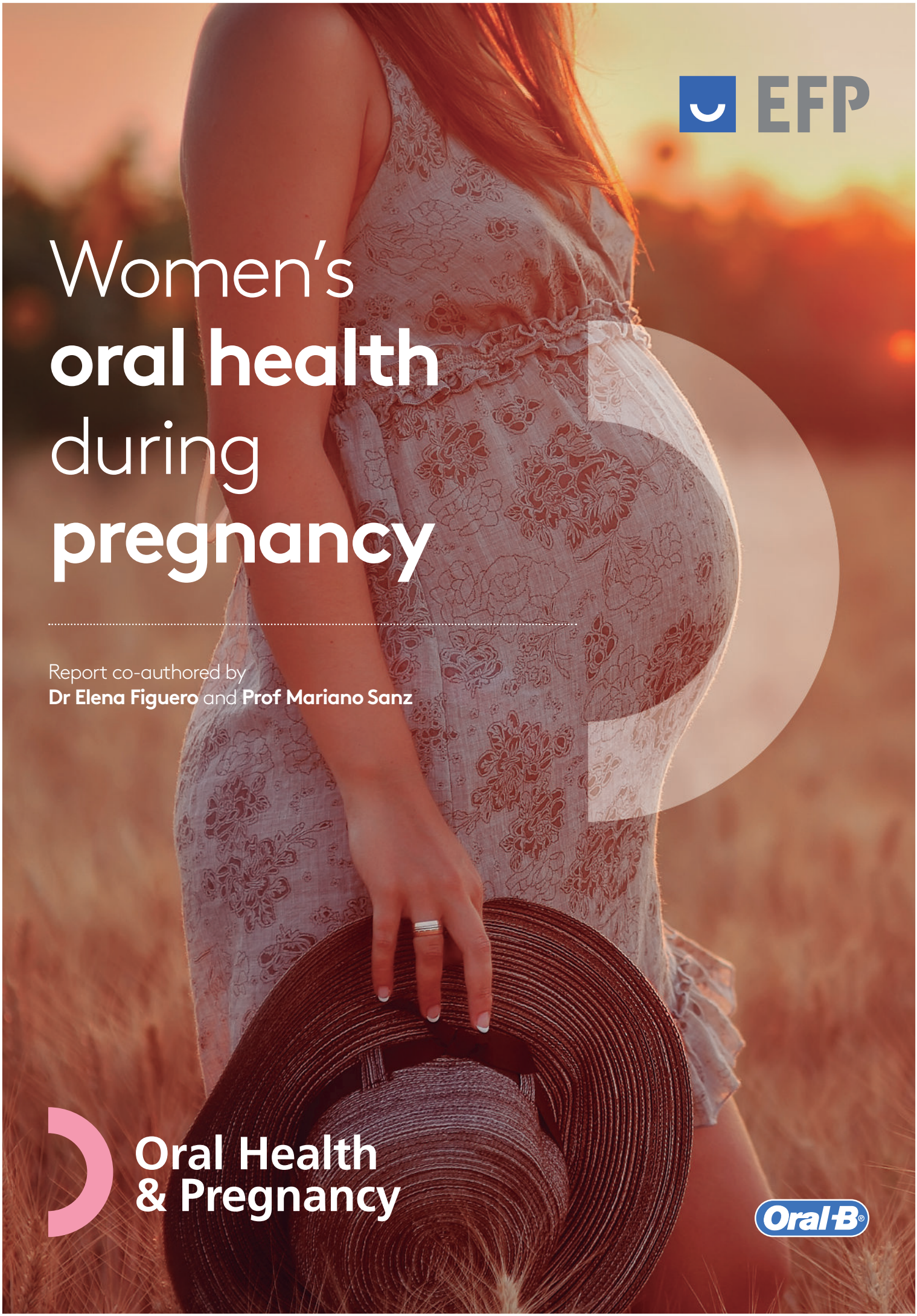

Women's **oral health** during **pregnancy**

Report co-authored by
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Oral Health & Pregnancy

EFP

European
Federation of
Periodontology

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Women's **oral health** during **pregnancy**

The main physiological and hormonal changes in the life of a woman occur during pregnancy (Laine, 2002), and the oral cavity is one of the main areas involved in these changes (Amar and Chung, 1994). Pregnancy gingivitis, granuloma gravidarium and periodontitis have been described as the entities that affect the periodontium of pregnant women.

