ISSN 2786-6661
eISSN 2786-667X

UDC: 618.2-089.888.11-053.31:616-036.88
https://doi.org/10.32345/USMYJ.3(157).2025.137-143

Received: March 21, 2025
Accepted: June 13, 2025

Late preterm infants: modern trends and challenges

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Abstract: *late preterm infants, born between 34 $^{0/7}$ and 36 $^{6/7}$ weeks of gestation, constitute a significant subgroup of preterm infants, accounting for nearly 75% of all preterm births. Although late preterm infants are often perceived as physiologically closer to term infants, they are at increased risk of morbidity and mortality due to developmental and structural immaturity. Recent studies suggest that preterm infants are at high risk of impaired postnatal adjustment and are prone to complications affecting multiple organ systems, including respiratory disease, feeding difficulties, hypoglycemia, hyperbilirubinemia, temperature instability, sepsis, nervous system damage, and neurodevelopmental delay. Late preterm infants are more likely to have neurodevelopmental impairment compared to term infants, with potential long-term consequences extending into later life, such as cognitive delay, language delay, higher risk of cerebral palsy and attention deficit hyperactivity disorder, autism. The incidence of late preterm birth is increasing worldwide, resulting in increased healthcare costs and resource utilization. The aim of this article is to present a literature review of current trends, challenges, and advances in the care of preterm infants, focusing on their unique comorbidities, developmental risks, and to demonstrate that these preterm infants are at increased risk of maladjustment, morbidity, and mortality during and after the neonatal period compared to term infants. A systematic search of scientific publications in various databases was conducted to identify modern approaches to the management of late preterm infants. The information obtained was systematized and integrated to identify the main risks of maladjustment and features of further development in this group of infants. Early diagnosis, observation and treatment of pregnant women with chronic diseases and pathologies during pregnancy and childbirth, timely detection of high-risk pregnancies, effective antenatal diagnostics and high-quality neonatal care are the main directions of modern perinatology that can improve the prognosis of "late preterm" newborns. A comprehensive approach, including minimizing unnecessary late preterm births, careful assessment, optimized treatment, parental education and follow-up care, is essential for improving outcomes and reducing long-term risks. This review highlights the importance of evidence-based prevention and treatment strategies, while calling for further research to improve outcomes in this vulnerable group of infants.*

Key words: Morbidity; Newborn; Premature Birth; Prognostic Factors; Early Diagnosis.

ISSN 2786-6661
eISSN 2786-667X

Introduction

Preterm birth, defined as birth before 37 completed weeks of gestation, is a major global health problem and a leading cause of neonatal mortality.

Although the risks associated with extremely preterm infants are well documented, attention is now increasingly shifting to late preterm infants (LPI). LPI are those born between 34 $^{0/7}$ and 36 $^{6/7}$ weeks of gestation and account for a significant proportion of these preterm births. LPI account for almost 75% of all preterm births.

Late preterm infants are physiologically less mature and have limited compensatory responses to the extrauterine environment compared with full-term infants. Although late preterm infants are the largest subgroup of preterm infants, research on this group is scarce. These infants are considered to be un– or minimally cared for. However, late preterm infants have a 2 – to 3-fold increased risk of complications such as hypothermia, hypoglycemia, respiratory distress, poor feeding, jaundice, sepsis, and rehospitalization after initial discharge [1,2].

The increasing incidence of LPI highlights the need for improved data collection, standardized definitions, and targeted medical interventions to address the unique challenges faced by this vulnerable population [3].

In this literature review, we review various aspects of late preterm infants, such as etiology, immediate, and long-term outcomes. This population has attracted increased attention over the past decade, prompting an increase in clinical research and the development of targeted policies and recommendations to optimize care and outcomes for these vulnerable infants [4,5].

Aim

The aim of this article is to present a literature review of current trends, challenges, and advances in the care of late preterm infants, focusing on their unique comorbidities, developmental risks, and to demonstrate that these preterm infants are at increased risk of maladaptive adaptation, morbidity, and mortality during and after the neonatal period compared with term infants.

