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Preventing Spontaneous Preterm Birth: Insights from Genomics

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Abstract

Mortality and morbidity due to infants being born preterm remains one of the greatest health burdens facing society.

Many factors influence the risk for spontaneous preterm birth, both genetic and environmental. To date, generally effective interventions to prevent preterm birth have not been identified.

In this paper, we discuss the impact of preterm birth and the challenges that have limited insights so far. New advances in genomics, systems biology, and population/personalized medicine show promise in overcoming previous barriers and leading to new insights and preventive treatments.

1. Introduction:

Preterm birth, defined as birth before 37 completed weeks of gestation, remains one of the greatest adverse public health outcomes globally. Preterm birth has for decades been the leading cause of infant mortality, and more recently it has been identified as the leading cause of death in children under 5 years of age (L. Liu et al., 2014). For those infants surviving preterm birth, a variety of lifelong complications are often incurred in neurologic, lung, gastrointestinal and visual function, along with compromised long-term growth (Committee on Understanding Premature Birth and Assuring Healthy Outcomes Board on Health Sciences Policy, 2006). Moreover, infants of low birth weight, whether growth restricted in utero or born early, are at increased risk for obesity, metabolic disorders, and hypertension as adults (de Boo & Harding, 2006). In addition, women experiencing a pregnancy complicated by preterm birth are themselves at increased risk for later cardiovascular disease (Lane-Cordova, Khan, Grobman, Greenland, & Shah, 2019). Clearly, the ability to prevent preterm birth would have enormous ramifications for both early and later life health.

The impact of preterm birth is widely recognized and increased funding to understand mechanisms and interventions to reduce preterm birth have been provided by several organizations including the US National Institutes of Health, the Burroughs Wellcome Fund, the March of Dimes, the Bill and Melinda Gates Foundation, amongst others. Despite this increased attention, little progress has been made in reducing the global incidence of preterm birth. Still, no generally effective interventions exist. Initial reports and experience with progesterone or 17-alpha hydroxyprogesterone caproate supplementation for women with a high risk of preterm birth (previous preterm birth or short cervix) suggested potential therapeutic benefit (for example, (Epppic Group, 2021; Meis et al., 2003). Other evidence, though, has called these earlier findings into question and has also revealed potential adverse consequences of progesterone treatment such as the risk for cancer in the offspring of treated pregnancies (Kuon, Berger, & Rath, 2021; Murphy, Cirillo, Krigbaum, & Cohn, 2022; Norman et al., 2016).

Despite the limited ability to prevent preterm birth thus far, considerable opportunities for new mechanistic insights and potential therapies have recently emerged. In this manuscript, the challenges in research designed to reveal mechanisms leading to spontaneous preterm birth will be described. Spontaneous preterm birth accounts for approximately two-thirds of all preterm births (Muglia & Katz, 2010), with the remaining preterm birth a result of early obstetric delivery for complications of pregnancy such as preeclampsia or severe fetal growth restriction. Direct causual mechanisms may differ at various stages of spontaneous preterm birth as well, with extreme preterm birth more often association with bacterial colonization of maternal-fetal tissues as previously described (Muglia and Katz 2010). Recent advances in 'omics' approaches to human pregnancy, evolutionary biology, and personalized and population medicine in overcoming previous limitations will then be presented.

2. Challenges in Pre-term Birth Research:

Lack of Understanding for Normal Term Delivery Mechanisms

Every mammalian species displays a characteristic timing for birth that has been shaped by evolution to optimize reproductive fitness (Rokas et al., 2020). This normal timing for birth – "term" gestation – takes into account factors such as maternal and fetal size/growth, number of fetuses per pregnancy, nutritional provisioning to the fetus, optimal readiness for extrauterine life and other factors. However, for no species do we fully understand how it recognizes it is at term gestation. Is there a biologic timing mechanism or clock that starts at conception that counts off the time until birth or are there signals transmitted between the mother and fetus that serve as signposts as to where in the gestational timeline the pregnancy is? For different species, the mechanisms could ultimately be different. For example, mice need to meter an approximately 19.5 day gestational period while human gestation (from last menstrual period) is approximately 280 days. Until the mechanisms governing normal term gestation are understood, it will be difficult to determine how preterm birth disrupts the normal trajectory for the birth process (parturition) to result in too early delivery of the fetus.

