

Infants Born Late Preterm: Definition, Physiologic and Metabolic Immaturity, and Outcomes

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Author Disclosure
Dr Engle has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives After completing this article, readers should be able to:

1. Define "late preterm," "early term," and "term" gestations.
2. Describe the rationale for use of the term "late preterm" rather than "near term."
3. Know the physiologic, anatomic, and metabolic basis for complications in infants born late preterm.
4. Explain the impact of late preterm birth on developmental, academic, behavioral, and social outcomes.

Abstract

Infants born late preterm are immature and have significant risks for short-term and long-term morbidities. During the birth hospitalization and first weeks after birth, hypothermia, respiratory distress, apnea, temperature instability, hypoglycemia, hyperbilirubinemia, and feeding problems may result in prolonged hospital stays or readmission for additional care. Mortality risk is also greater during the first postnatal year. A higher risk for long-term complications, including developmental delays, school failure, behavior disorders, and social disabilities, has been identified in children and young adults. Priorities in management of infants born late preterm include early identification of acute medical complications and long-term disabilities. Efforts to avoid late preterm birth, if medically safe for fetus and mother, also are warranted.

Introduction

Infants born at 34–0/7 to 36–6/7 weeks' gestation have been defined as "late preterm." This population of infants has been a focus of attention because of their large and growing contribution to the incidence of preterm births and recent investigations that have identified short- and long-term complications that differentiate late preterm and term infants. The focus of this review is to discuss the definition of "late preterm" as it relates to "near term" and to describe the physiologic and anatomic deficiencies that predispose to acute and long-term outcomes following late preterm birth.

Definition of Late Preterm

"Late preterm" was defined by participants of the 2005 Workshop on "Optimizing Care and Outcome of the Near-Term Pregnancy and the Near-Term Newborn Infant" sponsored by the National Institutes of Health (Fig. 1). The definition of "late preterm" birth, or birth at 34–0/7 through 36–6/7 weeks after the onset of the first day of the mother's last menstrual period, was developed to guide clinical care and research and emphasizes the premature nature of such infants. Prior to this workshop, "near term" frequently was used to describe this population because survival and outcomes were believed to be similar. "Near term" also implied that infants were physiologically "near enough" to term infants that late preterm pregnancy and offspring could be managed similarly. "Term" birth, as defined by the American Academy of Pediatrics, American College of Obstetricians and Gynecologists, and the World Health Organization, is birth during the first day of the 38th gestational week (37–0/7 weeks or 260 days) through the end of the 42nd week (41–6/7 weeks or 294 days) after the onset of the last menstrual period.

Late preterm infants account for greater than 70% of preterm births in the United States

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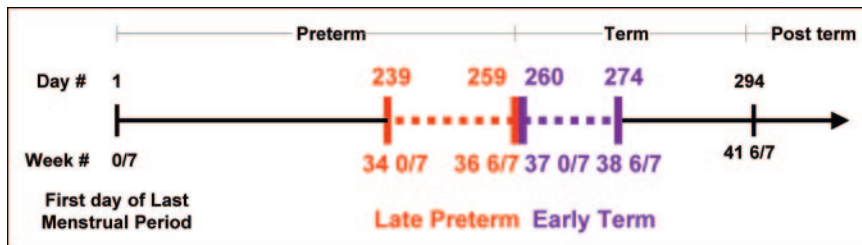


Figure 1. Definitions of "late preterm" and "early term." Adapted from Engle W, Kominiarek M. *Clin Perinatol*. 2008;35:325–341.

(Fig. 2). The proportion of births that were late preterm in 1990 was 7.3%; in 2005, the proportion had increased significantly to 9.1%, equal to approximately 377,000 infants. In comparison, the proportion of infants born at fewer than 34 weeks' gestation has remained relatively stable during this same time period. Thus, the increase in late preterm births is the dominant contributor to the increased rate of preterm births in the United States in recent years.

Physiologic and Metabolic Immaturity of Late Preterm Infants

Late preterm infants are physiologically and metabolically immature. A complete understanding of the extent of immaturity in such infants is largely unstudied. Management strategies, therefore, are extrapolated from knowledge about extremely preterm and term infants and general health-care principles.

