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CORD BLOOD LIPID PROFILE ABNORMALITIES IN INFANTS OF DIABETIC MOTHERS: A PROSPECTIVE CROSS-SECTIONAL STUDY ON EARLY PREDICTORS OF CARDIOVASCULAR DISEASE

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Abstract

Background: Gestational Diabetes Mellitus (GDM) affects approximately 7% of pregnancies globally, altering neonatal lipid profiles and indicating potential cardiovascular diseases (CVD) risks in infants(1,2). This study investigates the correlation between maternal GDM and cord blood lipid abnormalities as early predictors of CVD, based on the Barker hypothesis and emerging pediatric health concerns(3,4). **Methods:** This prospective cross-sectional study at Saveetha Medical College & Research Centre (September 2020 to September 2022) included 101 infants born to diabetic mothers. Cord blood samples were analyzed for lipid profiles, utilizing SPSS for statistical analysis. The research followed established protocols for sample collection and analysis, ensuring rigorous data integrity(5-17). **Results:** Significant findings reveal elevated triglyceride levels in SGA neonates (189 mg/dl), a trend towards lower HDL levels in LGA neonates, and significant variations in the cholesterol/HDL ratio and total cholesterol levels across neonatal groups, underscoring the impact of maternal glycemic control (HbA1c levels)(18,19). Approximately 93% of AGA neonates had mothers with HbA1c <6%, contrasting with LGA neonates, 50% of whom had mothers with HbA1c >8%, highlighting the critical role of maternal glycemic management(21,22). **Conclusion:** The study's findings emphasize the significant correlation between maternal GDM and neonatal lipid profile abnormalities, advocating for early intervention and comprehensive prenatal care to mitigate future health risks. This underscores the critical need for targeted care strategies and supports the pivotal role of maternal health management in pediatric and preventive medicine(3,4).

Keywords: Cord Blood Lipid Profile, Gestational Diabetes Mellitus (GDM), Cardiovascular Disease Predictors, Gestational Age.

INTRODUCTION

Gestational Diabetes Mellitus (GDM) is recognized as glucose intolerance initiated or first identified during pregnancy, prevalent in approximately 7% of pregnancies worldwide. The frequency of GDM varies between 1% and 14%, with projections suggesting an increase parallel to the rising rates of obesity(1,2). This condition emerges from the failure of pancreatic β-cell function to compensate for the heightened insulin requirements of pregnancy, leading to increased risks for both mother and offspring. These risks include cesarean delivery, macrosomia, and neonatal complications such as hypoglycemia. Moreover, GDM escalates the mother's risk of developing type 2 diabetes mellitus (T2DM) later in life and predisposes the child to early-onset obesity and T2DM (23,24).

The pathophysiology of GDM is primarily linked to an imbalance between insulin secretion and demand, exacerbated by the insulin resistance inherent to pregnancy. Normally, pregnancy reduces insulin sensitivity by about 50% to ensure an adequate glucose supply for the fetus, necessitating a 200%-250% increase in maternal insulin

production. However, this compensatory mechanism often fails in GDM, resulting in hyperglycemia(25). This resistance to insulin is believed to be influenced by placental hormones, obesity, and various pregnancy-related factors, though the exact mechanisms remain partially understood(25).

Adipose tissue metabolism sees significant alterations during pregnancy, which are further intensified in GDM cases. While the initial increase in adipose tissue mass supports the expansion of maternal and fetal structures by enhancing lipid synthesis, GDM-associated insulin action imbalance disrupts lipid metabolism, leading to elevated circulating lipid levels(26,27,28). These metabolic shifts carry important ramifications for fetal development, influencing nutrient transfer and predisposing the offspring to metabolic conditions in later life.

The Barker hypothesis posits that the intrauterine environment, especially in the context of GDM, plays a crucial role in fetal metabolic programming, impacting the likelihood of chronic diseases in adulthood. The lipid profiles in early life, as a result, are indicative of future cardiovascular diseases (CVD) and metabolic disorders, highlighting the critical need for effective GDM management(3,4).

