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Can oral bacteria cause pregnancy complications?

“Accumulating evidence demonstrates that oral bacteria play a significant yet previously unrecognized role in intrauterine infections.”

Intrauterine infection is a major cause of adverse pregnancy outcomes such as preterm birth and stillbirth. Accurate diagnosis of the infectious organisms and identification of the source of infection are key to patient management. The hospital laboratories still employ the traditional culturing methods, which severely limit the detection of uncultivated or microbial species that are difficult to culture. This explains at least in part some of the idiopathic adverse outcomes. In addition, the current paradigm indicates that the infectious microorganisms originate from the vaginal tract. Accumulating evidence demonstrates that oral bacteria play a significant yet previously unrecognized role in intrauterine infections. Studies in both humans and animals have demonstrated that oral bacteria can translocate to the pregnant uterus through hematogenous transmission. These recent discoveries shed new light on our understanding of pregnancy complications.

Pregnancy complications, such as miscarriage, eclampsia, preeclampsia, premature delivery, low birthweight and stillbirth constitute a major public health problem. They are costly not only financially but also emotionally. According to the March of Dimes, the USA has the highest preterm birth (before 37 weeks) rate among the industrialized countries. The prematurity rate in the USA has risen steadily during the past three decades from 9.4% in 1981 to 12.8% in 2006 [1]. Although the rate has shown a slight trend of decline, dropping to 12.3% in 2008 and to 12.2% in 2009, it is still substantially higher than the goal of 7.6% set by the federal government's Healthy People 2010 campaign [2]. With improvements in medical technology, the survival rate of the preemies has increased dramatically. However, this comes with a price. The survivors, especially the early preemies (born before 30 weeks), often suffer from complications such as cerebral palsy, learning difficulties, attention deficits and respiratory diseases, among others. The families usually carry a tremendous emotional burden owing to the loss of neonates

or the long-term care for the ones that manage to survive. As a result of the increased preterm birth rate and increased survival rate, our population of handicapped individuals has been rising steadily. Preterm births cost society more than US\$26 billion annually in maternal delivery, medical care, early intervention services, special education services and loss of household and labor market productivity [3]. Clearly, prevention is the key in improving the birth outcome and the quality of life. This is only achievable when we have a thorough understanding of the cause of these complications. So far, at least half of the preterm births occur with no known causes [4].

A series of risk factors have been associated with pregnancy complications, including but not limited to: race, maternal bodyweight and age, education, socioeconomic status, prenatal care, smoking, drug abuse, past pregnancy outcome and infection [4]. Among these, infection plays one of the major roles, especially among those early preterm births, accounting for as many as three quarters of the spontaneous premature deliveries before 30 weeks [5]. The early preemies constitute the most medically relevant population owing to the high fatality rate and the long-term morbidity of the survivors. The infection could be systemic, such as respiratory infections and malaria, among others, or localized inside the womb, an otherwise sterile environment. Infections inside the intra-amniotic cavity may involve some or all of the following placental microenvironments: between uterus and fetal membranes (deciduitis), within fetal membranes (chorioamnionitis), within the placenta (villitis), within the amniotic fluid, within the umbilical cord (funisitis) or within the fetus (sepsis) [5].

It is generally accepted in obstetrical practice that in cases with proven intra-amniotic bacterial infection, the risk of maternal and neonatal sepsis outweighs the risk of prematurity and such cases are unanimously managed by a medically indicated delivery and aggressive antibiotic treatment of the mother and newborn. Thus, accurate diagnosis of microbial infection in the amniotic

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cavity is critical for patient management. In this regard, we are faced with two challenges. First, the current approach to detect microbiological invasion of the womb relies on the traditional culturing methods, which severely limits the scope of detection since we are still unable to grow the majority of the microbes living on and within our bodies in a laboratory setting [6,7]. The uncultivated bacteria account for at least part of the idiopathic preterm births. Technologies have been developed to detect microbial species using the culture-independent methods. Studies have shown that some of the idiopathic preterm births were probably caused by uncultivated or difficult-to-culture microorganisms [6,7]. Unfortunately, these advanced technologies have not yet been applied to the clinical laboratories.

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Second, the source of infections inside the womb is usually unknown. The current paradigm indicates that the infectious organisms identified in intrauterine infection originate predominantly from the lower genital tract and ascend into the pregnant uterus. With the advancement of technology, an increasing number of microbial species are identified that do not belong to the normal vaginal flora [6,7]. Studies have demonstrated that infections inside the womb may originate from the mother’s mouth rather than her vagina [6–8].

