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Review

Oral environment, inflammation and preterm birth

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From the womb to the adult
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Abstract

Adverse obstetric outcomes are determinants of neonatal mortality and serious morbidity, often leading to neurologic and developmental alterations in early childhood and/or adult life. Several studies have focused the relationships between maternal inflammation and diseases and those conditions.

The role of oral inflammation and gingival diseases as factors with potential maternal and fetal detrimental effects on the outcomes of pregnancy is a relatively new area of investigation that has attracted a lot of interest and research in the last twenty years. The new evidences now strongly support a role for maternal infection and inflammation of the genital tract, as well as inflammation from sites distant from the pelvis, in the etiology of preterm birth.

The aim of the present paper is to outline and summarize the current knowledge about the relations between oral biofilms, periodontal inflammation and the pathogenic mechanisms linking periodontal diseases with adverse pregnancy outcomes, concluding with some practical advices for clinicians on the prevention and control of the oral inflammation and the related adverse outcomes in pregnant patients.

Keywords

Periodontal diseases, oral diseases, inflammation, gingivitis, periodontitis, mucositis.

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Oral biofilms, inflammation and periodontal diseases

Since over two centuries clinical observations make doctors consider the relations between oral infections and inflammations and the general health of patients; oral diseases and conditions can be markers for underlying health problems, and relevant determinants influencing the onset and management of adverse systemic conditions such as cardiovascular disease and diabetes and physiological events like pregnancy: poor maternal oral health status contributes to the incidence of preterm birth and low birth weight [1].

The oral cavity is a unique environment in which the microorganisms from oral biofilms, the oral epithelium and the host inflammatory substances and mechanisms play a key role in maintaining health and promoting several disease mechanisms which could affect locally and systemically human tissues and structures.

Oral microorganims colonize surfaces of oral soft and hard tissues and develop as three-dimensional biofilms composed by communities of thousands of different commensal and/or pathogenic species of bacteria, fungi and viruses. embedded in an exo-polysaccharide matrix (**Fig. 1**) [2].

Oral biofilms play the main causative role in infective periodontal diseases; they are mainly represented by gingivitis and periodontitis. Gingivitis is the reversible inflammatory disease of the marginal gingiva. It is originated by the

