

Changes of Oral Microbes during Pregnancy and Its Effect on Premature Birth

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Abstract. Premature birth, stillbirth, low birth weight babies, hypertension, and other negative pregnancy outcomes are all associated with women's dental health during pregnancy, according to several studies. Premature birth is a common complication of pregnancy. Premature birth refers to the birth of the fetus before 37 weeks of pregnancy, which is the main cause of death of children under 5 years old. Therefore, it is critical to comprehend the mechanism of premature birth and prevent it effectively. Existing studies have shown that pregnancy, especially in the early stage, promotes the proliferation of microbes in the mouth and promotes the colonization of periodontal pathogens. Gingivitis and periodontitis are more common in pregnant women than in non-pregnant women. The reasons for the changes of oral microbes during pregnancy may be the increase of maternal progesterone and estrogen, as well as the changes of immune system. The pH value of saliva will also decrease during pregnancy, which is related to oral diseases. At present, there are two mechanisms of premature birth caused by oral microbes. One is that oral bacteria reach the uterus through blood borne transmission, and intrauterine infection leads to premature birth. The other is that endotoxin released by bacteria will increase inflammatory mediators and trigger the release of inflammatory factors (such as interleukin and tumor necrosis factor) and prostaglandins in the uterus, leading to premature birth. This paper summarizes the changes and causes of oral microbes in women during pregnancy and the two mechanisms of oral bacteria leading to premature birth and puts forward some measures to prevent and treat oral diseases during pregnancy, so as to provide new ideas for the prevention and treatment of premature birth.

Keywords: Oral Microbes, Pregnancy, Premature Birth.

1. Introduction

Population aging has become a global problem, one of the effective measures to solve which is to increase fertility rate. The healthy and safe birth of a baby is a crucial part of the reproductive process. But even with advanced technology and medical care in this era, adverse pregnancy outcomes still occur from time to time, such as premature birth (PB), miscarriage, stillbirth, and low birth weight infants, among which premature birth is a common pregnancy complication. According to the "Global Report on Preterm Infants" released by WHO in 2014, there are about 15 million premature babies in the world every year, which is more than 10% of all newborns, and this number is still increasing year by year. Among these premature infants, there are about 1.1 million deaths from PB complications worldwide every year. According to research, premature complications are the main reason for death in kids under the age of five. PB is closely related to child morbidity, which has become a global public problem. Therefore understanding the causes of PB and preventing it is extremely important. PB is related to a variety of causes, such as twin or multiple pregnancies, chorioamnion infection, maternal malnutrition, especially folic acid deficiency, and so on. Researchers have found that some common microbes in the oral ecosystem can be detected in the placental system, suggesting that researchers can explore the mechanism of PB from oral microbes.

There are more than 500 kinds of microbes growing in the human oral cavity, including harmful bacteria that are not conducive to health, beneficial bacteria that are useful to the human body, and opportunistic pathogens in between. There is a dynamic balance between them to maintain the body's homeostasis. However, when the oral microbes change and break the original balance, it can cause not only oral infectious disorders including caries, periodontal disease, and apical periodontitis, but also atherosclerosis, diabetes, PB, and other serious illnesses. Existing research suggests that

pregnancy enhances the development of bacteria in the mouth cavity, especially in the early stage, such as periodontal pathogens [1]. If periodontitis is not treated in time, it will destroy the periodontal bone tissue and cause the teeth to become loose and detached. Moderate and severe periodontitis can even greatly increase the chances of premature and low birth weight babies. In addition to periodontitis, some bacteria in dental plaque can also be transferred to the uterus through the bloodstream, causing intrauterine infections that can lead to premature birth. The link of maternal oral inflammation and PB has now been shown on a consistent basis, but the data on its mechanisms leading to PB are sparse and inconsistent. This article will summarize the changes and causes of oral microbes in women during pregnancy, as well as the causes and mechanisms of oral bacteria leading to PB and provide new ideas for exploring the causes of PB and preventing PB.

