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REVIEW ARTICLE

The oral microbiome and dental health during pregnancy: Impact on maternal and foetal health outcomes

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Abstract

Hormonal and immune system changes during pregnancy may disrupt the resident oral microbiota causing dysbiosis that may render these women prone to gum health disease, such as gingivitis and periodontitis. This may in turn lead to systemic disorders, such as maternal gestational diabetes mellitus and hypertension, preterm birth, and low birth weight infants. Emerging evidence has associated dysbiosis of the oral microbiota during pregnancy with an imbalance and a preponderance of pathogenic bacteria such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum* that may cause both placental and systemic inflammation. To mitigate the consequential adverse effects originating from poor oral health, some strategies have been proposed which include the use of probiotics, antimicrobial agents, laser therapy, and nanotechnology aimed at regulating a healthier oral microbiota to promote better overall health and pregnancy outcomes. This paper also highlights the importance of routine maternal oral health examination and management as a crucial inclusive component of antenatal care, which could positively impact on both the maternal and neonatal health outcomes. Advances and further research in this area will unravel the molecular mechanisms underlying the oral dysbiosis, systemic interactions and the fundamental basis for newer therapies to curb oral health related disorders in pregnancy.

Keywords: dysbiosis, gingivitis, oral microbiota, periodontitis, probiotic, systemic inflammation, antenatal care, gum disease, entero-mammary, oral-gut axis

INTRODUCTION

The oral microbiota has about 700 bacterial species, and as of now, only 50%-60% have been isolated and identified.[1] These microorganisms live in different areas of the mouth, such as the gingival sulcus, the back of the tongue, oral mucosa and saliva,[2] and are mainly composed of the phyla such as, *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Proteobacteria* and *Clostridia*.[3] A healthy mouth and body are maintained by a balanced oral microbial community.

New studies have referred to oral dysbiosis being an emerging and serious health concern to women of child-bearing age. Pregnancy causes some remarkable changes in the body, and thus women may be more prone to disruption and deterioration in their oral health. The physiological changes may alter the composition and diversity of the oral microbiota, favouring the proliferation of pathogenic bacteria, and reducing the stability of the resident microbial community.[4] For example, studies have shown that the prevalence of *Porphyromonas gingivalis* (*P. gingivalis)* and *Fusobacterium nucleatum (F. nucleatum)* is relatively high during pregnancy. These bacteria are associated with systemic inflammation and adverse pregnancy outcomes.[5] With the progression of gestation, changes in hormone levels and the immune system can alter the structure of the oral microbial community and

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damage gum health, thus increasing the risk of gingivitis and periodontitis.[6,7] Both kinds of gum disease are known risks associated with heart disease, diabetes and respiratory problems.[8-10]

There is now considerable evidence to support the extended implications of pregnancy-associated oral dysbiosis beyond oral health. Inflammatory mediators released by periodontal infections are known to enter the bloodstream to significantly impair the function of the placenta; thus, preterm birth, low birth weight, gestational diabetes mellitus (GDM), and maternal hypertension are possible consequences.[11]

Alterations in the Oral Microbiota During Pregnancy

The oral microbial community is a diverse and relatively unstable ecological system that supports other microbial activities in the mouth, helps shape the local immune system, and enables nutrient acquisition. A disruption in this balance will lead to dysbiosis, characterised by a decrease in microbial diversity and an increase in pathogenic bacteria that could potentially be harmful to the health of pregnant women and the development of the foetus.[6,12] Commonly occurring bacteria in the oral microbiota and their effects on the host are presented in Table 1.

Changes in the oestrogen and progesterone levels are the main causes of alterations to the microbiota during pregnancy. Research has shown that these hormones change the composition of the oral microbiome by increasing the proportion of pathogenic organisms.[6,7,12] Oestrogen can regulate the expression of bacterial genes and their metabolism to promote the growth of some pathogens.[6,7] The microbe, *Prevotella intermedia*, for example, obtains hormonal metabolites as a source of nutrition for its own proliferation and pathogenicity. At the same time, alterations in the function of the immune system during pregnancy may reduce the stability of resident microbes and thus promote an imbalance in the oral microbiota.[6,12] Furthermore, many pathogenic bacteria can form biofilms and thus reduce the effectiveness of the host immune system response and antimicrobial agents (Table 1).

Another way that pathogenic bacteria cause poor gum health is by altering host cell function, such as in the case of *P. gingivalis*. Besides releasing proteases to damage periodontium tissues, *P. gingivalis* can enter gingival epithelial cells (GECs) and trigger apoptosis in a self-preservation mechanism. *P. gingivalis* also contributes to the pathogenesis of periodontitis by releasing outer membrane vesicles (OMVs). These vesicles are taken up by the human periodontal ligament cells; as a result, these cells undergo apoptosis and release inflammatory factors.[13] *P. gingivalis* can also degrade tight junction proteins, such as JAM1, increase the permeability of gingival epithelium, and thus promote the entry of bacterial virulence factors.[14] Therefore, *P. gingivalis* suppresses apoptosis to maintain its survival within host cells and perpetuate its harmful effects.[15] It is likely that evasion of the host defence mechanism and release of pro-inflammatory factors such as IL-1 and TNF-α will exacerbate oral dysbiosis and tissue injury.