Pregnancy gingivitis

The first cases of exaggerated gingival responses during pregnancy were described by Eiselt (1840) and Pinard (1877). Pregnancy gingivitis is a commonly recognised entity that is included in the most recent classification of periodontal diseases from the American Academy of Periodontology. It is defined as "a gingival disease induced by plaque and modified by systemic factors" (Armitage, 1999). It is characterised by a red gingiva that easily bleeds, by an enlargement of gingival margin, and by hyperplasia of interdental papilla, which could ultimately provoke pseudo-pockets (Laine, 2002; Amar and Chung, 1994; Sooriyamoorthy and Gower, 1989). The clinical features of pregnancy gingivitis do not differ from those of common gingivitis, except for the tendency to develop severe signs of gingival inflammation without concomitant increases in plaque levels (Löe & Silness, 1963; Silness & Löe, 1964; Hugoson, 1970; Arafat, 1974; Chaikin, 1977; O'Neil, 1979a; Tilakaratne *et al*., 2000; Gürsoy *et al*., 2008). An increment in the percent of locations with severe gingivitis between first and third terms of pregnancy has been described (2.5% to 10%) (Figuero *et al*., 2010). Related to the type of tooth and location, it has been postulated that the increase of gingival inflammation is more marked in anterior teeth and in interproximal locations (Figuero *et al*., 2010; Löe & Silness, 1963; Hugoson, 1971; Raber-Durlacher, 1994).

From a histological point of view, pregnancy gingivitis is an unspecific, proliferative, vascular inflammation with an extensive cellular inflammatory infiltrate (Maier & Orban, 1949). Maier & Orban (1949) studied 53 biopsies from pregnant women with gingivitis and concluded that none of their findings was characteristic of gingivitis in pregnancy. Therefore, plaque-induced gingivitis and pregnancy gingivitis are considered to be very similar entities, except that the latter presents the tendency to develop overt clinical symptoms of inflammation in the presence of relatively low amounts of plaque (Mariotti, 1999).

It has been traditionally stated that pregnancy gingivitis affects between 36% (Maier and Orban, 1949) and 100% (Löe and Silness, 1963) of pregnant women. More recent studies confirm these numbers, reporting a prevalence of pregnancy gingivitis ranging from 38% (Tellapragada *et al*., 2014; sample size=390) to 49% (Usin *et al*., 2013; sample size=150) to 93.75% (Cornejo *et al*., 2013; sample size=80).

Additionally, the prevalence of self-reported pregnancy gingivitis has been assessed through interviews or questionnaires. Christensen *et al*. (2003) in a group of 1,935 pregnant Danish women

reported (by telephone interviews) that 43% perceived signs of gingival inflammation. Similarly, Dinas *et al*. (2007), with a questionnaire involving 425 women in the first three days postpartum, reported that 46.8% perceived gingival inflammation during their pregnancy.

It has also been also reported that the prevalence of pregnancy gingivitis correlated with plaque levels, because in women with excellent plaque control the occurrence of this condition was minimal, with a prevalence of 0.03% (Chaikin, 1977). However, no additional research has confirmed these findings.

Detailed information on study design, outcomes, and results on gingival inflammation of case-control and cohort studies dealing with pregnancy gingivitis are presented in tables 1 to 3. Clinical studies have reported an increase in the severity and extension of gingival inflammation during pregnancy (Figuero *et al*., 2013). Reported gingival severity ranged from mild inflammation to severe hyperplasia, pain, and profuse bleeding (Samant *et al*., 1976; Thomson and Pack, 1982). Most of these studies did not consider the implication of plaque levels in gingival inflammation, although (Carrillo-de-Albornoz *et al*., 2012) reported plaque to be the main factor associated with the gingival index during pregnancy.

Three months after delivery, levels of gingival inflammation usually return to first-term values. So, pregnancy gingivitis does not usually imply irreversible damage to the periodontium (Figuero *et al*., 2013).

The gingival inflammatory pattern during pregnancy is a controversial subject, and studies have reported varying severities and timings of peak inflammation. Most studies have reported that gingival inflammation peaks in the third trimester (Tilakaratne *et al*., 2000; Taani *et al*., 2003; Kornman and Loesche, 1980; Hugoson, 1971; Cohen *et al*., 1969; Zaki *et al*., 1984; Löe & Silness, 1963), although others have observed the greatest inflammation during the second trimester (Samant *et al*., 1976; Muramatsu and Takaesu, 1994; Gürsoy *et al*., 2008; Arafat, 1974).

The source of the conflicting information about pregnancy gingivitis may be attributable to methodological differences among the studies, including variations in the measured periodontal indices, gingivitis severity, and study designs.