2. Changes in the Oral Microbes of Women During Pregnancy

2.1. Changes of Oral Microbes During Pregnancy

Oral disorders afflict roughly 3.5 billion people worldwide, according to the WHO. Oral problems are also linked to a number of severe illnesses, including adverse pregnancy outcomes. Premature birth (PB) and low birth weight newborns are more probable when mothers have oral disease during pregnancy, which are seven times more likely in pregnant women with periodontal disease [2]. Therefore, it is very important to study the oral microbes of pregnant women.

There are more than 500 kinds of bacteria in the human mouth, including harmful bacteria that are not conducive to health, and beneficial bacteria that has a good effect on the human body. The specific oral microbial community is shown in Table.1. Beneficial bacteria account for about 1% of the culturable microbes in the oral cavity, such as *Streptococcus salivarius*, *Bifidobacterium*, *Lactobacillus*, etc. Harmful bacteria account for 99% of the culturable microbes in the oral cavity, including *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Actinomyces viscosus*, which can cause periodontitis and dental caries. Human oral microbes always maintain a dynamic balance. As long as the number of bacteria is less than a certain amount, it is harmless to the body. However, when certain bacteria overproduce and break the original balance, it will cause harm to the body. In general, pregnancy enhances the development of microbes in the buccal cavity in women, especially in the first trimester.

Overall, the oral microbes of women change significantly during pregnancy. Compared with non-pregnant women, the total amount of culturable microbes in the mouth of pregnant women is higher at each stage of pregnancy. Particularly in the initial stage of gestation, contrasted to the women who are not pregnant, the level of total bacteria in the mouth increases significantly, and the prevalence of *actinomycetes* and *Porphyromonas gingivalis* is also significantly higher [3]. The number of some microbes in the oral cavity of pregnant females and non-pregnant females is shown in Figure 1. Another study has also confirmed this phenomenon. After quantitative determination of periodontal bacteria in pregnant women, it was found that the *actinomycetes* and *F. nucleatum* were observed in large quantities During the 12 to 24 weeks of pregnancy [4]. Thus, it can be seen that the prevalence of *actinomycetes* in pregnant women at each stage is significantly higher than that in non-pregnant women, and pregnant women are more likely to suffer from oral diseases.

There are also differences in oral microbes from pregnancy to postpartum, And the gross quantity of bacteria reduced considerably after delivery. In order to explore the changes of oral microbes during specific pregnancy, researchers sampled the subgingival samples of pregnant women at the 12th week, 28th week, 36th week of pregnancy and 4 to 6 weeks after delivery and obtained 37 kinds of bacteria. After comparative analysis, it was found that there was a considerable drop of the total bacteria count from the 12th week of pregnancy to the 4th-6th week after delivery. The total number of bacteria in the mouth at the 12th, 28th and 36th weeks of pregnancy and 4 to 6 weeks after delivery is shown in Figure 2. 17 of the 37 species decreased, but the subgingival levels of periodontitis related bacteria (*actinomycetes*, *Porphyromonas gingivalis*, *T. forsythia* and *T. denticola*) did not change. In addition, the distribution and growth of bacteria are not same in different oral parts, especially in the

place of exploratory bleeding (BOP) of gingivitis during pregnancy. Higher levels of bacteria associated with early colonization were found at the BOP site at weeks 12 and 28, which can be described as the time when periodontal tissue is susceptible to bacterial colonization and infection with inflammatory response [5]. This also reveals that the first trimester of pregnancy is a critical time for oral health management. It is also worth noting that BOP decreases between the 12th week of pregnancy and the first few weeks after delivery, and without any active therapy, mild gingivitis during pregnancy may diminish to some extent [6].

In addition, the pH value of female saliva will also change during pregnancy, which may be related to the prevalence of oral diseases during pregnancy. According to the study, the average pH value of saliva of women in non-pregnancy, early pregnancy, middle pregnancy and late pregnancy decreased successively, and the oral hygiene of pregnant women also deteriorated with time, from the first to the second trimester of pregnancy. Salivary pH and oral hygiene of pregnant and non-pregnant women are shown in Figure 3. Gingivitis and periodontitis were shown to be more prevalent in pregnant women than in non-pregnant women. The concentrations of *Streptococcus mutans* and *Lactobacillus* rose in the third trimester of pregnancy, as did the prevalence of dental caries.