Translatability of Animal Models

Advances in clinical medicine have often occurred as a consequence of insights gained from robust, translatable investigations from model organisms to humans. Pathways regulating growth, metabolism, and neural development have preserved conservation through evolution in many of their most fundamental physiologic characteristics. What is the situation for pregnancy and parturition? The attachment and implantation of the embryo to establish pregnancy have been revealed to be a relatively conserved inflammatory process in eutherian mammals that is followed by a prolonged anti-inflammatory phase of uterine quiescence that is not experienced, for example, in marsupial pregnancy (Griffith et al., 2017). After this period of anti-inflammatory uterine quiescence, the uterine environment reverts to active inflammation again in association with initiation of uterine contractions and expulsion of the fetus. For many mammalian species, pro-inflammatory mediators such as prostaglandins cause a fall in maternal plasma progesterone (systemic progesterone withdrawal) (Bezold, Karjalainen, Hallman, Teramo, & Muglia, 2013). Progesterone is the primary endocrine signal needed to maintain uterine quiescence and the continuation of pregnancy. The drop in circulating progesterone marks the initiation of labor in rodents and ruminants. In women, however, plasma progesterone does not fall at the end of pregnancy when it is at its highest concentration. Thus, it is hypothesized that women experience "functional progesterone withdrawal" rather than systemic progesterone withdrawal, and a number of molecular mechanisms have been implicated in this process. To date, though, no definitive mechanism for functional progesterone withdrawal has been established. Further complicating the translatability of many animal models is the source of the progesterone itself. In rodent pregnancy, the progesterone is

synthesized and secreted by the maternal ovary through gestation. In human pregnancy, there is a shift from maternal ovarian to predominantly placental progesterone expression at approximately 10 weeks of gestation. Thus, very divergent mechanisms, at least on the surface, make extrapolation from usual model organisms to humans problematic.

Diverse Risk Factors for Preterm Birth
Preterm birth may be the result of impaired programming or inappropriate timing for the mechanism leading to normal term birth or arise from an adverse exposure that disrupts normal gestational control mechanisms to initiate preterm labor and delivery. To establish the role of genetic programming in parturition timing, twin and family-based studies have demonstrated that approximately 30-40% of the variation in gestational duration in humans is due to genetic factors (primarily in the maternal genome), leaving the remaining 60-70% arising from environmental exposures (Kistka et al., 2008; Plunkett et al., 2009). Numerous epidemiologic studies have shown associations of nutrition, health behaviors, socioeconomic status, maternal stress, and pregnancy associated infections or microbial communities (maternal microbiome) with risk for spontaneous preterm birth (Cobo, Kacerovsky, & Jacobsson, 2020; Goldenberg et al., 1996; Goldenberg, Culhane, Iams, & Romero, 2008). Until recently, studies typically interrogated one or a small number of risk factors at a time. Every pregnancy, however, is exposed to a spectrum of risk factors that must be integrated to determine the overall likelihood that a preterm birth will occur. Several recent collections of longitudinal biological, demographic, and environmental exposures in pregnancy cohorts have shown the promise of these deep-phenotyping approaches to reveal new insights into adverse pregnancy outcomes, most recently, preeclampsia (Liang et al., 2020; Stelzer et al., 2021).

Incorporating human diversity into research
A recurring finding in human pregnancy is the range of preterm birth rates as a consequence of parental geographic ancestry and consideration of associations of preterm birth with race and ethnicity. Parental geographic ancestry may reflect components for genomic variation that alter birth timing. One study performed in the UK revealed shorter duration for term pregnancy in women of South Asian or African descent as compared to women of European descent (Patel, Steer, Doyle, Little, & Elliott, 2004). In considering social determinants of health and disease, the consideration of race, a social rather than biologic designation, has been repeatedly shown to be associated with preterm birth risk. Black women are at significantly increased risk for preterm birth and a nearly 4-fold increase in risk for recurrent preterm birth after accounting for many covariates such as socioeconomic status, prenatal care, and other risk factors (Kistka et al., 2007). The transgenerational consequences of structural racism and economic environment have emerged as targets for intervening and understanding health disparities across populations and must be incorporated into ongoing efforts to ensure the health and social justice (C et al., 2022; Collins, David, Prachand, & Pierce, 2003; Collins, David, Rankin, & Desireddi, 2009; Collins, Rankin, & David, 2011). Without incorporating biological,

social and environmental information and studies across diverse global cohorts, the potential to exacerbate rather than minimize health disparities may occur.