Materials and Methods

A systematic search of scientific publications for 2020-2024 was conducted in various databases to identify modern approaches to the management of late preterm infants. The information obtained was systematized and integrated to identify the main risks of adaptation and further development in this group of infants.

Review and discussion

The etiology of late preterm birth is multifactorial and includes a range of medical, obstetric, and lifestyle factors. Approximately 50–75% of late preterm births are the result of spontaneous preterm labor or spontaneous rupture of membranes [1].

Medical and obstetric factors leading to late preterm birth include:

- Having a history of a previous preterm birth significantly increases the risk of subsequent late preterm birth.
- Carrying twins or higher multiples increases the likelihood of preterm birth, including late preterm birth.
- Infections, particularly those affecting the amniotic fluid and lower genital tract.
- Maternal conditions such as hypertension, diabetes, and thyroid disease.
- Structural abnormalities of the uterus, placenta, or fetus can lead to preterm birth.
- Smoking and drug use.
- Physical trauma.
- Stress
- Air pollution.
- Certain medications, including NSAIDs and some antibiotics, may increase the risk of preterm birth.
- Maternal older age [6].

Some preterm births have medical indications due to maternal or fetal health problems. For example, a study of 2693 late preterm births found that 32.3% were iatrogenic and 56.7% were due to neonatal indications [7].

Late preterm infants have a higher mortality rate than term infants, but lower than very preterm infants. Recent studies have identified an increased risk of mortality among LPI during and after the neonatal period. A systematic review that included studies from 2003 to 2010 involving more than 2.2 million LPI and 25.5 million term infants found that LPI have a significantly higher risk of death in the first 28 days of life. This increased risk persists through the first

ISSN 2786-6661
eISSN 2786-667X

year of life. Although LPI are often perceived as physiologically closer to term infants, they still have an increased risk of morbidity due to developmental immaturity and structure [8].

Short-Term Clinical Outcomes

LPI are particularly vulnerable to respiratory problems, including respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), apnea, bradycardia, and other pulmonary complications. The incidence of these respiratory problems is significantly higher in LPI compared to term infants [3]. RDS affects 5.2–6.4% of LPIs, with its severity decreasing with increasing gestational age. Surfactant therapy is required for a small percentage of LPI, and mechanical ventilation is often necessary for patients with more severe respiratory disease. TTN, characterized by delayed alveolar fluid clearance, affects 3.9%–9.9% of LPI, with a marked decrease in incidence with antenatal steroid use. Apneic and hypoxic episodes are common in LPI, occur at a higher rate than in term infants, and may result in prolonged hospital stays. In addition, LPI face long-term respiratory risks, including increased risk of wheezing, pneumonia, and bronchiolitis. LPI are at increased risk of developing hyperbilirubinemia due to a combination of factors such as short red blood cell lifespan, immature liver function, and poor nutrition. Studies show that more than half of LPI require phototherapy for jaundice, and this condition is one of the leading causes of readmission after discharge. The risk of bilirubin-induced neurological damage, including cardiac jaundice, is higher in LPI, even when bilirubin levels are below therapeutic thresholds. Early intervention and close monitoring are important to prevent serious consequences such as long-term hearing loss. Feeding difficulties are common in LPI due to immaturity of oral motor skills, coordination and bowel motility, and poor postural control during breastfeeding. LPI also have higher energy requirements and are at risk of stunted growth and dehydration. These feeding problems contribute significantly to readmission, with the risk of feeding complications for LPI being six times higher than for full-term infants. Early intervention and support to optimize feeding practices are critical to improve outcomes and prevent further morbidity [9]. LPI are at increased risk of developing hypoglycemia due to low glycogen stores, immaturity of enzymes involved in glucose release, poor feeding and inadequate nutrient intake, cold stress, infection, and underlying respiratory problems. The physiological postnatal decline in blood glucose concentrations is more pronounced in LPI compared to term infants, and the lack of fully developed compensatory mechanisms further increases the risk of hypoglycemia. Numerous studies have consistently highlighted the higher incidence of hypoglycemia in LPI. The overall incidence of hypoglycemia in LPIs has ranged from 8.7% to 50% across studies and analysis also confirmed that LPIs have a significantly higher risk of hypoglycemia compared to full-term infants [10].