Given the emerging evidence on the impact of maternal diabetes on infant cord blood lipid profiles, this area of research is of paramount importance in pediatric health, especially for predicting CVD risks in infants. Cord blood lipid levels have been recognized as significantly influenced by maternal diabetes, suggesting an intricate interplay that affects infant health outcomes. Studies have expanded our understanding of the relationship between maternal dietary intakes, lipid levels, and subsequent cardiovascular risk in the early stages of life(5-17). This body of research underlines the necessity of early monitoring and intervention strategies to lower CVD risk from infancy, advocating for comprehensive prenatal and postnatal care to safeguard long-term health.

Aim and Objectives:

1. To assess the correlation between cord blood lipid profile and the incidence of cardiovascular disease predictors in infants of diabetic mothers.
2. To evaluate the abnormalities in the cord blood lipid profile among infants of diabetic mothers across different neonatal growth categories.

MATERIALS AND METHODS

Study Population

A total of 101 infants born to diabetic mothers were recruited for this study, spanning from September 2020 to September 2022. The study was approved by the Institutional Review Board committee prior to its initiation.(SMC/IEC/2020/09/028)

Study Design

The research was designed as a prospective cross-sectional study and was conducted at Saveetha Medical College & Research Centre.

Sample Size

The sample size was calculated using the formula:

$$N=z^2pq/e^2$$

where N represents the sample size, z is the confidence level set at 95%, pq indicates the variance in the population, and e denotes the allowable error.

Inclusion and Exclusion Criteria

Infants born to diabetic mothers were eligible for inclusion. Exclusion criteria encompassed newborns who suffered hypoxic insults or presented with congenital anomalies.

METHODOLOGY

Gestational age was determined utilizing the Ballard system. Based on gestational age and birth weight, infants were categorized into three groups: appropriate for gestational age (AGA), small for gestational age (SGA), and large for gestational age (LGA). AGA infants' weights were within the 10th to 90th percentile, SGA infants' weights were below the 10th percentile, and LGA infants' weights exceeded the 90th percentile, as per Fenton growth curves. Informed consent was obtained from the caregivers of each participant.

Sample Collection

Cord blood samples were collected immediately after cord clamping following delivery and before the delivery of the placenta. These samples were analyzed for lipid profiles, including total cholesterol (TC), triglycerides (TGL), high-density lipoproteins (HDL), low-density lipoproteins (LDL), and very low-density lipoproteins (VLDL).

Statistical Analysis

The study employed standard statistical methods to examine the relationship between cord blood lipid profiles and the incidence of cardiovascular disease predictors in infants born to diabetic mothers. Data were organized using MS Excel 2013 and analyzed with SPSS software (Version 20.0 for Windows, IBM Co.).

The Kolmogorov-Smirnov test assessed data distribution normality, while Levene's test evaluated the homogeneity of variances across groups. The Kruskal-Wallis H test, followed by Post-Hoc Dunn's test with a Bonferroni correction for pairwise comparisons, was used for non-normally distributed variables or unequal variances, reporting findings in terms of median, interquartile range (IQR), mean rank, and statistical significance.

Associations between categorical variables were explored using the chi-square test, with a p-value of less than 0.05 considered statistically significant for identifying meaningful differences or associations within the study's findings.

RESULTS

Lipid Profile Variations Across Gestational Age Groups Our study centered on analyzing triglyceride levels, high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), the cholesterol/high-density lipoprotein ratio (Chol/HDL ratio), and total cholesterol among neonates categorized by their gestational age.