A recent systematic review (Figuero *et al*., 2013) was designed to obtain an overall quantitative estimate of the association between pregnancy and gingival inflammation in observational studies. It included 14 prospective cohort studies (involving between 14 and 903 women, with a total of 1,353 pregnant women and 197 non-pregnant women) and 19 cross-sectional studies (involving between 37 to 5,537 women, with a total of 4,824 pregnant women, 205 postpartum women, and 8,324 non-pregnant women) which assessed gingival inflammation either by gingival index (GI) or by the bleeding on probing (BOP) index. This review revealed: (1) an increase in gingival inflammation throughout pregnancy with a peak in the second or third terms, depending on the publication or when comparing pregnant women to postpartum or non-pregnant women; (2) probing pocket depth (PPD) and plaque index (PI) did not undergo great variation throughout pregnancy or at postpartum, although tended to be lower in non-pregnant women than in pregnant or postpartum women; (3) different results in terms of microbiological or immunological parameters were retrieved; however, discrepancies in outcome variables preclude the description of tendencies in this area.

Meta-analyses on the primary outcome were conducted in only a few studies and revealed: (1) a lower GI in pregnant women in the first term compared to those in their second or third terms of pregnancy in both cohort (weighted mean difference [WMD]: 0.140-0.415) and cross-sectional (WMD: 0.242-0.320) studies; (2) reduced GI scores in postpartum women when compared to women in their second (WMD = 0.143; 95% Confidence Interval (CI) [0.031; 0.255]; $p = 0.012$) or third term (WMD = 0.256; 95% CI [0.151; 0.360]; $p < 0.001$) of pregnancy, only when considering

cohort studies; (3) a significantly reduced GI when comparing non-pregnant women to women in any term of pregnancy in both cohort and cross-sectional studies (WMD 0.385-0.741). Regarding secondary outcomes, no significant differences could be found in the PI among pregnancy trimesters (WMD 0.001-0.027) and between the pregnancy and postpartum groups (WMD 0.003-0.144) in cohort studies. Small but significant changes in PI (Silness and Löe, 1964) were observed between pregnancy trimesters in the case of cross-sectional studies (WMD 0.048-0.109). In the case of PPD or clinical attachment loss (CAL), only some comparisons could be analysed due to a lack of articles. In addition, BOP, microbiological, immunological, and patient-centred outcomes could not be subjected to meta-analysis, because different indices were employed by the authors or there was a scarcity of retrieved data.

Since this systematic review was published, new articles regarding this topic have been published, some of them representing additional outcomes to those in previously published research (Bieri *et al*., 2013; Gürsoy *et al*., 2013, 2014, 2016).

Bieri *et al.* (2013) is the second publication from Adriaens *et al*. (2009). The researchers added information on gingival crevicular fluid (GCF) cytokine messenger RNA levels and subgingival bacteria from the same participants as Adriaens *et al*. (2009). They reported that associations between bacterial counts and cytokine levels varied greatly in pregnant women with gingivitis and a normal pregnancy outcome. Postpartum associations between GCF cytokines and bacterial counts were more consistent.

Gürsoy *et al*. (2013), Gürsoy *et al*. (2014) and Gürsoy *et al*. (2016) represent the fifth, sixth, and seventh manuscripts from the research first published by Gürsoy *et al*., 2008. In these articles, information on salivary oestrogen levels (Gürsoy *et al*., 2013) salivary inflammatory markers (Gürsoy *et al*., 2014) and antimicrobial defensin levels (Gürsoy *et al*., 2016) are presented. Gürsoy *et al.* (2013) reported that simultaneous enhanced oestrogen levels and plaque scores during second and third terms brought an additional risk of developing gingivitis compared to high plaque index alone. This result is further reinforced in 2014, with a complex in silico network model (Gürsoy *et al*., 2014). Gürsoy *et al*. (2016) demonstrated that pregnancy has a suppressive effect on salivary concentrations of of human beta-defensins-1 (hBD), hBD-2 and human neutrophile peptide (HNP-1), while hBD-3 remains unaffected.

Probably, the most recent and innovative research dealing with pregnancy gingivitis is the one published by Wu *et al*. in 2016. It has a very similar methodology to the series of Figuero *et al*. (2010) and Gürsoy *et al*. (2008), with the exception that participants had an *excellent plaque control, obtained by oral-hygiene instructions* during the whole study period (PI<1). The researchers followed 30 women throughout each term of pregnancy and 20 non-pregnant women during two consecutive months. Clinical parameters, hormone levels in saliva, and inflammatory mediators [interleukin (IL)-1B and tumour necrosis factor (TNF-α) were measured. They reported that, independently of the extremely low plaque levels maintained, gingival and bleeding index increased significantly in the second (increase in GI=0.15) and third (increase in GI=0.28) terms of pregnancy. These results are in agreement with those obtained in the meta-analyses mentioned above (Figuero *et al*. 2013) where the WMD: 0.14-041. on GI increased (0.14-0.41) between the second and third terms. No significantly changes on PPD and CAL were reported throughout pregnancy. Regarding inflammatory mediators, IL-1B levels increased during pregnancy, but no changes in TNF-α were observed. A positive correlation between serum hormone (progesterone and oestradiol) levels and gingival inflammation was found during pregnancy.