Nutrition and diet may also affect the composition of oral bacteria in the mouth. Many women change their diet and are more likely to consume refined carbohydrates during pregnancy. This may incite the proliferation of more cavity-causing bacteria, thus increasing the risk of dental caries.[16,17] A high-fibre, low-sugar diet is more likely to maintain microbial diversity and promote better oral health.[18]

In short, the fluctuations of oral microbiota in pregnancy are due to various reasons such as hormonal changes, immune system modifications and preferential dietary choices.[19] Based on these factors, strategies need to be developed to maintain good oral health and prevent other diseases during pregnancy.[17,20]

Common Oral Diseases in Pregnancy and the Oral Microbiota

Pregnancy-associated Gingivitis

Gingivitis is a relatively common oral disease of pregnant women. It is known to occur frequently, and there have been reports indicating that they occur in 100% of cases.[29] Gingivitis is a condition that causes inflammation of the gums, so it may appear red, swollen, bleeding and tender. The underlying cause of the increased sensitivity of the gingival tissue to injury in pregnancy is attributed to hormonal changes. High levels of oestrogen and progesterone promote the formation of blood vessels in the gums and may enhance local inflammatory responses. Therefore, the gingival tissue is more easily irritated by plaque and subject to microbial infection.[30]

Pregnancy-associated gingivitis is a local disease of the gums during pregnancy that may also be linked to other health problems. Inflammation in gingivitis induces the

release of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), into the circulation. These cytokines have been linked to impaired placental function and an increased risk of adverse pregnancy outcomes, such as preterm birth and low birth weight infants.[31] As such, periodontal inflammation may lead to systemic inflammatory response, indicating that the health of the oral cavity and overall systemic health are interconnected, especially in pregnancy.

Some of the modifiable risk factors that exacerbate gingivitis in pregnancy include poor dental hygiene - not brushing the teeth regularly and failing to floss or clean between the teeth, causing plaque to accumulate. Smoking and malnutrition are also predisposing factors that increase the risk of gum disease. Disadvantaged socioeconomic status and the lack of access to preventive dental care are also some factors that contribute to this pervasive condition.[32]

There is a cumulative body of evidence to suggest that the prompt diagnosis and treatment of pregnancy gingivitis is translated in a preventive strategy involving regular dental check-ups for pregnant women to control plaque accumulation and gum disease through professional periodontal care. There are various published guidelines on focused and basic periodontal examination, objective scoring of the state of the gum, and recommended treatment to help dental practitioners work more efficiently during busy antenatal health care appointments.[33] Research has shown that the management of periodontal diseases during pregnancy is safe for both the mother and the baby, and it does not harm the foetus.

Pregnancy-associated Periodontitis

Periodontitis is a long-standing inflammatory disease of the supporting tissues that damages the gums and bones, causing gum disease and bone loss. About 10% - 15% of pregnant women have this condition, and it is more common among those with poor oral hygiene, a habit of smoking, stressful lifestyles and some peculiar behavioural or environmental risks.[34,35] While gingivitis is mostly reversible, periodontitis in pregnancy is a chronic and more serious condition, resulting from a combination of altered microbial populations and immune system dysregulation causing more extensive tissue damage. An increase in pathogenic bacteria, such as *P. gingivalis*, *Prevotella intermedia* and *F. nucleatum*, produces virulence factors such as lipopolysaccharide (LPS) and proteolytic enzymes to disrupt the normal state of periodontal tissue causing advanced disease (Table 1).

The systemic problems linked to pregnancy-associated periodontitis are serious. There are two biologically plausible pathways involved in this process that have been widely studied. Periodontal pathogens may enter the bloodstream as bacteria in the blood (bacteraemia) through direct spread. Bacteria then invade the trophoblasts in the placenta and cause inflammation at the decidua and chorionic interface. A Japanese study has identified several periodontal pathogens in placenta samples associated with *F. nucleatum* and threatened preterm labour.[37] Additionally, *P. gingivalis* has been found in the placenta villous stroma and umbilical cord samples of preterm births.[37] LPS in bacterial toxins can also activate Toll-like receptors on the placenta to release pro-inflammatory cytokines, such as interleukin-1 beta (IL-1β), IL-6 and TNF-α into the circulation. These inflammatory mediators could induce uterine contractions and precipitate preterm birth. In the indirect pathway, severe periodontal inflammation causes the release of pro-inflammatory factors into the maternal circulatory system, which then reaches and crosses the placenta to affect the development of the placenta, reduce its function in providing nutrients and oxygen for the foetus, and cause growth retardation and small-for-gestational-age infants.[20,31,38,39] Another study revealed that the pathogen, *P. gingivalis* activates the JNK and p38 signalling pathways to induce apoptosis in the uterine artery and impair placental perfusion of the foetus.[39] Recently, even GDM and hypertension (preeclampsia), have been linked to periodontitis in some research reports.[40] Shared inflammatory pathways in periodontal disease and other diseases have been identified, so timely intervention and treatment for this condition in pregnant women is essential.[41,42]

