

## The “Late Preterm” Birth—Ten Years Later

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It is now 10 years since the phrase *late preterm* entered the medical lexicon.<sup>1</sup> The impact of this milestone on perinatal patient care and research and a brief note concerning the unresolved issues on this topic are the focus of this Pediatric Perspective.

In 1969, the World Health Organization proposed that a preterm birth should be defined as “childbirth occurring at less than 37 completed weeks, or 259 days of gestation counting from the first day of the last menstrual period in women with regular (28-day) menstrual cycles.”<sup>2</sup> However, in the mid-1970s through the 1980s, researchers began identifying their research participants close to term gestation as “near-term.” Although no specific lower gestational age limits were stated, the implication was that such participants were fully mature and did not differ from full-term infants in any respect.<sup>3</sup>

Coincidentally, the US preterm birth rate, calculated from the last menstrual period, increased 31% between 1981 and 2003 (9.4% in 1981 and 12.3% in 2003).<sup>4</sup> Most of this increase was due to births between 32 and 36 weeks. The distribution of gestational age at delivery had shifted toward lower gestational ages, such that in 2002 the peak gestational age for US singleton births was 39 weeks, compared with 40 weeks in 1991. During this period, for pregnancies between 32 and 36 weeks, there was a 22% increase in medical interventions, defined as inductions or cesarean births in the absence of prolonged rupture of the membranes.<sup>4</sup>

Thus, at the turn of the 21st century, some startling perinatal epidemiologic data had emerged. There was a steady increase in US preterm births. The fastest-growing segment was births between 34 and 36 weeks’ gestation, accounting for 74% of preterm births. The ethnic and racial disparity in US preterm births had continued. In 2008, 8.2% of births were late preterm for non-Hispanic white compared with 11.3% for non-Hispanic black women.<sup>5</sup> There were significantly more medical interventions for deliveries between 32 and 36 weeks’ gestation, with no evident increase in the known causes of prematurity, such as multiple gestation, preeclampsia, or chorioamnionitis.

These trends were alarming. Therefore, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) convened a panel of experts to address issues related to near-term births. The panel reviewed the sparse yet compelling available data and concluded that infants born even a few weeks before term were at

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higher risk for short and long-term morbidity and mortality, and calling them “near-term” wrongly implied that they were almost fully mature. The expert panel recommended discontinuing the phrase near-term and replacing it with late preterm, defined as 34 weeks and 0/7 days through 36 weeks and 6/7 days (239th–259th day) of gestation. Research priorities and practice guidelines were offered.<sup>1</sup>

The publication of the NICHD executive summary of the workshop proceedings led to a high-impact paradigm shift in many domains. In addition to the milestones noted in Table 1, the national and international research community responded vigorously. More than 500 articles have appeared on this topic since 2007, including observational and case-controlled studies, short-term and long-term follow-up reports, comprehensive and systematic reviews, editorials, and opinion pieces. Most studies underscored the vulnerability of late preterm infants reported by the NICHD workshop panel.<sup>1</sup> They confirmed that late preterm birth per se was associated with higher morbidity in the absence of any identifiable maternal or fetal risk factors. Adverse outcomes included respiratory distress, hypoglycemia, feeding difficulties, problems of temperature control, jaundice, apnea, and seizures during the neonatal period and higher risk for short-term mortality and morbidity.

Late preterm infants are also at higher risk for readmission after initial hospital discharge and during infancy and higher risk for pulmonary disorders during childhood and adolescence, and they manifested subtle, minor deficits in cognitive function and learning difficulties compared with their term counterparts at school age. Some of these disorders and deficits persisted into adulthood, probably because of arrested growth of organ systems,

**TABLE 1** Major Advances in Late Preterm Birth, 2006–2016

| Year | Milestones   |
|------|--|
| 2006 | Introduction of the phrase <i>late preterm</i> to replace <i>near-term</i> , recommended in an executive summary of a 2005 NICHD workshop. <sup>1</sup>  |
| 2007 | Practice guidelines are issued by the American Academy of Pediatrics Committee on Fetus and Newborn, and the Committee on Obstetric Practice of the ACOG.  |
| 2007 | NCHS begins tracking late preterm birth statistics; the March of Dimes Foundation begins research support and educational activities to prevent non-medically indicated deliveries at late preterm gestations.   |
| 2011 | Guidelines to manage “indicated late preterm and early term deliveries” published after an NICHD and SMFM workshop. <sup>6</sup>   |
| 2012 | Additional classifications published defining and refining the definition of <i>term birth</i> at a working group convened by NICHD, in collaboration with ACOG, the American Academy of Pediatrics, SMFM, the March of Dimes Foundation, the World Health Organization, and the NCHS. The subgroups were “early term” as births between 37 wk 0 d and 38 wk 6 d, “full term” as those at 39 wk 0 d through 40 wk 6 d, “late term” as deliveries at 41 wk 0 d through 41 wk 6 d, and, by implication, “post term” as those at 42 wk and 0 d and beyond. <sup>7</sup> |
| 2014 | NCHS continues to note decreases in US singleton preterm and late preterm birth rates beginning in 2007. <sup>8</sup>  |
| 2016 | From 2007 through October 2016, >500 publications and review articles confirm that late preterm infants are at higher risk for pulmonary, metabolic, and neurologic disorders; feeding difficulties during the neonatal period; elevated risk for hospital readmissions for jaundice and bilirubin-induced brain injury; respiratory syncytial virus and other pulmonary infections during infancy childhood; cognitive deficits and learning issues at school age; and small but measurable negative effects in adult age groups.                                   |
| 2016 | Decreasing rates of inductions at late preterm and early term pregnancies in 6 high-income countries in North America and Europe. <sup>9</sup>   |
| 2016 | Attempts to improve fetal pulmonary maturity in late preterm early term gestations for elective cesarean birth and in other clinical settings (reviewed in Kamath-Rayne et al <sup>10</sup> ). Publication of a large trial to increase fetal lung maturation with antenatal betamethasone therapy <sup>11</sup> in late preterm pregnancy and endorsement of this practice by the SMFM <sup>12</sup> and ACOG. <sup>13</sup>  |

