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Research Article

Neonatal Hyperbilirubinemia in Babies Born to Hyperglycemic Mothers

Dr. Pramod Padasalimani[1*], Dr. Savitri Honakeri[2], Dr. G Basant Kumar Patil[3]
[1*]Senior Assistant, Department of Pediatrics, Koppal Institute of Medical Sciences, Koppal, Karnataka, India.
[2]Assistant Professor, Department of Pediatric Surgery, Karnataka Institute of Medical Sciences and Research Institute (KMCRI), Hubli, Karnataka, India.
[3]Professor, Department of Pediatrics, J. J.M. Medical College, Davangere, Karnataka, India.
Corresponding Author: Dr. Pramod Padasalimani
Senior resident, Department of Pediatrics, Koppal Institute of Medical Sciences (KIMS), Koppal, Karnataka, India.
Email: pramodpadasali@gmail.com
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ABSTRACT
Background & Objectives: Gestational diabetes mellitus (GDM) alters the intrauterine metabolic environment, exposing the fetus to postnatal metabolic complications. Among these, neonatal hyperbilirubinemia and hypoglycemia represent the primary clinical challenges. This study evaluated the incidence, clinical spectrum, co-occurrence of hypoglycemia, and maternal onset-related determinants of neonatal hyperbilirubinemia in babies born to hyperglycemic mothers admitted to a tertiary care neonatal intensive care unit (NICU).
Methods: A prospective hospital-based observational study was conducted in the NICUs attached to J.J.M. Medical College, Davangere, over an 18-month period (March 2021 to October 2022). A cohort of 105 neonates born to GDM mothers was evaluated. Data were gathered regarding maternal GDM onset (early [<24 weeks] vs. late [≥24 weeks]), neonatal clinical profiles, total serum bilirubin levels, and blood glucose levels.
Results: The overall incidence of neonatal hyperbilirubinemia in infants of diabetic mothers (IDMs) was 43.8% (n = 46/105), while neonatal hypoglycemia was present in 64.8% (n = 68/105). Hyperbilirubinemia was observed in 35.0% (n = 7/20) of neonates born to mothers with early-onset GDM compared to 45.9% (n = 39/85) in those with late-onset GDM (p = 0.377). Hypoglycemia occurred in 75.0% (n = 15/20) of early-onset GDM infants compared to 62.4% (n = 53/85) in late-onset GDM infants (p = 0.287). The mean duration of NICU stay for affected neonates was 9.62 \pm 4.64 days.
Conclusion: Neonatal hyperbilirubinemia and hypoglycemia affect a major proportion of GDM-exposed newborns. Although the timing of GDM onset did not yield a statistically significant difference in jaundice or hypoglycemia incidence, the strong metabolic interplay between fetal hyperinsulinemia, delayed hepatic enzyme maturation, and early glucose instability underscores the necessity of universal early bilirubin screening, glucose monitoring, and prompt enteral nutrition.

Keywords: Neonatal Hyperbilirubinemia, Hypoglycemia, Gestational Diabetes Mellitus, Infant of Diabetic Mother, Jaundice, Bilirubin Metabolism.

INTRODUCTION

Diabetes mellitus represents one of the most frequent medical complications encountered during gestation, with gestational diabetes mellitus (GDM) accounting for approximately 85% to 90% of all diabetic pregnancies. Maternal hyperglycemia creates a continuous gradient of excess glucose transport across the placenta to the developing fetus, while maternal insulin fails to cross the placental barrier. Under the classic Pedersen hypothesis, persistent fetal hyperglycemia stimulates hyperplastic pancreatic \beta-cells, generating fetal hyperinsulinemia.

Fetal hyperinsulinemia acts as a key metabolic driver causing sudden postnatal glucose clearance failure (leading to severe neonatal hypoglycemia) while simultaneously impacting hepatic enzyme induction and erythrocyte turnover. Postnatally, the destruction of expanded fetal red cell mass releases a heightened hemoglobin load, which readily overwhelms the infant's immature hepatic bilirubin conjugation pathways.