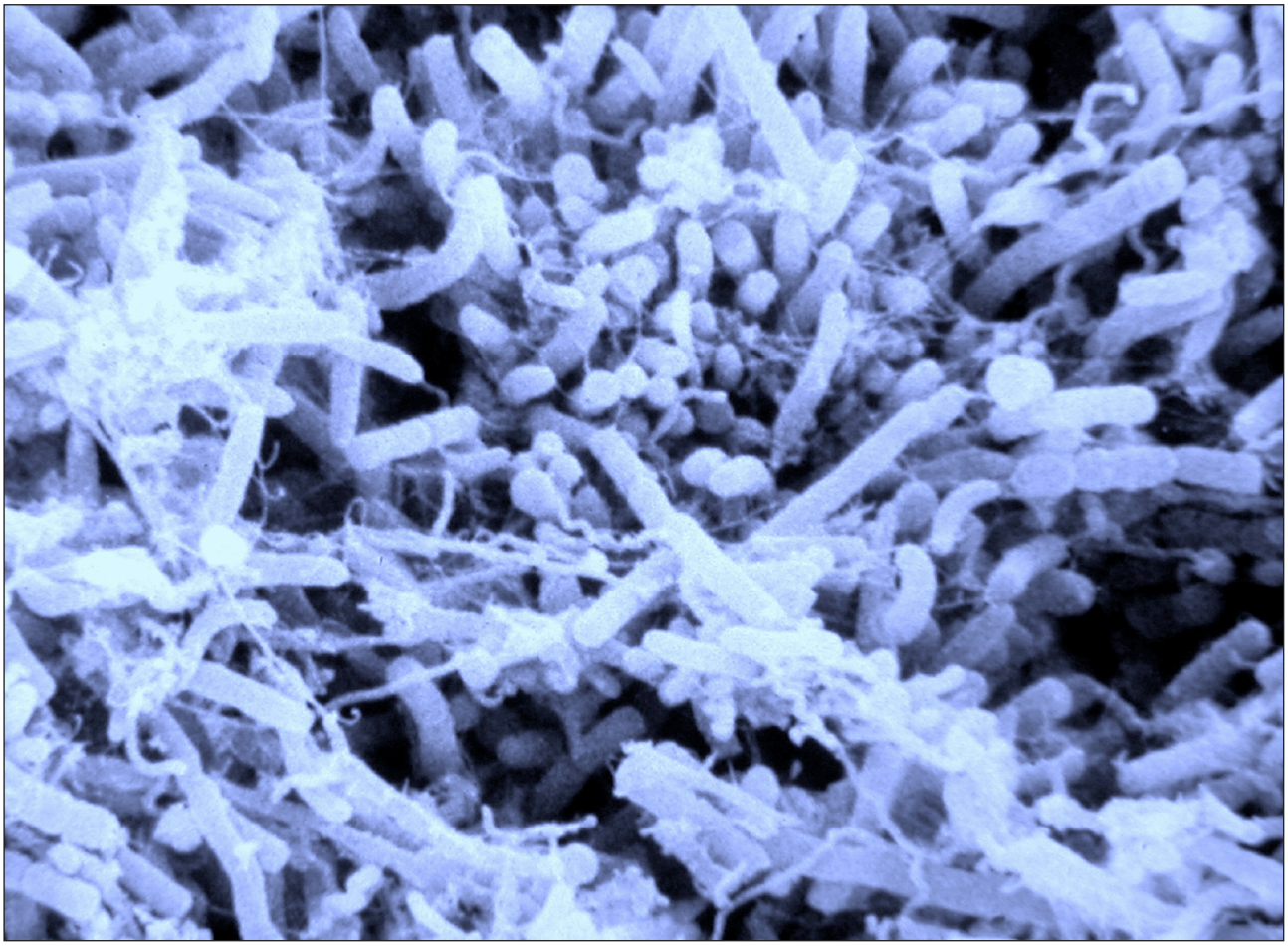

Figure 1. Subgingival oral biofilm – SEM, 13 kV, Original Magnification: 4,000 X
Composite biofilm of several species of periopathogenic bacteria adherent to the dental root in the deepened gingival sulcus.

accumulation of biofilms in the gingival sulci and is clinically characterized by gingival redness and swelling, spontaneous or induced ginvival bleeding, inconstant gingival pain, possible bad breath; periodontitis represents the irreversible spreading of inflammation and the eventual bacterial invasion in the deep periodontium, with progressive destruction of the tooth-gingival attachment, periodontal ligament, alveolar bone and developing mobility and definitively terminated with the loss of the involved teeth (**Fig. 2**) [3].

Specific pathogenic bacteria colonize the gingival sulcus within already formed commensal biofilms and form pathogenic microcolonies therein. Several studies showed the differences in composition and structure of biofilms in the different oral ecological niches. The dominance of *Actinomyces spp.*, *T. forsythia*, *F. nucleatum*, *Spirochaetes spp.*, as well as other anaerobic and gram negative genera like *Bacteroides spp.*, *Porphyromonas spp.*, *Prevotella spp.*, *Capnocytophaga spp.*, *Peptostreptococcus spp.*, *Aggregatibacterium spp.*, and *Eikenella spp.* and recently the phylum *Synergistetes* in subgingival plaque, has been strongly associated with destructive periodontitis. The subgingival localization of pathogenic bacteria proved their important role in host-pathogen interactions due to the localization in close proximity to immune cells; periodontal stability is indeed dependant from the presence of an health-promoting biofilm, involving a true symbiosis between resident microbial species and also with the host response. Species of the so-called perio-pathogenic bacteria that colonize and persistently grow in special complexes or co-infective associations can be associated with clinical parameters of disease. Besides the polymicrobial nature of periodontitis several reports now also establish a role for viral coinfection by herpesviridae in the promotion and initiation of periodontal inflammation [4, 5].

