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MATERNAL INFLAMMATORY AND ANGIOGENIC BIOMARKERS IN PROLONGED NEONATAL JAUNDICE

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ABSTRACT
Maternal obesity is characterized by low-grade inflammation and endothelial activation, which may influence neonatal metabolic adaptation and hepatic function. This study evaluated maternal C-reactive protein (CRP), procalcitonin (PCT), and vascular endothelial growth factor A (VEGF-A) across prepregnancy body mass index categories and explored their associations with biochemical profiles in term infants with prolonged neonatal jaundice. This single-center observational study included 140 mother-infant pairs examined at the Urgench City Maternity Complex, Uzbekistan, during 2023-2025. Mothers were classified as overweight (n = 57), obese class I-II (n = 21), underweight (n = 25), or normal weight (n = 37). An immunobiochemical subanalysis was performed in 80 pairs. Maternal CRP and PCT were measured using standard serum assays and VEGF-A by sandwich enzyme-linked immunosorbent assay. Infant total, direct, and indirect bilirubin, alanine aminotransferase, aspartate aminotransferase, total protein, and glucose were assessed. Compared with normal-weight mothers, mothers with obesity had higher CRP (2.34 ± 0.21 vs 1.76 ± 0.19 mg/L), PCT (0.28 ± 0.10 vs 0.05 ± 0.02 ng/mL), and VEGF-A (95.8 ± 7.3 vs 72.9 ± 3.9 pg/mL; $P < 0.05$ for reported comparisons). In the obesity group, infant total bilirubin correlated with maternal total cholesterol (r = 0.49) and atherogenic index (r = 0.45); direct bilirubin correlated with maternal low-density lipoprotein cholesterol (r = 0.52), and infant alanine aminotransferase correlated with maternal PCT (r = 0.42). Maternal obesity was associated with an inflammatory and angiogenic biomarker pattern in mothers of infants with prolonged jaundice. The exploratory maternal-infant correlations support further prospective investigation of metabolic inflammation and neonatal hepatic adaptation.

KEYWORDS: C-reactive protein; Maternal obesity; Neonatal jaundice; Procalcitonin; Vascular endothelial growth factor A

INTRODUCTION
Neonatal jaundice is among the most frequent clinical findings during the neonatal period. When hyperbilirubinemia persists beyond the expected physiological interval, clinicians must consider hemolysis, infection, endocrine disease, and cholestatic liver disorders (Memon et al., 2016; Fawaz et al., 2017; American Academy of Pediatrics Subcommittee on Hyperbilirubinemia, 2022). In addition to these immediate causes, maternal and antenatal metabolic exposures may influence neonatal bilirubin handling and hepatic adaptation.
Maternal obesity and metabolic syndrome are associated with insulin resistance, dyslipidemia, chronic low-grade inflammation, oxidative stress, and endothelial dysfunction. These disturbances may alter placental signaling and nutrient transport and contribute to developmental programming of offspring metabolism (Gluckman et al., 2008; Girardi and Bremer, 2022; Scheidl et al., 2023; Purcell and Glastras, 2023). C-reactive protein (CRP) reflects systemic inflammatory activity. Procalcitonin (PCT) is widely used as a marker of bacterial inflammation, although modest increases may occur in noninfectious inflammatory states. Vascular endothelial growth factor A (VEGF-A) is a hypoxia-responsive signaling protein involved in angiogenesis and vascular permeability (Apte et al., 2019; Schuetz et al., 2019). Taken together, these proteins represent complementary inflammatory and endothelial pathways that may be altered by maternal adiposity.
Few studies have assessed maternal CRP, PCT, and VEGF-A concurrently and related these biomarkers to the bilirubin and liver-associated biochemical profile of infants with prolonged jaundice. We therefore evaluated maternal serum CRP, PCT, and VEGF-A across prepregnancy body mass index categories and explored associations between maternal laboratory markers and infant biochemical characteristics.

MATERIAL AND METHODS
Study design and participants
A single-center observational study included 140 term infants with prolonged jaundice and their 140 mothers who were admitted to or evaluated at the Urgench City Maternity Complex, Uzbekistan, from 2023 through 2025. The infant cohort comprised 100 boys (71.4%) and 40 girls (28.6%). Eligibility required term birth, clinically persistent jaundice beyond the expected physiological period, and availability of maternal and infant laboratory data. An immunobiochemical subanalysis was performed in 80 mother-infant pairs.