neonatal illness, and postnatal care practices.<sup>14</sup>

Of particular note, after the NICHD workshop, the US singleton preterm birth rate, calculated based on obstetric estimate documented in birth certificates (as opposed to last menstrual period dating used in earlier reports), which was 10.44% in 2007, dropped to 9.56% in 2014, an 8% drop.<sup>8</sup> The National Center for Health Statistics (NCHS) noted that this drop “may be related to heightened understanding of the increased neonatal risk at these gestational ages.”<sup>8</sup>

Although many developments after the 2005 NICHD workshop were positive, there were concerns about unintended consequences. A desire to reduce late preterm births could lead to avoiding indicated late-preterm deliveries altogether, increasing the risks for the mother and her infant.

Therefore, to develop guidelines for optimal timing of deliveries, NICHD and the Society for Maternal Fetal Medicine (SMFM) organized a workshop in 2011. Its summary provided practical guidelines for managing indicated late preterm and early term deliveries based on the existing data and expert opinion.<sup>6</sup>

In a 2012 workshop convened by NICHD and the SMFM, refinements were recommended for the definition of term pregnancy to help in counseling, clinical management, and research (Table 1).<sup>7</sup> This workshop also had an impact on clinical practice. Between 2006 and 2014, late preterm and early term birth rates decreased in the United States, and a direct association was observed between lower early term birth rates and decreasing clinician-initiated obstetric interventions.<sup>9</sup> This effect could also be secondary to

recommendations by the American Congress of Obstetricians and Gynecologists (ACOG) to avoid non-medically indicated early-term deliveries before 39 weeks.<sup>15</sup>

In a large multicenter randomized controlled trial, researchers tested whether betamethasone administered to women at risk for late preterm delivery decreased the risks of respiratory and other neonatal morbidities.<sup>11</sup> The primary outcome of stillbirth, respiratory morbidities, or postnatal death within 72 hours of age occurred in 165 of 1427 infants (11.6%) in the intervention group and in 202 of 1400 (14.4%) in the placebo group (relative risk in the betamethasone group, 0.80; 95% confidence interval, 0.66–0.97;  $P = .02$ ). The number needed to treat to reduce 1 poor primary outcome was 35. The authors recommended administration of betamethasone to women at risk for late preterm delivery to reduce the rate of neonatal respiratory complications.<sup>11</sup>

However, there are concerns about the routine use of betamethasone in late preterm pregnancies, prompting the SMFM and the ACOG to recommend the use of betamethasone, but with caveats.<sup>12,13</sup> Some concerns include a significantly higher prevalence of neonatal hypoglycemia in the steroid-treated group, a need to treat a large number of women to reduce a single poor composite outcome, and the unknown long-term risks of fetal exposures to corticosteroids.<sup>10</sup>

There are other unresolved issues concerning late preterm births. Compared with the preterm birth rates of 2014, the US rates for 2015 and the first quarter of 2016 have been inching higher, especially among non-Hispanic black and Hispanic women.<sup>16,17</sup> These trends must be monitored and their causes explored. Additional studies are needed to understand and prevent persisting high preterm birth rates

among non-Hispanic black and Hispanic minority women in the United States.

Evidence-based practice guidelines are needed to refine management guidelines for medically indicated late preterm and early term pregnancies.<sup>6</sup> Although maturation is a continuum, the pace and trajectory of maturation vary between organ systems, and we still do not know all the factors that accelerate or impede specific fetal organ maturation. We need to improve methods to accurately date pregnancy duration and fetal organ maturity. Other obstetric and neonatal research and clinical management issues have been reviewed elsewhere.<sup>3</sup>

In summary, the care of late preterm births has improved since the introduction of the “late preterm” concept.<sup>1</sup> Nevertheless, more needs to be done. Reinforcing the awareness among health care teams that all newborn infants are vulnerable and that no specific pregnancy duration is an automatic assurance of full neonatal maturation is needed. Basic and translational research should continue to focus on preventing all preterm births, improving the quality of care, and reducing the short- and long-term burden of morbidity for preterm infants regardless of gestational age at birth.

#### ABBREVIATIONS

ACOG: American Congress of Obstetricians and Gynecologists  
NCHS: National Center for Health Statistics  
NICHD: Eunice Kennedy Shriver National Institute of Child Health and Human Development  
SMFM: Society for Maternal and Fetal Medicine

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