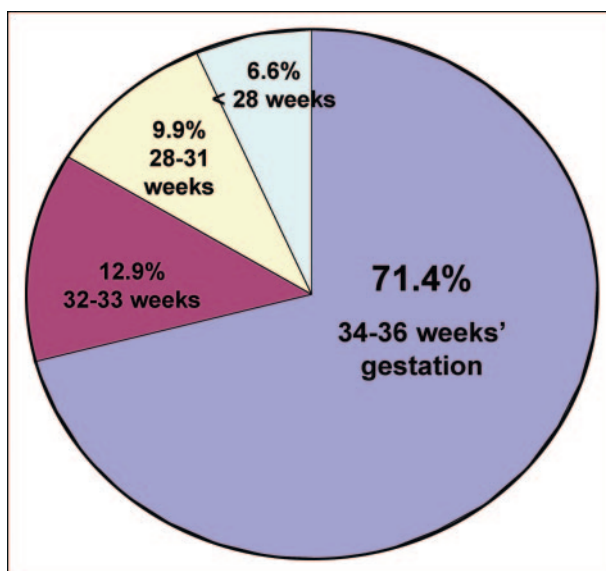


Figure 2. Percent distribution of preterm births: United States, 2005. Centers for Disease Control and Prevention. *National Center for Health Statistics Final Natality Data 2005*.

The continuum for development of physiologic maturity between preterm and term newborn populations can vary substantially. Such variability reflects the biologic differences encountered by infants who have identical gestational ages. Some infants born late preterm are as large as and behave physiologically like infants born early term or at 37–0/7 weeks' gestation to

38–6/7 weeks' gestation (Fig. 1). Other late preterm infants experience complications that are more common in infants born at fewer than 34 weeks' gestation (Fig. 3):

- Hypothermia
- Respiratory distress
- Apnea
- Hypoglycemia
- Hyperbilirubinemia and jaundice
- Feeding problems
- Developmental delays
- School failures
- Behavioral and social disabilities
- Mortality

Physiologic, anatomic, and biochemical deficiencies in late preterm infants predispose to both short- and long-term complications. Immature body structure and physiologic function of body systems may lead to respiratory distress, apnea, hypothermia, hypoglycemia, hyperbilirubinemia, poor feeding, developmental and behavioral difficulties, and poor social outcomes.

Respiratory Distress

Late preterm infants are born during the transition from the terminal sac period to the alveolar period of lung development. During the terminal sac stage, terminal respiratory units are composed of alveolar saccules lined with cuboidal type II (source of surfactant) and flat type I epithelial cells. Functional deficiencies in surfactant and management of lung water also occur in many late preterm infants. Such immature structural and functional deficiencies predispose late preterm infants to respiratory failure. The cardiopulmonary transition that is necessary immediately after birth for postnatal adaptation may be delayed in late preterm infants, which is reflected in higher rates of retained fetal lung liquid syndrome (transient tachypnea) and respiratory distress syndrome than in term counterparts (Fig. 3). During the alveolar stage of lung development, mature alveoli lined primarily with extremely thin type I epithelial cells appear. Pulmonary

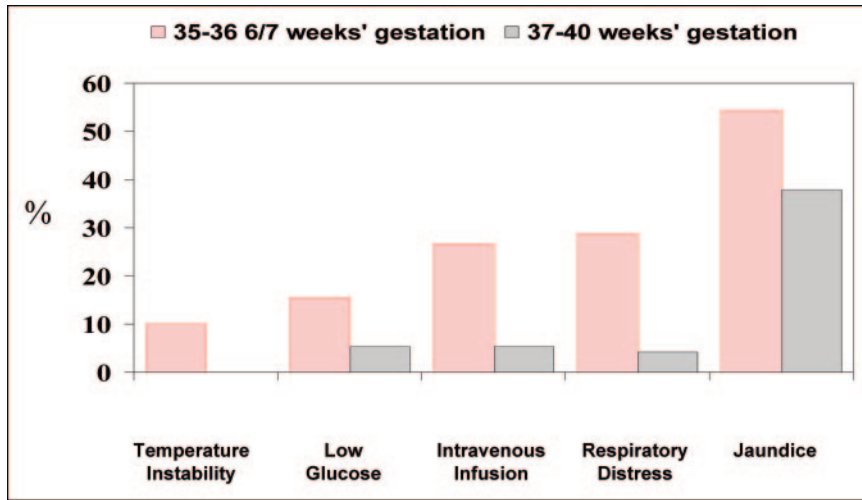


Figure 3. Morbidity during birth hospitalization among late preterm and term infants. Adapted from Wang ML. *Pediatrics*. 2004;114:372–376.

capillaries also begin to protrude into the space of each terminal sac, and adult surfactant pool sizes are attained. Because surfactant pool size and surfactant activity are established and mature alveolar structures are present, term infants are at significantly lower risk of respiratory compromise than late preterm infants.