The oral cavity, like the gut, skin and vagina, is a major microbial habitat in our body, thus can serve as a potential reservoir for microbial infections. Thus far, more than half of the bacteria in our mouth have not been cultivated in laboratories [9]. Using the sophisticated culture-independent and DNA finger printing technology, oral bacteria from the mothers’ mouths have been found to be responsible for causing infections inside their uteri leading to premature delivery and stillbirth [6,8].

The first such case was reported in 2006, when a mother delivered a premature infant at 24 and a half weeks [6]. Although the mother showed signs of intrauterine inflammation, no bacteria were detected in her amniotic fluid by the hospital laboratory despite repeated amniocentesis. Using the culture-independent methods, one

oral species, *Bergeyella*, that has not yet been cultivated was detected in her amniotic fluid. No *Bergeyella* was detected in the mother’s vagina. Instead, an identical clone of *Bergeyella* was identified in her dental plaque [6].

Recently, a case of stillbirth caused by a different oral bacterium, *Fusobacterium nucleatum*, was reported [8]. In this case, the mother was already at term (39 weeks) when she came down with a mild upper respiratory tract infection running a fever of 100°F. In a matter of days, her baby died inside the womb. *F. nucleatum* was cultivated from the stillborn infant’s lung and stomach, with no other bacteria detected. Again, no *F. nucleatum* was present in the mother’s vagina, and the same clone that killed the infant was identified in the mother’s dental plaque [8].

Both *Bergeyella* and *F. nucleatum* are common to the human oral cavity. However, when they migrate to other distant sites in our body, such as the uterus, they become harmful. *Bergeyella* has only recently been associated with intrauterine infection [6,7] because it is uncultivated; thus not detected by hospital laboratories. By contrast, *F. nucleatum*, a fastidious Gram-negative anaerobe absent in other normal human floras, has been frequently identified inside the infected womb [7,10,11].

How do these bacteria migrate from the mother’s mouth to her uterus? It appears that the bacteria translocate to the womb through blood circulation.

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Pregnancy causes many changes to a woman’s body. One of them is the change of her gingival conditions [12]. Women with gum disease may experience progression of the disease during pregnancy. Even women who normally have healthy gums may develop pregnancy-associated gingivitis. Gingivitis is a mild and reversible form of gum disease characterized by inflammation of the gingiva (swollen and bleeding gums), with no bone or attachment loss. Pregnancy-associated gingivitis is highly prevalent, affecting 30–75% of the pregnant population, which goes away after delivery [12]. Whatever the case (mild or severe), the bleeding gum provides an entry point for the bacteria in the mouth to enter the blood circulation, a

phenomenon called transient bacteremia. Under normal healthy conditions, our body can readily fend off such transient bacteremia. However, if the mother has other underlying conditions that compromise her immune system, the bacteria in the blood may escape her immune defense and invade into her womb.

It is likely that this is what happened in the stillbirth case described previously. The mother reported excessive gum bleeding during pregnancy, but had minimal signs of gingival inflammation postpartum, thus indicative of pregnancy-associated gingivitis [8]. As such, she might have experienced frequent transient bacteremia while pregnant. The upper respiratory infection she suffered at the end of her gestation apparently weakened her immune defense, providing a window of opportunity for the bacteria to survive long enough in the circulation to escape to the womb.

This explanation is supported by our observations of pregnant animals. We have demonstrated that once in the blood circulation, *F. nucleatum* can colonize specifically in the mouse placenta, without causing systemic infections [13]. The placental infection will then induce localized inflammation, which eventually kills the fetuses [13,14]. The pattern of infection in mice corroborated with that in the human case [8].

More recent work in animals has demonstrated that many different kinds of oral bacteria can follow this hematogenous route to the placenta [15]. Interestingly, the majority of these species have been associated with pregnancy complications in humans, although their sources of infection were not previously known [15]. Thus, the oral cavity may be a significant yet previously overlooked source of infection inside the womb.

Identification of the source of bacterial infection implicated in pregnancy complications is critical to improve the birth outcome. In the stillbirth case, one couldn't help but wonder: had oral bacteria-induced bacteremia been recognized as a potential risk, would prophylactic antibiotic therapy during the mother's upper respiratory tract infection have saved the baby? One urgent question to address now is: to what extent do oral bacteria impact the pregnancy outcome? Given that the majority of the oral bacteria are uncultivated, it is reasonable to speculate that a significant portion of intrauterine infection caused by oral bacteria have gone undetected. It is our hope that in the future we can identify women at risk for developing oral bacteria-associated pregnancy complications so that preventive measurements can be taken to manage each individual case. An in-depth knowledge of the disease mechanism is the basis of personalized medicine. Only when we have a clear understanding of the causes, can we then develop therapeutic and preventive measures to identify women at risk and to improve the birth outcome and ultimately the quality of people's lives.

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