In conclusion, pregnancy, especially in the early stage, promotes the proliferation of microbes in the mouth and the colonization of periodontal pathogens. Oral illnesses are more common in gravid women than women who are not gravid. The early stage of pregnancy (the first 12 weeks) is a critical period for intervention to improve oral health. If women have mild gingivitis during pregnancy, it can subside in the second trimester of pregnancy or postpartum through autoimmune regulation.

Table 1. The specific oral microbial community [7]

Oral site	Microorganism	Characteristics	Disease
Tooth surfaces	<i>Streptococcus sanguinis</i>	(+)	It is an integral part of the core microbiome of periodontal health
	<i>Streptococcus gordonii</i>	(+)	Cause infective Endocarditis Cocci with alpha-hemolytic chains that aid in the alkalization of the oral mucosa and the formation of protective biofilms
	<i>Rothia dentocariosa</i>	(+)	Cause periodontal lesions It is a natural component of the mouth's microbial flora.
	<i>Gemella hemolysans</i>	(+)	As opportunistic pathogens, they cause serious and widespread illness.
	<i>Granulicatella adiacens</i>	(+)	Bacteremia
	<i>Actinomyces Species</i>	(+)	Plaque formation and periodontal disease
Subgingival plaque	<i>Campylobacter showae</i>	(-)	Periodontal infections
	<i>Cryptobacterium curtum</i>	(+)	Periodontal disease and necrotic dental pulp
	<i>Prevotella multiformis</i> (PPPA21)	(-)	Periodontal disease
	<i>Gemella</i>	(+)	Isolated from the subgingival plaque in periodontitis
	<i>Campylobacter rectus</i>	(-)	Rectobacteria <i>Campylobacter</i> is a periodontal pathogen
The tonsil	<i>Prevotella</i>	(-)	Periodontal disease
	<i>Porphyromonas Species</i>	(-)	Periodontitis
	<i>Veillonella atypica</i>	(-)	Periodontitis
Tongue	<i>Porphyronas gingivalis</i>	(-)	Periodontal diseases
	<i>Selenomonas species</i>	(-)	Periodontal disease
	<i>Actinobacillus actinomycetemcomotans</i>	(-)	Oral and nonoral infections and periodontal disease
	<i>Prevotella intermedia</i>	(-)	Periodontitis gingivitis
Oropharyngeal region	<i>Streptococcus salivarius</i>	(+)	Dental caries and periodontal disease
	<i>Streptococcus mutans</i>	(+)	Dental caries and periodontal disease
	<i>Streptococcus anginosus</i>	(+)	Oral cancer

Note:

Gram-positive: (+)

Gram-negative: (-)