LPI are at increased risk of temperature instability and cold stress due to:

– Large surface area relative to body mass, which contributes to increased heat loss.

– LPI have less brown and white fat, which are necessary for insulation and heat retention. Research suggests that a significant number of LPI experience temperature instability during initial hospitalization. Wang et al. found that 10% of newborns developed hypothermia, while other studies reported that more than half of LPI were diagnosed with hypothermia during hospitalization [8]. Hypothermia is one of the leading causes of prolonged hospital stays for LPI. Recent findings highlight the importance of early detection and proactive thermal management. Strategies such as plastic wrap and bags have been shown to significantly reduce the incidence of hypothermia in LPI.

Late preterm infants are at increased risk of sepsis and infection due to several factors, including:

– immature innate immunity: the immune system of LPI is not fully developed, making them more susceptible to infections;

– poor immunological response: LPI have a weaker immune response compared to full-term infants, which hinders their ability to fight infections;

– internal infection: conditions such as chorioamnionitis during pregnancy increase the likelihood of LPI infections;

ISSN 2786-6661
eISSN 2786-667X

– invasive procedures: procedures such as catheterization or intubation also increase the risk of infection.

A large observational cohort study conducted by the Pediatrix medical group found that the combined incidence of early – and late-onset sepsis was 4.42 and 6.30 episodes per 1000 hospitalizations, respectively. Gram-positive organisms were the primary cause of early – and late-onset sepsis in LPI. LPI are five times more likely to have culture-positive infections than term infants [11].

LPIs experience lower incidences of severe IVH or PVL compared to very preterm or extremely preterm infants, but their risks remain elevated relative to term neonates. Due to the absence of universal screening guidelines for neuroimaging in LPIs, the reported rates of IVH and PVL vary widely. While severe cystic PVL is rare in LPIs, subtle forms may occur, often linked to maternal chorioamnionitis, cardiovascular instability, or hypoxic-ischemic events [12].

Long-Term Neurodevelopmental Outcomes

The period between 34 and 40 weeks of gestation represents a critical phase for brain development. At 34 weeks, the cortical volume is approximately half, and the brain weight is about 65% of that of a term neonate. Neuronal proliferation, synaptogenesis, and myelination occur at a rapid pace during this time, rendering the brain highly susceptible to injury. This vulnerability is amplified by hypoxic events, nutritional deficits, and maternal infections or inflammation [3]. Studies using advanced imaging have revealed widespread white matter microstructural alterations in LPI at term-equivalent age, indicative of delayed or disrupted brain development. Such disruptions may underlie the observed developmental challenges in this population. Epidemiological studies have consistently shown that LPI are at an elevated risk for long-term neurodevelopmental delays compared to term infants. While many of these studies are retrospective and include moderate preterm infants (32–34 weeks gestation), their findings highlight the significant neurodevelopmental challenges faced by LPI. Variations in assessment tools, ages of evaluation, and study designs - often conducted two decades ago—limit direct comparisons. However, the consensus is clear: LPI have increased risks for motor, cognitive, and behavioral delays compared to term neonates [13,14].

LPI are at an increased risk for cognitive delays, as highlighted by multiple studies. Research has reported higher rates of developmental delay in LPIs compared to term infants, with adjusted odds showing a significant association. Lower scores for both the Mental Developmental Index and Psychomotor Developmental Index have been observed in LPIs during early childhood. In addition, a greater proportion of LPI have been found to exhibit significant delays in development. These cognitive delays appear to persist into childhood, with LPI being more likely than term controls to have full-scale and performance IQ scores below the threshold for borderline intellectual functioning. These findings were noted to be independent of socioeconomic status and maternal IQ. However, some studies have not consistently found significant differences in cognitive outcomes between LPIs and term infants. This variability underscores the need for further research to understand the contributing factors and to identify strategies for early intervention to support cognitive development in LPI [10].

