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Infection and preterm birth

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SUMMARY

Preterm birth (PTB) remains a primary cause of neonatal morbidity and mortality. The purpose of this article is to outline the association between infection and PTB. We performed a search of the PubMed database for relevant scientific work published in English from 1995 to July 2015. Whereas there is substantial evidence regarding infection as a strong risk factor for preterm birth, the role of specific bacterial and viral infections is not totally conclusive. Newer high-dimensional biological technologies such as microbiomics and metabolomics offer hope to identify the causative pathogens. In addition, strategies have been developed to reduce PTB.

1. Introduction

Preterm birth (PTB), or birth prior to 37 weeks of gestation, is a major cause of neonatal morbidity and mortality both in the USA and worldwide. From 1996 to 2006, the PTB rate increased until peaking in the USA at 12.8%. More recently, the incidence has slightly decreased to 11.4% in 2013 [1]. Worldwide, an estimated 11.1% of all livebirths in 2010 were preterm [2]. Despite advances in the management of preterm labor and neonatal care, PTB continues to account for ~75% of neonatal mortality and ~50% of long-term neurologic impairment in children [3].

Preterm birth can be categorized into major subtypes including spontaneous PTB due to preterm labor (45%), preterm premature rupture of membranes (PPROM) (25%), or indicated PTB due to factors such as pre-eclampsia, eclampsia, or intrauterine growth restriction (30%) [3,4].

Numerous risk factors and proposed mechanisms for PTB have been described. Uteroplacental ischemia and uteroplacental hemorrhage have been linked to spontaneous PTB [5]. Other risk factors include, but are not limited to, prior PTB, shortened cervical length [3,4,6–9], polyhydramnios, low maternal body mass index, multiple gestation, and African-American ethnicity. Systemic and genital tract infections have a known association with PTB based on large epidemiologic studies. As such, this report reviews the role of specific infections in the epidemiology of PTB.

2. Methods

We implemented a literature review of infection and its relation to PTB to identify relevant contemporary articles on the topic. We searched the PubMed database for relevant articles, including recent review articles, published in English in the past three to five years, but also included widely referenced publications dating back as far as 1995. MeSH terms for this search included “preterm delivery” and “preterm birth” in combination with the terms “epidemiology”, “infection”, “bacterial vaginosis”, “ureaplasma”, “mycoplasma”, “sexually transmitted infections”, “trichomonas”, “Neisseria gonorrhoeae”,” Chlamydia trachomatis”, “periodontal infection”, “human papilloma virus”, “herpes”, “influenza”, “antibiotics”, “metabolome,” and “microbiome”. The bibliographies of relevant articles were reviewed to capture other manuscripts not discovered by the original search.

3. Infection and preterm birth

Genital tract infection is associated with ~25–40% of PTB based on microbiological studies. The range may be larger but is limited by methods for detection of infection [4–6]. Infection has been shown to shorten pregnancy latency in the case of PPROM and to increase adverse neonatal outcomes [7].

Multiple hypotheses exist regarding the mechanism for spontaneous preterm labor and PPROM and its relation to infection (Fig. 1). The initiation of term labor is believed to result from progesterone withdrawal, oxytocin secretion, decidual activation, and activation of the fetal immune response [4]. Decidual activation and the fetal immune response are the two mechanisms most likely

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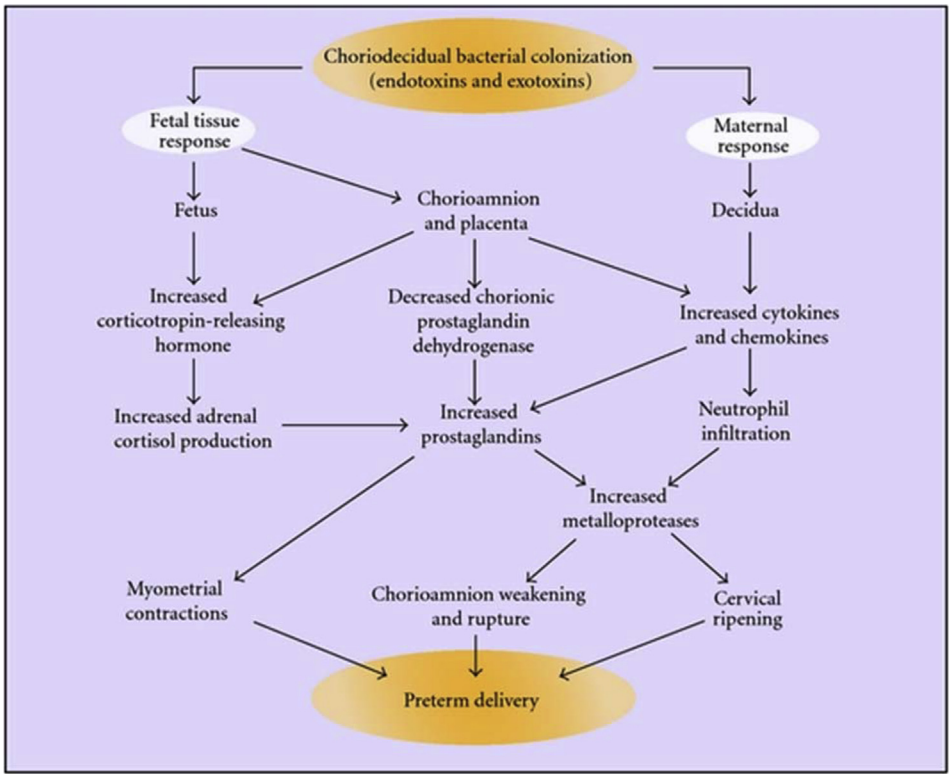

