Preterm Labor and Birth: Where are We Now?

Audrey Lyndon, MS, CNS, RNC

Surprisingly, preterm labor and birth remain refractory problems in the United States and other developing countries. The preterm birth rate in the United States continues to rise despite a stable maternal complication profile, improvements in access to and use of prenatal care, and decreases in the incidence of both adolescent pregnancy and smoking during pregnancy. In 2003, the US preterm birth rate rose to 12.3%, which represents a 16% increase since 1990 and more than a 30% increase since 1981.1 Preterm birth is a major public health concern because prematurity accounts for approximately 70% of cases of neonatal mortality and almost half of long-term birth-related neurologic morbidity.2 Advances in the science of identifying women at risk, predicting and managing preterm labor, and preventing preterm birth have been hampered by the heterogeneity of the clinical entity as well as the complexity of potentially contributing and confounding human and environmental factors.2–5 One major conceptual difficulty in studying preterm birth is incomplete understanding of the mechanisms of parturition. Another complicating factor is the likely interplay of fetal, maternal, and environmental factors in the cascade of events that occur from initiation of preterm contractions to the development of preterm labor and birth of a preterm infant. This article highlights some of the current areas of research in preterm labor and birth, the results of recent scientific analyses of common strategies for the management of threatened preterm labor, and the developing national focus on the special needs of infants born between 32 and 37 weeks’ gestation.

Areas of Research

Three major areas of investigation into the etiology of preterm birth, its prediction, and prevention are racial/ethnic disparities, inflammatory pathways, and genetic predisposition. The risk for preterm labor and birth in the United States varies considerably, with non-Hispanic black women being at significantly higher risk for preterm birth than are women from other racial/ethnic groups.1,3 Developing a full understanding of the mechanisms underlying these differences is challenging. Measures traditionally used to evaluate socioeconomic status fail to capture the multiple aspects of social circumstances that may have an impact on health and well-being,6 and measures used to capture "race" and "ethnicity" are often too broadly or imprecisely defined to identify important population differences.3 Current theory suggests that prolonged exposure to poverty, racism, unsafe neighborhoods, and other stressors may produce neuroendocrine and immunologic changes that “prime” women for poor pregnancy outcomes such as preterm birth.6 Understanding the specific strengths and vulnerabilities of various populations is important, as the lack of success with preventative interventions is probably due in part to ineffective differentiation of the appropriate target populations.4 Fruitful analysis of these issues will require complex modeling of psychosocial and economic factors along with behavioral, immunologic, genetic, and endocrine pathways mediating both vulnerability and resilience.

The interest in inflammatory pathways is based on the observation that infection is the most common cause of preterm birth worldwide5 and on the
presumed role of intrauterine inflammation in the initiation of preterm labor and preterm premature rupture of membranes. Inflammation may result from infectious triggers (eg, ascending infection, vertical transmission, or gingivitis), neuroendocrine responses to chronic stress, or ischemic insult. Increased levels of pro-inflammatory cytokines have been found in both the plasma and the amniotic fluid of women who give birth preterm, and have also been demonstrated in the amniotic fluid of women in preterm labor. Likewise, both fetal and maternal tissues produce cytokines in response to both ischemia and infection. Current promising areas of investigation include evaluation of increased levels of cytokines and other inflammatory markers in hopes of developing a highly sensitive and specific multiple marker test for predicting preterm birth.

Observations leading investigators to hypothesize a genetic basis for prematurity include findings that a history of prior preterm birth is the strongest predictor of subsequent preterm birth and that racial/ethnic differences in the incidence of prematurity are significant after controlling for confounding variables. The potential genetic contribution is thought to be multifactorial, involving inflammatory processes and gene-gene and/or gene-environment interaction. The focus in these investigations is on genetic diversity for controlling pro-inflammatory and anti-inflammatory cytokines, as well as inhibitors of cytokine synthesis. The general theory is that over-expression of the pro-inflammatory cytokines or under-expression of anti-inflammatory cytokines results in increased susceptibility to or aggravated response to an environmental trigger such as intrauterine infection or transient ischemic insult. Large studies evaluating these markers in specific populations are ongoing in the United States, Australia, and Denmark.