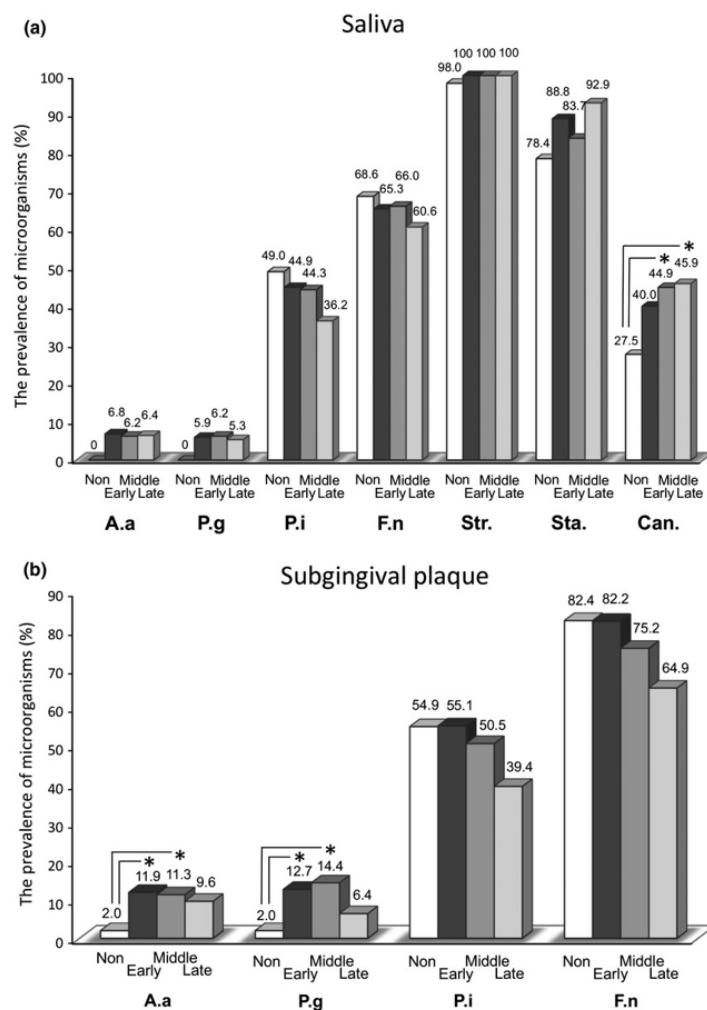


Figure 1. The number of microbes in saliva and subgingival part of pregnant females and non-pregnant females [3]

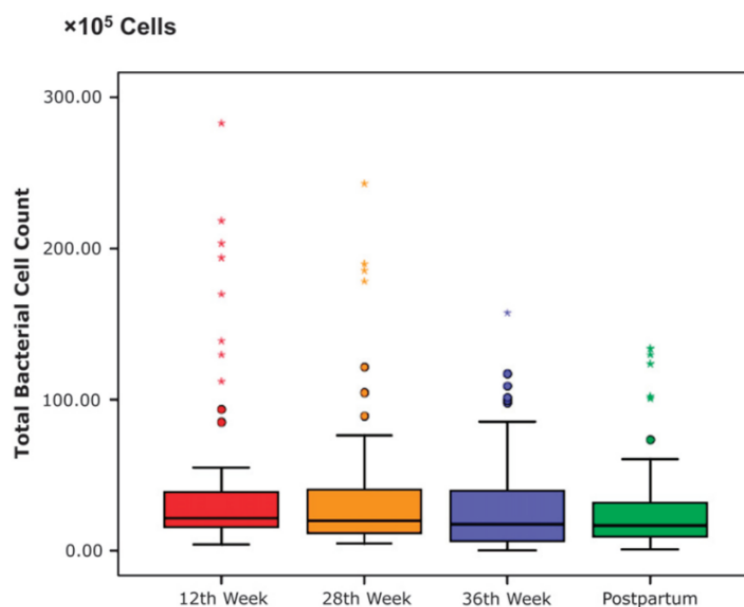


Figure 2. The total number of bacteria in the mouth at the 12th, 28th and 36th weeks of pregnancy and 4 to 6 weeks [5]