In their seminal 1963 investigation, Taylor and colleagues established that infants born to

diabetic mothers exhibit significantly higher mean serum bilirubin concentrations on the third day of life compared to gestational-age-matched controls born to non-diabetic mothers. Crucially, Taylor et al. demonstrated that this hyperbilirubinemia was non-hemolytic in origin, as reticulocyte counts, erythrocyte fragility, and Coombs tests remained normal, pointing instead toward metabolic factors, altered neonatal weight loss dynamics, and transient liver enzyme immaturity.

Despite advancements in modern obstetric surveillance and neonatal intensive care, neonatal hyperbilirubinemia and hypoglycemia continue to affect a substantial proportion of infants of diabetic mothers (IDMs). This study was undertaken to examine the clinical burden of hyperbilirubinemia and hypoglycemia in IDMs, investigate their relationship with maternal GDM onset timing, and analyze their co-occurrence in a tertiary care setting.

MATERIALS AND METHODS AND STUDY DESIGN

Study Design and Setting

This hospital-based prospective observational study was conducted in the Neonatal Intensive Care Units (NICUs) of Bapuji Child Health Institute and Chigateri General Hospital attached to J.J.M. Medical College (JJMMC), Davangere, Karnataka, India, from March 2021 to October 2022.

Study Population

The study cohort comprised 105 consecutive neonates born to mothers diagnosed with gestational diabetes mellitus (GDM) who were admitted to the NICU during the study period.

Eligibility Criteria

- **Inclusion Criteria:** Live neonates (inborn and outborn) born to mothers diagnosed with GDM as per standard diagnostic criteria (DIPSI / Carpenter-Coustan guidelines) admitted to the NICU.
- **Exclusion Criteria:** Neonates with major structural congenital malformations incompatible with life, infants with proven isoimmune hemolytic disease (such as severe Rh or major blood group incompatibility with positive Coombs testing), and cases with incomplete clinical data.

Clinical and Laboratory Evaluation

Maternal Profile: Maternal data were documented, including gestational age at GDM diagnosis. GDM onset was classified into Early Onset (<24 weeks of gestation) and Late Onset (≥24 weeks of gestation). Mode of delivery (normal vaginal, assisted, or lower segment cesarean section [LSCS]) and relevant antenatal events were recorded.

Neonatal Profile: Birth weight, gestational age (classified per Battaglia and Lubchenco criteria into Appropriate for Gestational Age [AGA], Small for Gestational Age [SGA], and Large for Gestational Age [LGA]), gender, and APGAR scores at 1 and 5 minutes were documented.

Hyperbilirubinemia Workup: Neonates were monitored daily for clinical jaundice. Total serum bilirubin (TSB) was measured using spectrophotometric micromethods or standard laboratory automated analyzers upon clinical appearance of icterus or routinely in high-risk infants. Direct Coombs testing, reticulocyte counts, and peripheral blood smears were performed to exclude hemolytic etiologies. Hyperbilirubinemia was defined and managed according to gestational-age and hour-of-life specific phototherapy thresholds based on American Academy of Pediatrics (AAP) guidelines.

Glucose Monitoring & Hypoglycemia Workup: Blood glucose levels were monitored systematically from birth (at 1, 2, 4, 6, 12, 24, and 48 hours of life, or prior to feeds) using point-of-care glucometers and confirmed via laboratory glucose oxidase methods. Neonatal hypoglycemia was defined as a blood glucose concentration <40 mg/dL (<2.2 mmol/L).

Statistical Analysis

Cateorical data were expressed as absolute frequencies and percentages. Associations between categorical variables (e.g., GDM duration vs. hyperbilirubinemia or hypoglycemia) were evaluated using the Chi-square test or Fisher's exact test where appropriate. Continuous variables were presented as Mean Standard Deviation (SD). A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographic and Clinical Characteristics

A total of 105 neonates born to GDM mothers were evaluated. Male neonates comprised 60.0% (n = 63) and female neonates comprised 40.0% (n = 42). Preterm births (<37 weeks) accounted for 19.0% (n = 20) of the cohort, while 81.0% (n = 85) were term neonates.

