidity, mode of delivery, weight of neonate at birth, any other non-cardiac problem, and record of mother on anti-glycemic treatment regimen were noted on the proforma. At the time of presentation, after initial clinical examination, all the neonates were screened by using echocardiography and neonatal cardiac anomalies were noted, if present. All the neonates with cardiac anomalies were followed-up in outpatient department (OPD) for spontaneous closure of defect for 3 months.

STATISTICAL ANALYSIS

The data was analyzed by the Statistical Package for the Social Sciences (SPSS) version 25. Mean±SD were used for numerical data and categorical data was reported as frequency and percentage. Fisher's exact test was applied to compare cardiac anomalies and various treatment modalities in mothers. A p-value $\leq$0.05 was taken as significant.

RESULTS

In this study, we enrolled a total 108 neonates delivered to mothers with gestational diabetes for echocardiographic assessment. The mean weight of neonates at presentation was 3.00±0.59 kg. Table 1 shows the clinical data of the study participants.

On 1st echocardiography (done after 72 hours), 80(74.1%) neonates had cardiac anomalies while 28(25.9%) had normal cardiac functioning. Out of 80 neonates diagnosed with cardiac anomalies, patent ductus arteriosus (PDA) was detected in 56(70%), ventricular septal defect (VSD) in 8(10%), septal hypertrophy with PDA in 8(10%) and VSD with PDA in 8(10%) cases (Figure 1).

On comparison, PDA (63.2%) was more common in neonates of diabetic females taking metformin as compared to other congenital cardiac defects (p=0.001). Among neonates born to diabetic mothers on insulin, PDA and VSD with PDA were observed in 33.3% of the neonates each. At follow-up, defect was spontaneously closed in 68(85%) neonates. Spontaneous closure of defect (88.2%) was also high in neonates of diabetic mothers on metformin (p=0.001) (Table 2).

Table 1: Clinical Data of Mothers enrolled in the Study (n=108)

Characteristics		Frequency & Percentage
Gravidity	**Primigravida**	24(22.2%)
	Multigravida (Gravida 2-4)	76(70.4%)
	Grand Multigravida (Gravida ≥5)	8(7.4%)
Mode of Delivery	**Vaginal Delivery**	8(7.4%)
	Cesarean Section	100(92.6%)
Time of GDM Diagnosis	**2nd Trimester**	72(66.7%)
	3rd Trimester	36(33.3%)
Treatment Modalities of Diabetic Mothers	**Insulin only**	12(11.1%)
	Metformin only	76(70.4%)
	Insulin with Metformin	16(14.8%)
	Diet Control	4(3.7%)

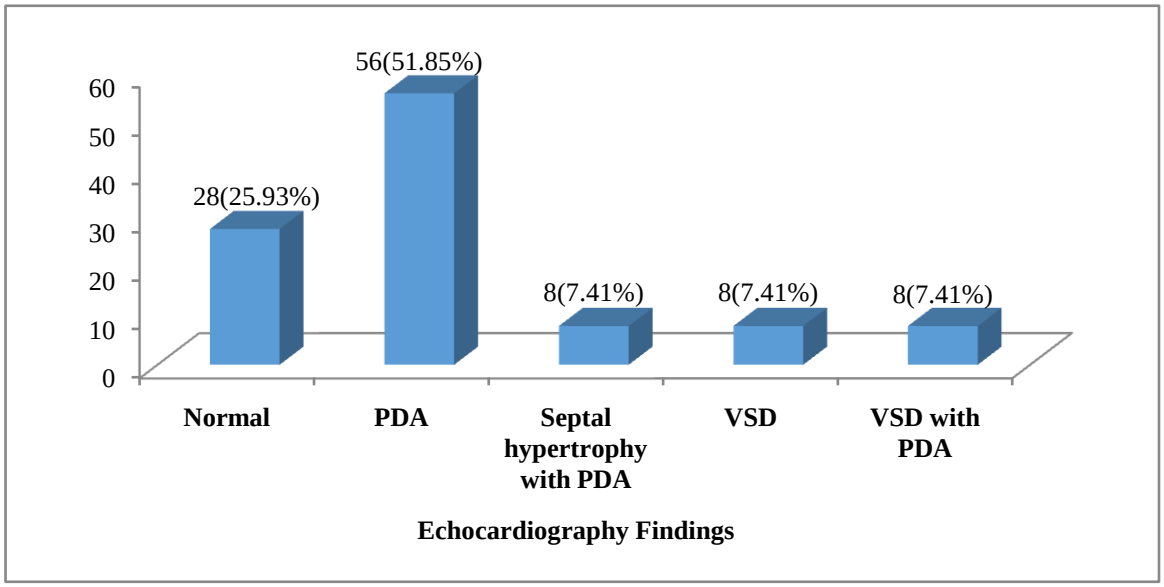

Figure 1: Distribution of Echocardiography Findings of Neonates

Table 2: Association of Neonatal Echocardiography Findings and Treatment Modalities of Diabetic Mothers