The host response to the bacterial infection of the teeth and subgingival environment also plays an important role in the tissue-denstruent pathogenic mechanisms of periodontal diseases, involving inflammatory cells and host inflammatory mediators like PGE_2, matrix metalloproteinases and the cytokines interleukin IL- 1, IL-6 and TNF-α. The last two decades of research have significantly changed the understanding of the pathogenic processes that

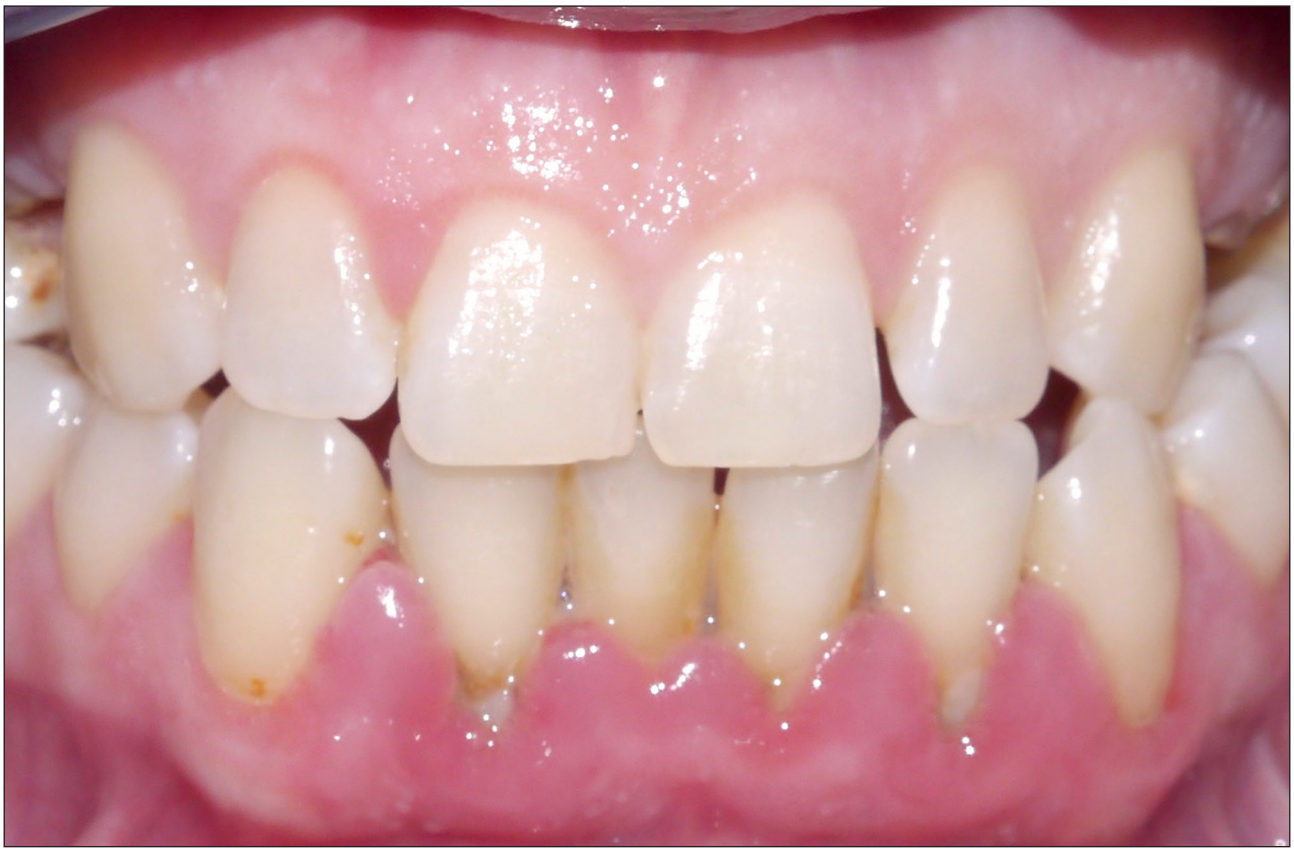

Figure 2. Gingivitis and periodontitis in a pregnant patient.

Marginal gingivitis in upper areas and severe inflammation in lower gingival tissues with acute inflammation, loss of periodontal tissue, gingival recession, pocket formation and accumulation of oral biofilm.

lead to periodontal tissue destruction; much about the dynamic molecular interactions between the various microbial and host factors has been revealed, as the influence of the combination of genetics, epigenetics, lifestyle and environmental factors on the pathological phenotype labeled as "periodontal disease".

