Placenta 57 (2017) 204–215

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

# The transformative potential of an integrative approach to pregnancy

Haley R. Eidem [a, 1], Kriston L. McGary [a, 1], John A. Capra [a, b], Patrick Abbot [a], Antonis Rokas [a, b, *]

[a] Department of Biological Sciences, Vanderbilt University, Nashville, TN 37235, USA
[b] Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN 37235, USA

ARTICLE INFO

*Article history:*
Received 23 September 2016
Received in revised form
8 July 2017
Accepted 15 July 2017

*Keywords:*
Preterm birth
Human evolution
Parent-of-origin effect
Functional genomics

ABSTRACT

*Background:* Complex traits typically involve diverse biological pathways and are shaped by numerous genetic and environmental factors. Pregnancy-associated traits and pathologies are further complicated by extensive communication across multiple tissues in two individuals, interactions between two genomes—maternal and fetal—that obscure causal variants and lead to genetic conflict, and rapid evolution of pregnancy-associated traits across mammals and in the human lineage. Given the multifaceted complexity of human pregnancy, integrative approaches that synthesize diverse data types and analyses harbor tremendous promise to identify the genetic architecture and environmental influences underlying pregnancy-associated traits and pathologies.

*Methods:* We review current research that addresses the extreme complexities of traits and pathologies associated with human pregnancy.

*Results:* We find that successful efforts to address the many complexities of pregnancy-associated traits and pathologies often harness the power of many and diverse types of data, including genome-wide association studies, evolutionary analyses, multi-tissue transcriptomic profiles, and environmental conditions.

*Conclusion:* We propose that understanding of pregnancy and its pathologies will be accelerated by computational platforms that provide easy access to integrated data and analyses. By simplifying the integration of diverse data, such platforms will provide a comprehensive synthesis that transcends many of the inherent challenges present in studies of pregnancy.



## 1. Pregnancy is an ensemble of complex traits subject to substantial genetic and environmental variation

A highly-interconnected network of physiological, cellular, and molecular pathways supports the development of a healthy fetus by maintaining homeostasis through pregnancy despite variation in maternal diet, stress, medical care, and other factors. When genetic and/or environmental variation of this network cannot be buffered to maintain a healthy state, complications arise. Like diseases of other complex traits, the most common complications of pregnancy – preeclampsia (PE), spontaneous preterm birth (sPTB), preterm premature rupture of membranes (PPROM), intrauterine growth restriction (IUGR), and spontaneous recurrent pregnancy loss (RPL) – involve multiple genetic loci and environmental factors [1–5].

Understanding the genetic basis of such complex traits is challenging. For example, although many pregnancy-related traits and pathologies, such as birth timing [1,6], birth weight [6,7], and propensity to develop PE [8], have substantial heritabilities, they are likely governed by numerous genetic variants with small effect sizes and that epistatically interact with each other [2]. Furthermore, pregnancy-related traits are also influenced, to varying degrees, by multiple environmental factors. For example, gestational diabetes [9,10], PE [10,11], and sPTB [9,10,12] are well known for their association with maternal obesity, and sPTB may also be associated with certain environmental exposures, such as bisphenol A [13]. Similarly, chronic and acute stress is thought to reduce birth weight and alter methylation levels of genes involved in the hypothalamic–pituitary–adrenocortical (HPA) axis in the placenta,

* Corresponding author. Department of Biological Sciences, Vanderbilt University, VU Station B 351634, Nashville, TN 37235, USA. Tel.: +1 615 936 3892; fax: +1 615 343 6707.
*E-mail address:* antonis.rokas@Vanderbilt.edu (A. Rokas).
*URL:* http://www.rokaslab.org
[1] Co-first authors.

http://dx.doi.org/10.1016/j.placenta.2017.07.010
0143-4004/

cord blood, and maternal blood [14].

Further complicating matters is that the genetic and environmental factors underlying pregnancy-associated traits and diseases do not act independently; rather, they exhibit gene by environment (GxE) effects, where the pathological phenotype is only observed with specific combinations of genetic variants and environmental conditions. For example, PPROM is often associated with inflammation due to bacterial infection, but recent studies argue that the fetal genotype also influences susceptibility [15]. Specifically, human fetuses with a null *SIGLEC14* genotype were more likely to be born prematurely, but only in conjunction with Group B *Streptococcus* (GBS) infection; in its absence, the *SIGLEC14* null variant did not appear to influence prematurity.

But what makes pregnancy-associated traits and diseases extremely, or maybe even singularly, complex is that they involve three additional dimensions. The first dimension of complexity is associated with the fact that pregnancy-associated traits require coordination and communication across many different tissues and organs in two individuals: the mother and the fetus. The interplay of tissues and organs from two individuals creates many of the distinctive complexities of pregnancy including immunosuppression, entwined physiology (respiration and metabolism), and shared endocrinology. For example, the production of progesterone, which maintains gestation in most placental mammals, must successfully shift from the ovary to the placenta [16]. Similarly, primary human trophoblasts have been shown to release exosomes containing microRNAs, proteins, and phospholipids with antiviral properties, facilitating communication between maternal and fetal tissues [17,18].