As a summary, it can be said that during pregnancy there is a clear tendency to increase the levels of clinical gingival inflammation (Figuero *et al*., 2013), even when excellent self-performed plaque control is maintained until delivery (Wu *et al*., 2016).

Granuloma gravidarium

Granuloma gravidarium, also called *pregnancy tumour*, has also been observed during pregnancy. In 1844, S. P. Hullihen described the first case of pyogenic granuloma in scientific literature in English, while Hartzell in 1904 coined the terms "pyogenic granuloma" or "granuloma pyogenicum". It is characterised by a proliferative red-to purple nodular mass arising mainly from the gingiva of a pregnant woman, with a tendency to have an ulcerated and haemorrhagic surface mucosa and it is usually a solitary lesion that bleeds easily. It usually appears during the second term of pregnancy and it continues growing until delivery (Ojanotko-Harri *et al*., 1991, Yuan *et al*., 2002). The typical lesion involves the interproximal gingiva and increases in size to cover a portion of the adjacent teeth. The maxillary gingiva (especially in the anterior region) is involved more frequently than the mandibular gingiva; the facial gingiva is involved more than the lingual gingiva (Raghavendra Reddy *et al*., 2014).

The true prevalence of pregnancy tumours is not established, because not all affected women seeks professional attention. The overall reported prevalence is 0.2-9.6% (Bhaskar and Jacoway, 1966). The etiopathogenesis of oral pyogenic granuloma is still a matter of debate (Neville, 2009). Although the exact cause is not clear, it seems that the combination of periodontal pathogens, local irritants (Kamal *et al*., 2012), and circulating hormones of the pregnant woman cause this lesion. No racial predilection is reported (Reddy *et al*., 2014).

Periodontitis during pregnancy

In contrast to the two previous entities (pregnancy gingivitis and *granuloma gravidarium*), there is not any specific type of periodontitis related to pregnancy in any of the current or previous classifications of periodontal diseases (Armitage, 1999; Ranney, 1993).

By contrast, periodontitis has been mainly considered as a potential risk factor for adverse pregnancy outcomes (Sanz and Kornman, 2013) or gestational diabetes mellitus (Abariga & Whitcomb, 2016) but there is not an abundant literature on the effect of pregnancy on pre-existing periodontitis (treated or not).

Data on the prevalence on periodontitis during pregnancy is scarce in the traditional literature. Recent cross-sectional studies have dealt with it, reporting a prevalence of periodontitis that ranges from 0% (Borgo *et al*., 2015) to 61% (Usin *et al*., 2013). These differences might be attributable to different definitions of periodontitis (Manau *et al*., 2008). A cross-sectional study of 150 healthy pregnant women with signs of gingival inflammation from the Provincial Maternity Hospital in Córdoba (Argentina) reported that gingivitis (PPD=4-5mm without CAL), mild periodontitis (PPD≥5mm and CAL=1-2mm), and moderate periodontitis (PPD≥5mm and CAL=3-4mm) were present in 49%, 50%, and 11% of participants (Usin *et al*., 2013). Cornejo *et al.* (2013), in a cross-sectional study including 80 pregnant women (age 18-39) in their first or second trimester from a health centre located in the south of Buenos Aires City, reported that 93.75% of the patients showed clinical signs of gingivitis and 2.5% showed clinical signs of periodontitis.

Tellapragada *et al*. (2014), in a cross-sectional study including 390 pregnant women (age 18-35 years old) within 8-24 weeks of gestation attending the department of Obstetrics and Gynaecology in Udupi, Karnataka, India, reported a prevalence of 10% of clinical periodontitis (CPI score >3 and a pathological pocket depth >4mm) and 38% of gingivitis (gingival index score 0.1 and 3). Basha *et*

al. (2015), in a prospective study conducted among 307 women (age 18-28) in their second term of pregnancy, found that 41.04% had periodontitis. Soucy-Giguère *et al*. (2016), in a cohort of 258 women (median gestational age of 16 weeks) reported a prevalence of periodontitis (presence of ≥1 sites with PPD≥4mm and ≥10% BOP) of 45%. By contrast, Borgo *et al*. (2015), in a cross-sectional study with nine pregnant women, did not find any women with periodontitis (defined as the presence of ≥4 teeth with ≥1 site of PPD≥4mm and CAL≥3mm).

Most of the articles dealing with the evolution of non-treated periodontitis during pregnancy are randomised clinical trials (RCTs) that looked for an association between periodontitis and adverse pregnancy outcomes. In these manuscripts, there is scarce information dealing with periodontal outcomes during pregnancy and after delivery. Therefore, in this section, only information regarding specific material on periodontal parameters during pregnancy or postpartum in pregnant women with untreated periodontitis will be reported.

