CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Updates on an At-Risk Population: Late-Preterm and Early-Term Infants

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The American Academy of Pediatrics published a clinical report on late-preterm (LPT) infants in 2007 that was largely based on a summary of a 2005 workshop convened by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, at which a change in terminology from "near term" to "late preterm" was proposed. This paradigm-shifting recommendation had a remarkable impact: federal agencies (the Centers for Disease Control and Prevention), professional societies (the American Academy of Pediatrics and American College of Obstetricians and Gynecologists), and organizations (March of Dimes) initiated nationwide monitoring and educational plans that had a significant effect on decreasing the rates of iatrogenic LPT deliveries. However, there is now an evolving concern. After nearly a decade of steady decreases in the LPT birth rate that largely contributed to the decline in total US preterm birth rates, the birth rate in LPT infants has been inching upward since 2015. In addition, evidence revealed by strong population health research demonstrates that being born as an early-term infant poses a significant risk to an infant's survival, growth, and development. In this report, we summarize the initial progress and discuss the potential reasons for the current trends in LPT and early-term birth rates and propose research recommendations.

INTRODUCTION

The American Academy of Pediatrics (AAP) published a clinical report on late-preterm (LPT) infants (born between 34 0/7 weeks' gestation and 36 6/7 weeks' gestation; Fig 1) in 2007[1] that was largely based on a summary of the 2005 workshop convened by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.[2] At this workshop, a change in terminology from "near term" to "late preterm" was proposed. This shift in the paradigm recommendation led to a remarkable impact: federal agencies (the Centers for Disease Control and Prevention), professional societies (the AAP and American College of Obstetrics and Gynecology), and organizations (March of Dimes) initiated nationwide

abstract

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Clinical reports from the American Academy of Pediatrics benefit from expertise and resources of liaisons and internal (AAP) and external reviewers. However, clinical reports from the American Academy of Pediatrics may not reflect the views of the liaisons or the organizations or government agencies that they represent.

Dr Stewart and the members of the Committee on Fetus and Newborn conceived the concept of updating the previous American Academy of Pediatrics publication on late-preterm infants, collaborated with Drs Barfield and Raju, and reviewed the manuscript; Drs Barfield and Raju collaborated with Dr Stewart and members of the Committee on Fetus and Newborn and reviewed the manuscript; and both authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

All clinical reports from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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monitoring and educational plans that had a significant effect on decreasing the rates of iatrogenic LPT deliveries, as noted in numerous publications.

Evidence revealed by strong population health research demonstrated that LPT or early-term (ET) births (between 37 0/7 weeks' gestation and 38 6/7 weeks' gestation; Fig 1) pose a significant risk to an infant's survival, growth, and development because of increased morbidities and mortality in these at-risk groups (Fig 2). The 2007 AAP clinical report on LPT births was an important milestone in helping health care providers understand the magnitude of these untimely births and their relative contribution to overall preterm birth and disparities. Neonatologists and pediatricians should be aware of the current and ongoing challenges infants face after being born LPT or ET. Understanding the current terminology, factors contributing to these early deliveries, and long-term implications for growth and development will help in prevention, clinical management, and population-based quality-improvement efforts.

Because LPT infants account for approximately 70% of preterm births in the United States, this is a costly and important public health matter.[3] LPTs represent 7% of all live births; ET infants represent 26% of all live births and 29% of all term infants[4] (Fig 3). Recognition of these at-risk subsets of preterm and term infants has affected perinatal care and launched a robust research endeavor to decrease the number of nonmedically indicated deliveries of infants born LPT and ET[5] while seeking methods to optimize care provided to these patients. There have been more than 500 publications investigating the reasons for LPT and ET while recognizing that there are a number of maternal, fetal, and placental complications for which either LPT or ET birth is warranted.[5]

