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Maternal Determinants of Pregnancy Success

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Pregnancy is a process describing the journey of *in utero* development of a life born from a fertilized egg called zygote.[1] The process is highly conserved to escape eutherians from environmental insults and thus evolutionally protecting these species from distinction.[2] In humans, a gestation normally takes ~40 weeks to complete to give birth of a healthy baby. In this long journey, there are a series of key maternal steps that can affect pregnancy outcomes, including embryo implantation, placentation, maternal adaptations to pregnancy, and myometrial quiescence and the timing of parturition, etc. Perturbation of a single or a combination of multiple steps leads to a multitude of pregnancy complications, including early pregnancy loss, miscarriage, spontaneous abortion, new onset hypertension in pregnancy (preeclampsia), gestational diabetes, fetal growth restriction, preterm birth, and placenta accrete. Experiencing a complicated pregnancy not only affects the well-being of pregnant woman and her fetus during pregnancy but also predisposes the mother and her child to a much greater risk for cardiometabolic diseases (cardiovascular diseases and type II diabetes) resulting in lifelong consequences later in their life.[3] Poor pregnancy outcomes not only psychologically affect the couples involved but also represent a huge economic burden for the society. Although advances in assistant reproductive technologies over the last three decades have greatly facilitated the treatment of millions of infertile couples, approximately 15% of couples still greatly suffer from pregnancy failures, often without any form of effective treatment. Insufficient to lack of understanding of normal pregnancy process and how complicated pregnancies occur must be blamed for these failures. Nonetheless, there are clear unmet medical needs for pregnancy complications, urging more basic and translational studies to fill knowledge gaps in physiology and pathophysiology of pregnancy. The purpose of this special issue is to revisit the specific events in maternal-fetal interface in both human and animal models encompassing decidualization, placentation, transplacental viral transmission, uterine vascular adaption to pregnancy, myometrial contractility, pertaining to preterm birth, preeclampsia, and infections in pregnancy.

To assure pregnancy health, every step of the entire gestation must be precisely regulated. Implantation, however, is the very first step to establish maternal-fetus communications via the formation of placenta involving cells of maternal and fetal origins. During and immediately after the blastocyst implantation under the influence of pregnancy hormones estrogens and progesterone, the endometrial stromal cells proliferate and differentiate into decidual stromal cells. These terminally differentiated cells are characterized by increased secretions to support the growing embryo and to protect excessive trophoblast invasion.[4–6] Depicting the mechanisms of decidualization is therefore critical for understanding normal pregnancy. Tong *et al*. (*Matern Fetal Med* 2022;4(1):24–35) summarized the dynamic and multi-step decidualization process in both mice and human by considering the regulatory and functional aspects based on data from mice and humans. Successful transformation of the fibroblast-like endometrial stromal cells into rounded decidualized stromal cells is marked by the induction of insulin-like growth factor binding protein 1 and prolactin in women and prolactin family 8, subfamily a, member 2 in mice, respectively. Except for the clear differences in these marker proteins, Tong *et al*. also highlighted other differences in human and mouse decidualization. In mice, polyploidization, characterized by more than 4N chromosomes in the cell, is a widely recognized hallmark of mature decidual cells. However, whether this process also occurs during decidualization in humans remains debatable. Decidualization occurs spontaneously in the menstrual cycle in reproductive aged women, whereas in mice the process appears to take place only after embryo has implanted. More complete decidualization in humans might be attributed to the more profound transformation of stromal cells to facilitate deeper invasion of trophoblast cells to facilitate maximun maternal-fetal blood exchanges can be executed. Nonetheless, there is an urgent need to illustrate the underlying mechanism of decidualization in view of its function in placentation, immune modulation, sensing embryo quality, and labor initiation. Single cell RNA-seq

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has been recently widely applied in recent studies to dissect early maternal-fetal interface cell-cell interactions in humans.[7] Similar approaches would be applied to analyze the spatiotemporal heterogeneity of stromal cells during menstrual cycle and pregnancy, which may provide insights in decidualization, endometrium regeneration, and surveillance of proper trophoblast invasion. In addition, animal studies have clearly shown that disturbed decidualization can propagate in late pregnancy will ultimately contribute to a variety of pregnancy complications. The specific contribution of disturbed decidualization to human pregnancy complications are yet to be determined. Further studies are warranted to explore the translational role of decidualization in pregnancy disease prediction and intervention.

