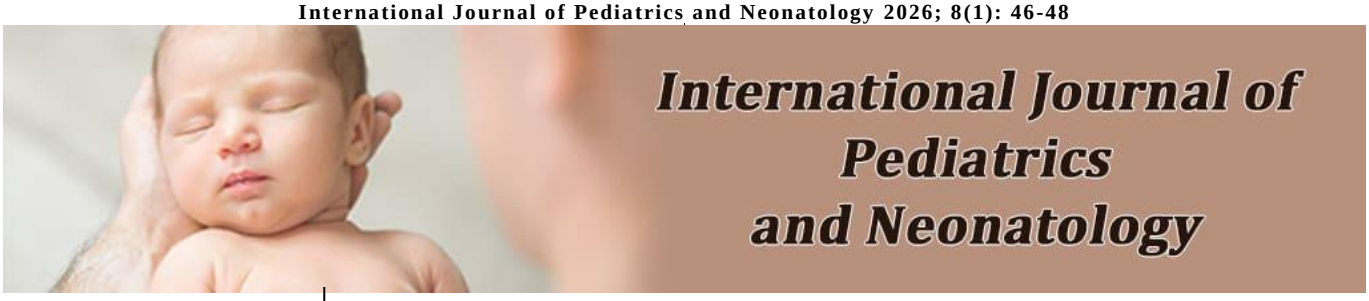

ISSN Print: 2664-8350
ISSN Online: 2664-8369
Impact Factor: RJIF 6.02
IJPN 2026; 8(1): 46-48
www.pediatricsjournal.net
Received: 15-11-2025
Accepted: 19-12-2025

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Postnatal glucose homeostasis and dysglycemia in newborns: A narrative review

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DOI: https://www.doi.org/10.33545/26648350.2026.v8.i1a.184

Abstract
Background: Glucose is the principal substrate for cellular energy production during fetal and neonatal life and is particularly critical for cerebral metabolism. The neonatal brain consumes glucose at a rate disproportionate to body size, rendering newborns especially vulnerable to disturbances in glucose availability. Following birth, the abrupt cessation of placental glucose transfer necessitates rapid metabolic, hormonal, and physiological adaptations to maintain glucose homeostasis. Failure of this adaptive process may result in neonatal hypoglycemia or hyperglycemia, both of which are associated with significant morbidity and potential long-term neurodevelopmental impairment [1, 2].
Objective: To review current evidence regarding postnatal glucose homeostasis in newborns, with emphasis on physiological adaptation after birth, mechanisms underlying neonatal hypoglycemia and hyperglycemia, screening challenges, and clinical consequences.
Data Sources: This narrative review is based on peer-reviewed literature cited in a master's thesis on neonatal glucose homeostasis, including clinical, physiological, and endocrinological studies.
Study Selection: English-language articles addressing neonatal glucose physiology, dysglycemia, screening strategies, management approaches, and outcomes were included.
Data Extraction: Relevant data were extracted and narratively synthesized, focusing on mechanistic insights and clinical implications rather than quantitative outcomes.
Conclusion: Neonatal glucose regulation is a dynamic, developmentally dependent process. Accurate interpretation of blood glucose values requires an understanding of normal physiological adaptation and pathological deviations to prevent adverse neurological outcomes.

Keywords: Neonatal glucose homeostasis, neonatal hypoglycemia, neonatal hyperglycemia, newborn metabolism, glucose regulation

Introduction
Glucose is the primary metabolic substrate for energy production during the perinatal, neonatal, and early postnatal periods. A substantial proportion of placental glucose transfer is utilized by the fetal brain, which relies almost exclusively on glucose for oxidative metabolism [1]. Prior to birth, the fetus depends entirely on continuous maternal glucose supply mediated by facilitated diffusion across the placenta, while endogenous fetal glucose production is minimal under normal physiological conditions [3].
Although enzymatic systems required for glycogenolysis and gluconeogenesis develop early in fetal life, endogenous glucose production occurs only under extreme conditions such as placental insufficiency or prolonged fasting [2]. Insulin secretion is detectable as early as 10-12 weeks' gestation; however, fetal insulin functions primarily as a growth-promoting hormone rather than a regulator of blood glucose concentrations [4].
At birth, the sudden interruption of placental glucose delivery represents a major metabolic challenge. In healthy term neonates, blood glucose concentrations undergo a transitional decline during the first hours of life before stabilizing over the subsequent 48-72 hours [5]. This physiological nadir reflects delayed activation of hepatic glucose production and transient alterations in insulin sensitivity. Premature, small-for-gestational-age, or metabolically stressed infants may fail to mount an adequate adaptive response, increasing their susceptibility to dysglycemia [6].
Neonatal hypoglycemia is the most prevalent metabolic disorder encountered in newborns, whereas neonatal hyperglycemia is more commonly observed in preterm and very low birth

weight infants. Both conditions have been associated with increased short- and long-term morbidity, underscoring the importance of understanding neonatal glucose physiology [7].

Materials and Methods

This narrative review was conducted through qualitative synthesis of the literature referenced in a master's thesis on neonatal glucose homeostasis. No primary data collection or statistical analysis was performed. Emphasis was placed on integrating physiological mechanisms, endocrine regulation, pathophysiology, and clinical implications of neonatal dysglycemia.