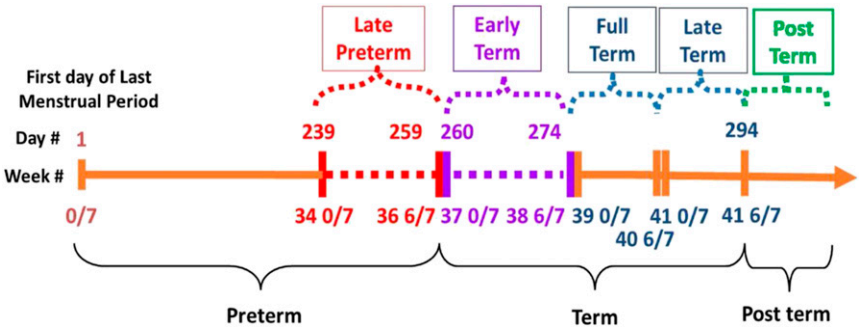

FIGURE 1
Definitions of gestational age periods from LPT to postterm. (Reprinted with permission from Engle WA, Kominiarek M. Late preterm infants, early term infants, and timing of elective deliveries. *Clin Perinatol.* 2008;35(2):325–341.)

After reaching a nadir of 9.57% in 2014, the preterm birth rate increased to 9.97% in quarter 3 of 2018 (Fig 4).[6] This report shows an emerging concern. After nearly a decade of steady decreases, the preterm birth rate is inching upward again. These trends are largely attributable to increases in the rate of LPT births, predominantly among non-Hispanic black and Hispanic women.[4,7] In 2018, the LPT birth rate rose to 7.28% (Fig 5). These trends must be continually monitored with an exploration of causality.[8] In this report, the initial progress is summarized, the potential reasons for the current trends in LPT birth rates are discussed, and practice

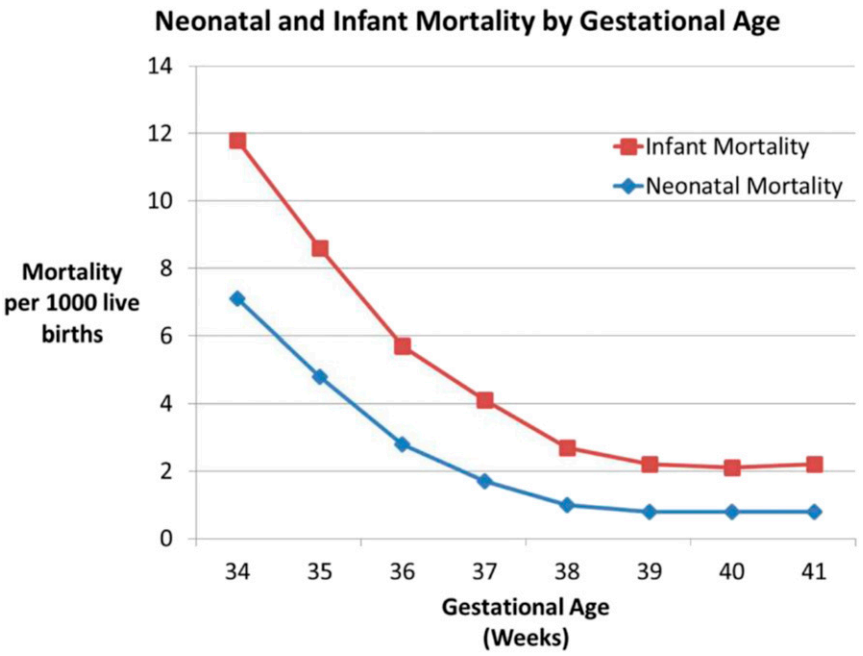

FIGURE 2
Neonatal and infant mortality by gestational age. Adapted from Reddy UM, Ko CW, Raju TN, Willinger M. Delivery indications at late-preterm gestations and infant mortality rates in the United States. *Pediatrics.* 2009;124(1):234–240. (Reprinted with permission from Kardatzke MA, Rose RS, Engle WA. Late preterm and early term birth: at-risk populations and targets for reducing such early births. *NeoReviews.* 2017;18(5):e265–e276.)

