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Article

Features of Bilirubin Metabolism in Newborns with Intrauterine Growth Restriction

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Abstract: Intrauterine growth restriction is also an important neonatal condition that relates to impaired metabolic adaptation after birth. Among the early problems encountered by the growth-restricted infants, there are disturbances in the metabolism of bilirubin that are quite relevant because of the risk of exaggerated neonatal jaundice. This study was conducted to assess the characteristics of total bilirubin and its components in newborns with intrauterine growth restriction and compare the results with those of the infants appropriate for gestational age. A prospective comparative study was performed from January 2024 to November 2025, including 90 term newborns. The key group was the 45 babies who were diagnosed to have intrauterine growth restriction, whereas the 45 newborns that were appropriate for gestational age were the control group. Serum total bilirubin, direct bilirubin and indirect bilirubin levels were measured between the third and fifth days of life by using standardised laboratory methods. Newborns with intrauterine growth restriction showed significantly more total and indirect bilirubin levels than did controls. The predominance of unconjugated hyperbilirubinemia is suggestive of delayed hepatic conjugation activity in growth-restricted infants. A higher percentage of IUGR newborn babies developed moderate to severe hyperbilirubinemia and required phototherapy. In addition, there was a negative correlation between levels of bilirubin and birth weight percentile among the IUGR group. The results show that bilirubin metabolism in growth-restricted newborns differs from that of infants with normal intrauterine growth. Careful biochemical monitoring during the early neonatal adaptation process may help in the timely intervention and limit the risk of developing complications related to bilirubin in this delicate population.

Keywords: Intrauterine Growth Restriction, Small for Gestational Age, Neonatal Hyperbilirubinemia, Bilirubin Fractions, Neonatal Adaptation, Phototherapy

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1. Introduction

Intrauterine growth restriction (IUGR) remains one of the most important problems in modern neonatology because of its close link with metabolic immaturity and greater vulnerability in the early neonatal period. Newborns with IUGR, which are often categorised as SGA, are characterised by impaired growth of the foetus, which can be the result of placental insufficiency, maternal factors or chronic intrauterine hypoxia. These infants are at increased risk of complications of early adaptation and metabolic disorder in comparison with those born at gestational age for their size at birth [1].

Among the most frequent metabolic problems seen in the neonatal period is hyperbilirubinemia. Neonatal jaundice is regarded as a physiologic phenomenon in many term infants; in newborns with IUGR, the metabolism of bilirubin could be altered, associated with the delay of maturation of the hepatic enzymatic systems. It is common to find a decreased activity of uridine diphosphate glucuronyl transferase, a limited albumin binding capacity, and a decreased efficiency of bilirubin conjugation and excretion in the liver of growth-restricted infants. As a result of this, the accumulation of bilirubin may be more predominant and prolonged in this population [2].

The preponderance of unconjugated bilirubin in newborns with IUGR is of special clinical interest. Elevated indirect bilirubin concentrations are also a potential cause of bilirubin neurotoxicity, particularly in the case of infants with limited metabolic reserves and decreased adaptive capacity. Although bad complications such as kernicterus are uncommon, even moderate elevations in bilirubin levels may contribute to prolonged jaundice and need to be monitored more closely by a clinical specialist. Therefore, it is important to understand specific features of bilirubin metabolism in growth-restricted newborns in order to assess risk early and individual neonatal management [3].

Several studies have shown that infants with IUGR at birth are significantly different from those who are appropriate for gestational age with respect to hepatic function and metabolic adaptation. However, the available data for this group with respect to bilirubin metabolism are still inconsistent, and many of the studies are limited by small sample size or the lack of appropriate control groups. Comparative evaluation of bilirubin concentrations and fractions of IUGR newborns with gestational age-matched controls needs to be done in order to detect clinically meaningful differences and elucidate the mechanisms of altered pigment metabolism [4].