Akalin *et al*. (2009), in a cohort study including 33 pregnant women with periodontitis, reported an increase in GI (Löe & Silness, 1963) from 1.26 in the first term to 1.84 in the third term of pregnancy. The magnitude of this increment (0.58) was similar to that reported in patients without periodontitis (Figuero *et al*., 2013). In the case of PPD & CAL, there was a statistically significant increment from the first to third terms of pregnancy, rising from 3.94mm (SD=0.34mm) to 3.77mm (SD=0.35) for PPD, and from 3.53mm (SD=0.40) to 4.01mm (SD=0.36mm) for CAL. These increments were similar to those observed by the same study for gingivitis and periodontally healthy groups.

Gumus *et al*. (2016) reported data on 59 pregnant women (second and third terms) who were followed six months' postpartum (n=47). Women were divided according to their periodontal diagnoses as healthy (n=14) [BOP<20%], gingivitis (n=21) [BOP>50% and PPD<3mm at ≥90% of the measured sites, but no more than one site had a PPD>4mm and CAL ≤1 and no clinical sign of periodontitis], and chronic periodontitis (n=12) [≥4 teeth in each jaw with a PPD ≥5mm, CAL ≥4mm and 50% alveolar bone loss in at least two quadrants]. No changes in PPD or CAL were observed between the pregnant and postpartum visit in any study group, nor in BOP in the case of the gingivitis group. However, in the case of gingivitis and periodontitis patients, a decrease in BOP levels was observed from the second-third terms of pregnancy to six-months postpartum, although no periodontal treatment was performed (from 60% to 50% in the gingivitis group, and from 100% to 80% in the chronic-periodontitis group).

Raga *et al*. (2016) in a longitudinal observational study of 117 pregnant women from a private gynaecologic and dental-care centre in Valencia (Spain) reported that periodontitis (≥5 locations with PD ≥5 mm and CAL ≥ 3 mm) was moderate to severe in 22 patients (18.8% of the total) and that BOP was frequent, with 50% of the women having ≥20%. Participants were seen in the third term of pregnancy (32-35 weeks of pregnancy) and 6-8 weeks postpartum and no periodontal treatment was performed during this time. Periodontal examination before childbirth showed that mean PI was 21.61% (SD=2.149%), mean BOP was 21.03% (SD=15.60%), mean probing depth (PD) was 2.62mm (SD=0.61 mm), and mean CAL 1.20mm (SD=0.29 mm) 16.06% for 4- to 5-mm pockets, and 2.62% for > 6-mm pockets. A significant statistical improvement ($p < 0.001$) was observed in all parameters postpartum, except for plaque index between third term of pregnancy and postpartum, with a reduction of 7.78% in BOP, 0.23mm in PPD, 0.06mm in CAL, 3.21% of sites with PPD 4-5mm, and 1.57% of sites with PPD ≥6mm.

Therefore, it can be concluded that, in postpartum, even women with periodontitis without any periodontal treatment had an improvement in all clinical periodontal parameters.

Etiopathogenesis

One of the first authors to suggest the existence of a potential correlation between hormonal levels (progesterone and oestradiol) and the severity of gingival inflammation was Ziskin *et al*. (1933). Since then, Gürsoy *et al*. (2013), Wu *et al*. (2016), Raga *et al*. (2016) have demonstrated a correlation of the level of these hormones and gingival inflammation.

The precise mechanism by which these hormones are responsible for the gingival changes is still unknown. Various hypotheses have been proposed (Sooriyamoorthy & Gower, 1989; Mascarenhas *et al*., 2003; Mealey & Moritz, 2003), including changes in oral biofilms (Kornman & Loesche, 1980; Jonsson *et al*., 1988; Raber-Durlacher *et al*., 1994), depression of the immune system (O'Neil, 1979a; Lopatin *et al*., 1980; Raber-Durlacher *et al*., 1991, 1993), increased vascularity and vascular flow (Lindhe & Attsfrom, 1967; Lindhe & Branemark, 1967; Lindhe *et al*., 1967; Hugoson, 1970; ElAttar & Hugoson, 1974), and cellular changes (Mariotti, 1994). The response of the periodontium is probably not related to a single mechanism but, rather, it is multifactorial in nature (Mariotti *et al*., 1994).

The explanation of an exacerbation of gingival inflammation as a consequence of changes in the subgingival biofilm is one of the most solidly based hypotheses. Direct and indirect etiopathogenic pathways have been proposed.