Apnea

Apnea of prematurity is present in nearly 100% of infants born at fewer than 28 weeks' gestation. The incidence of apnea in late preterm infants is 4% to 7%, significantly lower than in extremely preterm infants, but significantly greater than in term infants (<1% to 2%). Predisposition to apnea occurs because of an increased susceptibility to hypoxic respiratory depression, diminished central chemosensitivity to carbon dioxide, increased sensitivity to

respiratory depression with laryngeal stimulation, immature pulmonary irritant receptors, and decreased upper airway dilator muscle tone. Central nervous system immaturity also is suspected to contribute to apnea in late preterm infants. The brains of such infants are significantly smaller, less myelinated, and contain fewer gyri and sulci than term infants (Figs. 4 and 5).

Temperature Regulation

Thermoregulation by infants born late preterm is compromised by low amounts of brown and white fat, immature hypothalamic function, and low concentrations of hormones

responsible for brown-fat metabolism (such as prolactin, leptin, norepinephrine, triiodothyronine, and cortisol). Fat accumulation and associated hormone activity in the fetus peaks at term. During the cold stress that follows birth, hypothermia is experienced more often by late preterm infants than term infants because of a lower capacity to generate heat from brown adipose tissue and lower stores of white fat for insulation from the cold (Fig. 3). The larger surface area-to-weight ratio and smaller size of the late preterm infant also contributes to the higher incidence of hypothermia.

Glucose Metabolism

Hypoglycemia can occur in newborns at all gestational ages because of insufficient metabolic compensation after the maternal source of glucose is lost following birth. The incidence of hypoglycemia is correlated inversely

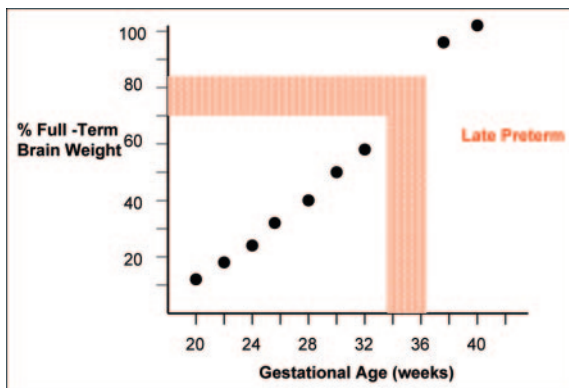


Figure 4. Brain weight versus gestational age. Adapted from Kinney HC. *Semin Perinatol*. 2006;30:81–88.

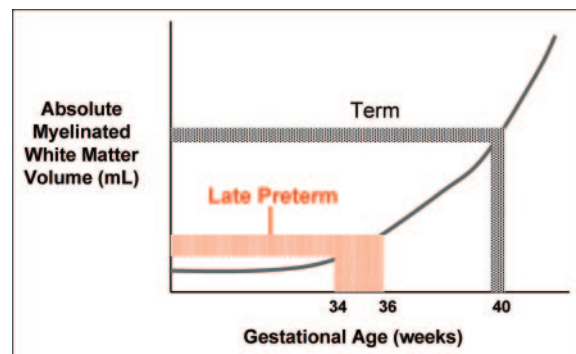


Figure 5. Myelination versus gestational age. Adapted from Huppi PS, et al. *Ann Neurol*. 1998;43:224–235.

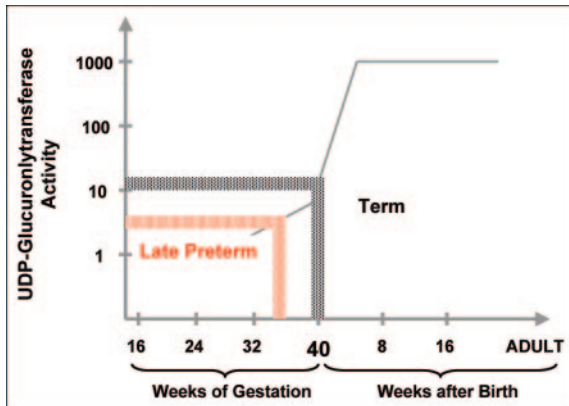


Figure 6. UDP-glucuronyltransferase activity. Adapted from Kawade N, Onishi S. *Biochem J*. 1981;196:257–260.

with gestational age, with late preterm infants having a greater risk than term infants (Fig. 3). The susceptibility for hypoglycemia decreases, usually within 12 to 24 hours after birth, because concentrations of enzymes responsible for gluconeogenesis and ketogenesis increase. Preterm infants, including those born late preterm, are predisposed to hypoglycemia because of immature hepatic glycogenolysis and adipose tissue lipolysis, hormonal dysregulation, deficient hepatic gluconeogenesis and ketogenesis, and low glucose reserves.