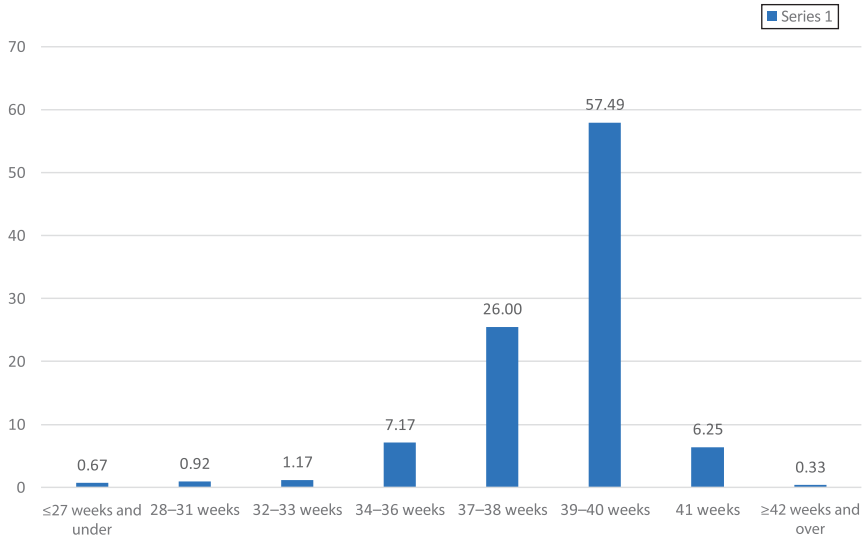

FIGURE 3

Percentage of births by gestational age at birth: United States 2017. (Adapted from Martin JA, Hamilton BE, Osterman MJ, Driscoll AK, Drake P. Births: final data for 2017. *Natl Vital Stat Rep.* 2018; 67:8.)

and research recommendations are proposed.

CURRENT DEFINITIONS

The national emphasis on reducing preterm births and the increase in scheduled deliveries has created confusion around the definition of term gestation.[9] The concept of "term" gestation provides guidance to clinicians and influences the public's perceptions about the optimal timing of delivery for a healthy pregnancy.[9] This nomenclature acknowledged that fetal maturation is a continuum, yet the use of the label of term for pregnancies spanning 37 weeks' 0 days gestation through 41 weeks 6 days' gestation remained unchanged. Recent data demonstrate that maternal and neonatal adverse outcome rates are not the same across the 5-week gestational age range that constitutes term.[9] Rather, the frequency distribution of adverse outcomes is U shaped, with the nadir being between 39 weeks 0 days' gestation and 40 weeks 6 days' gestation.[9] The Defining "Term" Pregnancy workshop recommended that births occurring between 37 weeks 0 days' gestation and 38 weeks 6 days' gestation be designated as ET, those between 39 weeks 0 days' gestation and 40 weeks 6 days' gestation be designated as term, and those occurring at 41 weeks 0 days' gestation through 41 weeks 6 days' gestation be designated as late term.[9,10]

According to the American College of Obstetricians and Gynecologists (ACOG), accurate dating of pregnancy is important to improve outcomes and is a research and public health imperative. As soon as data from the last menstrual period, the first accurate ultrasound examination, or both are obtained, the gestational age and the estimated due date should be determined, discussed with the patient, and documented clearly in the medical record. A pregnancy without an ultrasound examination that confirms or revises the estimated due date before 22 0/7 weeks' gestation should be considered suboptimally dated. For the purposes of research and surveillance, the best obstetric estimate, rather than estimates based on the last menstrual period alone, should be used as the measure for gestational age.[11]

"Implicit in any definition or subclassification of preterm or term birth is the need for accurate dating, which would likely lead to a lower proportion of deliveries categorized as postterm or early term."[8] The ACOG considers first-trimester ultrasonography to be the most accurate method to establish or confirm gestational age. Pregnancies without an ultrasonographic examination confirming or revising the estimated due date before 22 0/7 weeks' gestation should be considered suboptimally dated. There is no role for elective delivery in a woman with a suboptimally dated pregnancy. Although guidelines for indicated LPT and ET deliveries depend on an accurate determination of gestational age, women with suboptimally dated pregnancies should be managed according to these same guidelines because of the lack of a superior alternative.[12]

After the 2005 *Eunice Kennedy Shriver* National Institute of Child Health and Human Development workshop, there were concerns about unintended consequences, including an increase in stillbirths[13] and increasing the risks for the mother and her fetus by the avoidance of indicated LPT deliveries. Current ACOG and Society for Maternal-Fetal Medicine recommendations state that there are a number of maternal, fetal, and placental complications for which either an LPT or ET delivery is warranted. The timing of delivery in such cases must balance the maternal and newborn risks of LPT and ET delivery with the risks associated with further continuation of pregnancy. Deferring delivery to the 39th week is not recommended if there is a medical or obstetric indication for earlier delivery.