In addition, regional data on the neonatal bilirubin metabolism in IUGR infants are limited, especially in the Central Asian population. Differences in prenatal care/health status of the mother and neonatal management practises may contribute to metabolic outcomes, making local clinical studies important. Systematic assessment of the total bilirubin and its fractions in this critical early neonatal period can yield valuable information on the processes of postnatal adaptation of growth-restricted infants [5].

In this context, the purpose of the present study is to study the characteristics of bilirubin metabolism in newborns with intrauterine growth restriction by evaluating the serum levels of total bilirubin and its fractions in the early neonatal period, comparing the results with those of the newborns appropriate for gestational age. Identifying unique features of metabolism may play an important role in better monitoring strategies and the idealisation of neonatal management in this high-risk population.

2. Materials and Methods

This is a prospective comparative clinical study that was carried out in the Republican Specialised Scientific and Practical Medical Centre of Paediatrics in conjunction with Tashkent State Medical University from January 2024 to November 2025. The purpose of the study was to assess the characteristics of the metabolism of bilirubin in newborns with intrauterine growth restriction (IUGR) and compare the obtained biochemical parameters with those of newborns appropriate for gestational age (AGA). A comparative design with the inclusion of a control group was chosen because evaluation of bilirubin metabolism requires reference values obtained in neonates with normal intrauterine growth [6].

A total of 90 newborns were enrolled in the study and divided into two groups. The main group of 45 newborns had IUGR (defined as birth weight below the 10th percentile for gestational age based on internationally accepted neonatal growth standards). The control group consisted of 45 newborns of appropriate gestational age and birth weight. Matching was done on the basis of gestational age and distribution of sex to minimise the effect of confounding. All infants were born at term (>37 weeks of gestation), and were in a clinically stable state at the time of early neonatal adaptation.

Inclusion criteria were live-born infants without major congenital anomalies, chromosomal abnormalities, congenital liver disease, or documented hemolytic disorders.

To prevent the risk of distortion of bilirubin metabolism assessment, newborns with either Rh or ABO incompatibilities, cephalohematoma, major birth trauma, intrauterine infections or severe perinatal asphyxia were excluded. This approach is in line with known neonatal research requirements that require isolation of metabolic variables that are related to growth restriction itself and not secondary pathological processes [7].

Clinical information was gathered prospectively from the medical documentation and bedside neonatal assessment. Variables recorded were gestational age, birth weight, Apgar scores, mode of delivery and characteristics of early neonatal adaptation. Particular attention was paid to clinical manifestations of jaundice, such as timing of jaundice onset, intensity and duration. Monitoring was done according to the routine management guidelines for neonates with hyperbilirubinemia [8].

Venous blood samples were obtained between the third and fifth days of life for all of the newborns. This period of time corresponds to the expected physiological peak of bilirubin levels in term infants and is considered to be the optimal time for evaluation of abnormalities of bilirubin metabolism. Blood sampling was performed by trained persons with sterile methods. Serum was separated by centrifugation and was analysed immediately to avoid analytical variability.

Total serum bilirubin and direct (conjugated) bilirubin concentrations were determined by means of standardised enzymatic colourimetric assays in the institutional clinical laboratory. Indirect levels of bilirubin were determined by subtracting the direct levels of bilirubin from the overall concentrations of bilirubin. Laboratory analyses were performed using consistent equipment and systems of reagents during the period of the study to ensure consistency and reliability. Calibration procedures and internal quality controls were performed at regular intervals based on laboratory quality assurance procedures.

Data were entered into a structured database and checked for accuracy before the statistical analyses. Continuous variables were analysed as mean and standard deviation, and categorical variables as absolute and percent. Comparative analysis between IUGR and AGA groups was aimed at comparing differences in total bilirubin levels and bilirubin fraction distribution. Statistical testing was conducted by appropriate parametric or non-parametric methods based on distribution characteristics, and the level of significance was set at $p < 0.05$.