In the direct pathway, the increase in hormone levels would promote the overgrowth of specific pathogenic bacteria that are responsible for the increased gingival inflammation. *Prevotella intermedia* and (to a lesser extent) *Porphyromonas gingivalis* would play an important role in this theory, as they can replace vitamin K (an essential growth factor for these bacteria) by progesterone or oestradiol (Kornman & Loesche, 1982; Gibbons & MacDonald, 1960).

In the indirect pathway, the greater exposure to sex steroid hormones would transform the gingiva into a more susceptible environment because of greater gingival probing depths (Miyazaki *et al*., 1991), a higher gingival crevicular flow rate (Lindhe & Branemark, 1968a, b), lower keratinisation of the marginal gingival epithelium, and reduced immune-responsiveness, which would together favour the entry of more pathogenic bacteria into the subgingival biofilm. Accordingly, the presence of the pathogen would be the consequence and not the cause of the condition.

Exploring further the scientific evidence regarding this topic, various cross-sectional and longitudinal studies have evaluated the effects of sex steroid hormones on the subgingival biofilm. However, the results have been inconclusive and this issue remains controversial.

Several authors have proposed the increase in *P. intermedia* during pregnancy as an aetiological factor in pregnancy gingivitis. Kornman & Loesche (1980) were the first to describe an increase in *P. intermedia* during the second trimester concomitant with an increase in gingival inflammation. A cross-sectional study by Jensen *et al*. (1981) found a 55-fold higher level of *P. intermedia* in pregnant versus non-pregnant women. An association between higher *P. intermedia* levels and increased gingival inflammation was also reported using an experimental gingivitis model in pregnant patients (Raber-Durlacher *et al*., 1994).

However, Gürsoy *et al*. (2009) and Machado *et al*. (2016), in cohort studies including (respectively) 24 and 18 women, revealed – either by culture and polymerase chain reaction (PCR) (Gürsoy *et al*., 2009) or by florescence in situ hybridisation (FISH) (Machado *et al*., 2016) – the importance of *P. nigrescens* rather than *P. intermedia* in pregnancy gingivitis. Both studies remarked upon the importance of differentiating both bacteria by means of the appropriate technologies.

Some other authors found no microbiological differences between pregnant and non-pregnant women (Jonsson *et al*., 1988) and there are also authors who have reported a general qualitative shift of the subgingival microbiota in a group of non-periodontitis pregnant women that showed an increase in gingival inflammation during pregnancy (Carrillo-de-Albornoz *et al*., 2010). Significant differences in proportions were found for *Aggregatibacter actinomycetemcomitans*, *P. gingivalis*, *P. intermedia/nigrescens*, *Tannerella forsythia*, *Parvimonas micra*, *Campylobacter rectus*, and *Fusobacterium nucleatum* by culture techniques when comparing pregnancy to three months postpartum. Further analyses of this data undertaken, using exhaustive chi-square automatic interaction detection (exhaustive CHAID) to analyse the predictive value of the independent outcomes, revealed that the level of plaque was the strongest predictor implicated in gingival inflammation during pregnancy. In addition, during the second and third terms of pregnancy, the presence of *P. gingivalis* significantly contributed to the worsening of gingival inflammation (Carrillo-de-Albornoz *et al*., 2012).

Molecular-based technologies have also been introduced in studies with pregnant women. A cross-sectional study with 150 healthy pregnant women with signs of gingival inflammation from the Provincial Maternity Hospital in Córdoba (Argentina) revealed that the bacterial frequencies identified by PCR were 39.3% *P. gingivalis*, 34% *T. denticola*, 3.3% *A. actinomycetemcomitans*, 21.3% *T. forsythia*, and 3.3% *P. intermedia*. In the multivariate analysis, *P. gingivalis* and *T. denticola* were found to be risk factors for moderate periodontitis. The risk of an increased clinical attachment level (CAL) was 14 times higher with the presence of *P. gingivalis* (OR = 14.6, 95% CI = 4.2–50.6), and approximately five times higher with the presence of *T. denticola* (OR = 4.98, 95% CI = 1.6–15; Table 3). When the risk to gingival inflammation (GI) > 2 was analysed, the data showed that *P. gingivalis*, *T. forsythia*, or *P. intermedia* in pregnant women were independent risk factors. The presence of *P. gingivalis* might increase the risk of GI > 2 by as much as sevenfold (OR = 7.34, 95% CI = 1.3–43.0, P = 0.0270). *T. forsythia* might be associated with a sixfold increase (OR = 6.39, 95% CI = 1.3–31.7, P = 0.0232), and when *P. intermedia* was detected, the risk for GI > 2 could increase as much as 51-fold. (OR = 51, 95% CI = 6.51–51.86, P = 0.0008) (Usin *et al*., 2013).