PATHOGENESIS OF PRETERM BIRTHS

The pathogenesis of preterm birth is not completely understood. Two-thirds of preterm deliveries occur as

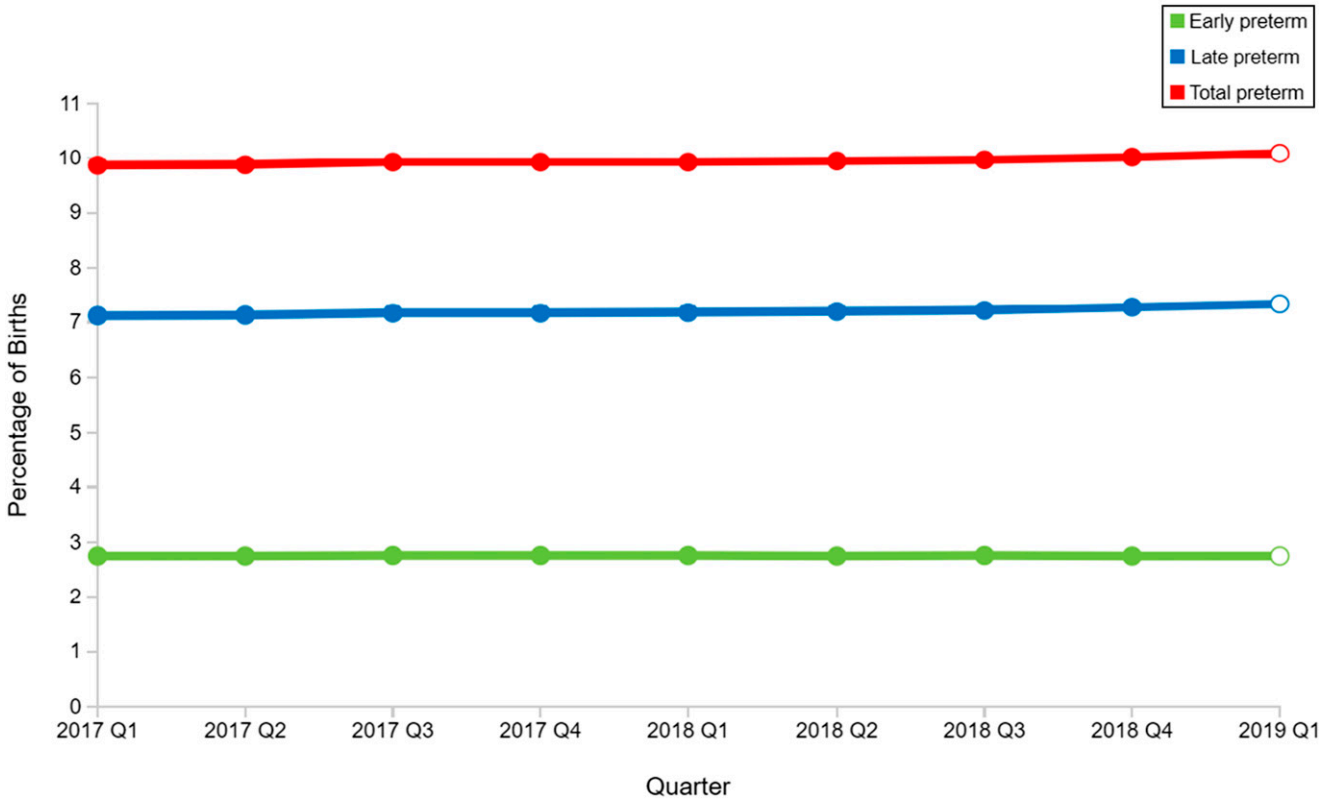

FIGURE 4

Quarterly preterm birth rates 2017 to quarter 1 of 2019. (Adapted from Rossen LM, Osterman MJK, Hamilton BE, Martin JA. Quarterly Provisional Estimates for Selected Birth Indicators, 2017–quarter 1, 2019. Hyattsville, MD: National Center for Health Statistics NVSS, Vital Statistics Rapid Release Program; 2019.)