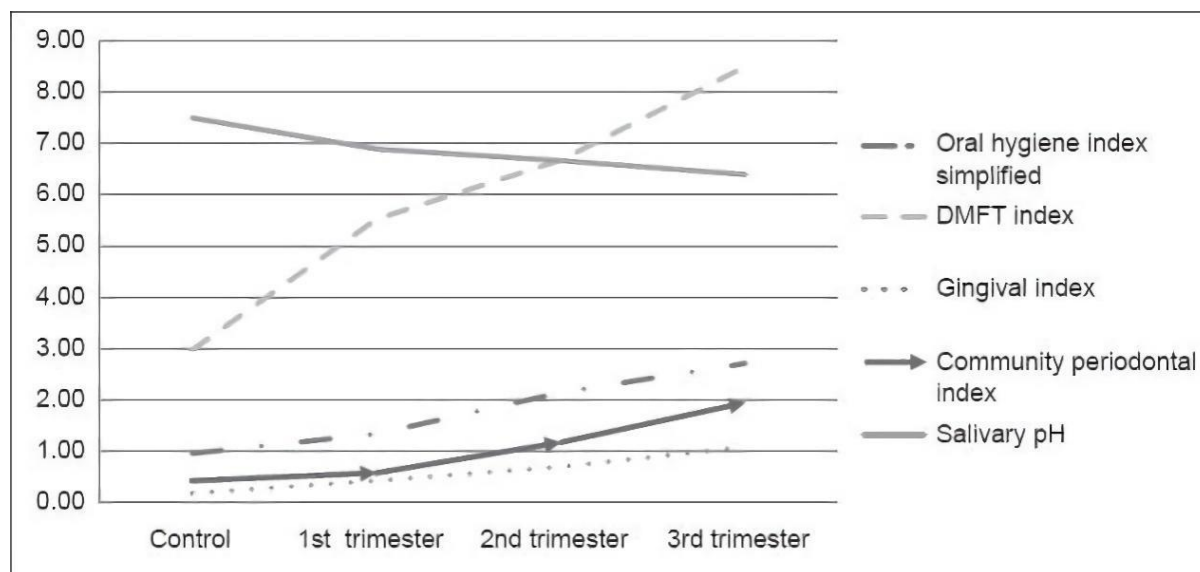


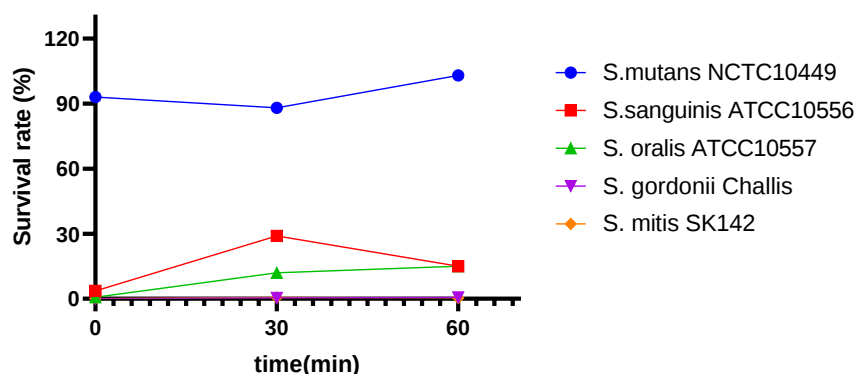
Figure 3. Salivary pH and oral hygiene of pregnant and non-pregnant women [8].

2.2. Causes of Oral Microbial Changes During Pregnancy

There are many reasons for the changes of oral microbes in women during pregnancy. One of the main reasons is the increased secretion of estrogen and progesterone during pregnancy and the changes of maternal immune system. Existing studies have shown that sex steroid hormones can diffuse into saliva and enter the mouth through capillaries and salivary tubes, affect the balance between human body and oral microbes, change the physiological and biochemical properties of the mouth, and lead to gingival inflammation and bleeding [9]. The specific mechanism may be that estradiol stimulates gingival inflammation, whereas progesterone promotes vascular permeability and lead to gingival bleeding. The levels of progesterone, estrogen, and prostaglandin E₂ in the gingiva rise in pregnancy, which alter the permeability of gingival blood vessels, resulting in the increase of gingival vascular exudate, the weakening of gingival epithelial shielding effect, and the excessive reproduction of dental plaque bacteria. As a result, it causes gingivitis and bleeding during pregnancy [10]. In addition, the increase of progesterone level in women during pregnancy will promote the growth and reproduction of periodontal pathogen *Prevotella intermediate* and *Porphyromonas gingivalis*. At present, researchers have found *Prevotella intermediate* and *Porphyromonas gingivalis* have a link to mothers' hormone levels [11], which may be due to the fact that these female sex hormones like progesterone and estradiol may be used as a part of the diet by two bacteria [12].

Secondly, as mentioned above, salivary pH of pregnant women will decrease, which is also related to oral hygiene. The possible reason for the decrease of pH is that women are prone to vomiting during pregnancy, and gastric acid flows back to the mouth, resulting in the decrease of salivary pH. In addition, salivary pH is also related to diet. Some pregnant women like to eat acidic food during pregnancy. The long-term intake of acidic food makes the oral environment acidic. Acidic oral environment will lead to demineralization of tooth surface and enhance the acid resistance of some oral bacteria. Once bacteria begin to adapt to acidic conditions, it will accelerate the potentially dangerous cycle, that is, enhance the acid continuity and acidity of bacteria, resulting in the deterioration of oral environment. The survival rate and acid production of *streptococcus* after acidification are shown in Figure 4.