The evidence-based management of periodontitis during pregnancy includes scaling and root planning therapy to reduce gum inflammation and improve pregnancy outcomes.[43] Additionally, antisepsis reduces both bacterial load and limits inflammation, such as with the use of chlorhexidine mouthwash. Oral health education should be introduced to improve awareness of good oral hygiene practices among pregnant women. Expanding access to affordable periodontal treatment may mitigate the harm sustained from periodontitis.

Table 1. Features and distribution of oral microbiota species during pregnancy and effects of host-microbeinteraction

Microorganism	Distribution and Location	Oxygen Demand	Changes during pregnancy	Health Implications	Mechanisms Influencing Health Outcomes
P. gingivalis [7,21]	Gingival groove and periodontal pocket	anaerobe	Significant increase	Periodontitis, preterm birth, low birth weight, gestational diabetes, preeclampsia	1. Tissue destruction: gingival proteinase and other virulence factors are produced, destroying the periodontal tissue structure. 2. Release of inflammatory mediators: induce the host to produce a large number of inflammatory factors (such as IL-1, TNF-α), which affect systemic health through blood circulation. 3. Haematogenous transmission: Bacteria enter the blood circulation, infect the placenta, and cause local inflammation.
F. nucleatum [21]	Gingival groove, periodontal pocket and tongue surface	anaerobe	Significant increase	Periodontitis, preterm birth, low birth weight, placental abruption, gestational diabetes	Bridge bacteria: Promote the aggregation and biofilm formation of other pathogenic bacteria, enhancing the pathogenicity of the microbiome. 2. Inflammatory induction: Systemic inflammatory response is induced through inflammatory mediators, affecting placental function. 3. Haematogenic transmission: Bacteria spread through the blood to the placenta, causing placental inflammation and dysfunction.
Prevotella intermedia [22]	Gingival groove, periodontal pocket and tongue surface	anaerobe	Significant increase	Periodontitis, gestational diabetes, hypertension, foetal development limitation	Hormone utilisation: The use of hormone metabolites during pregnancy as a source of nutrition to promote their own proliferation and pathogenicity. Inflammatory promotion: The production of inflammatory mediators, exacerbating periodontal tissue inflammation. Immune escape: Escape from the attack of the host immune system by altering surface proteins.

Prevotella nigrescens [23]	Gingival groove and periodontal pocket	anaerobe	multiplication	Periodontal disease, gingivitis, gestational diabetes	Tissue destruction: production of a variety of enzymes (such as proteases) that break down periodontal support tissue. Immunomodulation: interferes with the host immune response and promotes the persistence of inflammation.
Prevotella oris [24]	Gingival groove, periodontal pocket and tongue surface	anaerobe	Multiplication	Periodontal disease, gingivitis, gestational diabetes	Biofilm formation: A stable biofilm is formed through adhesion proteins to protect itself from the effects of antimicrobials. Release of inflammatory mediators: stimulates the production of inflammatory factors in the host, exacerbating local and systemic inflammatory responses.
Veillonella spp.[25]	Gingival groove, periodontal pocket and tongue surface	anaerobe	May fluctuate as a result of hormonal alterations during pregnancy.	Plays a crucial role in lactic acid metabolism and the regulation of acid-base balance, thereby influencing the stability of the oral microecological environment.	Metabolic regulation: Participates in the metabolism of lactic acid, regulates oral pH, and affects the growth of other bacteria. Competitive inhibition: Inhibits the proliferation of pathogenic bacteria by competing for nutrients.
Streptococcus mutans [26]	Tooth surfaces, especially caries spots	Facultative anaerobic	Partial increase	Dental caries, periodontitis	Acid production: Fermented sugars produce lactic acid, which leads to demineralisation of tooth enamel and the formation of dental caries. Biofilm formation: A stable biofilm is formed through adhesion proteins to protect itself from the effects of antimicrobials.
Candida spp.[27]	Tongue, cheek and under gum	Aerobic	Significant increase	Candida infection, oral mucosal inflammation, and possibly blood transmission affects islet function	Adhesion and invasion: adhesion to oral mucosa, forming biofilm, leading to local inflammation. Immune escape: evading recognition by the host immune system by altering surface antigens. Haematogenous transmission: Infection spreads throughout the body through the blood, affecting islet cell function

Table 1. (continued)

Lactobacillus spp.[16,28]	Tooth surface, tongue surface and oral mucosa	Facultative anaerobic	May decrease or change	Maintain the balance of oral microecology and inhibit pathogenic bacteria	Competitive inhibition: competition for nutrients and adhesion sites, inhibiting the growth of pathogenic bacteria. Acid production: Fermentation of sugars to produce lactic acid, reduce oral pH, inhibit pathogens. Immunomodulation: enhances the host immune response and reduces inflammation.
Bifidobacteria spp.[28]	Gingival groove, periodontal pocket and tongue surface	anaerobic	May decrease or change	Maintain the balance of oral microecology and promote probiotics	Probiotic action: inhibits the proliferation of pathogenic bacteria through competitive inhibition and acid production. Anti-inflammatory effect: regulates the host immune system and reduces inflammatory response. Nutritional support: breaks down complex carbohydrates to provide host nutrition.