The host response is now recognized as the major contributor to periodontal tissue damage as it could lead to a dysfunctional, poorly targeted and nonresolving inflammation and to the oral flora dysbiosis creating a biofilm that supports the growth of periodontopathogenic species capable of sustaining the gingival disease: the interplaying roles of signalling epithelial cells, natural killer cells, T-cell populations, specific B cells and neutrophils have been almost completely revised (**Fig. 3**). Neutrophils, as the main inflammatory population, are considered to play a major role not only as powerful synthesizers of proinflammatory cytokines but also as responders to prostaglandin signals triggering switches to a pro-resolving phenotype capable of regenerating the structure and function of healthy tissues. Key factors are the molecular signaling pathways that dominate at any one time and the influences of microRNAs capable of 'silencing' certain inflammatory genes [6].

The commensal bacterial community acts therefore to benefit the innate immune response and the regenerative potential of oral tissues; inflammation and dysbiosis impact on periodontal health and disease with an outcome driven toward acute resolution and stability, chronic resolution and repair, or failed resolution and ongoing periodontal tissue destruction [5].

Defending substances in oral epithelial cells, like α-defensins, β-defensins, LL-37, histatins, and other antimicrobial peptides and proteins, may be induced by non-pathogenic oral bacteria. This substances are fundamental in maintaining oral health and preventing bacterial, fungal, and viral adherence and infection [6].