Echocardiography Findings	Treatment Modalities				p-value
	Insulin (n=12)	Metformin (n=76)	Combination of Insulin with Metformin (n=16)	Diet Control (n=4)	
Normal	4(33.3%)	8(10.5%)	12(75.0%)	4(100%)	0.001*
PDA	4(33.3%)	48(63.2%)	4(25.0%)	0(0%)	
Septal Hypertrophy with PDA	0(0%)	8(10.5%)	0(0%)	0(0%)	
VSD	0(0%)	8(10.5%)	0(0%)	0(0%)	
VSD with PDA	4(33.3%)	4(5.3%)	0(0%)	0(0%)	

*****Significant p-value*

DISCUSSION

Pregnancy-related hyperglycemia is a hallmark of gestational diabetes. Gestational and pre-gestational diabetes have a negative impact on pregnancy and the postpartum period. The fetus develops hyperglycemia and hyperinsulinemia due to maternal hyperglycemia. This promotes anabolism, which in turn promotes the growth of connective tissue, muscle, and fat. When hyperglycemia and hyperinsulinemia coexist, fetal fat and protein accumulation increases, leading to macrosomia.[12] Paauw et al. also reported that hyperinsulinism had hyperglycemia, which can result leading to development of cardiac hypertrophy in neonates.[13] A

clinical review on diabetes during pregnancy found that both pre-gestational and gestational diabetes were associated with increased risk of congenital defects and cardiac anomalies were the most commonly observed defects.[14] Bayoumy et al. used tissue Doppler imaging to study cardiac function and found that fetal cardiac function at 30 weeks of gestation was compromised in diabetic pregnant females as compared to normal pregnant females.[15]

In this study, we observed that 80(74.1%) neonates had congenital cardiac defects. Patent ductus arteriosus was the most common congenital cardiac anomaly (70%), followed by VSD in 10% neonates, septal hypertrophy with PDA in 10% and VSD with PDA in 10% of the cases. Afridi et al. performed comparable research in Karachi and found that 67(45.57%) of the 147 newborns of mothers with GDM had a congenital cardiac abnormality. Unlike our study, patent foramen ovale (PFO) was the most prevalent cardiac abnormality (23%), followed by PDA (14.9%), VSD (5.4%), tetralogy of Fallot (TOF) (2.7%), hypertrophic cardiomyopathy (HCM) (2.7%), atrial septal defect (ASD) (2.7%), and transposition of the great arteries (TGA) (1.36%).[16]

A study done by Arjmandnia et al. in Iran also reported that 49% neonates born to diabetic mothers had congenital cardiac defects. Contrary to our results, TOF (69.5%) was most prevalent in neonates followed by PDA (41%).[17] Similar to our results, Sadiq et al. from Peshawar found that on echocardiographic assessment of neonates, PDA (32%) was the most common congenital heart defect, followed by PFO (29.33%), HCM (14%), ASD (10%), VSD (6.66%), TGA (4.66%) and TOF (3.33%).[18] According to a study conducted in Faisalabad, Pakistan, 47.3% of the children born to a diabetic mother had abnormal echocardiogram results. The most common abnormalities were PDA (32.6%), VSD (25.3%), ASD (14.5%), TGA (7.9%), and hypertrophic obstructive cardiomyopathy (5.7%).[19] Various approaches to control diabetes, different sampling populations and methods for detecting cardiac abnormalities might all contribute to the variation in regional, national and international frequencies.

Our statistically significant results showed that all congenital anomalies were more common among neonates of diabetic females taking metformin as hypoglycemic treatment. The most prevalent cardiac defect in neonates of GDM mothers on metformin was PDA (63.2%), followed by septal hypertrophy with PDA (10.5%), VSD (10.5%) and VSD with PDA (5.3%). This difference might be due to variation in glucose levels in mothers taking different regimes. Mothers taking insulin might have better glycemic control resulting in decreased frequency of anomalies in these patients. Similarly, a cohort study reported that children born to mothers with pre-existing diabetes who were exposed to second-line anti-diabetic medications during pregnancy had a higher incidence of major congenital anomalies or cardiac malformations compared to those exposed to insulin.[20] A study done in Saudi Arabia also reported that PDA (71.5%), followed by hypertrophic cardiomyopathy (36.5%) and VSD (11%) were the most common congenital cardiac anomalies among infants of diabetic mothers. Out of 293 diabetic mothers included in their study, 43.7% were on diet control, 33.1% were on insulin, 16.4% were on medications, and 6.8% had a combined treatment regimen. However, no significant association ($p=0.313$) was found between different treatment modalities and the frequency of congenital cardiac defects.[21]