Decidual maturation is accompanied by the formation of a placenta as the maternal-fetal interface, through which close communication between the mother and fetus is established.[8] The placenta functions as the lifeguard of the fetus as it provides all the support that the developing fetus needs. Yu and Wang (*Matern Fetal Med* 2022;4(1):36–51) summarized recent advances relating to the differentiation of human trophoblast and the construction of the placental unit. Moreover, Yu and Wang also discuss the placental and maternal factors contributing to the occurrence of preeclampsia. They describe distinct human placental trophoblast differentiation pathways and discuss how human and mouse trophoblast stem cells are established. They also elaborate the significance of trophoblast cells in spiral artery remodeling and immune intolerance of the semi-allograft placenta/fetus, the endocrine properties, and nutrient transport function of these cells and their role in the immune modulation of maternal-fetal interface. It is noted that exciting progress has been made over recent years with regards to the understanding of the regulation of trophoblastic cell lineage and placental development, the discovery of novel biomarkers, and potential therapeutic targets for pregnant complications including preeclampsia; however, many important questions have yet to be answered. For instance, we do not know how do trophoblast stem cells differentiate into different cell types or how the mammalian target of rapamycin signaling orchestrates the nutritional microenvironment in the placenta. Moreover, we do not know how trophoblast differentiation and metabolism maintain placental functional plasticity, how spiral artery remodeling is regulated, how the endothelial cells are replaced by invasive extravillous trophoblasts or the fate of the vascular cells during spiral artery remodeling. Exploration on the complicated and delicate roles of the placenta in pregnancy outcomes and the health of the mother and the offspring requires systematic intergradation of the multiple cellular events and their cascading regulation.

Preeclampsia is a human pregnancy-specific disease characterized by new onset hypertension and proteinuria after the 20th week of gestation. This disease affects approximately 10 million pregnant women annually worldwide, thus representing a major cause of maternal and fetal morbidity and mortality. The pathogenesis of preeclampsia is largely elusive due to the heterogeneity of the disease. However, most clinically defined preeclampsia cases have been reported to be originated from a two-stage hypothesis involving perturbations of placentation in the first trimester resulting in placental ischemia/hypoxia that further causes systemic inflammation and generalized vascular dysfunction in the rest of gestation.[9] Understanding of placentation is, undoubtfully, important for understanding human pregnancy and preeclampsia; however, theoretically correcting placenta defects appears to be too late for therapeutic interventions because a fully functional placenta is formed approximately 5 weeks before manifestations (new onset hypertension and proteinuria) of clinical preeclampsia can be diagnosed at 20th weeks of gestation. It is not a surprise that most preclinical studies and clinical trials for preeclampsia thus far have been targeted to lessen placenta ischemia through increasing uterine and/or placental blood flow and perfusion. Uterine blood flow is the lifeline for fetal development and survival because it provides almost all the nutrient needs of fetal and placental development and survival, and it also functions as the transportation system for the bidirectional maternal-fetal gas (O_2 and CO_2) exchanges and the exhaust of fetal metabolic wastes. Uterine Doppler flow is known to decrease in preeclampsia with intrauterine growth restriction, thus suggesting a crucial role for the uterine blood flow in pregnancy. Accompanied by the dramatic up to up to 20–50-fold rises in uterine blood flow, endogenous estrogens also significantly elevate in accord with gestational age, which is believed to be a driving force to increase uterine blood flow.[10] There is solid evidence that estrogen production is reduced, and that estrogen metabolism is dysregulated in preeclampsia. Li *et al.* (*Matern Fetal Med* 2022;4(1):52–60) discussed the nitric oxide pathway which has dominated our understanding of the mechanisms modulating estrogen-induced uterine vasodilation in pregnancy since the early 1990s. Thus far, the nitric oxide-mediated uterine and placental vasodilation, along with tissue perfusion, have been the major focus of therapeutic interventions in preeclampsia. However, clinical trails only achieved little success. Li *et al.* also provide us with a critical update relating to the emerging novel proangiogenic vasodilatory role of hydrogen sulfide (H_2S) in modulating estrogen-induced uterine vasodilation in pregnancy and preeclampsia, inciting a new field of perinatal research. This novel pathway provides an attractive and druggable target for therapeutic interventions in preeclampsia and fetal growth restriction. However, clinical trials targeting H_2S for treating these pregnancy disorders will become a realty only after a definite physiologic role of augmented H_2S production in modulating uterine hemodynamics and a pathophysiological role of dysregulated H_2S signaling in preeclampsia can be determined.