<u>*Dental Caries in Pregnancy*</u>

A recent review indicates that the occurrence of dental caries in pregnant women is roughly 1.5 to 2 times greater than in the general population.[44] Several factors can affect the development of dental caries during pregnancy, such as changes in diet and fluctuations in hormones, exacerbated by underlying health problems, such as GDM. One reason for the higher risk of caries during pregnancy is that more refined sugars and carbohydrates are consumed. These sugars are rich in nutrients for the bacteria that cause cavities; therefore, these bacteria proliferate and increase the risk of decay.[45,46] Changes in the levels of progesterone and oestrogen during pregnancy are recognised to alter salivary secretion and function. Consequently, the antibacterial function of saliva is limited, added to the risk of xerostomia with further reduction in the defence capability of the mouth against caries.[36] Pregnancy is also known to reduce calcium and phosphate in saliva, especially in the later stages of pregnancy; therefore, the buffering effect and pH of saliva may be lower, increasing tooth demineralisation and the risk of caries.[47]

In addition to carbohydrates in the diet and host-predisposing risk factors, acidogenic/acidophilic microorganisms in the mouth also play a crucial role in the development of dental caries. The oral microbial flora forms a biofilm in a dynamic state and maintains the pH and mineralisation-demineralisation of tooth enamel. Dysbiosis is a disruption of this balance that increases cariogenic microorganisms such as *Streptococcus mutans*, Actinomyces and Lactobacillus, which produce lactic, formic, acetic and propionic acids to lower the pH and damage the enamel.[48] A recent study of the oral microbiome of high-risk pregnant women found that *Streptococcus mutans*, *Streptococcus oralis* and Lactobacillus were associated with a larger number of decayed teeth.[16] Of note, there is strong evidence to suggest that *Streptococcus mutans* may also be vertically transmitted from the mother to child, thus extending the cycle of increased dental caries and poor oral health to newborns and future generations.[49]

Pregnant women with other concurrent health problems such as GDM need closer and more regular monitoring of their sugar control. A poor blood glucose control and poor oral hygiene

are more likely to exacerbate tooth decay and gum disease. It is crucial to practice good oral hygiene and optimise self-management of blood sugar not only to limit dental decay and its complications but also to promote positive pregnancy outcomes.[50]

Oral Candidiasis

Oral candidiasis is an opportunistic fungal infection in pregnant women caused generally by an overgrowth of the yeast, Candida, such as *Candida albicans*. Hormonal alterations and a suppressed immune system in pregnancy are the reasons for this increased vulnerability. An increase in oestrogen and progesterone induces the proliferation of Candida by strengthening their adhesion to oral epithelial cells and modifying the salivary environment, such as changes in the pH and some elements.[51] In addition, nausea and vomiting in some pregnancies may result in a decreased ability to maintain good oral hygiene, increasing the risk of fungal overgrowth. An increased quantity of carbohydrates that the mother eats may also lead to oral candidiasis.

A previous study of the types of fungi in the oral microbiome of a group of lower socio-economic pregnant women found a higher proportion of *Candida* in plaque. A significant bacterial-fungal interaction in limiting oral candidiasis has been observed in the microbiota populations; specifically, with *Veillonella* (Table 1). *Veillonella rogosae*, a common bacterial commensal, was associated with reduced plaque and salivary colonization by *Candida albicans*.[16] From this, it can be surmised that oral dysbiosis causing an imbalance in this bacterial-fungal interaction may increase the risk of oral candidiasis in pregnancy.

Some published studies also reported that Candida overgrowth may be associated with hypothyroidism. Affected individuals have different profiles of oral bacteria and altered metabolism.[52] Candida can circulate in the bloodstream and reach the placenta to affect the developing foetus. Several case reports have identified preterm birth due to chorioamnionitis associated with *Candida albicans*.[53]