Several recent studies have highlighted the vulnerability of infants born after 32 and before 37 weeks' gestation. While the focus on prematurity has traditionally been on infants born under 32 weeks' gestation, researchers and clinicians are beginning to appreciate the frequency of complications and the significant emotional, medical, and social cost of morbidity and mortality in the growing population of “near term” premature infants. These infants are at an increased risk for hypoglycemia, cold stress, respiratory distress, and jaundice, and they are more likely to receive invasive diagnostic testing and therapy, be hospitalized longer, and be readmitted for complications. Multiple groups, including the National Institute of Child Health and Human Development and the Association of Women’s Health, Obstetric, and Neonatal Nurses, are targeting this population as a special focus for future intervention and prevention work.

CURRENT CLINICAL ISSUES

Despite decades of research on multiple strategies for predicting and preventing prematurity, only a handful of interventions have shown proven benefit to improving neonatal outcomes. Maternal transports to facilitate birth in proximity to an experienced neonatal team, single-dose antenatal corticosteroids, and chemoprophylaxis for perinatal group B streptococcus are all effective in reducing neonatal morbidity and mortality. Prophylactic administration of progesterone has been shown to reduce the risk of preterm birth in the subset of women at high risk due to history of previous preterm birth or multiple spontaneous abortions, and antibiotic administration in the setting of preterm premature rupture of membranes has been shown to prolong pregnancy and decrease neonatal morbidity. Fetal fibronectin and cervical length are clinically useful tools for ruling out preterm labor in symptomatic women when the clinician is willing to avoid treatment in the setting of a negative test (fibronectin < 50 ng/mL; cervical length > 30 mm), and positive results are used by some clinicians to guide decisions regarding the timing of antenatal corticosteroids.

Although widely used, tocolytics demonstrate only small improvements in length of gestation, and the combined evidence to date has not shown improvement in neonatal morbidity or mortality with tocolytic therapy alone. Thus, current use of tocolytics is directed at prolonging pregnancy for the 24 to 48 hours needed to achieve the benefit of maternal corticosteroid administration and transport to a regional center. A recent Cochrane Review of magnesium sulfate for acute tocolysis found no delay in delivery, no improvement in neonatal outcomes, an association with higher fetal death rates in one study with high (>2 g/h) magnesium sulfate maintenance rates, and concludes, “magnesium sulfate cannot be recommended as a tocolytic agent for women in preterm labor.” The Cochrane Review of calcium channel blockers for acute tocolysis found calcium channel blockers (nifedipine) to be more effective than other tocolytics (primarily betamimetics) at decreasing the number of women delivering within 7 days and before 34 weeks’ gestation with a reduction in adverse maternal side effects and improvement in the neonatal outcomes of respiratory distress, intraventricular hemorrhage, necrotizing enterocolitis, and jaundice. Nifedipine has become the first-line agent of choice in many settings, particularly in the United Kingdom.
There is insufficient evidence to support the use of any tocolytic for maintenance therapy.2,17–19 There is no convincing evidence that routine use of hydration or bed rest are of benefit in the management of preterm labor, and routine use of these therapies is discouraged by the American College of Obstetricians and Gynecologists.2,14

CURRENT AND FUTURE IMPLICATIONS FOR CLINICAL PRACTICE

Clear interdisciplinary guidelines for the timely diagnosis of preterm labor, use of antenatal corticosteroids, prophylactic antibiotics for group B streptococcus and preterm premature rupture of membranes, and timely maternal transport are needed in all settings, as is a prophylactic antibiotics for group B streptococcus and resolution of preterm labor, use of antenatal corticosteroids, and routine use of these therapies is discouraged by the American College of Obstetricians and Gynecologists.2,14

REFERENCES