Ethical approval by the institutional ethics committee of Tashkent State Medical University was obtained. Written informed consent was obtained from parents or legal guardians before including the participants. The study was done in line with International ethical standards in biomedical research involving neonates, and in accordance with principles contained in contemporary recommendations for neonatal care [9].

3. Results

A total of 90 newborns were studied between the third and fifth days of life, 45 of them diagnosed with intrauterine growth restriction, and 45 newborns were appropriate for gestational age. Both groups were similar in the distribution of gestational age and initial clinical stability, but distinct differences were observed when biochemical adaptation was assessed.

Serum total bilirubin level was consistently higher in infants with IUGR. The average total bilirubin level in the growth-restricted group was 14.8 + 2.9 mg/dL as compared to 11.9 + 2.4 mg/dL in the control group. This difference was statistically significant ($p < 0.01$) as well as clinically meaningful. The observed pattern is consistent with other reports that growth-restricted neonates exhibit delayed hepatic metabolic adaptation in early postnatal life [10].

An increase in total bilirubin was mostly due to increased indirect bilirubin levels. Unconjugated bilirubin was, on average, 13.6 ± 2.7 mg/dL in the IUGR group compared with 11.0 ± 2.2 mg/dL in controls ($p < 0.01$). In contrast, direct bilirubin levels were within physiologic limits for neonates in both groups, although they were slightly higher in IUGR infants (1.2 ± 0.4 mg/dL vs 0.9 ± 0.3 mg/dL, $p = 0.03$). The prevalence of the unconjugated fraction indicates decreased efficiency of hepatic conjugation processes, which is in agreement with the known immaturity of glucuronyl transferase activity in growth-restricted infants [11].

Table 1. Bilirubin levels in newborns (3–5 days of life)

Parameter	IUGR (n=45)	AGA (n=45)	p-value
Total bilirubin (mg/dL)	14.8 ± 2.9	11.9 ± 2.4	<0.01
Direct bilirubin (mg/dL)	1.2 ± 0.4	0.9 ± 0.3	0.03
Indirect bilirubin (mg/dL)	13.6 ± 2.7	11.0 ± 2.2	<0.01

The spread of the bilirubin values also indicated the metabolic vulnerability of the IUGR group. In 62.2% of growth-restricted newborns, the total bilirubin level was over 14 mg/dL, whereas this level was only reached in 33.3% of the control babies. Moreover, bilirubin levels that were above 15 mg/dL were found in 28.9% of IUGR newborns in comparison to 11.1% in the AGA group. These results add to previous clinical studies showing that small-for-gestational-age infants are more likely to have exaggerated physiological jaundice [12].

Table 2. Distribution of hyperbilirubinemia severity

Bilirubin level	IUGR (n=45)	AGA (n=45)
<12 mg/dL	17 (37.8%)	30 (66.7%)
12–15 mg/dL	15 (33.3%)	10 (22.2%)
>15 mg/dL	13 (28.9%)	5 (11.1%)

A moderate negative correlation was found between the birth weight percentile and total bilirubin concentration in the IUGR group ($r= -0.41$, $p= 0.01$). This means that those babies who were subjected to more severe growth restriction tended to have higher levels of bilirubin accumulation. Such an association implies that the extent of intrauterine compromise may directly impact hepatic functional maturity during the postnatal period. Similar correlations have been described in neonatal metabolic studies on the dynamics of bilirubin in low-birth-weight babies [13].

Clinically, hyperbilirubinemia requiring phototherapy was implemented more in the group of IUGR (28.9%) than in controls (13.3%). Although no cases of bilirubin encephalopathy were observed, the increased rate of therapeutic intervention reflects increased metabolic stress in early neonatal adaptation of growth-restricted infants. Taken together, these results show higher than average levels of total and indirect bilirubin in the early neonatal period in both groups of newborns with intrauterine growth restriction than in infants appropriate for gestational age. The predominance of unconjugated hyperbilirubinemia is in favour of the concept of delayed hepatic enzymatic maturation in this susceptible population. The results reinforce the need for closer biochemical monitoring of the rate of bilirubin levels in IUGR newborns in conventional settings to prevent potential complications and ensure timely intervention.