a result of spontaneous preterm labor and/or premature rupture of membranes.[14] Risk factors that may contribute to these events include a history of a previous preterm delivery (risk is 1.5–2.0 times higher)[15]; infection; inflammation; maternal stress (acute and/or chronic); uterine, placental, and/or fetal anomalies; short cervix; as well as multifetal pregnancies.[16] Newnham et al[17] recently reviewed current strategies for prevention of preterm birth, which include decreasing smoking during pregnancy, cervical cerclage, judicious use of fertility treatments, prevention of nonmedically indicated deliveries, and the establishment of high-risk obstetric clinics. Public health efforts also contributed, using the Collaboration on Innovation and Improvement Network to reduce infant mortality. In these efforts, states focused on policies and practices to reduce tobacco use in pregnancy and reduce nonindicated preterm delivery.[18,19] State perinatal quality collaboratives, which consisted of teams of clinical and public health members, have also helped to reduce the rates of nonmedically indicated LPT and ET births.[20] Progress has been made in the rate for triplet and higher-order–multiple births, which has been on the decline since 1998 and presently is the lowest in more than 2 decades.[3,21–23] In part from the efforts from the March of Dimes program that no infant be delivered electively before 39 weeks' gestation, the cesarean delivery rate is down 3% from a peak of 32.9% in 2009.[3]

In a large randomized controlled trial, the benefits of a single course of antenatal betamethasone was investigated in women anticipated to deliver between 34 and 37 weeks of pregnancy.[24] Infants of women treated had significantly lower rates of respiratory complications. However, 35 women needed to be treated to improve outcomes in 1 infant, and 24% of steroid-exposed infants developed hypoglycemia compared with 14.9% of those in the placebo group. Thus, despite endorsements by the obstetric professional societies,[25–27] several experts have raised concerns about the routine use of antenatal steroids in women during LPT gestations.[27–29] Pediatric providers, too, need to review a history of antenatal steroid exposure while evaluating LPT infants, including checking for neonatal hypoglycemia.

Use of progesterone for women with a previous history of spontaneous

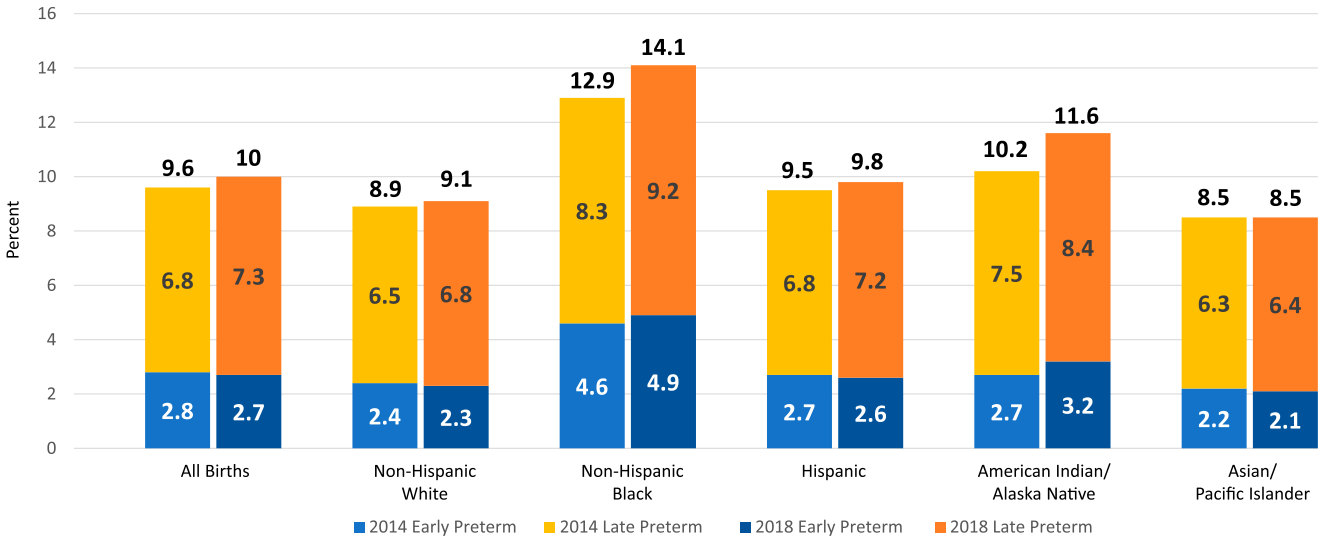

FIGURE 5
Preterm birth rates: United States, overall and by race and ethnicity, 2014 and 2018. Source: National Center for Health Statistics, National Vital Statistics System–Natality.