The risk of speech and language delays in LPI has been highlighted in several studies. Thus, LPIs were more likely to experience speech and language delays at 18 and 36 months compared to term infants. A retrospective cohort study by Rabie et al. observed that LPI had an increased risk of developmental speech and language disorders compared to term infants, with an adjusted hazard ratio of 1.36. Conversely, utilizing the Peabody Picture Vocabulary Test for children aged 4 to 5 years, reported no statistically significant difference in receptive vocabulary delays between LPI and term infants, with rates of 13.1% and 12.7%, respectively. These findings indicate variability in outcomes, suggesting the need for further research and tailored interventions [15,16].

LPI are at a higher risk for cerebral palsy (CP) compared to term infants, despite lower rates of severe IVH and PVL during the neonatal period. Key predictive factors for CP in LPIs included

ISSN 2786-6661
eISSN 2786-667X

birth resuscitation, antibiotic treatment during the initial hospitalization, a 1-minute Apgar score below 7, and the presence of intracranial hemorrhage. LPI were more than three times as likely to be diagnosed with CP by the age of five when compared to term infants. These findings emphasize the need for close monitoring and early intervention in this vulnerable population [17].

LPI often face challenges in school performance and readiness, as reported by several studies. By the end of the first year of school, 59% of LPIs had not reached a good level of overall achievement compared to 51% of full-term children. By the third year, LPIs were found to have a 36% increased risk of poor academic performance. LPIs were also found to have a 30% higher likelihood of requiring special education services and demonstrated lower math and English scores on standardized tests. Similarly, LPI were reported to have lower reading scores in kindergarten and first grade, with the risk for poor reading and math scores persisting into later grades. Teacher evaluations from kindergarten to fifth grade consistently rated LPIs below average in math and reading, and participation in special education programs was higher among LPIs. Additional research highlighted that LPIs were at a 19% higher risk of suspension in kindergarten and showed a 10–13% increased risk of disabilities in prekindergarten at 3 and 4 years of age. These findings underscore the long-term educational vulnerabilities of LPI and the need for targeted support to improve outcomes [18].

LPI have been found to have a higher risk of developing symptoms of attention deficit hyperactivity disorder (ADHD). A large-scale Swedish National Registry study found a gradual increase in the likelihood of ADHD medication use in childhood and adolescence, correlating with increasing immaturity at birth. Limited studies have reported the prevalence of autism spectrum disorder (ASD) in LPI. In a recent cohort study conducted researchers found that 14.5% of LPI scored above the clinical threshold for ASD on the Modified Autism Checklist for Early Childhood, compared with 9.3% in full-term infants. The positive failure rate for autism was higher in late preterm infants (2.4%) compared to term infants (0.5%) at follow-up assessments, suggesting an increased risk of ASD in this group. Although more research is needed, these findings highlight the importance of early screening for autism in late preterm infants [19,20].

LPI have higher rates of readmission compared to term infants, especially those born between 34–36 weeks. Studies in different regions consistently indicate jaundice as a major cause of readmission, with respiratory and gastrointestinal problems being more common after the neonatal period [3,7]. Management of LPI involves a multidisciplinary team that ensures clinical stability, adequate feeding, temperature control, and safe use of a car seat before discharge. High-risk LPI require referral to clinics for further neurodevelopmental monitoring for further management.

Significant progress has been made in reducing LPI through strategies such as smoking prevention, 17-hydroxyprogesterone administration, cerclage for short cervix, and prudent use of fertility treatments. Preventing unplanned births, improving prenatal care, and promoting increased spacing of pregnancies are also key. Interventions such as betamethasone for at-risk women may reduce respiratory complications of LPI. These interventions may improve both short-term and long-term outcomes for infants. Future research on LPI should focus on prospective studies to better understand its incidence and long-term outcomes [1,3].