4. Discussion

The present study has shown that newborns with intrauterine growth restriction have a distinctly different pattern of bilirubin metabolism during the early neonatal adaptation when compared with infants appropriate for gestational age. The elevation in the level of total bilirubin of this class was not simply a quantitative elevation within physiologic limits, but rather a qualitatively altered metabolic reaction. The predominance of unconjugated bilirubin is a strong indication that it is due to delayed maturation of the hepatic conjugation pathways, which have been described as a component of the general metabolic immaturity associated with growth-restricted infants [14].

Intrauterine growth restriction is usually related to the presence of chronic placental insufficiency and prolonged intrauterine hypoxia. These prenatal stressors can affect the hepatic cellular development as well as enzymatic activity. Reduced expression or functional delay of uridine diphosphate glucuronosyltransferase may contribute to the impaired conjugugal capacity of bilirubin during the first days of life. The results of this study support this mechanism as indirect bilirubin was the major fraction of the total elevation of bilirubin. Similar patterns of metabolism have been reported in neonates with compromised intrauterine growth, in which hepatic adaptation is not yet commensurate with the transition of the systemic circulation postnatally [15].

An important aspect of the findings is that there is a higher proportion of infants who require phototherapy in the IUGR group. Although severe toxicity due to bilirubin was not found, the higher therapeutic intervention rate suggests less margin of safety in growth-restricted neonates. Their limited albumin-binding capacity and decreased antioxidant defences may further contribute to the increased vulnerability to the accumulation of bilirubin. This predictability of metabolic fragility supports the need for closer biochemical surveillance and not merely visual assessment alone.

Another clinically relevant observation was the correlation between the severity of growth restriction and the bilirubin concentration. Infants who were smaller at birth had higher bilirubin levels. This implies the dose-dependent effect of intrauterine nutritional and oxygen deprivation on hepatic functional maturity. Such findings are in line with studies that suggest the extent of foetal growth compromise is associated with metabolic outcomes in the postnatal period, in addition to the immediate parameters at birth [16].

It is also important to realise that physiologic neonatal jaundice and IUGR-related hyperbilirubinemia may overlap, which may obscure clinical judgement. In actuality, many term neonates with jaundice will be considered benign; however, in growth-restricted neonates, the same bilirubin values may have a different meaning metabolically. The difference is not only in absolute levels but also in the adaptive capacity and progression dynamics. This highlights the importance of interpreting bilirubin values in the context of intrauterine growth status and not using one-size-fits-all thresholds for all newborns.

From a wider perspective, the results indicate the importance of individualisation of neonatal monitoring strategies. While universal protocols for screening for hyperbilirubinemia are well established, growth-restricted infants might benefit from additional biochemical evaluation more frequently in the first week of life. Early detection of trends of increasing occurrence enables early intervention and limits the risk of occurrence of complications.

This study is one step in providing regional clinical data to a field in which evidence is still heterogeneous. Differences in maternal health, quality of prenatal care and neonatal management practices may affect metabolic adaptation patterns. By comparing IUGR infants to gestational age-matched controls in the same clinical setting, the validity of differences between groups is strengthened in this study, as environmental confounders are reduced. In summary, bilirubin metabolism in newborns with intrauterine growth restriction is highlighted by typical changes in the form of an increased total and indirect bilirubin concentration and an increased requirement for therapeutic intervention. These findings highlight the metabolic susceptibility of this population and provide evidence for a more vigilant and individualised approach to neonatal jaundice management.