Fig. 1. Potential pathways from choriodecidual bacterial colonization to preterm delivery. (From Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery, New England Journal of Medicine vol. 342, p. 1500–7. Copyright © 2000. Massachusetts Medical Society. Reprinted with permission.)

responsible for infection-related PTB, as the innate immune system is theoretically triggered by infection, inflammation, or hemorrhage. Micro-organisms may reach the amniotic cavity and fetus by ascent from the lower genital tract, by hematogenous distribution, or through invasive medical procedures [8]. Micro-organisms may then be recognized by pattern-recognition receptors such as Toll-like receptors. Consequently, chemokines [interleukin (IL)-8, monocyte chemotactic protein-1] and cytokines [IL-1β, IL-6, granulocyte colony-stimulating factor, tumor necrosis factor (TNF)-α] induce neutrophil activity, prostaglandin production and release, stimulating uterine contractility and synthesis and release of matrix metalloproteinases [5]. This leads to extracellular matrix remodeling and breakdown within the cervix and maternal–fetal interface, resulting in labor and rupture of membranes. Prostaglandin stimulation may also result from a fetal response, whereby infection stimulates the placenta and fetal hypothalamus resulting in corticotropin-releasing hormone production and subsequent release of fetal corticotropin and fetal cortisol [9].

Infections of the developing pregnancy may occur within the choriodecidual space, amnion, chorion, placenta, amniotic fluid, umbilical cord, or the fetus [5]. Many infections present in a subclinical manner. These are confirmed primarily through histopathologic exam, but clinical, biochemical, and microbiological criteria have been utilized to diagnose intrauterine infection. Histologic chorioamnionitis is up to three times more prevalent than clinical chorioamnionitis diagnosed by amniotic fluid culture. Tita et al. attributed this to decreased sensitivity in the genital cultures used to test for genital mycoplasmas, which are the organisms most associated with chorioamnionitis [6]. Similarly, Holzman et al. microscopically analyzed the placentas of 1053 patients, 239 of whom were delivered preterm. Histologic chorioamnionitis was defined by placental components involved, number of polymorphonuclear leukocytes per high-powered field, or by using polymorphonuclear leukocyte characteristics to assign low/high maternal, fetal inflammation stage and grade. Histologic chorioamnionitis was found in 12% of Caucasians/others and 55% of black patients that had a spontaneous PTB before 35 weeks [6,11].

4. Specific infectious organisms

Both mechanisms linking infection to preterm labor and epidemiologic data identifying infection as a major risk factor have been well documented in the literature. The role of specific pathogens as causative organisms, however, remains less conclusive.

5. Bacterial vaginosis

Bacterial vaginosis (BV) has been associated with spontaneous abortion, PPROM, chorioamnionitis, and amniotic fluid infection [12]. BV results from the replacement of typical vaginal flora, most abundantly *Lactobacillus* species, with anaerobes including *Gardnerella vaginalis*, *Bacteroides* spp., *Mobiluncus* spp., and *Mycoplasma hominis* [12]. Two methods are used to evaluate for BV: Amsel's criteria (vaginal pH 3.8–4.2, presence of discharge, amine odor, and presence of clue cells) and the Nugent's score (a Gram-stain scoring system). Risk factors include environmental exposures as well as ethnic differences [12].

Bacterial vaginosis is known to be associated with an increased risk of PTB. Present in 15–42% of pregnant women, BV confers a two- to four-fold independent increase in the risk of spontaneous PTB and PPROM [13]. In a case–control study by Macones et al., maternal blood was analyzed for the TNF genotype in 125 women with a prior PTB and 250 control subjects. Women with BV and a susceptible TNF-α genotype had a two-fold increased incidence of PTB (OR: 2.7; 95% CI: 1.7–4.5) [14]. In a multicenter prospective case–cohort analysis by Nelson et al. of women with a prior PTB,