preterm birth decreases mortality and the need for admission to the NICU. Unfortunately, this improvement is limited to singleton pregnancies, not multiples.[15,30,31] Likewise, 17-hydroxyprogesterone has shown efficacy in women with a short cervix documented by ultrasonography.[32] Screening of women with a previous preterm birth at less than 34 weeks' gestation may identify women with a cervical length <25 mm before 24 weeks' gestation who might potentially benefit from a cervical cerclage.[33,34] Variable access to 17-hydroxyprogesterone, antenatal steroids, prenatal ultrasonography, and early treatment and/or management of preterm prolonged rupture of membranes and/or signs of infection may be contributing to racial disparities in preterm birth rates.[35,36] In addition, lack of adequate prenatal care may delay appropriate management of conditions that develop before and during pregnancies, such as diabetes, hypertension, preeclampsia, and others.[23]

Since the birth of the first US infant conceived with assisted reproductive technology (ART) in 1981, the use of advanced technologies to overcome infertility has resulted in millions of pregnancies and subsequent live births.[37] Since 1995, the number of ART procedures performed in the United States and the number of infants born as a result of these procedures have nearly tripled.[22] Because many ART procedures involve transferring multiple embryos, ART results in multiple-gestation pregnancies and multiple births. The percentage of infants born preterm and very preterm is higher among ART-conceived infants than among infants in the total birth population even with elective single-embryo transfers, which involves the transfer of a single embryo. The contribution of ART to preterm births, the majority of which are also low birth weight, is a factor in the increases observed in the LPT and ET population (Table 1).[38,39]

SHORT- AND LONG-TERM MEDICAL AND NEURODEVELOPMENTAL SEQUELAE FOR LPT AND ET INFANTS

LPT infants are at increased risk for a number of adverse events, including respiratory distress, hypoglycemia, feeding difficulties, hypothermia, hyperbilirubinemia, apnea, seizures, and a higher rate of readmission after initial discharge.[40,41] In addition, LPT infants have higher rates of pulmonary disorders during childhood and adolescence, learning

TABLE 1 The Percentage of Preterm Births by Gestational Age Groups Attributable to ART, 2015

Region	Preterm (<37 wk) Births Attributable to ART, %	Very Preterm (<32 wk) Births Attributable to ART, %	LPT Births (34 + 0/7–36 + 6/7 wk) Attributable to ART, %	ET Births (37 + 0/7–38 + 6/7 wk) Attributable to ART, %
United States and Puerto Rico	5.3	5.4	5.0	2.1

Preterm: <37 wk; very preterm: <32 wk; LPT: 34 0/7–36 6/7 wk; ET: 37 0/7–38 6/7 wk. Source: Analyses of the National ART Surveillance System (NASS) data. Written communication with the Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, April 19, 2018.

difficulties, and subtle, minor deficits in cognitive function.[42] As adults, LPT and ET infants have higher blood pressure and more often require treatment of diabetes.[43] In a Swedish cohort, former LPT infants at 18 to 36 years of age showed an increased mortality rate compared with infants born at 37 to 42 weeks' gestation (hazard ratio, 1.31; 95% confidence interval, 1.13–1.5).[44] Several studies have described an increased risk of neurologic, psychiatric, and developmental conditions in this subset as they mature into adulthood (Table 2).[45] The United States does not have registries tracking outcomes of infants born at LPT gestations into adult age groups. However, on the basis of its national registry, the Swedish National Cohort Study reported a stepwise increase in disability rates in young adulthood, which increased with the degree of preterm birth.[46]