In terms of weight for gestational age, 53.3% (n = 56) were AGA, 33.3% (n = 35) were LGA, and 13.3% (n = 14) were SGA. Macrosomia (birth weight >4.0 kg) was identified in 3.8% (n = 4) of neonates. The mean birth weight of the study population was 2.97 \text{ kg}. The primary mode of delivery was LSCS (48.6%, n = 51), followed by normal vaginal delivery (43.8%, n = 46) and assisted delivery (7.6%, n = 8).

Parameter	Sub-category	Frequency (N = 105)	Percentage (%)
Gender	Male	63	60.0%
	Female	42	40.0%
Gestational Age	Preterm (<37 weeks)	20	19.0%
	Term (≥37 weeks)	85	81.0%
Growth Classification	Appropriate for GA (AGA)	56	53.3%
	Large for GA (LGA)	35	33.3%
	Small for GA (SGA)	14	13.3%
Mode of Delivery	LSCS	51	48.6%
	Normal Vaginal Delivery	46	43.8%
	Assisted Delivery	8	7.6%

Incidence of Neonatal Hyperbilirubinemia and Hypoglycemia

Evaluating the primary metabolic profile of the cohort revealed that hypoglycemia occurred in 64.8% (n = 68/105) of neonates, making it the most frequent metabolic derangement, followed by neonatal hyperbilirubinemia in 43.8% (n = 46/105). A notable proportion of neonates experienced both hyperbilirubinemia and hypoglycemia concurrently during their initial days of life.

Primary Metabolic Derangement	Frequency (N = 105)	Percentage (%)
Hypoglycemia	68	64.8%
Neonatal Hyperbilirubinemia	46	43.8%

Relationship between Maternal GDM Onset, Hyperbilirubinemia, and Hypoglycemia

Maternal GDM duration was categorized into early onset (n = 20) and late onset (n = 85).

- **Neonatal Hyperbilirubinemia:** Occurred in 35.0% (n = 7) of neonates in the early-onset GDM group and 45.9% (n = 39) in the late-onset GDM group (chi^2 = 0.781, p = 0.377).
- **Neonatal Hypoglycemia:** Occurred in 75.0% (n = 15) of neonates in the early-onset GDM group and 62.4% (n = 53) in the late-onset GDM group (chi^2 = 1.134, p = 0.287).

Clinical Parameter	Early Onset GDM (n = 20)	Late Onset GDM (n = 85)	\chi^2 value	p-value
Neonatal Hyperbilirubinemia	7 (35.0%)	39 (45.9%)	0.781	0.377
Neonatal Hypoglycemia	15 (75.0%)	53 (62.4%)	1.134	0.287

NICU Stay

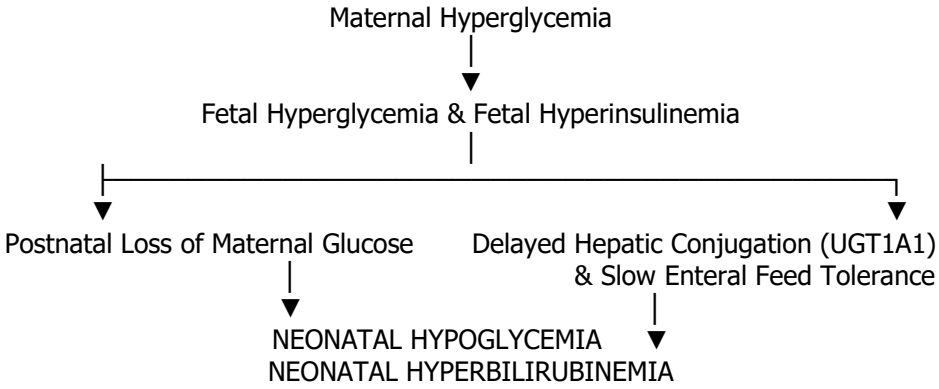
The overall mean duration of NICU hospitalization for the cohort was 9.62 \pm 4.64 days (range: 1 to 25 days). Neonates presenting with hyperbilirubinemia and persistent hypoglycemia required specialized phototherapy, frequent feeding schedules, and intravenous dextrose infusions, contributing to their total hospital stay.