Tellapragada *et al*. (2014), in a cross-study including 390 pregnant women 18-35 years-old within 8-24 weeks of gestation attending the Department of Obstetrics and Gynaecology in Udupi, Karnataka, India, reported that the most frequently detected bacterial agents among the study population were *P. gingivalis* (36%), *E. corrodens* (28%), *A. actinomycetemcomitans* (28%), and *C. rectus* (26%).

Therefore, an evolution in the concept of microbiological changes is observed, from the restricted relation of pregnancy gingivitis to *P.intermedia* or *P. nigrescens* to a more general quantitative and qualitative change in the subgingival biofilm, probably reflecting the new concept of periodontal disease as a dysbiosis reflected by an increment in bacterial diversity as disease progresses (Sanz *et al*., 2017).

According to the immune-system theory, immune-modulative changes developed for foetal tolerance would render periodontal tissues more prone to develop gingival inflammation during pregnancy (O'Neil, 1979a; Lopatin *et al*., 1980; Raber-Durlacher *et al*., 1991).

It has been postulated that changes in the maternal immune system during pregnancy may contribute to a greater susceptibility to develop gingival inflammation (O'Neil, 1979a; Lopatin *et al*., 1980; Raber-Durlacher *et al*., 1991).

Four main research lines have traditionally been distinguished in relation to this issue, based on the type of study design (Figuero *et al*., 2010):

(1) In the first, peripheral blood lymphocytes or monocytes from pregnant women were stimulated in vitro with different antigens or mitogens (O'Neil, 1979a, Lopatin *et al*., 1980, Polan *et al*., 1990, Raber-Durlacher *et al*., 1991). Some authors reported a reduced responsiveness of maternal T-lymphocytes to antigenic stimulation (O'Neil, 1979a, Lopatin *et al*., 1980, Polan *et al*., 1990), but others found no such evidence (Raber-Durlacher *et al*., 1991).

(2) In the second group of reports, peripheral blood lymphocytes from men and non-pregnant women were stimulated with lipopolysaccharide (LPS) and incubated with different concentrations of progesterone and oestradiol (Miyagi *et al*., 1993, Morishita *et al*., 1999). Both hormones enhanced the production of prostaglandin E2 (PGE2) (Miyagi *et al*., 1993) and suppressed the production of interleukin-1b (IL-1b) (Morishita *et al*., 1999).

(3) In a third research line, Raber-Durlacher *et al*. (1993) induced a 14-day experimental gingivitis during pregnancy and postpartum and studied the local immune response in the gingiva, finding a decreasing number of B-cells and macrophages in consecutive gingival biopsies.

(4) Finally, human biopsies of healthy and inflamed gingiva have been incubated with oestradiol and progesterone, finding that both hormones enhanced PGE2 synthesis (ElAttar & Hugoson, 1974).

However, more recent human studies have examined the association between increased gingival inflammation during pregnancy and changes in the local immune system by measuring different components of gingival crevicular fluid (GCF).

Kinnby *et al*. (1996) observed a higher gingival inflammatory reaction in women during pregnancy and proposed that changes in hormone levels might have a suppressive effect on local plasminogen activator inhibitor-2 (PAI-2).

Yalcin *et al*. (2002a) found lower GCF PGE2 levels during the second and third trimester in pregnant women treated with scaling and root planing. They concluded that PGE2 levels could be used as a marker of gingival inflammation during pregnancy, although they acknowledged the lack of a control group of untreated pregnant women.

Akalin *et al*. (2009) reported a decrease in GCF total antioxidant activity and superoxide dismutase enzyme concentrations from the first to the third trimester of pregnancy.

Figuero *et al*. (2010), Carrillo-de-Albornoz *et al*. (2010) and Wu *et al.* (2016) reported an exacerbated gingival inflammation during pregnancy, but they did not find statistically significant changes in IL-1α, Prostagaldine PGE2, or IL-6 throughout pregnancy, although their levels significantly decrease from the third term of pregnancy to three months after delivery. TNF-α underwent a down-regulation throughout pregnancy. It was statistically significantly reduced at the third trimester, and increased after delivery. Levels of TNF-α and PGE2 have also been studied in the saliva of pregnant women and non-pregnant women in a case-control study (Gumus *et al*., 2015). In saliva TNF-α and PGE2 were significantly lower when comparing pregnancy and postpartum. By contrast, 25-hydroxy-vitamine D3 were significantly higher during pregnancy.

However, the most complex study regarding inflammatory markers in saliva during pregnancy gingivitis is the one published by Gürsoy *et al*. (2014) using an in silico network model and

determining the complex interaction between these markers and oestradiol levels. Seven inflammatory mediators were measured: metalloproteinase MMP2, MMP8 and MMP9, myeloperoxidase (MPO), and inhibitor of MMP (TIMP-1), IL-1b, IL-8. In saliva were steady during pregnancy and postpartum, whereas MMP-8 and MPO levels increased significantly after delivery. The model revealed the activation of IL-1b and IL-8 and the inhibition of IL-1 receptor antagonist by oestradiol.