Maternal nutritional status
Prepregnancy body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Mothers were classified according to World Health Organization categories: underweight, BMI <18.5 kg/m²; normal weight, BMI 18.5-24.9 kg/m²; overweight, BMI 25.0-29.9 kg/m²; and obesity class I-II, BMI 30.0-39.9 kg/m².

Laboratory measurements
Maternal blood was collected within the first 3 days after delivery. Serum CRP and PCT were measured using the standard diagnostic assays available in the institutional laboratory. VEGF-A was measured using a solid-phase sandwich enzyme-linked immunosorbent assay (Cytokine, St Petersburg, Russia), and optical density was read on a microplate photometer according to the manufacturer's instructions. The infant biochemical profile included total, direct, and indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, and glucose. ALT and AST activities were measured by the kinetic International Federation of Clinical Chemistry method without pyridoxal phosphate activation, using reagents from Human Gesellschaft fur Biochemica und Diagnostica (Wiesbaden, Germany).

Statistical analysis
Continuous variables are presented as means ± standard error (SE) for biomarker measurements and means ± standard deviation (SD) for maternal age, following the source dataset. Distributional assumptions and homogeneity of variance were assessed before parametric testing. Between-group comparisons used Student's t-test when its assumptions were satisfied and an appropriate nonparametric test otherwise. Associations were evaluated using Pearson or Spearman correlation coefficients, as appropriate. Statistical significance was set at $P < 0.05$. Correlations for which exact P values and 95% confidence intervals were unavailable were treated as exploratory and were not interpreted as confirmatory evidence.

Ethical considerations
The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the mothers and from the legal representatives of the newborn infants.

RESULTS

Participant distribution
The distribution of mother-infant pairs by maternal nutritional status is shown in Table 1. Overall, 78 of 140 infants with prolonged jaundice (55.7%) were born to mothers with overweight or obesity.

Table 1. Characteristics of groups according to maternal nutritional status

Maternal group	BMI criterion (kg/m²)	n (%)	Maternal age, years (mean ± SD)
Overweight	25.0-29.9	57 (40.7)	28.2 ± 4.7
Obesity class I-II	30.0-39.9	21 (15.0)	27.1 ± 4.2
Underweight	<18.5	25 (17.9)	28.9 ± 4.6
Normal weight	18.5-24.9	37 (26.4)	27.4 ± 4.0

BMI = body mass index; SD = standard deviation.

Maternal inflammatory and angiogenic biomarkers
The most pronounced inflammatory and endothelial biomarker differences were observed among mothers with obesity (Table 2). Compared with the normal-weight group, CRP was 1.33-fold higher, PCT was 5.6-fold higher, and VEGF-A was 1.31-fold higher ($P < 0.05$ for the reported comparisons). In mothers with overweight, PCT was threefold higher than in the normal-weight group ($P < 0.05$), whereas the increase in VEGF-A to 80.2 ± 4.6 pg/mL was not reported as statistically significant.

Table 2. Maternal serum inflammatory and angiogenic biomarkers

Biomarker	Overweight	Obesity class I-II	Underweight	Normal weight
CRP (mg/L)	2.10 ± 0.20	2.34 ± 0.21*	1.87 ± 0.18	1.76 ± 0.19
PCT (ng/mL)	0.15 ± 0.04*	0.28 ± 0.10*	0.06 ± 0.02	0.05 ± 0.02
VEGF-A (pg/mL)	80.2 ± 4.6	95.8 ± 7.3*	73.4 ± 4.1	72.9 ± 3.9

*Values are mean ± SE. *P < 0.05 versus the normal-weight group. CRP = C-reactive protein; PCT = procalcitonin; SE = standard error; VEGF-A = vascular endothelial growth factor A.*

Exploratory maternal-infant correlations
Within the obesity class I-II group, maternal metabolic and inflammatory characteristics showed moderate correlations with infant biochemical measurements (Table 3). Infant total bilirubin correlated positively with

maternal total cholesterol and atherogenic index, while infant direct bilirubin correlated positively with maternal low-density lipoprotein cholesterol. Infant glucose correlated inversely with maternal low-density lipoprotein cholesterol. Infant ALT correlated positively with maternal PCT.