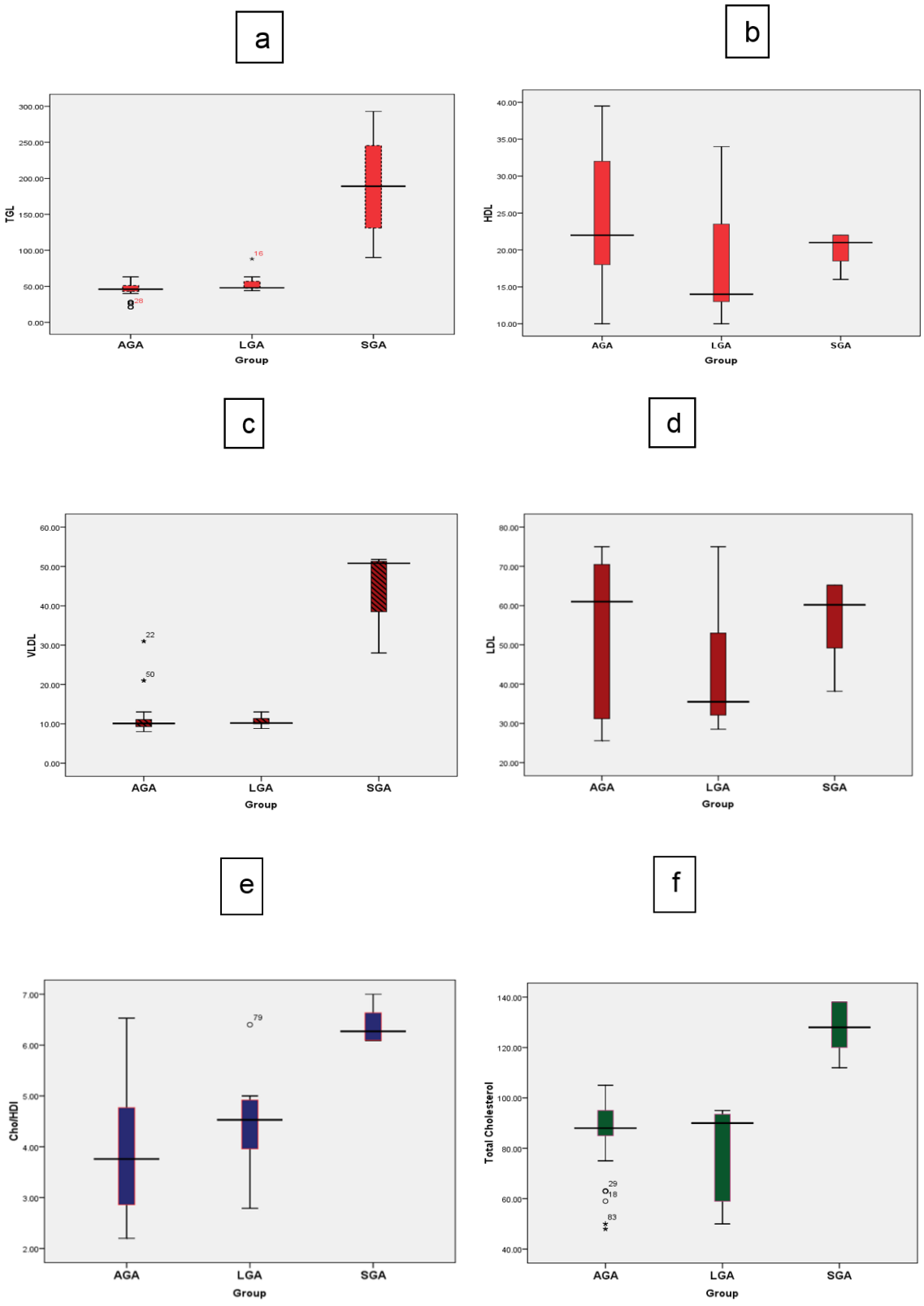

Figure 1:Comparison of Lipid Profile among different Gestational Age Group by Kruskal- Wallis Test

Figure 1a-TGL-triglyceride, Figure 1b HDL- High Density Lipoprotein, Figure 1c LDL- Low Density Lipoprotein , Figure 1d VLDL- Very Low Density Lipoprotein , Figure 1e Chol/HDL ratio -Cholesterol / High Density Lipoprotein Ratio, Figure 1f Cholesterol