Pyogenic Granuloma

Pyogenic granuloma, or a pregnancy "tumour", is a very common benign hyperplastic lesion of the gum in pregnant women. In tandem with the changes in hormones during pregnancy, such as increased progesterone and oestradiol, gingival blood vessels expand and inflammation occurs. This enhances granuloma formation by promoting the proliferation of blood vessels and endothelial cells in the gums.[54-56] Increased stimulating hormones and the lack of inhibiting factors for angiogenesis are the possible reasons. Histological staining of the tissue of pyogenic granuloma showed an increase in expression of vascular endothelial growth factor and basic fibroblast growth factor, and a decrease in angiostatin and thrombospondin-1.[57] Although the exact pathogenesis is largely unclear, it is believed that a combination of hormonal changes, local irritation from dental plaque, and immune dysfunction leads to the occurrence of such lesions. Altered granuloma tissue metabolism of progesterone may act as an immunosuppressant, causing a more suppressed acute inflammatory response to dental plaque with a preponderance of *Prevotella intermedia*, *P. gingivalis* and *F. nucleatum* as shown in Table 1.[58,59]

Clinically, pyogenic granulomas are red, hypervascularised tumours that usually occur on the gingiva. Although they are generally not painful, these lesions can be uncomfortable or bleed easily and are unsightly if they are large. The incidence of pyogenic granulomas in pregnancy is approximately 5%. and it is more frequent among women with poor oral hygiene or pre-existing gingivitis.[17] Most cases spontaneously regress after childbirth due to the normalisation of hormone levels; however, if there is a persistent or symptomatic lesion, surgical excision by laser ablation or curettage may be required.

Other Oral Diseases in Pregnancy

Changes in hormones and alterations to the immune system during pregnancy modify the oral environment, and thus pregnant women are more susceptible to tooth sensitivity and oral ulcers. At higher levels of oestrogen and progesterone during pregnancy, new blood vessels are formed in the gums, and thus, pathogens such as *P. gingivalis* are more likely to proliferate. Hormones modify the structure and function of the oral microbiome and also alter commensal-pathogen relationships. This will worsen gingival inflammation and cause increased tooth sensitivity; at the same time, the exposed dentinal tubules of inflamed gingival tissue are more likely to be stimulated.[50]

Oral ulcers are also relatively common in pregnancy and have multiple causes. Stress during pregnancy and changes in the diet are some factors associated with the development of

oral ulcers. Recently, some research has shown that bacteria such as *Mycobacterium avium* and Campylobacter are thought to cause oral ulcers by inhibiting the local immune system and damaging the mucous membrane of the mouth.[55]

Oral Microbiota and Systemic Connections

The extent of harm from pregnancy-related oral diseases is not limited to the mouth. Recently, some studies have also found that there is a two-way interaction between oral and gut microbiota. Oral bacteria, such as *P. gingivalis*, potentially enter the systemic circulation to reach the intestine, disrupt the composition of gut microbiota and induce systemic inflammation.[56]

Maternal Oral-Gut Microbiome Transmission to Infant

The second-largest pool of diverse and rich commensal bacteria in the body after the gut is the mouth, which has more than 700 species. While the resident microbiota of these two sites are quite different and diverse, the ecosystems of these two sites appear to be connected. Oral microbiota transfer to the gut presumably occurs via the bloodstream or food ingestion. Translocation of pathogenic oral microbiota may lead to gut dysbiosis and increase the risk of various gut diseases, such as irritable bowel syndrome and inflammatory bowel disease.[60] The maternal gut microbiome is known to be transmitted to the newborn infant through perineal contact during vaginal delivery.[61] The gut microbiome of these infants is different from the predominantly skin-type microbiome in infants delivered by caesarean section, and the dysbiosis in the latter group has been associated with diseases such as childhood asthma and obesity.[62] Therefore, maternal periodontal disease and oral dysbiosis could be factors involved in the early programming of health and disease for the newborn child. To date, few studies have explored the impact of maternal periodontitis on the health of infants, except preterm birth and low birth weight as discussed earlier.

Maternal to Infant Microbiome Transmission via the Entero-mammary Pathway

The entero-mammary pathway is a proposed biological route by which resident bacteria in the maternal gut translocate to the mammary glands and are secreted in breast milk. It is thought that the translocated bacteria are carried by immune cells, such as dendritic cells and macrophages; these cells having engulfed the bacteria in the maternal gut, are then transported through the lymphatic or circulatory systems to the breast tissue.[63,64] These cells and bacteria are then transferred to the baby through breast milk during breastfeeding. Therefore, microbial signals from the maternal gut may help shape the composition of the infant's gut microbiota and immune system.[45] The notion of the entero-mammary pathway has seen substantial development over the past twenty years. Initially, Martin and colleagues disputed the widespread idea that human milk is sterile, arguing that the bacteria present in breast milk should be seen as natural commensals rather than contaminants.[63] The researchers proposed that some microorganisms may originate from the mother's gastrointestinal tract and reach the mammary gland through an entero-mammary route. Subsequently, Perez *et al*. presented mechanistic evidence in favour of this hypothesis, indicating that maternal immune cells, such as dendritic cells and macrophages, could help transport bacteria or bacterial parts from the maternal intestine to the mammary gland in late pregnancy and lactation.[64] The process might aid in the imprinting of the neonatal immune system and in establishing tolerance to commensal microbes. Additional direct evidence was presented by Jost *et al*., who used molecular fingerprinting techniques to identify genetically identical strains of *Bifidobacterium breve* in maternal faeces, breast milk, and neonatal faeces.[65] The findings offer convincing evidence for the vertical transfer of microbes through breastfeeding and further substantiate the entero-mammary pathway. The whole process starts with the mother's gut and possibly her oral cavity, then breast milk transfer occurs, and finally, the infant's gut is colonised, as shown in Figure 1.