Table 3. Exploratory correlations in the maternal obesity class I-II group

Maternal variable	Infant variable	r	Direction
Total cholesterol	Total bilirubin	0.49	Positive
Atherogenic index	Total bilirubin	0.45	Positive
LDL cholesterol	Direct bilirubin	0.52	Positive
LDL cholesterol	Glucose	-0.33	Inverse
PCT	ALT	0.42	Positive
Triglycerides	ALT	0.33	Positive
Triglycerides	AST	0.32	Positive
VEGF-A	AST	0.30	Positive

Exact P values and 95% confidence intervals were not available for these coefficients; the correlations are therefore exploratory. ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDL = low-density lipoprotein; PCT = procalcitonin; VEGF-A = vascular endothelial growth factor A.

DISCUSSION

The principal finding was a concurrent increase in maternal CRP, PCT, and VEGF-A among mothers with obesity whose infants had prolonged neonatal jaundice. This pattern is consistent with obesity as a state of chronic low-grade inflammation, endothelial activation, and metabolic dysregulation (Girardi and Bremer, 2022; Scheidl et al., 2023; Purcell and Glastras, 2023). The absolute PCT concentrations remained below thresholds commonly used to support severe bacterial infection; consequently, these values should not be interpreted as evidence of neonatal or maternal sepsis in the absence of clinical and microbiological findings (Schuetz et al., 2019).

Higher maternal VEGF-A may reflect activation of hypoxia-sensitive angiogenic and endothelial signaling. VEGF-A expression and signaling are influenced by tissue oxygenation, inflammatory mediators, and metabolic state, and an isolated measurement is therefore not disease-specific (Apte et al., 2019). Nevertheless, the parallel elevation of CRP, PCT, and VEGF-A suggests a multi-pathway biomarker phenotype that warrants mechanistic and longitudinal evaluation.

The observed correlations between maternal lipid characteristics and infant total or direct bilirubin are biologically plausible. Maternal dyslipidemia and insulin resistance can influence placental function, fetal substrate exposure, and developmental programming of offspring hepatic metabolism (Gluckman et al., 2008; Girardi and Bremer, 2022; Scheidl et al., 2023; Purcell and Glastras, 2023). However, the cross-sectional and exploratory analyses cannot establish causality. The associations may also be affected by gestational diabetes, hypertensive disorders, intrahepatic cholestasis of pregnancy, delivery mode, feeding practices, and treatment of neonatal jaundice.

The results do not support using any single maternal biomarker as a diagnostic test for prolonged neonatal jaundice. A more clinically relevant approach may be to combine maternal metabolic risk stratification with timely fractionated bilirubin and liver-associated biochemical assessment in the infant. Direct hyperbilirubinemia should prompt evaluation for neonatal cholestasis in accordance with current clinical recommendations (Fawaz et al., 2017; American Academy of Pediatrics Subcommittee on Hyperbilirubinemia, 2022).

Strengths and limitations

This study evaluated three complementary maternal proteins and paired them with infant biochemical measurements in a clinically relevant cohort. Its limitations include the single-center observational design, absence of multivariable adjustment, incomplete inferential statistics for the correlation analysis, and lack of diagnostic-performance and longitudinal outcome data. The study did not measure gene expression, genetic variants, or downstream VEGF signaling; molecular mechanisms discussed here are therefore interpretive and require direct investigation. These limitations preclude causal inference and the establishment of clinical decision thresholds.

CONCLUSION

Among mothers of term infants with prolonged neonatal jaundice, obesity class I-II was associated with higher early postpartum CRP, PCT, and VEGF-A than normal maternal weight. Exploratory correlations linked maternal lipid and inflammatory characteristics with infant bilirubin, glucose, and transaminase measurements. These findings support prospective, adequately powered studies incorporating multivariable adjustment and direct molecular characterization of inflammatory, angiogenic, placental, and hepatic pathways.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS
SM Sharipova: conceptualization, investigation, data curation, laboratory work, formal analysis, and writing of the original draft. MR Khudayberganov: supervision, methodology, and critical revision of the manuscript. Both authors approved the final manuscript and agree to be accountable for the work.

DATA AVAILABILITY
De-identified data supporting the findings may be made available by the corresponding author upon reasonable request, subject to institutional and ethical requirements.

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