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Moderately Preterm, Late Preterm and Early Term Infant: Research Needs

Tonse N. K. Raju

Medical Officer and Program Director, Pregnancy and Perinatology Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, USA

Synopsis

In spite of increased appreciation that all preterm infants and early term infants are at higher risk for mortality and morbidities compared to their term counterparts, there are many knowledge gaps affecting optimal clinical care for this vulnerable population. In this paper a research agenda is presented focusing on the systems biology, epidemiology and clinical and translational sciences on this topic.

Keywords

Preterm; immaturity; respiratory distress; apnea; hypothermia; hypoglycemia; jaundice; infection; research

Introduction

In 1969 the World Health Organization defined prematurity as childbirth occurring at less than 37 completed weeks, or 259 days of gestation, counting from the last day of the last menstrual period in women with regular (28-day) menstrual cycles.¹ Births beyond this period were implied to be term and those after 42 completed weeks, post-term.

However, during the mid-1970s through the 1980s, for unknown reasons, the phrase “near term” began to appear in research publications.^{2–5} The phrase referred to experimental animals that were very close to their species-specific term gestations, and preterm infants in clinical trials who were also ‘close’ to term gestations with an undefined lower boundary^{2–5}. The reports did not provide gestational-age specific outcomes data, suggesting that the investigators considered their cohorts fully mature, homogenous term.

Over time, the phrase ‘near term’ acquired a physiologic connotation. This shift was perhaps due to practice recommendation that antenatal steroid to enhance fetal lung maturation are recommended for women between 24 and 33 completed weeks of gestation.⁶ An unstated implication was that the lungs and the surfactant system of infants born beyond 34 weeks of

Address for Correspondence: Tonse N. K. Raju, MD, DCH, Pregnancy and Perinatology Branch, NICHD/NIH, 6100 Executive Blvd, Room 4B03, Bethesda, MD, 20892-MS 7510, rajut@mail.nih.gov.

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gestation would be fully mature, and hence there should be no concerns about the maturity of other organs.

However, this was not to be. An expert panel in a 2005 workshop convened by the *Eunice Kennedy Shriver* National Institute of Health and Human Development (NICHD), reviewed the literature and recommended that the vague and imprecise phrase “near term” be replaced with “late preterm,” to reflect the developmental immaturity of infants born between 34^{0/7} and 36^{6/7} weeks’ gestation.⁷ The new term and its definition were endorsed by the Committee on Fetus and Newborn (COFN) of the American Academy of Pediatrics (AAP)⁸ and by other professional entities in the USA and in other countries.⁹

In recent years, many studies documented that all term infants are not equally mature. Compared to those born between 39^{0/7} and 40^{6/7} weeks’ gestation, those born between 37^{0/7} and 38^{6/7} weeks’ of gestation were at higher risk for mortality,¹⁰ as well as for short and long-term morbidities.^{11–13}

In spite of the above developments, there are many knowledge gaps, addressing which could help further improve patient care. This paper provides a list of possible research topics, largely based on the research agenda proposed by the NICHD expert panel,⁷ and the COFN of the AAP noted above.⁸

Some Aspects of Developmental Maturation

Maturation is a continuous process with no specific “goals” to be achieved. By contrast, maturational milestones are useful signposts developed by us to assess the pace and the trajectory of maturation to help make clinical decisions when they deviate from normal. Milestones also define stages of maturation into concrete intervals—a valuable tool for epidemiological research and for developing treatment guidelines.

The duration of gestation (or “time”) is only one of the many factors that influence fetal and neonatal maturational pace and its trajectory. Others include intrauterine environment, maternal health and the medications she takes, diet, nutrition, and lifestyle (e.g. exercise, stress, smoking, and drug abuse), the number of fetuses, fetal sex, and fetal health/diseases.