Survival rate (%) at pH 4.0 for 60 min after an exposure to pH 5.5 for:



pH decrease in the presence of 90 mM glucose for 160 min after an exposure to pH 5.5 for:

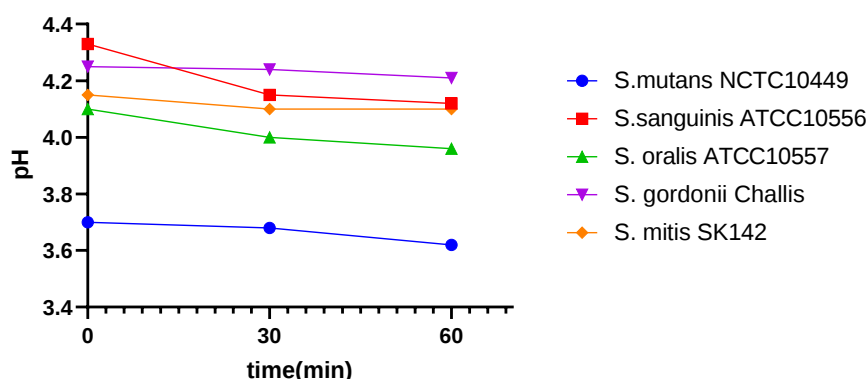


Figure 4. The survival rate and acid production of *streptococcus* after acidification [13]

3. Oral Microbes Cause PB

At present, there are two mechanisms for oral microbes to cause PB: 1. Oral microbes reach the uterus through blood-borne transmission to cause PB. 2. Lipopolysaccharide of oral microbes can increase inflammatory mediators, triggering the release of inflammatory factors and prostaglandins in the uterus, and leading to PB.

3.1. Oral Bacteria Trigger Uterine Infection

Current research suggests that oral microbes can reach the uterus through bloodborne transmission, leading to uterine infection. Uterine infection usually occurs through the ascending route, which means microbes that start in the lower genital tract ascend through the female vagina, enter the uterus and lead to infection. However, many cases have shown that women give birth prematurely due to uterine inflammation. Microbes from the lower reproductive tract are not detected in their uterus, but from the mouth, such as an uncultivated strain *Bergeyella* sp. clone AF14. A previous woman was diagnosed with a uterine infection of *Bergeyella* sp. clone AF14 resulting in premature birth at 24 weeks of gestation, this strain was also detected in the patient's subgingival plaque. After excluding oral, vaginal, and enteric sources, it was finally speculated that the uncultivated *Bergeyella* strain

originated in her oral cavity and caused infection through hematogenous transmission into the amniotic fluid [14]. There are also several cases involving PB due to *Capnocytophaga* infection. *Capnocytophaga* is found in the natural bacterial communities of the human mouth, and can cause chorioamnionitis and neonatal infections. Amnionitis may be the cause of most PB [15]. However, the bacteria did not produce vaginal cultures in the above cases, which has been suggested that blood borne transmission was used to spread it from the mouth to the uterus [16]. Many oral bacteria that do not belong to the reproductive tract have been detected in the uterus and placenta, including *Clostridium nucleatum*, which causes periodontal disease [1, 3]. *Clostridium nucleatum* is among the most typical amniotic fluid species and placental infection. There was a case of a lady with pregnancy-related gingivitis had a respiratory system infection at pregnancy and gave birth to a stillborn baby just several days later. *F. nucleatum* obtained from placenta and fetus originated from the mother's subgingival plaque. When the mother's immune system was compromised by the respiratory infection, it spread to the placenta and fetus, producing intrauterine infection and fetal death [17]. These all suggest that in addition to the ascending route, the bacteria can also reach the uterus through hematogenous transmission, leading to adverse pregnancy outcomes. This infection mechanism has been validated in animals. When *F. nucleatum* was given into pregnant mice via the caudal vein, the bacteria were found in the mouse placenta's blood vessels before expanding into the amniotic fluid to cause infection, which resulted in PB, stillbirth and non-sustained live birth. The bacterial infection is only restricted to the uterus, and placental infection subsequently induces local inflammation, activating inflammatory pathways, and ultimately leading to adverse pregnancy outcomes. This infection pattern is similar to that in humans.