Parturition is the final step of pregnancy, which is controlled by intricated maternal-fetal crosstalk directed by sophisticated signaling cascades; the dysregulation of these cascades can lead to preterm birth which can compromise the health of future generations.[11] Preterm birth occurs in 5%–18% of pregnancies and is the leading cause of infant morbidity and mortality. There are three types of preterm birth: infection-induced preterm birth, iatrogenic preterm labor, and spontaneous preterm labor with intact membranes. Among them, spontaneous preterm labor is a syndrome caused by multiple pathological processes, accounting for approximately 70% of all preterm births. Liu and Gao (*Matern Fetal Med* 2022;4(1):61–71)

summarized the current understanding of the potential mechanisms implicated in this disease and describe a range of newly identified risk factors that contribute to preterm birth, including maternal and fetal genetic variations, cervical and myometrium modifications, the placenta, the fetal membrane, the fetal lung and the intensive maternal-fetal interaction as well as food, nutrition, and heavy metals pollution, are newly identified risk factors that contribute to preterm birth. Among them, maternal-fetal interactions are attracting more and more attention in view of protecting the semi-allogeneic placenta/fetus from rejection, implicating that both fetal and maternal immune systems have developed unique strategies to silence maternal immune system during pregnancy, although these strategies have yet to be characterized. It is highly suspicious that preterm birth may be a consequence of abnormal maternal-fetal immune tolerance in the middle and late stages of pregnancy. Currently, the diagnosis of preterm birth represents a formidable scientific challenge. Although some clinical trials, that use metabolites and cell-free RNAs as biomarkers, are promising, their ultimate clinical application still needs to be determined.

The human placenta is formed by 15–20 functional units called cotyledons. Each cotyledon is formed from the branches of one main villous stem covered by the decidua basalis. The villous stem is occupied by fetal blood vessels and covered by a single layer of highly specialized terminally differentiated cells referred to as syncytiotrophoblasts (STB). The STBs are directly bathed in the maternal blood in the intervillous space to facilitate maximum maternal-fetal exchanges. The cell-cell junctions are diminished in the STB layer which functions as the physical blood-placental barrier to separate maternal blood from fetal blood, thus preventing direct blood-blood transfusion (which might include pathogens). While certain viruses can still weaken the placental barrier to trigger severe maternal and fetal health issues especially through vertical transmission. Yu and Cao (*Matern Fetal Med* 2022;4(1):72–86) summarized the classic and emerging viruses associated with frustrating maternal-fetal outcomes, including the hepatitis B virus, human immunodeficiency virus, influenza virus, Zika virus and severe acute respiratory syndrome coronavirus-2. Yu and Cao enumerated the potential underlying mechanism of virus vertical transmission, ranging from cellular structure, physical defense mechanisms, autophagy, the secretion of antimicrobial immunomodulators and the neonatal Fc receptor mediated antibodies transplacental transfer. Despite debates with regards to transplacental viral transmission attributing to the restricted recognition of these viruses or uncertain technical issues, there is a continuous need to decrypt the approaches utilized by viruses to infect fetus cross maternal-fetal interface. For ethical and safety concerns, comprehensively estimating the fundamental mechanisms of vertical transmission crossing placenta is challenging. Yu and Cao advocated that more attention should be paid to the fundamental mechanisms of transplacental viral transmission to arm us to combat the next emerging and re-emerging infectious diseases in pregnancy.

In this special issue, research articles (*Matern Fetal Med* 2022;4(1):7–16; 17–23) also present new data regarding the engagement of different signaling pathways in ethynylestradiol-induced intrahepatic cholestasis pregnant rats under various stressful stimuli, providing insightful mechanisms for pregnancy complications.

Above all, human pregnancy is a very complicated process with many knowledge gaps that need to be filled by future research endowers to assist the development of therapeutic interventions. The articles in this special issue provide insightful updates on various aspects of human pregnancy with relevant knowledge obtained from animal studies to advance the physiology and pathophysiology of pregnancy. Yet, many basic and fundamental processes of pregnancy remain unaddressed. Emerging new technologies, such as high-throughput single cell RNA-seq, three-dimensional organoid culture, and spatial transcriptome, will advance our understanding on these enigmatic processes. Future research must strive to depict the vital questions casted by the authors of this series to improve reproductive health. The creation of suitable animal models will be valuable to better understand human pregnancy events and pave the way to clinical translation and the improvement of pregnancy outcomes.

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None.

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