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Review

Maternal microbiome – A pathway to preterm birth

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SUMMARY

Despite great medical advances in preventing maternal and infant mortality in the past century, one issue remains unresolved: why do so many women give birth prematurely? A major new field of human microbiome studies has begun to shed light on the impact of microbes (of both the commensal and pathogen varieties) on pregnancy outcomes. Recent advances in next-generation sequencing and metagenomic analysis have revealed that maternal microbiomes at a variety of niches including the oral, vaginal, gut, cervical, and even the placenta itself govern pregnancy outcomes. In this review, we describe how alterations in the microbial biomasses impact preterm birth and we discuss the major research questions concerning the cause and/or interdependent relationships between microbiome, infection, and preterm delivery.

1. Introduction

In spite of tremendous research efforts, the puzzle of preterm birth (PTB) is far from being solved. PTB affects 1 in 10 pregnancies, resulting in ~15 million preterm deliveries worldwide [1]. Infants born preterm are at high risk of neonatal mortality and face multiple short- and long-term major health morbidities, which potentially impede childhood development and increase health care expenditures [1]. PTB continues to challenge clinical practice: only a few strategies are available to detect women at risk of delivering preterm, and current interventions to prevent preterm delivery are largely ineffective [2]. This is partly because of the heterogeneous etiology of PTB. Apart from provider-initiated PTB, two-thirds of PTB occur after spontaneous onset of preterm labor due to various pathological processes including preterm premature rupture of membranes (PPROM), intrauterine infection/inflammation, cervical insufficiency, uterine anomalies and pathologic uterine distention (polyhydramnios, multiple gestation), decidual senescence [3,4]. In addition, the interplay of environmental risk factors (stress, smoking, heavy work) [5] and the interrelated biological pathways of parturition [6] create challenges in understanding the mechanisms underlying PTB, hindering the opportunities to translate the research findings into effective interventions.

2. Microbial etiologies for preterm birth

A widely proposed hypothesis links infection and inflammation with spontaneous PTB, including associations with subclinical intrauterine infection, intra-amniotic, and extrauterine maternal infections, such as kidney infection and periodontal disease [7–11]. The micro-organisms most widely associated with PTB have been postulated to originate from one of two places: (i) the reproductive or genitourinary tract, ascending upward through the cervix; or (ii) they may reach the uterus through a haematogenous route [7,8,12]. Substantial data from more than three decades ago provide evidence for a causal role of lower genital tract infection in the etiology of a portion of PTB cases [4,7]. The conventional paradigm suggests

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that the initiating infection, either clinical or subclinical, mono- or polymicrobial, usually ascends from vagina and cervix to the choriodecidual space and may affect the myometrium, fetal membranes or amniotic fluid, resulting in intra-amniotic infection and immune stimulation within the otherwise sterile intrauterine environment [9]. As noted above, the infection may be haematogenous, either from periodontal disease and oral flora from periodontal niche [12,13], through fallopian tube, or seeding during manipulations such as amniocentesis. Further experimental evidence for an unequivocal association between infection and PTB included data showing that antibiotic treatment of ascending intrauterine infections may prevent PTB in experimental models of chorioamnionitis, that treatment of asymptomatic bacteriuria prevents PTB, and that systemic administration of microbial products to pregnant animals results in spontaneous preterm labor and delivery [3,14].

However, the inflammatory/infectious pathway does not fully explain the mechanism of PTB, and anti-inflammatory and antibiotic treatments have not reduced the rates of PTB. The underlying assumption of this hypothesis was that the uterus, and presumably placenta and fetal membranes, are sterile, thus any presence of bacteria is pathologic. This has been a dogma in medicine for over 100 years, implying that the presence of bacteria in the amniotic fluid is related to imminent preterm delivery and poor outcome for the fetus [15–17].

Emerging literature suggests that this long-held belief of a sterile womb may not be correct. New theories promoting a role for the bacterial content, the microbiome of reproductive organs in regulation of the timing of parturition, have been launched [18,19]. Evolving data suggest that the placenta and fetal membranes might not be sterile even in absence of infection [9]. A wealth of bacterial species has been shown to reside within the placenta [20–24]; yet, the microbiome of the placenta is different from other organ systems. It is more similar to the oral cavity than to the vagina, which was the general belief until recently [18]. Studies in both animal models and humans showed that specific bacteria may also be detected in the meconium [25] and umbilical cord blood of healthy newborns [19]. On the other hand, presence of bacteria in amniotic fluid specimens of asymptomatic women at term suggested that, rather than the presence of bacteria, the quantity of bacteria, or perhaps changes in proportion of various bacteria species, may initiate the cascade leading to inflammation, infection, and PTB.