Review of Literature

Postnatal Glucose Homeostasis in Neonates

Blood glucose concentrations are tightly regulated throughout life; however, in neonates, marked physiological variability is observed. Beyond the neonatal period, fasting blood glucose levels are maintained within a narrow range of 3.5-5.5 mmol/L, but during the immediate postnatal period, transiently lower values are considered physiologically normal [1, 5].

Following birth, endogenous glucose production is initiated primarily through hepatic glycogenolysis and gluconeogenesis. Hepatic glycogen stores accumulated during late gestation serve as an initial source of glucose, while gluconeogenesis becomes increasingly important as glycogen is depleted [8]. In addition to the liver, the kidney has been recognized as a significant gluconeogenic organ in neonates [3].

Hormonal regulation of glucose homeostasis involves a complex interplay between insulin, glucagon, catecholamines, cortisol, and growth hormone. Insulin predominates in the fed state, whereas glucagon and catecholamines serve as the primary defenses against hypoglycemia during fasting [9].

Perinatal Glucose Physiology

Maternal glucose is transferred to the fetus via facilitated diffusion mediated primarily by the GLUT1 transporter, which is highly expressed on placental syncytiotrophoblast membranes [10]. In the second half of pregnancy, fetal glucose demand increases substantially, promoting deposition of hepatic glycogen and fat stores [5].

Fetal glucose concentrations are typically slightly lower than maternal levels, with a fetal-maternal gradient of approximately 0.5 mmol/L at term [11]. Glucose contributes nearly 80% of fetal energy requirements, with the remaining energy supplied by lactate, amino acids, and glycerol [12].

Physiological Adaptation after Birth

The transition to extrauterine life requires coordinated metabolic and endocrine changes. Immediately after birth, blood glucose concentrations decline to a physiological nadir within the first 2-4 hours, stimulating release of counter-regulatory hormones [6].

Catecholamines, glucagon, cortisol, and thyroid hormones promote glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis, providing alternative substrates for energy production [13]. Healthy term neonates typically tolerate this transitional hypoglycemia without clinical consequences, whereas vulnerable infants may develop pathological hypoglycemia [14].

Neonatal Hypoglycemia

Definitions and Classification

Neonatal hypoglycemia is not a diagnosis but a biochemical marker indicating inadequate glucose availability for cerebral metabolism (neuroglycopenia) [15]. Operational thresholds are used to guide intervention, commonly ranging between 2.0 and 2.6 mmol/L [15].

Hypoglycemia may be classified as transitional, prolonged transitional, or persistent, depending on duration and underlying etiology [16].

Pathophysiology

The most common mechanism underlying neonatal hypoglycemia is inadequate suppression of insulin secretion at low glucose concentrations. This results in reduced hepatic glucose output and impaired ketogenesis, depriving the brain of alternative energy substrates [17]. Additional contributing factors include limited glycogen stores, immature enzymatic pathways, and increased cerebral glucose utilization [12].

Neuropathology and Outcomes

The neonatal brain is highly dependent on glucose for ATP generation. Neuroglycopenia may trigger excitotoxicity, oxidative stress, mitochondrial dysfunction, and neuronal injury [15]. Clinical studies have demonstrated associations between neonatal hypoglycemia and later cognitive impairment, learning difficulties, and executive dysfunction, particularly following severe or recurrent episodes [18].

Screening and Monitoring Challenges

Neonatal hypoglycemia is frequently asymptomatic, limiting the reliability of clinical assessment [19]. Most guidelines recommend targeted screening of infants with known risk factors; however, evidence suggests that hypoglycemia may also occur in infants without identifiable risk factors [14].

Management of Neonatal Hypoglycemia

Initial management includes early feeding, maintenance of normothermia, and monitoring. Oral dextrose gel has been shown to reduce treatment failure, neonatal intensive care admission, and need for intravenous therapy while supporting breastfeeding [14]. Intravenous dextrose is reserved for severe or refractory cases [20].

Neonatal Hyperglycemia

Neonatal hyperglycemia is typically defined as blood glucose concentrations exceeding 150-180 mg/dL and is most commonly observed in preterm and very low birth weight infants [7]. It is associated with insulin resistance, stress responses, infection, and excessive glucose infusion.

Hyperglycemia has been linked to increased risk of intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, sepsis, and mortality [7].

Conclusion

Postnatal glucose homeostasis is a complex and developmentally regulated process requiring coordinated metabolic and hormonal adaptation. While transient glucose fluctuations are physiologically normal, failure of adaptation may result in neonatal hypoglycemia or hyperglycemia with significant clinical consequences. Improved understanding of neonatal glucose physiology, careful interpretation of glucose measurements, and evidence-based management

strategies are essential to reduce morbidity and long-term neurodevelopmental impairment.

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How to Cite This Article
Hassan HM, Shahin AM, Zaki SES, Fayed SM. Postnatal glucose homeostasis and dysglycemia in newborns: A narrative review. International Journal of Pediatrics and Neonatology. 2026;8(1):4648.