Maturation is non-linear. It is programmed to meet the needs of the organism for an independent extra-uterine existence at different stages in life. Thus, organs tend to mature at trajectories independent of each other. For instance, most late preterm infants breathe with no external support and manifest no evidence of respiratory distress at birth—a reflection of their mature breathing apparatus and surfactant systems. However, many of them are prone to develop hypoglycemia^{14–16} coupled with difficulty in initiating and maintaining breastfeeding—a reflection of their immature perinatal glucose homeostasis as well as coordinating breathing, sucking and swallowing mechanisms.^{17–20}

Definition and Epidemiology

Large vital statistics databases, such as those in the National Center for Health Statistics of the Centers for Disease Control and Prevention,²¹ Consortium for Safe Labor,²¹ California Perinatal Quality Care Collaborative²³ are invaluable resources for epidemiological research. These and similar sources can be harnessed to address additional areas on this topic as listed below.

- Develop a risk-based system to sub-classify the heterogeneous category of preterm and term infants to improve the precision of risk assessment and comparability of outcomes.

- Refine methods to assess pregnancy duration and fetal/neonatal gestational ages and maturity.
- Develop gestational-age-specific anthropometric indices for singleton and multiple gestations among different ethnic groups to classify infants into appropriate risk categories.
- Study the national and regional epidemiological data on gestational-age specific birth and death vital statistics among different ethnic and sociodemographic subgroups, and their trends over time.
- Study the etiology of moderate and late preterm and early term births, assessing how many were from indicated causes, and how many were possibly preventable. Explore their relation to mother's payer status, and levels of hospital care where the infant was delivered.
- Study the contribution of the gestational-age-specific preterm birth rates on the overall neonatal and infant mortality and morbidity, and their regional variations.
- Study the Post-discharge outcomes for all preterm and term infants treated in special care or intensive care units.

Obstetric issues

The management of women in labor at any preterm gestation presents many challenges for the obstetrician. The best time to deliver has to be based on the anticipated risks to the mother and the fetus from expectant management, versus the risks and benefits to the mother and the newborn of early delivery. While preterm birth increases neonatal morbidity and mortality, expectant management of the pregnancy when the fetus is in a potentially hostile intrauterine environment can lead to fetal compromise, including organ dysfunctions, neurologic injury, or death.

A panel of obstetric and neonatal experts developed specific guidelines to inform clinicians about optimal management of indicated late preterm births. However, they noted that there is a need for more evidence-based research.¹³ Some research areas are listed below.

- Develop improved methods to assess pregnancy duration enhancing the precision of gestational age estimates to within 5 days.
- Assess the risks and benefits for diagnosis-specific indications for delivery at all gestations periods prior to 39 weeks.
- Study the factors accelerating or delaying fetal organ maturation.
- Improve the accuracy of estimating fetal well-being in the presence of maternal diseases (e.g., hypertension, diabetes, prolonged rupture of membranes, and chorioamnionitis) for choosing appropriate time for and route of delivery.
- Develop strategies to identify fetuses at risk for mid and late-pregnancy stillbirth.

NEONATAL ISSUES

Compared to those born prior to 32 weeks of gestation, moderate and late-preterm and early term infants are at lower risks for numerous medical problems, but compared to those born at 39 and 40 weeks' gestation, they are at higher risks for mortality and morbidities.^{10–13, 24–30} Potential areas for research are listed below.

Cardiovascular and Pulmonary Systems

- Study the risk factors for transient tachypnea of the newborn, respiratory distress syndrome, and severe respiratory failure, and their treatment options at these gestations.
- Study the mechanisms for impaired or delayed maturation of breathing and deglutition functions (central as well as peripheral apparatus) that lead to apnea of prematurity and feeding difficulties.
- Study the epidemiology of later onset apnea and bradycardia, and paroxysmal oxygen desaturation events, their detection and treatment.
- Study the role of caffeine therapy beyond the hospital stay to prevent unexplained oxygen desaturations and improve neurological outcomes.
- Evaluate the risk factors for sudden infant death syndrome in in preterm and early term infants

Nervous System

- Study the nature of vulnerability of preterm and early term infant to white matter injury and evaluating their functional consequences on neurodevelopmental outcomes.
- Study the incidence and natural history of intraventricular hemorrhage, periventricular leukomalacia, periventricular leukomalacia, and perinatal stroke.
- Assess the role of routine use of standard and functional magnetic resonance imaging to understand the ontogeny of brain growth and maturation and to assess their value in identifying babies at risk for long-term poor outcomes.
- Study to learn how intrauterine fetal environment promotes white matter growth, synaptic growth and arborization, potentially affecting neurobehavioral development.
- Develop strategies to improve neurological and behavioral outcomes.