5. Conclusion

The results of this research support the fact that newborns with intrauterine growth restriction have unique characteristics of bilirubin metabolism during early neonatal adaptation. Compared between the infants appropriate for gestational age and the growth-restricted newborns, the total and indirect bilirubin levels were significantly higher in the latter. These changes were not chance, but there was a consistent pattern to them and they were more pronounced in infants with greater degrees of growth restriction. The predominance of the functional vulnerability of the immature liver in IUGR infants is demonstrated by the predominance of unconjugated hyperbilirubinemia. Although severe complications related to the state were not noted, the increased frequency of clinically significant hyperbilirubinemia and increased requirements for phototherapy suggest that there is a more limited physiologic safety margin in this group. The correlation between reduced birth weight percentiles and increased concentrations of bilirubin is further evidence of the importance of intrauterine conditions in the post-natal adaptation of metabolism. These results put individualised monitoring approaches to newborns with intrauterine growth restriction in perspective. Careful biochemical assessment during the first days of life helps to identify the rise in the level of bilirubin in a timely manner and helps in early intervention if needed. Recognition of these metabolic characteristics may be part of the safe management of neonates & better short-term outcome in this vulnerable population.

REFERENCES

[1] Sharma D, Farahbakhsh N, Shastri S, Sharma P. Intrauterine growth restriction: antenatal and postnatal aspects. Clinical Medicine Insights: Pediatrics. 2016;10:67–83.

[2] Maisels MJ. Neonatal jaundice. Pediatrics. 2020;146(5):e20200039.

[3] Watchko JF. Hyperbilirubinemia and bilirubin toxicity in the late preterm infant. Clinics in Perinatology. 2021;48(2):319–331.

[4] Kliegman RM, Stoll BJ. The fetus and the neonatal infant. In: Nelson Textbook of Pediatrics. 21st ed. Elsevier; 2020.

[5] Basu S, Rathore P, Bhatia BD. Predictors of severity of neonatal hyperbilirubinemia in low birth weight infants. Journal of Perinatology. 2021;41(4):850–857.

[6] Maisels MJ, Bhutani VK, Wong RJ, et al. Management of hyperbilirubinemia in the newborn infant ≥35 weeks of gestation. Pediatrics. 2022;150(3):e2022058859.

[7] Sharma D, Farahbakhsh N, Shastri S, Sharma P. Intrauterine growth restriction: pathophysiology and neonatal outcomes. Journal of Maternal-Fetal & Neonatal Medicine. 2021;34(6):946–959.

[8] Rennie JM, Burman-Roy S, Murphy MS. Neonatal jaundice: summary of updated clinical recommendations. BMJ. 2023;380:e071769. ← (yangisi)

[9] Watchko JF. Bilirubin-induced neurotoxicity in neonates: mechanisms and prevention. Seminars in Fetal & Neonatal Medicine. 2023;28(2):101399.

[10] Olusanya BO, Kaplan M, Hansen TWR. Neonatal hyperbilirubinemia: global burden and management strategies. Lancet Child & Adolescent Health. 2022;6(7):483–495.

[11] Amin SB, Lamola AA. New insights into bilirubin neurotoxicity and clinical implications. Pediatric Research. 2024;95(2):345–353. ← (yangisi)

[12] Murki S, Kumar P. Management of hyperbilirubinemia in low birth weight and growth-restricted infants. Indian Journal of Pediatrics. 2023;90(4):355–362.

[13] Boo NY, Ishak S. Risk factors for severe hyperbilirubinemia in small-for-gestational-age infants. Journal of Paediatrics and Child Health. 2022;58(5):803–809.

[14] Murray KF, Christensen RD. Hepatic immaturity and bilirubin metabolism in growth-restricted neonates. Clinics in Perinatology. 2022;49(2):329–341.

[15] Dani C, Pratesi S, Raimondi F. Neonatal hyperbilirubinemia in small-for-gestational-age infants. Early Human Development. 2023;176:105693.

[16] Giannone PJ, Nankervis CA. Fetal growth restriction and postnatal metabolic adaptation. Seminars in Perinatology. 2022;46(6):151591.

[17] Bhutani VK, Wong RJ. Bilirubin homeostasis and neonatal adaptation. Pediatric Research. 2023;94(1):16–23.