Breast milk is known to provide complete nutritional support for term infants. Cumulative evidence has shown that various bioactives including beneficial microbes are also transferred from the mother to the infant. These components contribute to immune maturation and overall infant development. Bifidobacteria and Lactobacillus are the typical genera of bacteria that are abundant in breast milk and have shown immunomodulatory and gut-health-regulating effects for infants. Research has shown that breastfed infants have a more diverse and stable gut microbiome than formula-fed infants, and in the long run, they are less likely to develop infections or allergies and metabolic dysfunctions.[66,67] The microbial community of

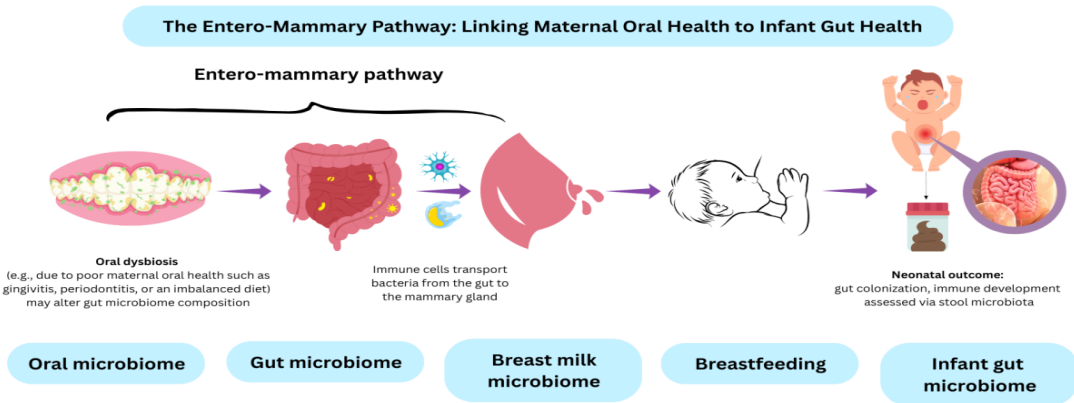

Figure 1. The Entero-mammary Pathway: An interconnection of maternal oral health and infant gut microbiome with immune development.

breast milk is shaped by changes in the mother's oral and gut microbiota; thus, neonatal health can be negatively affected by dysbiosis in the mother.

In supporting this, Kordy *et al*.[68] identified a specific strain of *Bifidobacterium breve* in the maternal rectum, breast milk and stool of an infant. Given that there was no contact with vaginal microbes at any of the three sites, the presence of this anaerobic species arguably supports microbial migration to the breast from other sites. Together, this suggests that the composition of breast milk microbiota may be influenced by maternal gut microbiome, and therefore, its disruption may transmit dysbiosis to the infant through breastfeeding.

Maternal diet may also influence the composition of oral and gut microbiota. A diet high in saturated fat and fat-soluble vitamins reduces microbial diversity. On the other hand, a diet rich in fibre and phytonutrients reportedly fosters a healthy gut microbiota.[26] These changes affect the general health of the mother, the microbial composition of her breast milk, and thus the gut microbiome and health of the infant.

Improving breastfeeding success rate also promotes the development of a favourable resident microbiota in infants through enhancing maternal oral health and nutrition during pregnancy.

Impact of Maternal Oral Health on Systemic Diseases

Periodontal Disease and Pregnancy Complications

Various studies have reported the systemic effects of periodontal pathogens with regard to maternal health and foetal-neonatal outcomes.[69,70] These are backed by systematic reviews and meta-analyses that have also shown that periodontal disease is associated with medical disorders during pregnancy and could also, in extreme cases, be associated with perinatal death, although a causal relationship has not been established.[71] In mitigating this problem, primary prevention to maintain good oral hygiene during pregnancy is crucial and implementing routine dental hygiene practice and care plan for pregnant women in their first trimester during antenatal clinic visits should be prioritised.[72,73]

Gestational Diabetes Mellitus

Bidirectional connections exist between periodontal disease and GDM with regard to inflammation and altered glucose metabolism. Periodontal inflammation is associated with elevated levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, and has been shown to increase the risk of systemic insulin resistance by inhibiting insulin signalling pathways. Hyperglycaemia in GDM promotes chronic low-grade inflammation and increases the formation of advanced glycation end-products (AGEs), thus damaging periodontal tissue and worsening periodontal disease.[74,75] Studies have identified specific gene pathways associated with ferroptosis, a type of regulated cell death caused by iron-dependent lipid peroxidation, that appear in chronic inflammation and insulin resistance states. It is possible that periodontal inflammation may be a risk factor predisposing to GDM.[76] Interestingly, periodontal treatment was able to improve blood glucose control in some diabetic patients. Scaling and root planning, with other non-surgical periodontal treatments,

reduced glycated haemoglobin (HbA1c) levels by 0.27% - 0.48% according to a clinical trial.[77]

