Available online at www.sciencedirect.com

Seminars in Perinatology

www.seminperinat.com

The genetics of preterm birth: Progress and promise

Nagendra K. Monangi, MD[a,b], Heather M. Brockway, PhD[b], Melissa House, MD[a], Ge Zhang, MD, PhD[c], and Louis J. Muglia, MD, PhD[a,b,*]

[a]Division of Neonatology, Perinatal Institute, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, MLC 7009, Cincinnati, OH 45229

[b]Center for Prevention of Preterm Birth, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

[c]Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

ARTICLE INFO

Keywords:
Preterm birth
Prematurity
Birth timing
Genetics
Genomics

ABSTRACT

Preterm birth is the single leading cause of mortality for neonates and children less than 5 years of age. Compared to other childhood diseases, such as infections, less progress in prevention of prematurity has been made. In large part, the continued high burden of prematurity results from the limited understanding of the mechanisms controlling normal birth timing in humans, and how individual genetic variation and environmental exposures disrupt these mechanisms to cause preterm birth. In this review, we summarize the outcomes and limitations from studies in model organisms for birth timing in humans, the evidence that genetic factors contribute to birth timing and risk for preterm birth, and recent genetic and genomic studies in women and infants that implicate specific genes and pathways. We conclude with discussing areas of potential high impact in understanding human parturition and preterm birth in the future.

Introduction: The global challenge of preterm birth

Preterm birth (PTB), defined as live birth before 37 weeks of completed gestation, presents the greatest global challenge to maternal, infant and child health.[1] Preterm birth is the leading cause of neonatal death and has also become the leading cause of under-five mortality worldwide.[2] An estimated 15 million neonates are born prematurely every year, and approximately 1 million of those children die each year due to complications of preterm birth.[3]

Preterm infants are at increased risk of short and long-term health sequelae as a result of immaturity of multiple organ systems. Neonates born before 37 weeks of gestation are more likely than their term counterparts to experience complications including respiratory distress syndrome, patent ductus arteriosus, feeding difficulties, necrotizing enterocolitis, intraventricular hemorrhage and sepsis. Although the incidence of these complications are lower in infants born at 37 weeks than those born at less than 34 weeks, those infants categorized as late preterm infants (34–36 weeks of gestation), still have higher rates of mortality and morbidity compared to their term counterparts.[4] In addition, prematurity leads to many long-term health impairments including growth restriction, chronic lung disease, and developmental delay. Further, there is a growing body of evidence suggesting that these infants are at increased risk of adult-onset diseases such as obesity, diabetes, and hypertension.[5–7]

The Institute of Medicine reported that the costs associated with preterm birth in US were $26.2 billion annually as assessed in 2005.[8] This includes $16.9 billion in medical and health care costs for the newborn, $1.9 billion in labor and

*Corresponding author at: Division of Neonatology, Perinatal Institute, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, MLC 7009, Cincinnati, OH 45229.

E-mail address: louis.muglia@cchmc.org (L.J. Muglia).

http://dx.doi.org/10.1053/j.semperi.2015.09.005
0146-0005/

delivery costs for mothers, $611 million in early intervention services, $1.1 billion for special education services, and $5.7 billion in lost work and pay for families with infants born prematurely.[9] Globally, lower income countries have an estimated 12% of babies born prematurely, compared with 9% in higher income countries. In the United States, over the last 8 years, rates of preterm birth have declined since its 2006 peak, from 12.8% to its current rate of ~11.4% of all live births.[10]