3. Opportunities:

The past decade has seen the expansion of approaches and cohorts being applied to better understand the mechanisms for normal birth timing and preterm birth. Here, we will briefly expand upon three of these areas: Evolution and Comparative Genomics; Human Multi-omics; Social Determinants – personalized and population health. We recognize that important advances that have also been made in investigations regarding the microbiome, immune system, pathogens, and bioengineering show considerable promise as well.

Evolution and Comparative Genomics
As discussed above, mammalian species have evolved divergent physiologic patterns associated with duration of gestation, optimizing reproductive fitness as a consequence of the environment occupied and pregnancy characteristics such as singleton versus multi-gestation pregnancies, maternal size, and ability to provide nutrients, circadian activity profiles and other contributors (Rokas et al., 2020). While these pregnancy differences in endocrine, immune and general strategies have historically provided barriers to translating findings from animal model systems to humans, recent advances in whole genome sequencing and comparative genomics capitalize on these differences in relating them to genome evolution and selection in the context of organismal phylogeny.

One example of a comparative genomics approach to parturition biology was provided by Plunkett et al (Plunkett et al., 2011). Because of the rapid evolution of increased brain size in humans, the hypothesis was tested that genes involved in determining gestational duration would be positively selected to ensure brain size or energetics would not exceed the ability for passage through the birth canal or limitation of overall fetal growth and development. Comparing genome sequences of humans to other primates and mammals in this study, rapid evolution of specific coding regions and conserved noncoding regions were identified as rapidly evolving along the lineage leading to modern humans. These genomic regions were then targeted to determine whether genetic variation (single nucleotide polymorphisms, SNPs) would associate with risk for preterm birth. In this way, *FSHR*, encoding the follicle stimulating hormone receptor was identified as a risk locus for preterm birth.

As reviewed recently, the expansion of sequenced mammalian genomes also provides other opportunities to exploit comparative genomics for new insights into birth timing (Rokas et al., 2020). By comparing more closely related species with different parturition patterns, genomic differences are likely to be more reflective on influences on reproduction and birth timing as opposed to more broad influences on genome evolution such as metabolic/nutritional regulation, pathogen exposures and immune system evolution, organism size and lifespan, as well as other life history traits. As one example, the spiny mouse (Acomys carihinus), Mongolian gerbil (Meriones unguiculatus), and house mouse (Mus musculus) diverged

phylogenetically over the last 18–24 million years. Surprisingly, the spiny mouse has a pregnancy of 39 days and delivers precocial (relatively mature) pups, while house mice and Mongolian gerbils have much shorter pregnancies of 19.3 days and 25 days, respectively, and deliver altricial (relatively immature) neonates. We postulate that comparative genomic analysis in these closely related species are likely to elucidate the gene selection resulting in the longer gestation of the spiny mouse. The function of these genes could be then analyzed in these organisms and used to formulate subsequent studies to determine their relevance to human pregnancy. Whether directly translatable to humans or not, the insight into control of gestational duration would be of substantial biological interest.