Cardiovascular Diseases in Pregnancy

Periodontal disease in pregnancy has been linked to the occurrence of other cardiovascular diseases, such as atherosclerosis, hypertension and preeclampsia, via the systemic inflammatory pathway, possibly mediated by pro-inflammatory markers such as IL-6 and TNF-α, which could act to cause vascular endothelial dysfunction, promote the development of atherosclerotic plaques, and increase arterial stiffness. Maternal periodontal disease is also associated with preeclampsia, as a consequence of endothelial dysfunction from systemic inflammation.[78] Oxidative stress and immune dysregulation, induced by periodontal pathogens such as *P. gingivalis* and *F. nucleatum* may also increase the risk of periodontal and cardiovascular diseases.[79,80]

Interventions to Enhance the Maternal Oral Microbiome and Prevent Oral Dysbiosis

Probiotic Supplementation

Lactobacillus and *Bifidobacterium* are the two types of probiotics that have shown good results in enhancing the oral microbiome of pregnant women. They help to maintain the health of the oral cavity by competing with and inhibiting pathogenic microorganisms through attachment, regulating microbial populations, and enhancing the barrier function of the oral mucosa. Probiotics occupy the adhesion sites of oral epithelial cells to inhibit the attachment and pathogenicity of bacteria, such as *P. gingivalis* and *F. nucleatum*, involved in pregnancy gingivitis and periodontitis. Probiotics can also stimulate the production of antimicrobial peptides and enhance the integrity of tight junctions to strengthen the barrier function of the mucosa and reduce the risk of oral infections in pregnancy.[81]

Probiotics also play a role in regulating the immune system, and as such have been used as adjunct therapy to modify the inflammatory processes present in pre-eclampsia and GDM. Regulating the release of pro-inflammatory cytokines, such as IL-6 and TNF-α, not only reduces systemic inflammation but also improves the health of the oral cavity. Moreover, the probiotic anti-inflammatory properties may help to maintain a normal, healthy state of the mouth and reduce the risk of gingivitis and other diseases of the mucous membranes during pregnancy.[7] Even so, the beneficial effects of different probiotic strains in enhancing the oral microbiota during pregnancy may differ due to various reasons, such as in bacterial viability and dosage.[82]

Antimicrobial Therapy

Copper nanoparticles possess good antimicrobial properties that could reduce the incidence of pregnancy-related oral diseases, such as gingivitis and periodontitis. This agent has been shown to inhibit the proliferation of bacteria by disrupting its cell membrane. Copper nanoparticles reportedly inhibit the multiplication of pathogens such as *P. gingivalis* and *F. nucleatum* in the diseased gum tissues of pregnant women.[83] However, further studies are required to evaluate their biocompatibility, safety and clinical efficacy before routine use during pregnancy can be recommended.

Antibiotics administered to pregnant women potentially alter the maternal and neonatal microbiota; therefore, they should be prescribed judiciously and only when necessary. Non-selective or extended antibiotic use can upset the normal microbial balance, cause harm such as the emergence of antimicrobial resistance, maternal dysbiosis, and an increased risk of neonatal sepsis and altered gut microbiota composition.[84] Future research aims to develop more non-antibiotic antimicrobials, such as copper nanoparticles, to combat the increasing emergence of antimicrobial resistance.

Probiotic supplementation is gradually introduced as adjunct therapy to improve oral health in pregnant women. *Lactobacillus* and *Bifidobacterium* strains may help restore the disturbed microbial balance induced by antibiotic treatment administered for various causes during pregnancy. These two probiotic strains have a synergistic effect that suppresses pathogenic bacteria, enhances the stability of the microbial community and strengthens the mucosal barrier.[85]

Laser Therapy

Laser therapy is emerging as a non-invasive method to treat periodontal disease in pregnancy. High-intensity light energy can kill or reduce the number of harmful bacteria in the mouth and thus reduce inflammation. It may be targeted to specific periodontitis causing bacteria, such as *P. gingivalis* and *Treponema denticola*, to reduce their numbers while protecting the surrounding healthy tissues. Laser therapy also reduces the production of the pro-inflammatory cytokines

such as IL-1β and TNF-α, decreases the extent of inflammation, and protects the periodontal tissue.[86,87]