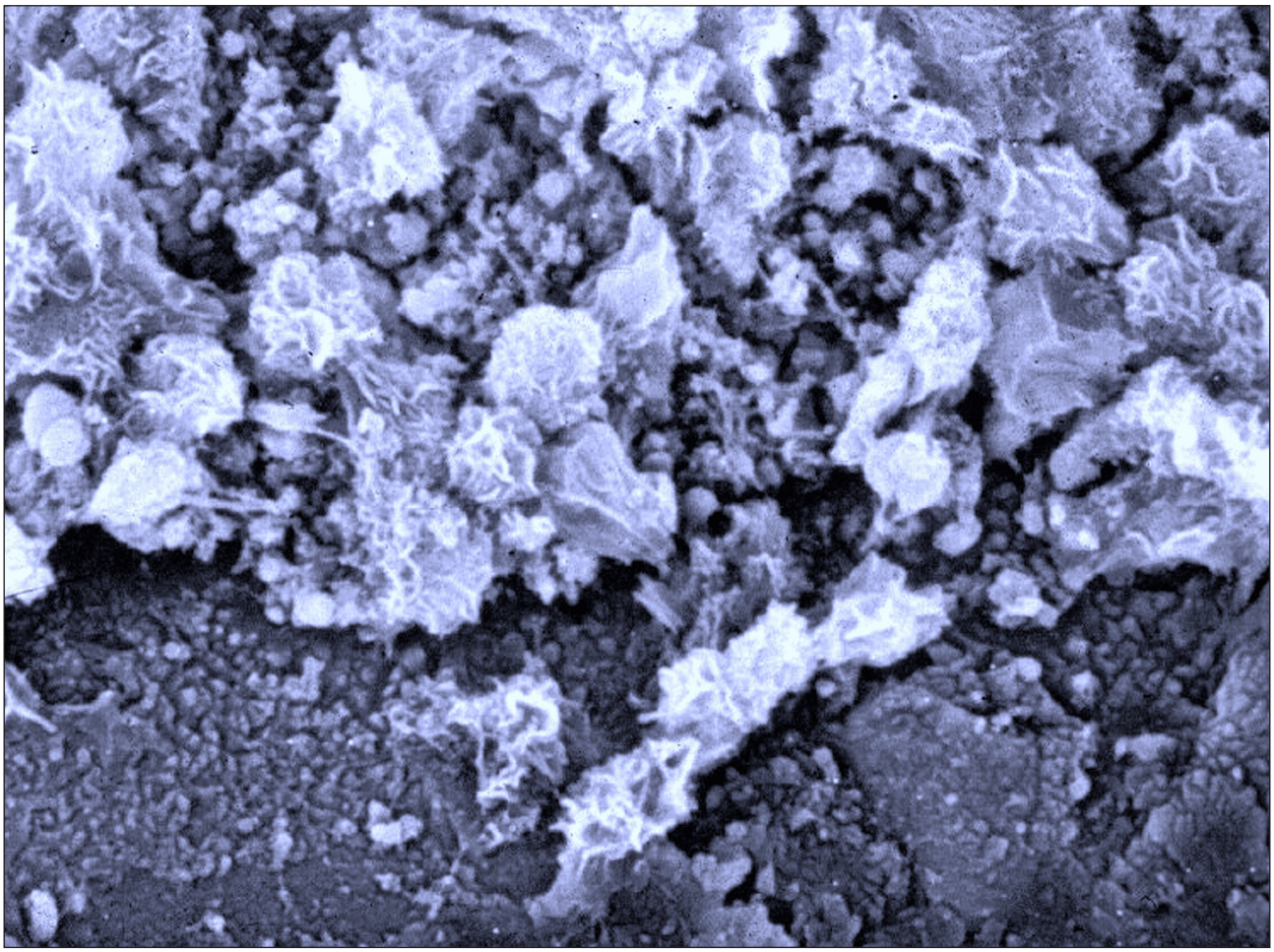

Figure 3. Host-parasite relations in the gingival sulcus – SEM, 15 kV, Original Magnification: 950 X.
The neutrophil granulocytes form a barrier at the plaque–tissue interface controlling the number of bacteria and keeping them out of the gingival tissues.

In relation to the presence and effect of genetic, predisposing, or acquired risk factors periodontal diseases could affect younger or adult patients, be acute or chronic in progression and involve one or multiple teeth; in the same way systemic health and the medical status of the patient may significantly influence the development of periodontal diseases and the approach to the outcome of periodontal treatment.

Periodontal diseases, preterm birth and other adverse outcomes in pregnancy

A large part of humans are affected by some degree of periodontal pathology: 5% to 20% of the population suffers from severe and generalized periodontitis, while gingivitis or mild to moderate periodontitis affects the majority of adults in Western countries [7].

Periodontal problems are common in pregnant women. In pregnancy the hormonal, immunologic and subsequent oral microbial modifications increase the risk to develop or worsen existing periodontal disease by the end of the first trimester and therefore periodontal pathology could affect about 3 out of every 4 pregnant women [8].

Preterm birth (PTB), defined as birth before 37 weeks of gestation, accounts for 75% of perinatal mortality and more than half of long-term morbidity. Despite extensive literature on the subject and improved antenatal care, there has been no significant decrease in the incidence of PTB in developed societies. There are several recognized predisposing and causative factors for preterm and low birth weight as well as for other adverse events like hypertensive diseases or premature rupture of membranes. Local genital and systemic infections of the pregnant patient may be responsible for these complications. Maternal infections may also compromise fetal wellbeing and lead to PTB through the activation of the innate immune system, leading to an increased expression of prostaglandins and inflammatory cytokines and other mechanisms [15].

Periodontal disease is a low-grade infection dominated by Gram-negative bacteria resulting in local and systemic inflammatory and immune responses. Periodontal microorganisms could act as pathogens not only in the oral cavity but also at distant sites in other body areas. These characteristics include (i) the ability to colonize, (ii) the ability to elude the host's defence mechanisms, and (iii) the ability to produce substances leading directly to tissue destruction. Inflamed periodontal tissues serve therefore as reservoirs for periodontal pathogens, endotoxins, and inflammatory mediators [9].

Proinflammatory cytokines, such as IL-1, IL-6, and TNF-α, may activate the mechanisms of labor through placental and chorion amnion production of PGE_2. Increased levels of intraamniotic cytokines have indeed been reported in pregnancies complicated by preterm delivery; these mediators can cross fetal membranes, so it is possible that high levels of these cytokines synthesized in the periodontal infection could interfere with fetoplacental functions and contribute to the onset of preterm labor or anyway complicate the regular progression of pregnancy. The detection of oral pathogens in amniotic fluids by polymerase chain reaction tests suggests a possible hematogenous spread of these infections. In addition, some bacterial products such as LPS, present at the level of amniotic fluid in women with chorioamnionitis, can increase the amnios, chorion, and decidual production of interleukins. The increase in these mediators can be associated with preterm and/or low weight births [10, 11].

The pioneering studies in animals and humans of the nineties showed significant associations between periodontal pathogens, periodontal diseases and PTB [10].

Since then the possible role of periodontal infection and inflammation in PTB causation has been investigated extensively: a number of studies found an association [12-18], whereas other studies did not [19-23]. The strength of any observed result may have been considerably influenced by the study design employed by the investigators and several systematic reviews have been carried out in this field, leading to the general conclusion that a modest association appears to exist between maternal periodontitis and the outcomes of low birth weight, PTB and pre-eclampsia [24-26].

