



Published in final edited form as:

Anaerobe. 2018 April ; 50: 55–59. doi:10.1016/j.anaerobe.2018.01.008.

***Fusobacterium nucleatum* and adverse pregnancy outcomes: Epidemiological and mechanistic evidence**

Emilie L. Vander Haar^a, Jeewon So^b, Cynthia Gyamfi-Bannerman^a, Yiping W. Han^{c,d,e,f,*}

^aDivision of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Columbia University Medical Center, New York, NY, USA

^bInstitute of Human Nutrition, College of Physicians & Surgeons, Columbia University Medical Center, New York, NY, USA

^cDivision of Periodontics, College of Dental Medicine, Columbia University Medical Center, New York, NY, USA

^dDepartment of Microbiology & Immunology, College of Physicians & Surgeons, Columbia University Medical Center, New York, NY, USA

^eDepartment of Obstetrics & Gynecology, College of Physicians & Surgeons, Columbia University Medical Center, New York, NY, USA

^fDepartment of Medicine, College of Physicians & Surgeons, Columbia University Medical Center, New York, NY, USA

Abstract

Fusobacterium nucleatum is a Gram-negative anaerobic oral commensal associated with periodontal disease. *F. nucleatum* has been implicated in a wide spectrum of systemic diseases, including oral, gastrointestinal, rheumatologic, and vascular pathologies. As pregnancy risk has been linked to periodontal disease, there has also been significant research into the effects of periodontal disease on adverse pregnancy outcomes. This article reviews the epidemiological and mechanistic evidence of the role of *F. nucleatum* in adverse pregnancy outcomes.

Keywords

Oral anaerobe; Pregnancy complications; Preterm birth; Stillbirth; Neonatal sepsis; VE-cadherin; Placenta; Chorioamnionitis; *Fusobacterium nucleatum*; FadA

1. Introduction

Intrauterine infection has long been associated with adverse pregnancy outcomes, including preterm delivery, chorioamnionitis, and stillbirth [1–3]. Preterm birth is a significant problem in the United States, as the March of Dimes reports a preterm birth rate of 9.6% for

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*Corresponding author. Department of Microbiology & Immunology, 701 W. 168th St. HHSC 15-1516, New York, NY 10032, USA., ywh2102@cumc.columbia.edu (Y.W. Han).

2016, well above the 7.6% goal set by the Healthy People 2010 campaign [4]. Moreover, neonatal morbidities associated with preterm birth cost the U.S. over 26 billion dollars annually [5]. Thus, as these adverse pregnancy outcomes are both common and costly, understanding the link between intrauterine infection and adverse pregnancy outcomes is critical for determining future preventive measures.

Currently, there are two major pathways by which bacteria and other pathogens may trigger an inflammatory response leading to pregnancy complications [1,6]. The direct pathway is thought to be via spread of microorganisms to the genitourinary tract. The indirect pathway is thought to occur due to a pathogenic inflammatory response mediated by locally produced pro-inflammatory cytokines, such as interleukin-6, interleukin-8, and tumor necrosis factor α , in the absence of detected pathogens [7–10]. Intrauterine infection is thought to arise most commonly from vaginal organisms, however non-genital-tract pathogens, and specifically oral commensal microorganisms, have also been increasingly detected in poor pregnancy outcomes, due in part to the advancement of culture-independent detection technologies [6,11–13]. Moreover, pregnancy renders women susceptible to periodontal disease, as the hormonal changes lead to weakened gingival epithelial barriers and increased inflammation, evidenced by increased rates of gingivitis and progression of periodontitis during gestation [14].

Literature linking poor oral health to preterm birth, chorioamnionitis, stillbirths, miscarriage, and preeclampsia has been steadily increasing for the past 20 years [4,6,11,12,15–17]. Evidence suggests that significant alteration of the bacterial load in the placenta may negatively affect pregnancy outcomes, as the placental microbiome seems to vary between preterm and term gestations [18–20]. Although the presence of a placental microbiome in healthy term pregnancies has been debated [21], recent research suggests that the placental microbiome most closely resembles the human oral microbiome [22]. This finding is consistent with detection of oral bacteria in pregnancy complications including preterm birth, stillbirth and neonatal sepsis [23–26]. Understanding how and which bacterial species transition from the oral cavity to the genitourinary tract may lead to novel therapies for preventing adverse pregnancy outcomes.