Human Multi-Omics

With the advent of genome-wide association studies, transcriptomics, proteomics, metabolomics, metagenomics and systems biological and artificial/machine learning advances, new genes and biomarkers associated with gestational duration or risk for preterm birth have been revealed (Zhang et al., 2018). Perhaps the longest standing of these approaches have been candidate gene association studies where common variants in plausible contributory pathways were interrogated for associations with preterm birth. As has been reviewed extensively elsewhere (Bezold et al., 2013; Plunkett & Muglia, 2008), candidate gene studies proved uninformative, with initial suggestive associations consistently unable to be replicated. Initial genome-wide association studies (GWAS), taking a hypothesis-free approach to detect associations across the genome, similarly did not reveal associations despite the previous evidence of genetics contributing 30-40% of the risk for preterm birth. In this case, the GWAS were substantially underpowered to find the changes in risk conferred by common variants as they only analyzed 2000-4000 pregnancies. The first successful GWAS capitalized on pregnancy data from the direct-to-consumer genotyping company 23andMe in collaboration with genotype data from 3 Northern European cohorts compromising a discovery dataset of approximately 44,000 mothers and a replication cohort of over 8,000 mothers. In this study, six independent loci associated with gestational duration were found, 3 of which showed strong association for preterm birth risk (Zhang et al., 2017). These loci were biologically plausible, and the functional SNPs revealed have shed mechanistic insight into how they regulate birth timing by modulating estrogen responsiveness, for example, in *WNT4*. In a similar fashion, the fetal genomic locus encompassing the proinflammatory cytokine IL-1 beta, has been found to be linked to gestational duration, in this case associating more with post-term gestation than preterm birth (X. Liu et al., 2019).

Using whole-exome sequencing of families or sister pairs concordant for preterm birth to detect rare, potential more penetrant gene variants, several additional risk alleles have been identified. These include variants in *HSPA1L*, a nuclear steroid hormone receptor chaperone, the androgen receptor (*AR*), and the insulin-like growth factor 1 receptor (*IGF1R*) (Haataja et al., 2011; Huusko et al., 2018; Karjalainen et al., 2012). The GWAS and whole exome sequencing studies demonstrate the power of these

nonbiased methods to detect true risk variants in this complex disorder.

An important complement to the DNA-based studies are recent biomarker studies performing longitudinal sampling during pregnancy. These investigations, also performed in a pathway agnostic manner, have identified signatures of gestational duration and time to delivery that should prove clinically useful in the future for predicting the risk of preterm birth and possibly developing new therapeutic strategies. These biomarkers include both cell-free RNAs and circulating metabolites or proteins (Liang et al., 2020; Rasmussen et al., 2022).

Social Determinants – personalized and population health

Racism and social injustice have gained increased attention as fundamental contributors to health disparities including adverse pregnancy outcomes such as preterm birth (C et al., 2022; David & Collins, 1991; Murrell, 1996; Slaughter-Acey et al., 2016). The individual health impact of the chronic stress associated with transgenerational racism requires substantial reorientation of societal voices and leadership well beyond the healthcare system. These efforts are growing in number and impact as evidenced by prioritizing diversity, equity and inclusion globally. Incorporating social determinants of health in electronic medical record dashboards is possible, which will guide care providers in individualizing the health care that will especially be powerful as broad areas of biological factors can simultaneously be assessed and intervened (Abraham et al., 2020) (Fig. 1).

Several targets for intervention as modifiable risk factors in pregnancy have been established and should be part of routine obstetric care for all pregnant women. These include pre-pregnancy body mass index (low BMI with the greatest risk for preterm birth), pregnancy weight gain, and interpregnancy interval (Lengyel, Ehrlich, Iams, Muglia, & DeFranco, 2017). Tracking and incorporating these factors into preventive strategies has considerable supportive evidence for impacting population attributable risk for preterm birth. Further, we hypothesize that the genetic regions we identify in our genome-wide studies that associate with preterm birth risk will be targets for epigenetic and post-transcriptional regulation that will arise from consequences of structural racism, social injustice and adverse environmental exposures including infection.

4. Summary and Future Considerations:

To make progress in the challenging area of preterm birth, new teams incorporating diverse disciplines will be advantageous. Bringing together molecular biologists, 'omics investigators, obstetricians, pediatricians, engineers, social scientists, mathematicians, economists, and others for collaborative research planning, implementation and analysis holds tremendous promise for new insights into this long-standing problem. Taking findings in human populations beyond associations but into mechanisms will require appropriate animal models and cell-based investigations. Further, we must partner with and learn from communities of those most severely