Conclusions

Late preterm infants are at high risk of postnatal maladjustment and are prone to complications affecting multiple organ systems, including respiratory disease, feeding difficulties, hypoglycemia, hyperbilirubinemia, temperature instability, sepsis, and neurodevelopmental delay.

Therefore, late preterm infants are a high-risk group and require special attention during their hospital stay, including delayed discharge and follow-up pediatric follow-up very soon after discharge.

A comprehensive approach that includes minimizing late preterm birth, thorough clinical and laboratory assessment, optimized care pathways, parent education, and follow-up care is essential to reduce short – and long-term risks in this group of infants.

ISSN 2786-6661
eISSN 2786-667X

Financing

The investigation of this clinical case did not receive any specific grants from financial institutions in the public, commercial, or non-profit sectors.

Conflicts of Interest

There were no conflicts of interest during the conduct of the study.

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article

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Ukrainian Scientific Medical Youth Journal
Issue 3 (157), 2025
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ISSN 2786-6661
eISSN 2786-667X

Пізні передчасно народжені діти: сучасні тенденції та виклики

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Анотація: *пізні недоношені діти, народжені між 34 0/7 і 36 6/7 тижнями вагітності, становлять значну підгрупу недоношених дітей, на них припадає близько 75% усіх новонароджених від передчасних пологів. Хоча пізні недоношені діти нерідко сприймаються як фізіологічно ближчі до доношених дітей, але вони мають підвищений ризик захворюваності та смертності через незрілість розвитку та структуру. Останні дослідження свідчать про те, що недоношені немовлята мають високий ризик порушення післяпологової адаптації та схильні до ускладнень, що впливають на численні системи органів, включаючи респіраторні захворювання, труднощі з годуванням, гіпоглікемію, гіпербілірубінемію, нестабільність температури, сепсис, пошкодження нервової системи та затримку нервового розвитку. Пізні недоношені немовлята мають більшу ймовірність порушення нейророзвитку порівняно з доношеними немовлятами з потенційними віддаленими наслідками, які поширюються на подальше життя, включаючи когнітивну затримку, відставання в мовному розвитку, вищий ризик розвитку церебрального паралічу та синдрому дефіциту уваги з гіперактивністю, аутизму. Захворюваність на пізні передчасні пологи зростає в усьому світі, що призводить до збільшення витрат на охорону здоров'я та використання ресурсів. Метою цієї статті є представити огляд літератури про сучасні тенденції, проблеми та досягнення у догляді за пізніми недоношеними немовлятами, зосередивши увагу на їхніх унікальних супутніх захворюваннях, ризиках розвитку, а також продемонструвати, що ці недоношені немовлята мають підвищений ризик дезадаптації, захворюваності та смертності під час і після періоду новонародженості порівняно з доношеними немовлятами. Проведено системний пошук наукових публікацій у різних базах даних з метою виявлення сучасних підходів до ведення пізніх недоношених дітей. Отриману інформацію було систематизовано та інтегровано з метою виявлення основних ризиків дезадаптації та особливостей подальшого розвитку у цієї групи немовлят. Рання діагностика, спостереження та лікування вагітних із хронічними захворюваннями та патологіями під час вагітності та пологів, своєчасне виявлення вагітності високого ризику, ефективна антенатальна діагностика та якісний неонатальний догляд є основними напрямками сучасної перинатології, які можуть покращити прогноз «пізніх недоношених» новонароджених. Комплексний підхід, включаючи мінімізацію пізніх передчасних пологів, ретельну оцінку, оптимізоване лікування, освіту батьків і подальший догляд, мають важливе значення для покращення результатів і зниження довгострокових ризиків. Цей огляд підкреслює важливість стратегій профілактики та лікування, заснованих на фактичних даних, водночас закликаючи до подальших досліджень для покращення результатів у цій вразливій групі немовлят.*

Ключові слова: захворюваність, новонароджений, передчасні пологи, прогностичні фактори.