- **Triglyceride Levels:** Elevated triglyceride levels were significantly higher in the SGA neonates, approximately 189 mg/dl, compared with the LGA group, marking a statistically notable increase ($\chi2(2) = 31.6$, $p < .001$) (Fig.1a).
- **High-Density Lipoprotein (HDL):** No statistically significant differences in HDL levels across gestational age groups were observed, although a trend towards lower HDL levels in the LGA group (Fig.1b)was noted ($\chi2(2) = 4.64$, $p = .098$).
- **Low-Density Lipoprotein (LDL) and Very Low-Density Lipoprotein (VLDL):** Significant elevation in VLDL levels was observed in the SGA group (Fig.1c)compared to others ($\chi2(2) = 28.2$, $p < .001$), while differences in LDL levels did not reach statistical significance, indicating a complex relationship with gestational age.
- **Cholesterol/High-Density Lipoprotein Ratio (Chol/HDL Ratio) and Total Cholesterol:** The Chol/HDL ratio was significantly higher in both LGA and SGA groups compared to AGA neonates ($\chi2(2) = 21.7$, $p < .001$), suggesting a potential risk factor for future cardiovascular conditions. A marked elevation in total cholesterol was noted in the SGA group (Fig.1f), indicating possible early markers of metabolic syndrome ($\chi2(2) = 29.51$, $p < .001$).

These findings underscore distinct variations in lipid profiles across gestational age groups, pointing towards potential long-term health implications.

Glycemic Control and Gestational Diabetes Impact

- **HbA1c Levels and Gestational Age Groups:** The study highlighted a significant impact of maternal glycemic control on neonatal outcomes. Notably, mothers with HbA1c levels less than 6 had a majority of children in the AGA group (Fig. 2), while elevated HbA1c levels were associated with shifts towards SGA or LGA groups, indicating the critical role of maternal glycemic control.
- **Types of Diabetes Mellitus During Pregnancy:** The presence of gestational diabetes mellitus (GDM) significantly influenced neonatal size at birth, with a noticeable distribution of neonates in the SGA and LGA categories among mothers diagnosed with GDM.

Maternal Health Complications

Table 1: Comparison of Associated Complication between the Different Gestational Age Group by using Chi –square Test

Parameter	AGA	LGA	SGA	Total	X2	p - value
Nil	68 (81.9)	05 (07.1)	01 (63.6)	80 (79.2)	**15.18**	**0.255 (ns)**
Anemia	07 (08.4)	01 (14.3)	02 (18.2)	10 (09.9)		
Anemia /PIH	03 (03.6)	0	0	03 (03)		
Anemia/RHD	0	0	01 (09.1)	01 (01)		
IHCP	01 (01.2)	0	0	01 (01		
PIH	03 (03.6)	01 (14.3)	01 (09.1)	05 (05)		
Seizure disorder	01 (01.2)	0	0	01 (01)		
Total	83 (100)	07 (100)	11 (100)	101 (100)		

A comprehensive analysis revealed variations in the prevalence of maternal complications across gestational age groups. Notably, 82% of the AGA group experienced no complications, contrasting sharply with only 7% in the LGA category.

This marked distinction underscores the profound impact of gestational age on pregnancy outcomes(Table 1).

Anemia Prevalence: Anemia's occurrence varied significantly with gestational age, being notably higher in the SGA and LGA groups compared to the AGA category.

Anemia and Rheumatic Heart Disease: Anemia coupled with rheumatic heart disease was exclusively observed in the SGA group, indicating specific maternal health challenges affecting this category.

Pre-eclampsia (PIH): A higher incidence of PIH in the LGA group suggests a correlation between increased gestational age and the risk of this condition.

These findings elucidate the complex relationship between maternal health issues and neonatal gestational categories. The statistically significant data points to the necessity of customized prenatal care aimed at mitigating complications in mothers of SGA and LGA neonates. Special attention to anemia, rheumatic heart disease, and pre-eclampsia management is crucial for enhancing pregnancy outcomes and neonatal health.

DISCUSSION

Our study provides a nuanced view into the complex relationship between maternal gestational diabetes mellitus (GDM) and its subsequent impact on neonatal health, focusing on cord blood lipid profiles. This aligns with the burgeoning pediatric health field that emphasizes the importance of early-life predictors for cardiovascular diseases (CVD), especially in the context of maternal diabetes (3,4).

One significant observation was the elevation of triglyceride levels in the SGA group, averaging at 189 mg/dl. This stark increase, statistically significant compared to the LGA group ($p=0.001$), echoes findings from Aletayeb et al., highlighting elevated serum triglycerides and cholesterol in low birth weight infants, suggesting these infants may have a predisposition to cardiovascular issues later(18). The significant lipid accumulation in SGA neonates underscores the need for early monitoring and intervention to mitigate future cardiovascular risks.