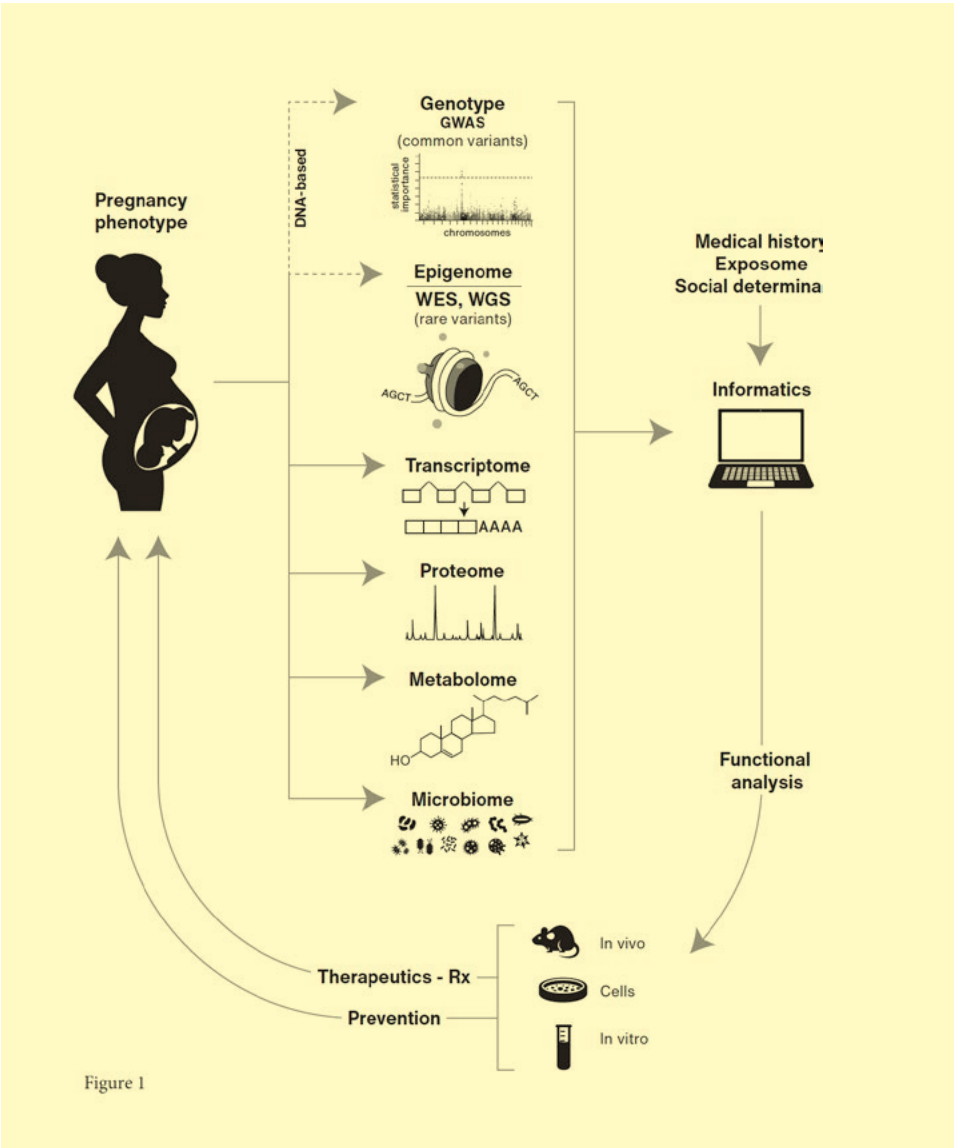

Figure 1. The cycle of discovery through new preventive strategies to prevent adverse pregnancy outcomes. Human populations with new technologies and omics platforms, integrated with medical history, social determinants and environmental data provide unparalleled opportunities for precision and population medicine. WES: whole-exome sequencing; WGS: whole-genome sequencing; GWAS: genome-wide association study. Reproduced with permission from (Sadovsky et al., 2020).

affected by the consequences of historical marginalization, racism, and social injustice. To accomplish this connection will require creative mechanisms of science communication as a dialogue to build trust and engagement. A great opportunity to utilize the arts to better convey scientific messages in a clear and inspiring manner is one that is gaining momentum. Ultimately, new preventive strategies will emerge from the innovative science now being performed to impact health and social equity. Demonstrating their effectiveness and uptake during pregnancy will require public understanding and trust – a priority for progress across all of public health.

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