The second dimension of complexity in pregnancy is that it involves multiple genomes (maternal, paternal, and fetal), which gives rise to the potential for conflicts of interest over parental investment [19,20]. Parent-of-origin effects on gene expression or genomic imprinting, for example, may have evolved as a result of differences in the consequences of resource investment for paternally and maternally-derived alleles [21,22]. When females mate more than once and offspring are half-sibs, paternally-derived alleles in the fetus may be evolutionarily favored to sequester more resources than optimal from the mother's perspective, favoring imprinting of the maternal allele [23,24].

The third and final dimension of complexity is that of rapid evolutionary change. Pregnancy and its associated tissues evolve rapidly in mammals [25–28], and the placenta is arguably the most diverse mammalian organ [29]. Out of this history of rapid evolutionary change emerged human pregnancy, which is distinctive in its own right [28], as a consequence of several evolutionary events and processes spanning the course of mammalian evolution, including the existence of genetic conflict [30], the primate-specific expansion of cranial size [31], and the human-specific evolution of bipedalism [32].

The importance of considering these additional dimensions of complexity is apparent in hypotheses proposed to explain puzzling facts of human pregnancy. Birth in humans appears to occur sooner than would be expected, given development of the neonate. A much larger fraction of brain growth occurs postnatally in humans than in any other primate. Why? The “obstetrical dilemma” (OD) hypothesis aims to explain gestation length based on two observations unique to human pregnancy – labor that poses risks to both mother and fetus, as well as birth at a point when fetal brain size is only 30% of adult size. The OD hypothesis holds that bipedal locomotion and large cranial capacity, both of which evolved in recent human history, act in opposing ways on the human pelvis, with the result being selection for shortened gestation lengths that preclude cranial expansion beyond pelvic capacity [23,24,33–38]. An alternative hypothesis, known as the “energetic and metabolic constraints on fetal growth and gestation” (EGG) hypothesis, aims to explain gestation length by invoking physiological limitations to metabolic provisioning *in utero*. Here, the primary controlling factor is physiological limits to the transfer of energy and metabolites between the mother and an encephalized fetus [39]. At some point, it is simply more efficient to transfer resources outside of the womb than within.

As these scenarios make clear, neither the genetic basis of pregnancy-associated traits and pathologies nor the proximate or ultimate hypotheses that explain them can be adequately understood from a single experimental approach, data source, or perspective. The history of efforts to decipher the genetic basis of a wide variety of complex traits and diseases offers numerous examples of the perils associated with reliance on a single experimental vantage point [40–42], and the complexities of pregnancy only amplify the need for integrative approaches that combine multiple data types, approaches, or model systems [25,43,44]. In this review, we examine some of the complexities that make human pregnancy-associated traits and pathologies unique and synthesize recent progress in integrative efforts to understand their genetic and environmental dimensions.

## 2. Integrating multiple maternal and fetal tissues

Pregnancy is singular among human processes in involving coordination of many different tissues and organs from two individuals (Fig. 1), including maternal pregnancy-specific (e.g., decidua, myometrium, and cervix), maternal non-specific (e.g., immune system, metabolism, and endocrine system), and fetal (e.g., lungs, adrenal glands, and fetal membranes). These interactions are responsible for many of pregnancy's unique physiological features, such as immune system modulation [45], entwined respiration and metabolism [46], and shared endocrinology (e.g., progesterone production). True for most placental mammals, the classic example of coordination between maternal and fetal tissues is ensuring that progesterone – a key hormone required for maintenance of gestation – is continuously produced during pregnancy even though the underlying tissue responsible for its production shifts from the ovary to the placenta [16].

The placenta is the nexus of this network of communicating tissues and dedicates a large fraction of its energy budget to secretion and coordination of maternal and fetal needs [47], while also providing the functions of the kidney, the lungs, and the liver for the fetus. Much of this communication occurs locally at the maternal-fetal interface and appears to have evolved early during the evolution of placental mammals by regulatory rewiring of the cAMP signaling pathway in endometrial stromal cells to facilitate decidualization and implantation [48–50]. There are many examples of the importance of communication at the maternal-fetal interface. For example, interaction between maternal immune cells and trophoblasts modulates macrophage inflammatory responses in human pregnancy, which in turn may play a role in implantation and proliferation [51]. Later in gestation, remodeling of the spiral arteries requires successful communication between maternal endothelium and migrating interstitial trophoblasts, which involves both chemotaxis and shifts in cytokine production [52]. Surprising recent work has demonstrated that placental secretion of microRNAs in exosomes at this interface appears to directly increase the resistance of maternal and fetal cell types against viruses implicated in perinatal infections by boosting autophagy [18,53,54].

In addition to local effects at the apposition of maternal-fetal tissues, inter-tissue communication also affects non-adjacent maternal and fetal tissues during gestation. For example, placental production of the neurotransmitter serotonin is crucial