DISCUSSION

Neonatal hyperbilirubinemia and hypoglycemia represent the predominant metabolic features observed in infants born to gestational diabetic mothers. In the present study, clinical hyperbilirubinemia was identified in 43.8% of newborns, while hypoglycemia was observed in 64.8% of cases. These rates confirm that

maternal glucose intolerance imposes a major postnatal metabolic burden on the neonate.

The physiological mechanisms underlying hyperbilirubinemia in IDMs are distinct from classic isoimmune hemolytic disease. As demonstrated by Taylor et al. (1963), infants of diabetic mothers exhibit significantly higher total serum bilirubin levels at 48 to 72 hours of life compared to non-diabetic controls. Taylor et al. proved that this hyperbilirubinemia occurs without evidence of increased hemolysis (Coombs tests negative, normal reticulocyte counts), attributing it instead to altered fluid balance, hepatic clearance delays, and increased red cell turnover.



In IDMs, fetal hyperinsulinemia suppresses glucagon secretion and inhibits gluconeogenesis and glycogenolysis immediately after umbilical cord clamping, precipitating early neonatal hypoglycemia. Simultaneously, hyperinsulinemia interferes with the normal enzymatic induction of hepatic uridine diphosphate glucuronosyltransferase (UGT1A1). Furthermore, early neonatal hypoglycemia often necessitates close feeding monitoring or delayed enteral intake, which prolongs intestinal transit time and enhances the enterohepatic reabsorption of unconjugated bilirubin.

Evaluating maternal GDM onset timing showed that hyperbilirubinemia occurred in 35.0% of early-onset vs. 45.9% of late-onset GDM pregnancies ($p = 0.377$), while hypoglycemia occurred in 75.0% of early-onset vs. 62.4% of late-onset GDM pregnancies ($p = 0.287$). Neither parameter showed statistically significant differences based on onset timing alone, indicating that metabolic derangements are common across all gestational diabetic pregnancies regardless of whether GDM was detected early or late in gestation.

The high incidence of hyperbilirubinemia (43.8%) and hypoglycemia (64.8%) observed in our study aligns with findings across contemporary neonatal literature in developing regions. Prabhavathi et al., Shirazi et al., and Anjum et al. have similarly documented high rates of jaundice (25–48%) and hypoglycemia (50–68%) in IDMs. The persistence of these clinical findings emphasizes that hyperbilirubinemia and hypoglycemia remain the core metabolic challenges facing neonates born to hyperglycemic mothers.

CONCLUSION

Neonatal hyperbilirubinemia and hypoglycemia are the key metabolic complications in infants born to gestational diabetic mothers, affecting 43.8% and 64.8% of exposed newborns, respectively. Their onset is closely linked to the metabolic consequences of fetal hyperinsulinemia, including impaired neonatal glucose regulation, delayed hepatic enzyme conjugation, and transient feed intolerance.

Because the risks of hyperbilirubinemia and hypoglycemia remain high regardless of whether GDM develops early or late in gestation, mandatory metabolic monitoring must be maintained for all IDMs. Strict maternal glycemic control throughout pregnancy, early glucose screening, routine bilirubin surveillance, and rapid establishment of enteral nutrition are essential to prevent severe hyperbilirubinemia and neurodevelopmental sequelae in this vulnerable population.

Limitations of the Study

1. **Heterogeneous Cohort:** The study included both inborn and outborn neonates; for outborn mothers, detailed maternal glycemic logs and serial trimester-specific HbA1c values were

not uniformly accessible.

2. **Methodological Screening**: Blood glucose screening initially utilized point-of-care glucometers before laboratory confirmation, which carries minor inter-device variability.
3. **Feeding Variables**: Variations in the exact volume and timing of enteral feed initiation were dictated by individual clinical stability, which influenced enterohepatic bilirubin clearance.
4. **Follow-up Duration**: Long-term neurodevelopmental follow-up of neonates who experienced significant hyperbilirubinemia or recurrent hypoglycemia was beyond the scope of this hospital-based study.

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