Bilirubin Metabolism

Jaundice occurs more frequently in late preterm infants than term infants (Fig. 3). The duration of jaundice is often more prolonged, and peak concentrations of indirect bilirubin frequently are higher than found in term infants. The primary factors causing physiologic indirect hyperbilirubinemia are delayed maturation and lower concentrations of uridine diphosphoglucuronate glucuronosyltransferase, the rate-limiting enzyme for conjugation of bilirubin (Fig. 6). The enterohepatic circulation of bilirubin also contributes to bilirubinemia in late preterm infants, especially those infants whose feeding skills are insufficient or whose gastrointestinal motility is slow or impaired. Late preterm infants are twice as likely as term infants to have significantly elevated bilirubin values during the birth hospitalization. In addition, the peak in bilirubin concentration may occur 5 to 7 days after birth in late preterm infants, a time when many such infants are at home. Parental education and follow-up with a health-care professional within 2 or 3 days of discharge for those late preterm infants discharged fewer than 3 days after birth are important care management priorities.

Feeding and Gastrointestinal Function

Feeding behavior and gastrointestinal function are immature in late preterm infants. They can have feeding difficulties because of low oromotor tone, incoordination of the suck-swallow-breathe sequence, and gastrointestinal dysmotility. Importantly, breastfeeding late preterm infants may be discharged before being challenged with the volume of milk released when the mother's milk supply is established. Inability to handle human milk volume may be exacerbated by difficulty sustaining oral feeding coordination. It is important to assess the late preterm infant for feeding success during the first days and weeks after birth, whether in the hospital or home.

Brain Development and Long-term Development, Education, Behavior, and Social Function

Brain development progresses throughout the fetal and childhood periods. The late preterm brain weighs about two thirds that of a term infant, has significantly fewer gyri and sulci, and is less myelinated (Figs. 4 and 5). Furthermore, preterm infants at term ages have relatively immature microstructural cerebral white matter than term infants, indicating that preterm birth has a negative

Table 1. Maternal and Fetal Conditions Predisposing To Late Preterm Birth and Associated Complications and Outcomes

Maternal

- Preterm labor
- Preterm premature rupture of membranes
- Chorioamnionitis
- Preeclampsia
- Diabetes
- Antepartum hemorrhage
- Multiple gestation
- Thrombophilia
- Cardiac disease
- Chronic pulmonary disorders (such as asthma)
- Renal disease
- Teenage mother
- Maternal tobacco use

Fetal

- Intrauterine growth restriction
- Fetal distress

Table 2. School-Age Outcomes and Healthy Late Preterm Infants

Outcome	Age (years)	% Near term (n=22,552)	% Term (n=164,628)	Relative Risk (95% Confidence Interval) Adjusted
Developmental delay/disability	0 to 3	4.8	3.2	1.46 (1.42–1.50)
PreK at 3 years*	3	4.8	4.0	1.18 (1.14–1.21)
PreK at 4 years*	4	7.7	6.6	1.15 (1.13–1.18)
Not ready to start school	4	4.7	4.1	1.09 (1.05–1.12)
Special education	5	13.6	11.8	1.13 (1.11–1.15)
Retention	5	7.6	6.2	1.11 (1.08–1.14)
Suspension	5	1.3	1.2	0.97 (0.91–1.04)

*Referral to Florida Part B program, Prekindergarten Program for Children With Disabilities. Adapted from Morse SB, Tang Y, Roth J. *Pediatr Res.* 2006;1(suppl):158.

Table 3. Gestational Age and Risk of Hyperkinetic Disorder

Gestational Age (weeks)	Controls (n=20,100)	Attention-deficit/Hyperactivity Disorder (n=834) (%)	Adjusted Relative Risk (95% Confidence Interval)
<34	298	34 (11.4)	2.7 (1.8–5.4)
34 through 36	544	37 (6.8)	1.7 (1.2–2.5)
37 through 39	6,629	298 (4.5)	1.1 (0.9–1.3)
40 through 42	12,365	465 (3.8)	Reference
43 through 44	264	9 (3.4)	1.0 (0.5–2.0)

Adapted from Linnet KM, et al. *Arch Dis Child.* 2006;9:655–660

Table 4. Social Outcomes in 23- to 29-year-old Swedish People By Gestational Age

	Gestational Age (%)					P value
	24 to 28 weeks (n=317)	29 to 32 weeks (n=2,630)	33 to 36 weeks (n=19,166)	37 to 38 weeks (n=68,541)	39 to 41 weeks (n=431,656)	
Post secondary education	26	34	36	38	40	0.001
Employed in 2002	68	70	73	73	74	0.001
Social welfare in 2002	5.0	3.0	2.8	2.2	1.8	0.001
Lives with parents	18	18	17	17	15	0.001
Disability (sickness pension, disability allowance, disability assistance)	13.2	5.6	2.7*	1.9*	1.5	0.001