Periodontitis alone might underestimate the total inflammatory burden from oral microorganisms and inflammation in the oral cavity: one interesting report evaluated the so-called oral inflammation score as the total inflammatory burden coming from acute gingival infection, periodontitis and mucositis and mucosal irritation from calculus deposits. This comprehensive assessment of potential oral inflammation seemed to be significantly associated with PTB [27].

It is not clear how treatment of the periodontal disease will reduce the risk of PTB. A recent study of periodontal treatment in pregnant women revealed a strong link between unsuccess in the treatment and PTB [28].

Similarly to periodontal diseases, maternal pregestational obesity has also been associated with gestational diabetes, hypertension, pre-eclampsia and delivery complications; obesity induces a chronic, low-grade inflammation with elevated levels of circulating inflammatory markers such as C-reactive protein [29]. Thus, maternal obesity may lead to fetal inflammatory response via placental inflammation, compromising placental function and altering fetal growth and development. Recent clinical and epidemiological evidence suggests that obesity is a risk factor for periodontitis, with gingival inflammatory responses and altered periodontal microbial compositions [30]. As both preterm delivery and pregnancy induce inflammation and immunological changes, the interplay between pregnancy, obesity and preterm delivery can be particularly harmful for both mother and fetus.

In our recent studies in pregnant patients we could not confirm a significant positive association between periodontal pathology and adverse pregnancy outcomes; however, there was an associative trend connecting clinical signs of oral inflammation and negative outcomes [23]. Moreover, in our pregnant patients, reported gingival symptoms like swelling and teeth looseness were significantly associated with the presence of oral pathologies [31]. We are now investigating whether conditions increasing sistemic inflammation such as maternal obesity may favor oral inflammation and thus represent summing risk factors for pregnancy pathologies [32].

Conclusions

Pregnancy complications, such as preeclampsia, intrauterine growth restriction, and PTB, represent one of the major unsolved public health problems because of their prevalence associated with high neonatal and maternal mortality, long-term pediatric disability, and consequences in adulthood.

Oral diseases could have an important impact on the oral, general, and reproductive health of women, their quality of life, and the oral health of their children.

This has lead to increasing scientific and clinical interest of professional institutions on possible preventive measures in the field of oral health.

Pregnancy is a unique moment in a woman's life and is characterized by complex physiological changes. Maintaining optimal conditions of the oral cavity of women is crucial for the best outcome of their pregnancy and for the promotion of oral health of the newborns. Adequate oral hygiene is mandatory to control the development of perio-pathogenic oral biofilms which have been reported to be associated with poor obstetric outcomes.

Control of oral diseases before and during pregnancy improves women's quality of life, decreases the incidence of dental diseases in children and has the potential to promote better oral health into adult life of the unborn child [33].

Perinatal health information and care of dentists, dental hygienists, physicians, gynecologists, obstetricians and pediatricians can have a significant impact on health, for the influence they have on the state of oral health and on preventive behaviors for oral and general health of the pregnant woman and her child [34] (**Tab. 1**).

Declaration of interest

The Authors declare that there is no conflict of interest.

Table 1. Guidelines for oral care in pregnancy (adapted from: Italian Ministry of Health, 2014 [35]).

All health professionals should advise and counsel pregnant women about the importance of maintaining good oral health and function to reduce the risk of having complications during pregnancy and ensure good oral health in the newborn:
- brush the teeth twice a day with fluoride toothpaste and use dental floss or other help every day;
- limit the intake of foods containing cariogenic sugars;
- choose water or low fat milk as a beverage; avoid carbonated drinks during pregnancy;
- choose fruits rather than fruit juices to meet the recommended daily intake of fruit;
- by the end of the third trimester obtain from a qualified dentist an oral clinical examination and a professional oral hygiene session, unless it has been done in the last six months or if there was a new condition;
- in case of health problems to the teeth or gums, immediately consult the dentist where to perform the necessary and indicated treatment, even during the pregnancy if needed;
- the majority of dental and periodontal treatments are safe and effective during pregnancy: the ideal period for treatment is between 14 and 20 weeks; other oral therapies may however be postponed until after delivery;
- oral symptoms and signs like bleeding or swollen gums, dental pain, cavities in the teeth, loose teeth, that arise during the pregnancy should not be considered as normal and indicate the need of dental evaluation;
- the delay in providing the necessary treatment for existing medical conditions may pose a significant risk to the mother and indirectly to the fetus.

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