One such oral species of interest is *Fusobacterium nucleatum*, a Gram-negative anaerobe commonly found within the oral cavity and implicated in various forms of periodontal diseases [27,28]. *F. nucleatum* has also been implicated in a wide variety of systemic diseases, including GI disorders, atherosclerosis, rheumatoid arthritis and respiratory tract infections [29,30], which is well summarized in a prior review [31]. Here, we review the current literature regarding the link between *F. nucleatum* and adverse pregnancy outcomes, including preterm birth, chorioamnionitis, neonatal sepsis, stillbirth, and preeclampsia.

2. *Fusobacterium nucleatum* and adverse pregnancy outcomes

2.1. Preterm birth, preterm premature rupture of membranes, and chorioamnionitis

The majority of literature regarding the link between periodontal bacteria and adverse pregnancy outcomes focuses on preterm birth and preterm premature rupture of membranes (PPROM). Early studies using traditional culturing techniques have documented intra-

amniotic *F. nucleatum* infection in patients with preterm birth [32–34]. More recently, using 16S rRNA-based culture independent methods, *F. nucleatum* has been detected in placental and fetal tissues, including amniotic fluid [24], cord blood [26], fetal membranes [35], and neonatal gastric aspirates [36], from pregnancies affected by PPROM as well as preterm birth with intact membranes. A study comparing term versus preterm deliveries found that *F. nucleatum* was more prevalent in the placental membranes of preterm deliveries [37]. Interestingly, *F. nucleatum* has also been associated with chorioamnionitis at term, as documented in a case of *F. nucleatum* found in the amniotic fluid of a term patient diagnosed with severe acute chorioamnionitis with intact membranes [25].

The site of origin of *F. nucleatum* in these tissues has been called into question, as both oral and vaginal *Fusobacterium spp.* have been identified [38]. The strains of *F. nucleatum* identified in amniotic fluid and placenta appear to match those from the maternal or the partner subgingival sites, rather than the lower genital tract [23,39,40]. Moreover, animal studies show that injecting saliva or subgingival plaque samples into mice leads to infection of the murine placenta with oral commensal species, including *F. nucleatum*, demonstrating that the oral bacteria are capable of translocation to the fetal-placental unit [41].

2.2. Neonatal sepsis

Neonatal sepsis has also been linked to poor maternal oral health [42], although the literature supporting this association is less robust. A recent study using culture independent methods has documented compelling evidence supporting a microbial link between intra-amniotic infection and early-onset neonatal sepsis (EONS) [26]. In this study, paired amniotic fluid and cord blood samples from 44 singleton pregnancies were analyzed by culture-dependent and independent methods. Several oral species, including *F. nucleatum*, were detected in the cord blood from those with presumed EONS, defined as clinical manifestations of EONS (lethargy, apnea, respiratory distress, hypoperfusion and shock) in newborns despite negative microbial cultures. *F. nucleatum* was the most prevalent species detected in the cord blood associated with presumed EONS, placing it on par with *E. coli* as an important neonatal pathogen. As this was the first study to document this association, further research is needed to better understand the link between *F. nucleatum* and neonatal sepsis.

2.3. Stillbirth

F. nucleatum has also been implicated in stillbirth. In a case study reported in 2010 [23], a strain of *F. nucleatum* identified in the placenta and the stillborn infant was also detected in the maternal subgingival plaque, while no fusobacteria were detected in the maternal vaginal or rectal floras, suggesting translocation of the bacteria from the oral cavity to the maternal-fetal unit. Subsequently, work by Ebersole et al. [43] found that women with miscarriages or stillbirths had significantly higher serum antibody levels to *F. nucleatum* compared to those with live births. As the quantity of antibodies in serum is related to the severity of periodontal disease [44], these findings support a link between oral *F. nucleatum* and stillbirth. Further research is needed to better categorize the severity of periodontal infection associated with this adverse outcome.

2.4. Hypertensive disorders of pregnancy

Periodontal disease has been linked to hypertensive disorders in pregnancy, including preeclampsia. In one study, pathogenic bacteria, including *F. nucleatum*, were found to be significantly enriched in the placentas of women with preeclampsia compared with controls [45]. Another case-control study reported that at the time of cesarean section, women with hypertensive disorders were more likely to have higher levels of oral pathogens in both the oral cavity and the placenta, when compared to the gestational age-matched controls [46].