3.2. Oral Bacteria Produce Inflammatory Mediators and Cause PB

Another mechanism of oral microbes triggering PB is that endotoxins released by oral bacteria can increase local inflammatory mediators in the oral cavity. These inflammatory mediators and endotoxins enter the blood circulation. Local inflammatory mediators stimulate the production of systemic inflammatory mediators and trigger the release of inflammatory cytokines and prostaglandins in the uterine fetal membranes [18]. Uterine contractions and rupture of membranes lead to PB. The mechanism of PB caused by bacterial endotoxin is shown in Figure 5.

The researchers detected significant rises in inflammatory cytokines like IL-6 and TNF- α in amniotic fluid samples obtained at PB. It was also found that in other asymptomatic patients, the level of IL-6 in amniotic fluid raised, and they delivered before 34 weeks of pregnancy [19]. The mechanism of PB induced by inflammatory mediators has also been verified in animals. After vaccination of *Porphyromonas gingivalis* in pregnancy mice, local infection of gingival porphy cells activates the parent inflammatory reaction, induces a particular maternal immunoglobulin reaction, increases maternal TNF- α and inhibits the mother IL-10, leading to the growth limit and reconnection of the fetus [20]. Apart from that, bacterial endotoxins may also enter the placenta through the blood circulation, causing the release of inflammatory cytokines in the uterus and leading to adverse pregnancy outcomes. Bacterial endotoxins in amniotic fluid were first identified in 1987, and subsequent research have found significantly higher concentrations of these bacterial products in premature women than those women who had normal delivery without bacteria invasion. Vitro experiments have also confirmed this mechanism. Immortalized cervical cancer and endometrial cells were treated with LPS, and LPS-induced inflammation significantly elevated IL-6 and IL-8 concentrations, damaged the cervical epithelial barrier and promoted cervical remodeling, triggering PB of the fetus [21]. Based on this inflammatory mechanism, the quantity of IL-6 in amniotic fluid is presently the most researched diagnostic technique for diagnosing intrauterine inflammation.

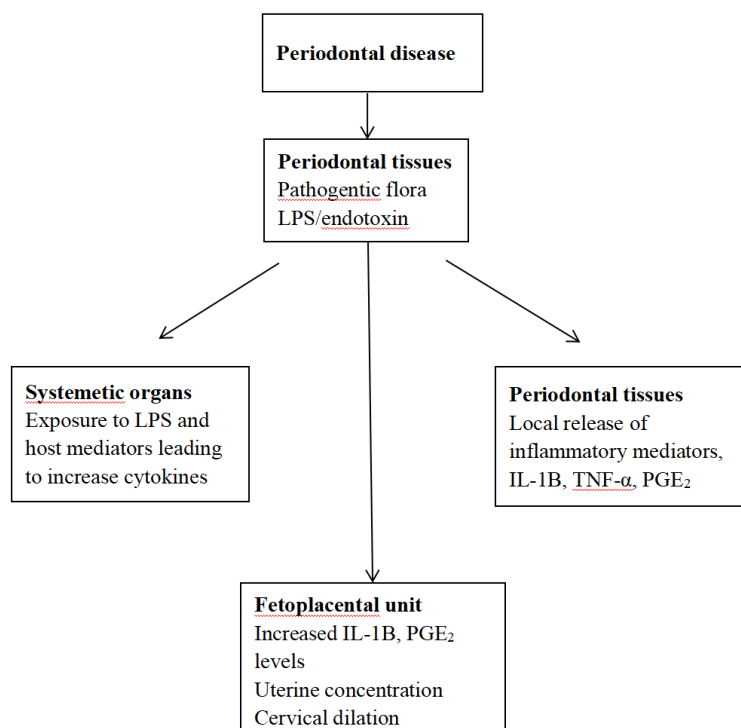


Figure 5. The mechanism of PB caused by bacterial endotoxin [22]