Due to these novel findings, the classic dogma of "sterile womb" and PTB initiated by an ascending infection from the vaginal cavity has been challenged [13,17] and the theory of resident bacterial flora in organ systems, including reproductive organs, makes headway (Fig. 1). This emerging hypothesis led to the development in 2008 of The Human Microbiome Project whose purpose is to describe the structure, function, and diversity of the human microbiome across multiple sites of the human body and to understand its role in human health and disease (www.hmpdacc.org). Characterization of the human microbiome may also be critical in understanding the physiology of human parturition. Evidence suggests that the functional alterations resulting from the hormonal and physical changes during pregnancy are accompanied by consequent changes in "normal" microbiota signature of reproductive organs [7]. Distortion of the fine balance in the composition of the bacterial communities from within reproductive organs may play an important role in triggering and sustaining early uterine contractions.

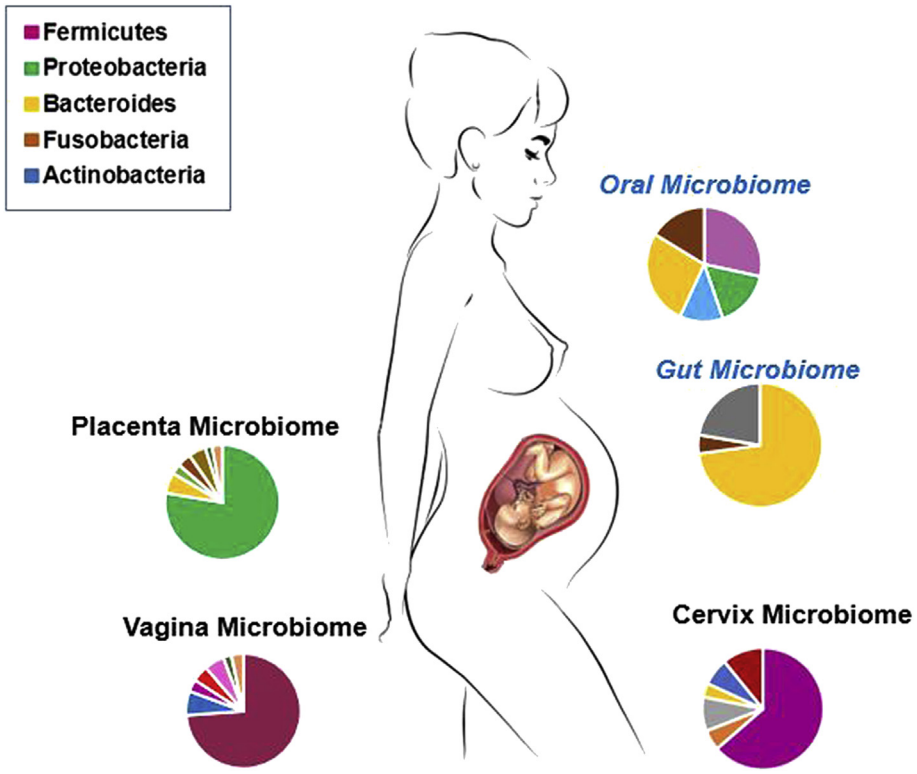

Fig. 1. Microbiomes during pregnancy. The conventional paradigm is that the placenta is a sterile organ and that adverse pregnancy outcomes are associated with microbes that originate from the reproductive tract (vaginal) and ascend through the cervix to colonize the placenta. However, evidence also suggests that other microbial communities including oral and gut may impact pregnancy health by routing hematogenously to the placenta. (Adapted with permission from Belizário JE, Napolitano M. Human microbiomes and their roles in dysbiosis, common diseases, and novel therapeutic approaches. Front Microbiol 2015;6:1050. http://dx.doi.org/10.3389/fmicb.2015.01050.)