Conversely, a study by Chaparro et al. [47] found no difference in the rates of periodontal infection or presence of *F. nucleatum* between hypertensive cases and controls; however, they did observe increased expression of Toll-like receptor (TLR) 2 in the placentas of hypertensive cases. TLRs are involved in the immune responses against pathogens, and stimulation of TLR2 within the placenta has been shown to induce pro-inflammatory cytokines [48]. This observation suggests that the hypertensive cases could be associated with microbial stimuli. Further investigation is required to better establish the link between periodontal infection and hypertensive disorders in pregnancy.

3. Mechanisms of virulence

Uncovering the virulence mechanisms of *F. nucleatum* is key to understanding its association with such a broad spectrum of adverse pregnancy outcomes. *F. nucleatum* is an invasive microorganism and can bind and invade both epithelial and endothelial cells, whereas the vaginal isolates, e.g. *F. gonidiaformans*, cannot [49]. The causative role of *F. nucleatum* in pregnancy complications has been demonstrated in a mouse model. Injection of *F. nucleatum* into the tail vein (mimicking dental bacteremia) of pregnant mice led to preterm and term fetal loss within 72 hours [49]. Rather than spreading systemically, *F. nucleatum* was found to be confined to the murine fetal-placental units, originating in the decidua basalis, followed by colonization in the placenta, fetal membranes, amniotic fluid and fetuses. This pattern parallels the pathophysiology of chorioamnionitis in humans, and demonstrates a clear hematogenous route of infection. The kinetics of this acute infection model corroborates with the afore-mentioned human stillbirth case [23]. Control experiments of infection of pregnant mice with *E. coli* DH5 α did not cause fetal loss, indicating the effect on pregnancy is species-specific [49].

Further study led to the discovery that *F. nucleatum* infection of the murine placenta induced an inflammatory response similar to those observed in humans [50]. Although *F. nucleatum* activates both TLR2 and TLR4 in vitro, in murine placentas, it elicits inflammatory responses through TLR4, accompanied by neutrophil infiltration into the decidua [50]. In TLR4-knockout mice, as well as in wild-type mice treated with a TLR4 antagonist, *F. nucleatum* colonizes the placenta to a similar extent as in untreated wild-type mice, however the fetal loss was significantly reduced, suggesting that inflammation rather than the bacteria per se is the cause of fetal demise. In contrast, TLR2 plays an insignificant role because there was no change in fetal loss or inflammatory response in the TLR2-knockout mice compared to the wild-type mice.

A few adhesin molecules have been identified that are required for *F. nucleatum* to colonize the murine placenta, including Fap2 and Fusobacterium adhesion A (FadA) [51–54]. Among them, FadA is the best characterized and plays a critical role in the murine model of infection [31].

FadA is required for *F. nucleatum* to attach and invade host epithelial and endothelial cells [54–56]. It is uniquely encoded in *F. nucleatum*, absent in most other species of *Fusobacterium* [54]. The strains detected in the vaginal tract mostly do not belong to the species of *F. nucleatum*, thus they do not possess FadA, which may be why the vaginal species such as *F. gonadiformans* do not invade host cells [39].

FadA exists in two forms, the intact pre-FadA, consisting of 129 amino-acid residues, and the mature FadA (mFadA), consisting of 111 amino-acid residues. The crystal structure of mFadA reveals a predominantly alpha-helical hairpin structure, with the monomers linked together head-to-tail via a novel leucine-chain motif [57]. It has been shown in vitro that pre-FadA and mFadA form an active and heterogeneous complex (FadAc) for binding and invasion [55]. In vivo, an *F. nucleatum* mutant without FadA is severely deficient in colonizing the murine placenta, while its complement clone restores the colonization [49,58].