LENGTH OF STAY AND DISCHARGE CRITERIA

The duration of birth hospitalization correlates with gestational age at birth.[47,48] Among 235 LPTs at 1 birth center, the length of the birth hospitalization (mean ± SD) was 12.6 ± 10.6 days at 34 weeks' gestation, 6.1 ± 5.8 days at 35 weeks' gestation, and 3.8 ± 3.6 days at 36 weeks' gestation. The usual hospital stay for a term infant is 2 days for a vaginal delivery and 3 days for a cesarean delivery. In addition, hospital readmission rates are increased for LPT (3.5%) versus term (2.0%) infants.[49] Even among infants who were never in a NICU, the readmission rate was threefold higher in LPT than in term infants.[50] Many LPT infants are discharged early but require readmission for jaundice, feeding problems, respiratory distress, and proven or suspected sepsis because of physiologic and metabolic immaturity.

Early discharge among LPT infants affected by discharge criteria established for term infants show an increase in morbidities. In statewide data from Massachusetts, all state-resident infants discharged after a hospital stay of less than 2 nights were analyzed. In the LPT group (1004 infants), 4.3% were readmitted or required an observational stay versus 2.7% of the term infants (n = 24 320). LPT infants were also 1.5 times more likely to require hospital-related care. This study suggested that LPT infants discharged early experience significantly more neonatal morbidity than term infants; however, this may be true only for breastfed infants. The authors concluded that evidence-based recommendations for appropriate discharge timing and postdischarge follow-up are needed.[49]

Moderately preterm infants are also at increased risk for acute bilirubin encephalopathy. Clinical manifestations may be more subtle in the LPT infant versus the term infant.[51,52] Chronic bilirubin encephalopathy (kernicterus) secondary to high concentrations of unconjugated bilirubin can result in permanent neurologic damage. Even exposure to moderate concentrations of bilirubin may lead to more subtle yet permanent neurodevelopmental impairment, which is labeled as bilirubin-induced neurologic dysfunction.[51] Auditory neuropathy spectrum disorder is a common manifestation of bilirubin-induced neurologic dysfunction in the LPT infant.[53]

Quinn et al[54] recently published a review of the literature concerning discharge criteria for the LPT infant. They found few differences in discharge criteria between infants in the newborn nursery and those in the NICU.[55] Previously published discharge criteria from the AAP evolved over time and include physiologic stability and completed screenings for hearing loss, hyperbilirubinemia, car seat safety, hypoglycemia, critical congenital heart disease, and sepsis. Parental education was also a major component of discharge planning, including umbilical cord care, feeding, voiding and/or stooling, and weight gain. In addition, Quinn et al[54] recommended maternal screening assessments for depression, drug use, a safe home environment, and the existence of a support system.

A major difference between newborn discharge and discharge criteria for the LPT infant is the transition to safe sleep before discharge (supine position). Given that LPT and ET infants are at an increased risk of morbidity and mortality, greater efforts are needed to ensure safe and healthy posthospitalization and home care practices for these vulnerable infants.[56] Finally, standardized criteria for discharge may improve outcomes and reduce maternal stress in these high-risk groups.

TABLE 2 Neurologic, Psychiatric, and Developmental Disorders in LPT Infants as Adults

Neurologic and Psychiatric Conditions	Relative Risk of LPT Versus Term (95% CI)
Attention-deficit/hyperactivity disorder	1.7 (1.2–2.5)
Any psychiatric disorder	3.74 (1.59–8.78)
Any anxiety disorder	3.85 (1.52–9.52)
Cerebral palsy	2.7 (2.2–3.3)
Cognitive disability	1.6 (1.4–1.8)
Schizophrenia	1.3 (1.0–1.7)
Any disorder of psychological development, behavior, and emotion	1.4 (1.3–1.5)

Adapted from Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. *N Engl J Med*. 2008;359(3):262–273; and Kardatzke MA, Rose RS, Engle WA. Late preterm and early term birth: at-risk populations and targets for reducing such early births. *NeoReviews*. 2017;18(5):e265–2376. CI, confidence interval.