During 3 months follow-up, we also observed that spontaneous closure of defect was high in neonates of mothers treated with metformin (78.9%), compared to those treated with insulin (33.3%), or with combination treatment (25%) ($p <0.05$). Patent ductus arteriosus is a congenital cardiac condition in which the ductus arteriosus of a newborn does not shut after birth. Usually, the PDA closes 48 hours after delivery.[22] In literature, the rate of spontaneous closure of PDA was about 66% within the first year of life that increased to 80% during the first five years of life.[23]

Another study reported that out of all pediatric cardiomyopathies, 25-40% of neonates had cardiac hypertrophy. The ventricular function after delivery had been associated with elevated maternal lipid and glucose indices. These results pointed to a possible link between future cardiovascular health and in-utero cardiac development.[24]

CONCLUSION

Neonates born to diabetic mothers had a high frequency of cardiac abnormalities (74%). The risk of cardiac anomalies was significantly high in neonates born to females with GDM who were treated with metformin alone.

LIMITATIONS & RECOMMENDATIONS

The study had a few limitations including single-centered and cross-sectional study design. The data on glycemic control of mothers during pregnancy is lacking. The risk of cardiac defects in mothers taking metformin was high which needs to be investigated in relation to glucose levels and

glycemic control of mothers. We recommend screening of the neonates of diabetic mothers for congenital heart disease. Furthermore, it is also recommended to conduct a multi-centered trial on different methods for the prevention of congenital heart disease in newborn and plan strategies for early cure.

Conflict of interest: None.
Source of funding: None.

Authors' Contributions:
A.S: Topic selection, study design, and methodology.
M.U.R: Data collection and entry.
R.N: Literature review, referencing, and quality assurance.
A.M: Statistical analysis and result interpretation.
S.N: Plagiarism check and clearance.
S.H: Proofreading and final approval.

REFERENCES

1. Sweeting A, Hannah W, Backman H, Catalano P, Feghali M, Herman WH, et al. Epidemiology and management of gestational diabetes. Lancet. 2024; 404(10448):175-92. doi:10.1016/S0140-6736(24)00825-0.

2. Candido R, Toffoli B, Manfredi G, Turisani A, Delfauro V, Petrucco A, et al. Retrospective cohort study on treatment outcomes of early vs late onset gestational diabetes mellitus. Acta Diabetol. 2024. doi:10.1007/s00592-024-02405-y.

3. Adnan M, Aasim M. Prevalence of gestational diabetes mellitus in Pakistan: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2024; 24(1):108. doi:10.1186/s12884-024-06290-9.

4. James-Allan LB, Rosario FJ, Madi L, Barner K, Nair S, Lai A, et al. A novel technique using chronic infusion of small extracellular vesicles from gestational diabetes mellitus causes glucose intolerance in pregnant mice. Clin Sci (Lond). 2022; 136(21):1535-49. doi:10.1042/CS20220484.

5. Szlapinski SK, Hill DJ. Metabolic adaptations to pregnancy in healthy and gestational diabetic pregnancies: the pancreas - placenta axis. Curr Vasc Pharmacol. 2021; 19(2):141-53. doi:10.2174/1570161118666200320111209.

6. Nair S, Ormazabal V, Lappas M, McIntyre HD, Salomon C. Extracellular vesicles and their potential role inducing changes in maternal insulin sensitivity during gestational diabetes mellitus. Am J Reprod Immunol. 2021; 85(2):e13361. doi:10.1111/aji.13361.

7. Seedat F, Kandzija N, Ellis MJ, Jiang S, Sarbalina A, Bancroft J, et al. Placental small extracellular vesicles from normal pregnancy and gestational diabetes increase insulin gene transcription and content in β cells. Clin Sci (Lond). 2024; 138(22):1481-502. doi:10.1042/CS20241782.

8. Mittal R, Prasad K, Lemos JRN, Arevalo G, Hirani K. Unveiling gestational diabetes: an overview of pathophysiology and management. Int J Mol Sci. 2025; 26(5):2320. doi:10.3390/ijms26052320.