Despite the profound global health significance and recognition that the optimal mechanism to improve child health compromised by complications of prematurity is to prevent preterm birth, there has only been limited progress in preventing prematurity. In large measure, the failure to make more substantial progress arises from limited insight into the normal control mechanisms for parturition and the ways in which these mechanisms are disrupted to cause prematurity. PTB can be classified as iatrogenic/medically-indicated or spontaneous. About 2/3rds of PTBs are spontaneous with or without premature rupture of membranes occurring for an unidentifiable reason.[11] Although the pathogenesis of PTB is not well understood, multiple maternal risk factors associated with increased incidence of PTB have been identified. In the US, disparities in PTB are evidenced by the rate in non-Hispanic white women at 10.5% compared to the rate in non-Hispanic black women at 16.7%.[10] Well-established risk factors include maternal age, short inter-pregnancy interval, multiple pregnancy, uterine or cervical anomalies, assisted reproduction, gestational bleeding, abnormal placentation, urogenital infection, African-American race, substance abuse, smoking, maternal socioeconomic status, late or no prenatal care, low maternal pre-pregnancy weight, bacterial vaginosis, periodontal disease, and poor pregnancy weight gain.[11] (Table 1). Despite efforts to address these risk factors and the implementation of various intervention measures to prevent or treat preterm labor, such as nutritional supplementation, treatment of bacterial vaginosis, tocolytics, bed rest, home uterine monitoring, home nursing care, cervical cerclage, and antibiotic treatment, have proved to be of little or no benefit.[12] In women with a previous preterm birth or a short cervix at mid-gestation, progesterone supplementation has been found to reduce the risk for preterm birth, but the mechanism by which this occurs remains unclear.[13]

Pathogenesis of preterm birth

Preterm birth is a complex disorder, that is, a health condition caused by multifactorial influences and the interplay of numerous risk factor, and represents the aggregation of heterogeneous phenotypes[14] (Fig. 1). The Institute of Medicine acknowledged multiple factors that contribute to preterm birth, including behavioral, psychosocial, socio demographic, genetic, environmental influences, and medical and pregnancy-related conditions.[8] Figure 1 illustrates the major etiological factors involved in PTB, including inflammation, hemorrhage, activation of maternal or fetal hypothalamic pituitary axis (stress), immune dysregulation, distension of the myometrium and cervical insufficiency. Each of these pathways has a distinct profile and mechanism of initiating parturition but share a common pathway of activation of fetal and maternal tissues. Ultimately, the release of mediators that stimulate myometrial contraction, degradation of extracellular matrix components, inflammation and apoptosis, promote membrane rupture, cervical ripening, and uterine emptying resulting in PTB.[15,16]

A wealth of evidence suggests that one of the most important risk factors for PTB may be grounded in genetics. A woman's risk of delivering preterm is up to four times higher if one of her previous infants was delivered preterm.[11,17] Epidemiological studies reveal that mothers who were themselves born preterm or has sisters that have had preterm children are more likely to deliver preterm.[18,19] Genetic studies of offspring of twins and segregation analysis of traits in families demonstrate that 25–40% of the variation in birth timing is due to genetic factors.[20]

The aim of this article is to review the current studies that implicate maternal and fetal genetics, and specific genes or pathways, to the risk of preterm birth in humans. We will describe the mechanistic findings that have emerged from animal studies, their limitations as applied to human parturition, available evidence for genetic contributors to the risk of PTB in humans, and results from the human genetic and genomic investigations.

Animal studies

The use of animal models to study the initiation and progression of parturition has provided significant insights into the mechanisms involved in term and preterm birth for the particular species studied, however, the differences between model systems and humans often precludes direct extrapolation of findings. Some characteristics of an ideal model organism for relevance to humans while still allowing molecular genetic dissection include (1) displaying endocrine

Table 1 – Risk factors associated with preterm birth.

Risk factor	Example	References
Age at pregnancy	Adolescent pregnancy, advanced maternal age	70
Pregnancy spacing	Short inter-pregnancy interval	71
Multiple pregnancy	Increased rates of twins, higher order pregnancies with assisted reproduction	72
Life style related	Tobacco smoking	73
Infection	UTI, chorioamnionitis, bacterial vaginosis, syphilis, asymptomatic bacteriuria, HIV	74
Ethnicity	African-American	75
Nutritional	Undernutrition, micronutrient deficiencies	76
Behavioral health	Depression, violence	77
Genetics	Previous preterm birth, maternal family history of preterm birth	19