Metabolic

- Study how to prevent and treat hyperbilirubinemia and bilirubin-induced brain injury.
- Studies to understand the prevalence of hypoglycemia, and its long-term consequences.
- Prevalence and etiology of electrolyte abnormalities and their impact on water balance, with implications for fluid and nutritional therapy.

Nutrition, Breastfeeding and Lactation, and Gastrointestinal

- Optimal nutritional and feeding practices for preterm and early term infants, and their potential role in the etiology of necrotizing enterocolitis.
- Mechanisms of acid secretion, the etiology diagnosis and treatment of gastro-esophageal reflux, and the understanding of gut motility and their impact on feeding strategies and hospital discharge practices.
- Improving breastfeeding success rates; assessing the role of lactation consultants during prenatal and postnatal periods, and studying the health and economic impact of increased intensity of breastfeeding in this vulnerable populations.

- Causes and treatment of lactation failure among women who delivery preterm infants.
- Studies in the evolving filed of microbiome,^{31–34} including assessing the development of gastrointestinal microbiome in relation to the mode of delivery, feeding strategies, antenatal and postnatal antibiotic use; the influence of microbiome on long-term immunological functions.

Immunology and Sepsis

- Understanding how immune system immaturity may lead to impaired inflammation and responses to infections.
- Evaluating the effects of preterm birth on developmental immune programming and its role in allergy and asthma in later life.
- The temporal trends in maturation of T-cell and granulocyte functions, other immune mediators, and their role in host-defense mechanisms in late-preterm gestations.
- Continued efforts to reduce nosocomial sepsis, and methods to prevent excessive use of antibiotics in infants “suspected of sepsis”.

Renal and Genitourinary

- Gestational age-specific definition for acute kidney injury and bio-makers to detect them.
- Timely management of acute kidney injury.
- The short and long-term consequences of acute kidney injury on the development of chronic kidney disease in later life.

Development Pharmacology

- Gestational age-specific studies to understand drug disposition, maturational changes in drug metabolism and elimination, and the factors that induce or inhibit these processes.
- Drug dosing guidelines taking into account the immaturity of the liver and kidney, and their dysfunctions resulting from disease states, and cholestasis associated with parenteral nutrition.
- Strategies to prevent medication errors during neonatal care.

Miscellaneous

- The risk factors for readmission of preterm and early term infants.
- Education of physicians, nurses, and other healthcare personnel that even seemingly healthy, moderate and late preterm infants, and early term infants are physiologically immature and should be diligently evaluated, monitored, and followed.
- The availability of expert healthcare teams in units of various levels obstetric and neonatal care, and their effect on obstetric and neonatal treatment practices and referral patters.
- The economic impact of the maternal and neonatal care of preterm and early term infants during their hospitalizations and during follow-up care; this may include

costs due to early intervention and other medical and social services, and various strategies to reduce such costs.

Summary and Conclusions

The above review is obviously not comprehensive—but an expanded version of the template suggested by the NICHD workshop expert panel,⁷ and the COFN of the AAP.⁸ One hopes that results from future research help continue to improve outcomes women and newborn infants of all gestational age groups.

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KEY POINTS

- Maturation is a continuum, and not all newborn infants are equally mature
- There is a need for better understanding of the epidemiology of moderate, late, and early term births, among various ethnic groups, as well as its geographic variations.
- We need to develop more precise measures of assessing gestational age, so that infants will be categorized into appropriate subgroups based on evidence-based risk levels.
- Many knowledge gaps in obstetric and neonatal topics need to be addressed with research to optimize the care of all preterm and term newborn infants.