Evaluating 161 804 infants in Florida between 34 and 41 weeks' gestation with a length of stay of ≤72 hours revealed that LPT infants, compared with term infants, had a 36% higher risk for developmental delay or disability and a 19% higher risk of suspension in kindergarten after adjustment for 15 potential confounders. Disability in prekindergarten at 3 and 4 years of age, exceptional student education, and retention in kindergarten all carried a 10% to 13% increased risk among LPT infants. "Not ready to start school" was borderline significant. The authors concluded that healthy LPT infants have a greater risk for developmental delay and school problems than term infants through the first 5 years of life.[57]

School performance is also a concern in LPT and ET infants. School performance in this group was evaluated in a cohort study at 7 years of age in the population-based prospective UK Millennium Cohort Study with >6000 children. This study used the statutory key stage 1 teacher assessment performed in the third school year in England. The primary outcome was not achieving the expected level (≥2) in reading, writing, and mathematics. There was a statistically significant increased risk of poor performance in those born LPT (adjusted relative risk, 1.36; 95% confidence interval, 1.09–1.68). ET infants performed statistically significantly worse than the term children in 4 of 5 individual subject domains but not in the primary outcome. This study concluded that LPT, and to a lesser extent ET, birth negatively affected academic outcomes at 7 years of age as measured by key stage 1 assessments.[58]

After review of 126 publications, Raju et al concluded that the overwhelming majority of adults born at preterm gestation remain healthy and well, but adult outcomes in a small but significant fraction of infants born preterm are concerning. This population is at a slightly higher risk for neuropsychological and behavioral problems, hypertensive disorders and metabolic syndrome, and developing at an earlier age when compared with term infants. Preterm birth should be considered a chronic condition, and the primary care physician should glean this information; this would potentiate early diagnoses and timely intervention.[59] Because of the research gaps that exist, the US National Institutes of Health convened a multidisciplinary conference with experts on adult diseases in infants born preterm and proposed a research agenda.[60]

PRACTICAL CONSIDERATIONS

Acceptance that early birth is not an inevitable and natural feature of human reproduction is the first step in ameliorating the societal burden of LPT and ET births.[17] LPT and ET births are not caused by a single entity but are the result of a heterogeneous group of conditions that affect the mother and/or fetus.[61] Potential interventions to reduce LPT births include the following:

1. prevention of exposure of pregnant women to cigarette smoke,[19]
2. judicious use of non-ART fertility treatments and ART treatments (eg, elective single-embryo transfer),[39]
3. improvement of preconception health to reduce chronic medical conditions such as diabetes, obesity, and poor nutrition,[15] and
4. encouragement of longer interpregnancy interval because a short interpregnancy interval of <6 months poses a higher risk of LPT delivery.[62–64]

Further success can be anticipated in the future as other research discoveries are translated into clinical practice, including new approaches to treating intrauterine infection, improving maternal nutrition, and lifestyle modifications to decrease stress.[17]

RECOMMENDATIONS

Accounting for approximately 32% of nearly 4 million live births annually, LPT and ET births remain a challenge, with a recent increase seen in rates in the United States. Pediatricians can continue to play an important role in the reduction of these at-risk births.

1. LPT and ET infants have increased risks of adverse medical, neurodevelopmental, behavioral, and social sequelae into and through adulthood. Neonatologists and pediatricians can continue to understand these risks and inform parents, educators, and adult care clinicians.
2. Continued use of population data within hospitals, states, regions, and networks will help to monitor rates of LPT and ET births for trends, changes in practice, and need for intervention.
3. Promising interventions exist to prevent LPT and ET births, but these interventions need to be adopted and disseminated equitably and financed by payers adequately to reduce disparities.
4. Multidisciplinary discussions and planning with obstetric providers will improve the understanding of the causes of and indications for LPT and ET deliveries with the intention of preventing iatrogenic deliveries.[18, 65]
5. Health care providers for all age groups should consider obtaining a patient's birth history to include gestational age as a comprehensive means of evaluating and predicting current and future health.[48,49]
6. Because these at-risk populations of LPT and ET infants are at risk

for adverse health outcomes, these groups should be added to payment models that better finance practitioners who have to increase their outreach, screening, and treatment to provide appropriate care to these patients.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
ACOG: American College of Obstetricians and Gynecologists
ART: assisted reproductive technology
ET: early-term
LPT: late-preterm

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