FadA binds to cadherins, a large family of cell-junction molecules [59,60]. When FadA binds to the vascular endothelial cadherins (VE-cadherin), it causes VE-cadherin to migrate away from the cell-cell junction, thus increasing the endothelial permeability allowing microorganisms to penetrate through the endothelium [59]. This is likely the mechanism utilized by *F. nucleatum* for systemic dissemination. It may also explain how *F. nucleatum* can overcome such obstacles as the placental barrier. It is plausible that the tight junctions loosened by FadA permit other species to disseminate, as studies show that co-incubation of *E. coli* in the presence of wild-type but not the *fadA*-deletion mutant of *F. nucleatum* resulted in enhanced endothelial cell penetration by *E. coli* [59]. This observation indicates that *F. nucleatum* can serve as a ‘facilitator’ and helps explain why it is frequently detected concurrently with other oral species in intrauterine infections in humans [13]. FadA-assisted systemic dissemination of oral bacteria through loosened endothelial junctions and subsequent placental colonization is depicted in Fig. 1.

4. Concluding remarks

Employment of culture independent techniques for bacterial identification has substantiated our understanding of the involvement of oral commensal species such as *F. nucleatum* in adverse pregnancy outcomes. Current literature supports the link between *F. nucleatum* and preterm birth, intra-amniotic infection, stillbirth, neonatal sepsis, and hypertensive disorders of pregnancy. *F. nucleatum* possesses key virulence mechanisms that allow it to attach and disseminate across endothelium, enabling its hematogenous spread. Understanding the mechanisms involved in transformation of this oral commensal organism into systemic pathogens lays the foundation for developing prevention and treatment strategies to circumvent bacterial-induced pregnancy complications.

Acknowledgments

This work was supported in part by NIH grants RO1 DE014924, DE023332, and CA192111 to Y.W.H.

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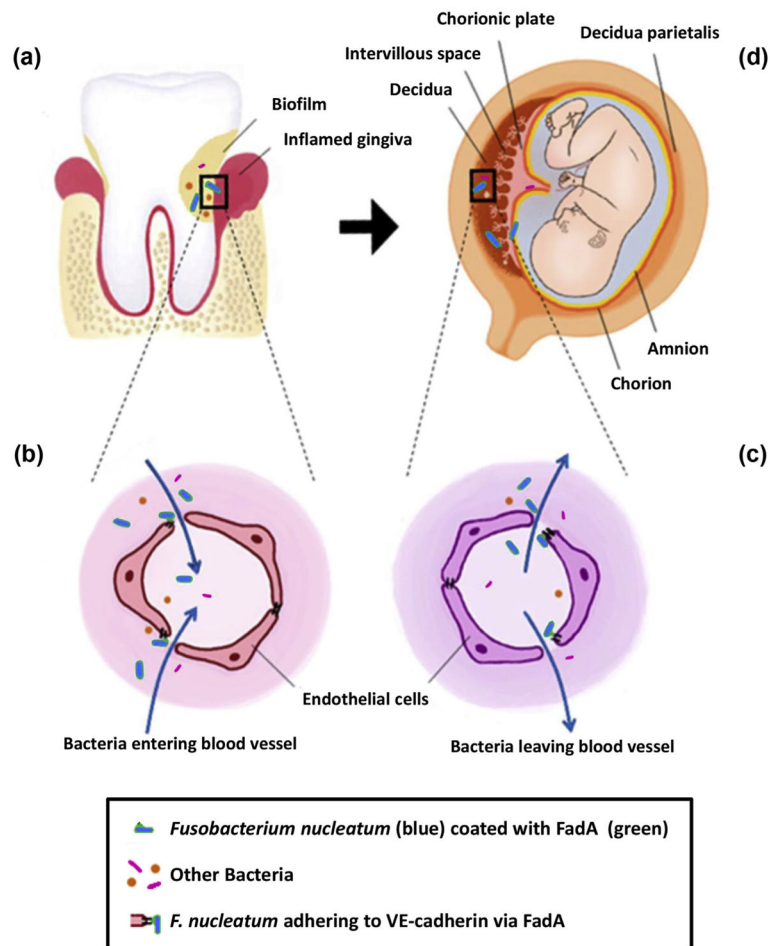


Fig. 1. Schematic presentation of oral bacteria translocation to the fetal-placental unit. Bacteria enters the circulation through the inflamed gingival tissue (a) and (b). Hematogenously spread bacteria invade the fetal-placental unit through the vasculature in the decidua basalis (c) and (d). Binding of *Fusobacterium nucleatum* adhesin A (FadA) to vascular endothelial cadherin (VE-cadherin) increases the endothelial permeability, allowing *F. nucleatum* and other oral bacteria to disseminate into and from the circulation (b) and (c).