Furthermore, laser therapy may emerge as alternative treatment to antibiotics. Laser therapy can also boost the immune system, stimulate the production of growth factors, such as transforming growth factor-beta (TGF-β), to aid in the repair of damaged tissues and improve oral health conditions.[88] Not only could it reduce periodontal inflammation and microbial dysbiosis, but laser therapy may also cause whole-body changes via the oral-gut axis. It has been shown to modulate gut microbiota and systemic immune function indirectly, such that systemic pro-inflammatory mediators are decreased. This could potentially alleviate pregnancy-related disorders such as preterm birth and pre-eclampsia. Therefore, it is proposed that laser therapy may be a new approach to all-around care for mothers and babies.[89]

Nanotechnology and Nano-antimicrobial Agents

Nanotechnology offers new ideas for oral health management in pregnancy by using the special features of nano-antimicrobial agents and nanomaterials for tissue repair. Functionalised nanoparticles, such as silver nanoparticles (AgNPs), have shown good antibacterial properties against periodontal pathogens such as *P. gingivalis* and *F. nucleatum*. Nanoparticles damage bacterial cell membranes, inhibit biofilm formation, stop metabolism, and are non-toxic to host cells.[90]

Nanomaterials also have other functions, such as helping to repair damaged tissues and organs.[91] Hydroxyapatite-based nanocomposites of bioactive nanoparticles promote the regeneration of periodontal tissue by enhancing osteogenesis and collagen synthesis.[92] The above materials are added to dental scaffolds, gels and coatings to help repair the periodontal structure damaged in pregnancy gingivitis and periodontitis. The nanoscale characteristics of these materials also enhance their biocompatibility with the body's tissues, thus improving treatment effectiveness.[91,93]

Conclusion

Hormonal changes, alterations in the immune system and metabolism during pregnancy together impact the oral microbiome. These changes may disrupt the normal balance of the resident microbiota causing dysbiosis, which leads to increased risk of developing dental problems, such as gingivitis, periodontitis and dental caries, which in turn, may contribute to systemic complications. Cumulative research evidence suggests that disruption and alteration in this oral microbiome are associated with adverse pregnancy outcomes, such as preterm birth, low birth weight infants, GDM and hypertensive disorders of pregnancy.

The systemic effects of oral microbiota are mediated through complex mechanisms, including inflammatory pathways, microbial translocation, and host-microbial interactions. These processes highlight the importance of addressing pregnancy-associated changes in oral microbiota to prevent both localized and systemic complications. A combination of targeted interventions such as probiotics, antimicrobial agents, laser therapy, and nanoparticles technology offers promising strategies for enhancing oral microbiota and improving health outcomes during pregnancy. Advanced molecular techniques, such as metagenomics and transcriptomics, could provide deeper insight into the interactions between probiotics, pathogenic bacteria, and the host immune system, while clinical trials are needed to assess the optimal strains, dosages, and delivery formats for achieving positive oral health outcomes during pregnancy. Such investigations would inform the development of targeted probiotic therapies as part of comprehensive maternal health programs, promoting both maternal and neonatal well-being.

The non-invasive nature and minimal discomfort from laser therapy serves as an attractive alternative for managing periodontal disease during pregnancy. The integration of nanotechnology into oral care products provides novel preventive and therapeutic options tailored to the unique needs of pregnant women. Nano-antimicrobial agents incorporated into toothpaste, mouth rinses, and dental sealants offer enhanced protection against oral pathogens while reducing inflammation and promoting microbial homeostasis. The safety and efficacy of nanotechnology-based oral care products have been supported by preliminary studies, highlighting their potential for routine use in prenatal care.[94] Clinical trials are needed to evaluate the efficacy, long-term safety and practicality of these emerging interventions, particularly in a global sense involving multi-ethnic populations and across different socio-economic demographics with real-world data collection.

Not forgetting, a primary preventive approach involving lifestyle modifications is critical for mitigating oral health problems during pregnancy. Adopting a nutrient-rich diet, such as the Mediterranean diet, has been shown to support both oral and systemic health by reducing inflammation and promoting a balanced microbiota.[6] Regular oral hygiene practices, including twice-daily brushing with fluoridated toothpaste, interdental cleaning/flossing, and the use of alcohol-free mouth rinses, are essential for maintaining microbial balance and reducing gingival inflammation. There have been promising anecdotal reports on the use of olive oil mouthwash as adjunct therapy to remedy gingivitis but need further large clinical trials.[95] Routine dental check-ups provide opportunities for early identification and management of oral conditions, while healthcare providers play a vital role in educating pregnant women about the importance of maintaining optimal oral health during pregnancy. Early identification and management of gingival inflammation is essential, and pregnant women should be encouraged to undergo routine dental screening as part of a comprehensive antenatal care visit.

Finally, public health initiatives aimed at improving oral health awareness during pregnancy and providing affordable dental care are particularly important in underserved populations. This is in line with the Sustainable Development Goals (SDG3 and SDG10). By addressing modifiable risk factors and ensuring timely interventions, the burden of pregnancy-related oral health problems and their potential complications can be effectively mitigated. Integrating periodontal care into a holistic antenatal care program is essential for ensuring positive maternal and foetal health outcomes.

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