4. Oral Care During Pregnancy

Although the increase of oral microbes during pregnancy may lead to oral diseases and PB, certain treatments and prevention methods can effectively alleviate oral diseases and avoid adverse pregnancy outcomes. For periodontitis, researchers have found that non-surgical and non-drug periodontitis treatments for pregnant women, such as scaling, root planer and tooth polishing, can improve periodontal disease and are safe for the fetus. However, PB, low birth weight, and fetal growth restriction are not effectively diminished by this therapy [23]. In order to improve the mother's periodontitis and reduce the incidence of PB, pregnant women can use mouthwash to treat periodontitis, which is more economical and convenient. Existing studies have shown that the use of nonalcoholic antibacterial mouthwash containing cetylpyridine chloride by pregnant women can reduce the probability of PB before 35 weeks [24]. In addition, during pregnancy, dental caries is also a common cause of oral disorders. Increased dental caries in newborns is associated with the accumulation of cariogenic bacteria in mothers. Women can use oral topical antibiotics to treat dental caries during the pregnancy's third trimester, such as xylitol as well as chlorhexidine, in order to minimize the mother's oral bacterial burden and the transfer of germs to her children [25].

Appropriate time should also be selected for the treatment of oral diseases during pregnancy. Early pregnancy (the first three months) is the key period of embryonic development. Effective dental treatments are not recommended at this stage, and unnecessary intervention may lead to abortion. The second trimester of pregnancy (4-6 months) is a suitable period for the treatment of oral diseases. In terms of the treatment of dental caries, filling teeth and root canal treatment can be carried out at this stage. In the third trimester of pregnancy (7-9 months), oral treatment should be avoided as much as possible. At this stage, the uterus is more sensitive, and external stimulation is easy to cause uterine contraction. The lying posture during treatment may also cause supine hypotension in pregnant women. If it is impossible to avoid the treatment of oral diseases in the third trimester of pregnancy, it is recommended to lie on the left side or change the posture occasionally and try to take simple treatment methods [26].

In addition to the necessary treatment, dental care during pregnancy is also essential. For instance, fluoride toothpaste can effectively prevent and control dental caries [27]. Apart from that, cleaning

teeth with sugar free gum is also an effective way, such as xylitol gum. Xylitol can reduce dental plaque and inhibit the growth and metabolism of *Streptococcus* leading to dental caries [28]. According to a recent report by the associated press in New York, researchers found that chewing xylitol gum can prevent PB through a controlled experiment. The mechanism is unclear, and it is not determined whether other forms of xylitol have the same effect. However, they believe that xylitol has "probiotic" properties that can stimulate the growth of healthy bacteria in the mouth, which may be related to the mechanism of preventing PB.

In conclusion, women should not only pay attention to fetal growth, but also pay attention to oral care during pregnancy. In case of oral diseases, seek medical attention in time. If pregnant women with periodontal disease desire to lower the incidence of adverse birth outcomes through periodontal intervention, such intervention should be carried out in the first trimester of pregnancy (before the 12th week).

5. Conclusion

In conclusion, during pregnancy, especially in the early stage of pregnancy, microbes in women's oral cavity will proliferate greatly, and oral illnesses are more common in pregnant women than in non-pregnant women. The reasons for the changes of oral microbes during pregnancy may be the increase of maternal progesterone and estrogen, as well as the changes of immune system. The pH value of female saliva will also change during pregnancy, which may be related to the prevalence of oral diseases during pregnancy. Acidic oral environment will lead to demineralization of tooth surface and enhance the acid resistance of some oral bacteria. At present, there are two mechanisms of PB caused by oral microbes: one is that oral microbes reach the uterus through blood borne transmission, and uterine infection leads to PB. The other is that the endotoxin released by oral microorganisms will increase the local inflammatory mediators in the oral cavity. The local inflammatory mediators stimulate the production of systemic inflammatory mediators and cause the release of inflammatory factors (such as IL-6, TNF- α) and prostaglandins in the uterus, leading to PB. Although the changes of oral microbes during pregnancy will increase the risk of PB, certain treatment and prevention methods can effectively alleviate oral diseases and reduce the probability of PB. Most studies have shown that periodontitis treatments without surgeries are suitable for pregnant women and can help them develop their periodontal health. The use of nonalcoholic antibacterial mouthwash containing cetylpyridine chloride by pregnant women can not only improve oral hygiene, but also reduce the probability of PB. In order to avoid adverse pregnancy outcomes, women should detect and treat oral diseases before and early in pregnancy. At present, there is still a large space to explore the relationship between oral microbes and PB.

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