Prevention of Prematurity
Advances and Opportunities

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KEYWORDS

• Preterm birth prevention • Preterm prevention clinic • Progesterone • Cerclage • Aspirin • Clindamycin • Clotrimazole • Nifedipine

KEY POINTS

- Preterm birth (PTB) rate varies widely with significant racial and ethnic disparities. Causal mechanisms are ill understood, but phenotype and genotype provide insight into pathways for preventing PTB.
- Varied response to medical interventions is explicable by underlying pharmacogenomics. Prevention should focus on minimizing iatrogenic PTB and risk reduction, especially those with prior PTB.
- Current PTB prevention includes reduction of non-medically indicated delivery less than 39 weeks, smoking cessation, implementation of preterm prevention clinic and appropriate use of cerclage and medications (progesterone, antimicrobials, and nifedipine). Aspirin and oral magnesium are currently under study.
- Placental health requires optimal management of diseases in pregnancy, smoking cessation, omega 3 supplements if smoking continues during pregnancy, anti-platelet agents, and non-medically indicated uterine manipulation.
- Future preventive approaches should focus on better understanding of sociodemography, nutrition, dysbiosis, lifestyles, phenotype, risk factors, and underlying individual genetic, pharmacogenomics, and epigenetic variation.

INTRODUCTION

Preterm birth (PTB) occurs with a prevalence ranging from less than 5% to greater than 15% worldwide. The widespread variability is well emphasized in the United Nations/World Health Organization (WHO) report entitled "Born Too Soon."[1] All countries with PTB rates greater than 15% are in sub-Saharan Africa,[2] and PTB rates in African Americans have traditionally been significantly greater than for other ethnic and racial groups. In the United States, the rate increased for 14 consecutive years followed by a

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decline for 7 consecutive years. Unfortunately, now US PTB rates have been increasing for 2 consecutive years to 9.84% in 2016.[3]

PREMATURITY PREVENTION AND INSIGHTS INTO CAUSE

Prevention of PTB has been attempted for several decades and in several settings with mixed success,[4–8] most likely related to the poorly understood heterogeneity of disease. Studies in the late 1990s showed some promise of interventions to prevent PTB with the publication of the injectable[9] and vaginal[10] progesterone trials. A population-based, multiethnic, cross-sectional study in 8 countries[11] over a 12-month period examined 60,058 births. Prevalence of PTB ranged from 8.2% in Muscat, Oman and Oxford, England to 16.6% in Seattle, Washington. Twelve PTB clusters were identified using phenotypes that included signs of presentation at hospital admission and a predefined conceptual framework. The distribution of clinical phenotypes in PTB across these multiethnic populations suggests that in 22% of these births, parturition started spontaneously and was unassociated with any of the phenotypes considered. A current genome-wide association study of 43,568 women with greater than 97% European ancestry demonstrates putative genetic and mechanistic insights into prematurity.[12] Six maternal genomic loci identified and replicated were robustly associated with gestational duration and contain genes whose established functions are consistent with a role in the timing of birth. Three of these loci are also associated with PTB with genome-wide significance. Furthermore, it is known that some of the variation in response to medications used in PTB prevention and treatment may be attributable to pharmacogenomic effects. Currently, greater than 50 genes are implicated in genomic biomarkers most commonly pertaining to polymorphisms in cytochrome p450 (CYP) enzyme metabolism. Polymorphisms in CYP enzymes are relatively common. For example, CYP2D6 is estimated to metabolize ~25% of drugs (including fluoxetine, metoprolol, codeine), and greater than 70 alleles have been identified in this highly polymorphic gene. As a result, CYP2D6 activity ranges widely even within populations, and up to 8% of European Americans may be identified as poor metabolizers.[13] Specific to 17-hydroxy progesterone caproate (17-OHPC) metabolism, Caritis and colleagues[14] examined plasma concentrations in 315 women at 25 to 28 weeks' gestation and grouped their 17-OHPC levels into quartiles. Women in the lowest quartile were significantly more likely to have recurrent PTB than those in the upper 3 quartiles (46% vs 29%; $P = .03$). Lowest PTB rates were seen when median 17-OHPC concentrations exceeded 6.4 ng/mL. Women in the second, third, or fourth quartiles had a 50% reduction in delivering preterm (hazard ratio: 0.48; 95% confidence interval [CI] 0.31–0.75; $P = .001$). Two specific pharmacogenomics studies have been performed to study the relationship between genotype and the response to 17-OHPC. Similarly, Nifedipine concentrations linked to CYP3A5 genotype are correlated with high clearance of Nifedipine and thus lower levels.[15] Women with high expression of CYP3A5 had less improvement in contraction frequency at several time points, including after the loading dose, at the steady state, and in the first hour after study dose.[16] No pharmacogenomics data are currently available for indomethacin or magnesium sulfate, although it is known that indomethacin is metabolized in the liver by polymorphic CYP2C9 and CYP2C19. Maternal and fetal genetic variance in several single nucleotide polymorphisms including CYP3A5 and CYP3A7*1E are associated with variation in neonatal respiratory outcomes, including need for surfactant and ventilator support. Thus, it has been surmised that genetic variation in betamethasone genes can be