*Attributable risk for disability: 74% of all disability is associated with birth at 33 to 38 weeks' gestation (late preterm and early term groups) due to large number (versus high incidence in more preterm infants) (n=522,310, 23 to 29 years old). Adapted from Lindstrom K, et al. *Pediatrics.* 2007;120:70–77

impact on brain development. Immature nervous system structure and function, an adverse intrauterine milieu in pregnancies shortened for maternal or fetal conditions (Table 1), and complications of preterm birth likely contribute to the developmental, behavioral, educational, and social disabilities described in late preterm infants (Tables 2 through 4).

In a large population of late preterm infants considered healthy at birth and assessed in prekindergarten and kindergarten, significantly more had developmental delay and were unsuccessful in school compared with healthy term infants (Table 2). The incidence of attention-deficit/hyperactivity disorder is 1.7 times more frequent in late preterm than in term infants (Table 3). Furthermore, in a large cohort of Swedish young adults, late preterm birth was associated with greater rates of disability and need for welfare support and lower rates of post secondary education and employment (Table 4). The Swedish cohort of late preterm and early term infants (defined at 33 to 36 weeks' gestation and 37 to 38 weeks' gestation, respectively) significantly contributed to the overall rates of disabilities in the Swedish population; more than 74% of disabilities occur in the 33 to 38 weeks' gestation cohort. Norwegian adults between 20 and 36 years of age who were born late preterm also were found to have higher rates of medical morbidities: cerebral palsy (2.7 times); intellectual disability (1.6 times); disorders of psychological development, behavior, and emotion (1.5 times); schizophrenia (1.3 times); other major disabilities (1.5 times); and any medical disability severely affecting working capacity (1.4 times) than term infants.

Summary

Late preterm infants are born at 34–0/7 through 36–6/7 weeks after the onset of the first day of the mother's last menstrual period. Such infants are premature physiologically, anatomically, and metabolically. Because of immature body systems and exposure to adverse intrauterine environments that often precipitate late preterm birth, late preterm infants have higher risks for acute medical complications, mortality, and long-term disabilities than do term infants. The risks associated with late preterm birth suggest the need for strategies to diagnose and manage complications during the birth hospitalization and first weeks after birth (especially hyperbilirubinemia and feeding dysfunction). Refinement of obstetric paradigms for management of late preterm pregnancies to extend pregnancy duration, if benefits outweigh risks for fetus and mother, also should

be considered because of the recently described complications and outcomes of infants born late preterm.

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the approximate relative risks of learning disabilities and school behavioral problems in high risk and preterm infants.
- Know the prenatal, perinatal, and neonatal risk factors associated with school and behavior problems.



Suggested Reading

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NeoReviews Quiz

4. The rate of preterm births, defined as births at a gestational age of fewer than 37 weeks after the onset of the last menstrual period, has continued to increase in the United States in recent years. Of the following, the overall increase in preterm births in the United States is attributed *most* to an increase in the rate of births of infants of gestational ages:
 - A. 22 to 24 weeks.
 - B. 25 to 27 weeks.
 - C. 28 to 30 weeks.
 - D. 31 to 33 weeks.
 - E. 34 to 36 weeks.

5. Late preterm infants, defined as infants born at a gestational age of 34 to 36 weeks after the onset of the last menstrual period, are physiologically and metabolically immature relative to infants born at term. Whereas some late preterm infants may behave physiologically like infants born at term, others experience perinatal complications similar to those seen commonly in preterm infants of fewer than 34 weeks' gestation. Of the following, the *most* common perinatal complication seen in late preterm infants relative to term infants is:
 - A. Apnea.
 - B. Hyperbilirubinemia.
 - C. Hypoglycemia.
 - D. Hypothermia.
 - E. Respiratory distress.

6. The brain of a late preterm infant weighs about two thirds that of a term infant, has significantly fewer gyri and sulci, and is less myelinated. Late preterm birth has a negative effect on brain development, which increases the risk of developmental, behavioral, educational, and social disability in adulthood. This increased risk of medical morbidities has been confirmed in a Norwegian study of adults, 20 to 36 years of age, who were born late preterm compared with those born at term. Of the following, the relative risk of medical morbidities in adults born late preterm relative to those born at term is *highest* for:
 - A. Cerebral palsy.
 - B. Impaired work capacity.
 - C. Intellectual disability.
 - D. Psychosocial disorder.
 - E. Schizophrenia.

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