9. Kouhkan A, Najafi L, Malek M, Baradaran HR, Hosseini R, Khajavi A, et al. Gestational diabetes mellitus: major risk factors and pregnancy-related outcomes: a cohort study. Int J Reprod Biomed. 2021; 19(9):827-36. doi:10.18502/ijrm.v19i9.9715.

10. Shamsad A, Kushwah AS, Singh R, Banerjee M. Pharmaco-epi-genetic and patho-physiology of gestational diabetes mellitus (GDM): an overview. Health Sci Rev. 2023; 7:100086. doi:10.1016/j.hsr.2023.100086.

11. Lee KS, Choi YJ, Cho J, Lee H, Lee H, Park SJ, et al. Environmental and genetic risk factors of congenital anomalies: an umbrella review of systematic reviews and meta-analyses. J Korean Med Sci. 2021; 36(28):e183. doi:10.3346/jkms.2021.36.e183.

12. Loeken MR. Mechanisms of congenital malformations in pregnancies with pre-existing diabetes. Curr Diab Rep. 2020; 20(10):54. doi:10.1007/s11892-020-01338-4.

13. Paauw ND, Stegeman R, de Vroede MAMJ, Termote JUM, Freund MW, Breur JMPJ. Neonatal cardiac hypertrophy: the role of hyperinsulinism-a review of literature. Eur J Pediatr. 2020; 179(1):39-50. doi:10.1007/s00431-019-03521-6.

14. Ornoy A, Becker M, Weinstein-Fudim L, Ergaz Z. Diabetes during pregnancy: a maternal disease complicating the course of pregnancy with long-term deleterious effects on the offspring. A clinical review. Int J Mol Sci. 2021; 22(6):2965. doi:10.3390/ijms22062965.

15. Bayoumy S, Habib M, Abdelmageed R. Impact of maternal diabetes and obesity on fetal cardiac functions. Egypt Heart J. 2020; 72(1):46. doi:10.1186/s43044-020-00077-x.

16. Afridi SB, Khan M, Shaikh M, Shaikh AS. Frequency and pattern of congenital heart defects in infant of diabetic mother at tertiary care hospital. LNJPC. 2023; 5(2):82-6. doi:10.37184/lnjpc.2707-3521.5.17.

17. Arjmandnia MH, Yousefi M, Rezvan S, Vahedian M, Noori E, Mohammadi A, et al. Evaluation of congenital heart diseases in neonates with diabetic mothers who referred to teaching hospitals in Qom, Iran. J Vessel Circ. 2020; 1(1): 33-6. doi:10.29252/jvesselcirc.1.1.33.

18. Sadiq F, Shah SMA, Khan A, Nisar S, Iqbal M, Khan A. Pattern of congenital heart disease in 0 to 28 days infants of diabetic mothers. KJMS. 2024; 17(2):67-70. doi:10.70520/kjms.v17i2.483.

19. Shamaoon M, Zunaira, Ahsan M, Maqbool T, Aslam R, Yaseen A. Congenital heart defects in neonates born to diabetic mother (IDM): a single center experience. Professional Med J. 2020; 27(5):950-6. doi:10.29309/TPMJ/2020.27.05.3924.

20. Andrade C. Exposure of pregnancy to pregestational diabetes, gestational diabetes, and antidiabetic medications with especial focus on major congenital and cardiac malformations in offspring. J Clin Psychiatry. 2024; 85(1):24f15318. doi:10.4088/JCP.24f15318.

21. Al Ghadeer HA, Alherz AH, Albattat FS, Alkhamis MA, Alamer MH, Almulaifi LF, et al. Pattern and frequency of congenital heart defects among infants of diabetic mothers. Cureus. 2024; 16(12):e76184. doi:10.7759/cureus.76184.

22. Backes CH, Hill KD, Shelton EL, Slaughter JL, Lewis TR, Weisz DE, et al. Patent ductus arteriosus: a contemporary perspective for the pediatric and adult cardiac care provider. J Am Heart Assoc. 2022; 11(17):e025784. doi:10.1161/JAHA.122.025784.

23. Nielsen MR, Aldenryd AE, Hagstrom S, Pedersen LM, Brix N. The chance of spontaneous patent ductus arteriosus closure in preterm infants born before 32 weeks of gestation is high and continues to increase until 5 years of follow-up. Acta Paediatr. 2022; 111(12):2322-2330. doi:10.1111/apa.16541.

24. Codazzi AC, Ippolito R, Novara C, Tondina E, Cerbo RM, Tzialla C. Hypertrophic cardiomyopathy in infant newborns of diabetic mother: a heterogeneous condition, the importance of anamnesis, physical examination and follow-up. Ital J Pediatr. 2021; 47(1):197. doi:10.1186/s13052-021-01145-x.