Additionally, our analysis highlighted a trend towards lower HDL levels in the LGA group. This finding resonates with previous literature that establishes a negative correlation between end-of-pregnancy HDL-C concentrations and birth weight, marking lower HDL-C concentrations as a predictive marker for large-for-gestational age infants(19). This corroborates the potential metabolic imprinting effects of maternal lipid metabolism on neonatal growth patterns and health trajectories.

The study also noted differential LDL levels across groups, with a notable reduction in the LGA cohort and an elevation in the SGA group. This complements the study by Ramy et al., which indicated a more atherogenic lipid profile in SGA neonates(20). These insights spotlight the intricate nature of fetal metabolic programming and its implications on neonatal lipid metabolism.

Crucially, our analysis showed that approximately 93% of AGA neonates were born to mothers with HbA1c levels less than 6, within the normal range. In contrast, 50% of LGA neonates came from mothers with HbA1c levels exceeding 8. This stark contrast not only emphasizes the significant impact of maternal glycemic control on neonatal

outcomes but also indicates potential metabolic and cardiovascular challenges these infants might encounter(21).

Our findings further reveal that over 65% of neonates born to mothers with GDM fell into the SGA or LGA categories, a significant and indicative statistic of the broad spectrum of risks associated with maternal diabetes(22). This highlights the nuanced risk profiles for neonates based on the type of maternal diabetes, emphasizing the need for targeted prenatal care and monitoring to address these risks effectively.

In conclusion, our study underscores the importance of early detection and intervention strategies for neonates at risk of cardiovascular diseases, particularly those impacted by maternal GDM. The detailed understanding of how maternal diabetes affects neonatal lipid profiles and overall health outcomes is vital for developing effective prevention and management strategies.

CONCLUSION

Our comprehensive study explored the connection between maternal gestational diabetes mellitus (GDM) and its impact on the offspring's lipid profiles and anthropometry. Through examining a cohort of 101 infants divided into AGA, LGA, and SGA groups, we discovered significant links between altered neonatal lipid profiles—namely, the increased triglycerides in SGA neonates and reduced HDL levels in LGA neonates—and the risk of cardiovascular diseases (CVD) later in life. Our research emphasizes the significant effect of the in-utero environment and maternal glycemic control on the long-term health of newborns, supporting the Barker hypothesis and underlining the critical need for early preventive measures and targeted care strategies.

Future Directions:

The implications of our findings suggest a vital shift towards proactive, comprehensive prenatal care, especially designed to meet the challenges diabetic mothers face, focusing on optimizing maternal glycemic levels. To decrease the likelihood of neonatal and adult-onset metabolic and cardiovascular diseases, implementing targeted prenatal interventions is crucial.

Moreover, the path forward calls for the initiation of multicenter, longitudinal studies to validate the clinical implications of our findings and to explore the evolution of risk factors across the lifespan of individuals born to GDM mothers. These studies are essential for developing robust strategies aimed at the early prevention and management of CVD, thereby fundamentally altering the health trajectory for future generations

Limitations and Strengths:

Limitations: Our study's insights, while impactful, stem from a single-center investigation, potentially affecting the broader applicability of our findings across different populations. Future studies should embrace a multicenter, longitudinal format to more comprehensively assess the effects of gestational diabetes on neonatal lipid profiles and anthropometry.

Strengths: Our research stands out by focusing on cord blood lipid profiles as indicators of future CVD risk, providing a detailed analysis of lipid abnormalities across neonatal groups. This approach not only sheds light on the specific impacts of the

intrauterine environment on neonatal health but also supports the crucial need for tight glycemic control during pregnancy to prevent negative long-term health outcomes for the offspring.

Summary: This study contributes significantly to the field by highlighting early-life physiological and metabolic indicators as predictors of future health risks. It shows the critical role of managing maternal health during pregnancy within pediatric and preventive medicine. Moving forward, an interdisciplinary approach involving obstetrics, pediatrics, and chronic disease epidemiology is essential to reduce the intergenerational risk of CVD and promote better health outcomes for mothers and their children.

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