Therefore, the landscape of inflammatory changes occurring throughout pregnancy is not yet known. New technologies are given new mechanisms to study the complex world of inflammatory markers that extends far beyond clinical gingival inflammation reported in pregnancy.

An increase in the volume of GCF has been reported, which might be mediated by an increase in the permeability of the sulcus mediated by sexual hormones (Hugoson, 1970). As a general principle, oestrogens are mainly related to the alterations in blood vessels in target tissues in pregnant women. However, in the periodontium, progesterone seems to be the main hormone responsible for the clinical changes (Mealey and Moritz, 2003). Progesterone is able to induce dilation of the gingival capillaries, the increase of the capillary exudate, and capillary permeability, which translates clinically as erythema and edema of the gingival margin. This is mediated by a direct action on the endothelial cells, on the syntheses of prostaglandins, and by a suppression in the cellular response associated with pregnancy.

In the case of cellular changes, there is reduction in the keratinisation of the gingival epithelium, an increase in the epithelial glucogen, a proliferation of the fibroblasts, and an impairment in collagen degradation and in the proliferation of the basal layer. All these changes lead to a reduction in the epithelial layer and, therefore, to a greater response against the irritants present in the dental plaque (Sooriyamoorthy and Gower, 1989; Deasy and Vogel, 1976).

Periodontal therapy during pregnancy

Oral-hygiene habits during pregnancy have scarcely been reported. Christensen *et al*. (2003), in a group of 1,935 pregnant Danish women reported (by telephone interviews) that 96% brushed their teeth twice a day and nine out of 10 were regular users of the dental-care system. Similarly, Dinas *et al*. (2007) reported, in a questionnaire involving 425 women in the first three days postpartum, that 27.3% visit the dentist during pregnancy, and 72.2% believed that dental treatment during pregnancy might have a negative effect on pregnancy outcome. Finally, a cross-sectional study of 93 pregnant women from Brunei, which relied on self-reporting data (questionnaires), revealed that 40.9% pregnant women flossed daily, 31.2% brushed after meals (breakfast and dinner), and 26.9% had a dental check-up at least twice a year. While 48.4% of pregnant women agreed that oral and dental treatment should not be avoided during pregnancy, the rest disagreed or were not sure. A comparison between the knowledge and practice of oral and dental healthcare was made, revealing that knowledge about frequency of brushing, flossing, and brushing after meals was significantly associated with practice (Bamanikar *et al*., 2013).

Therefore, taking into consideration the high prevalence of gingivitis in pregnant women, it would be of interest to implement proper education on oral and dental healthcare among pregnant women in order to lead to the correct practice of oral and dental health.

One of the first randomised control trials (RCT) to deal with the treatment of pregnancy gingivitis, and the one with the biggest sample size, was published by López *et al*. in 2005, including women with ≤22 weeks gestation and with gingival inflammation (≥ 25% of sites with BOP, and no sites with clinical attachment loss > 2 mm). In the test group (n=580), plaque-control instructions, supra- and

subgingival scaling and crown polishing, 0.12% chlorhexidine rinse once a day from 22nd week of pregnancy, and maintenance therapy every two to three weeks until delivery were carried out. No treatment was performed on the control group (n=290). A clear reduction in the bleeding index was observed in the treatment group (BOP: 55.09% to 15.09%) while an increase was observed in the control group (BOP: 51.42% to 56.52%), with statistically significant differences between the groups in the final visits (after 30 weeks of gestation).

Some other RCT studies have also been performed involving pregnant women to determine the efficacy of triclosan-copolymer (Kraivaphan *et al*., 2006, 2007), chlorhexidine rinses (Vasiliauskiene *et al*., 2007) and probiotics (*Lactobacillus reuteri*) (Schlagenhauf *et al*., 2016) on pregnancy gingivitis.

Kraivaphan *et al*. (2006) determined the efficacy of 0.03% triclosan-copolymer dentifrice adjunctive to non-surgical therapy versus placebo (Kraivaphan *et al*. 2006). One-hundred and twenty healthy pregnant women, three months' gestation, who received routine prenatal care at Taksin Hospital, Thailand for the presence of gingivitis were included and followed over nine months (three months postpartum). The triclosan dentifrice was associated with a statistically significant reduction in gingival inflammation – 19.73% (second term), 27.91% (third term), and 38.45% (three months postpartum) – compared to placebo ($p<0.05$). One year later, this same research group tested the same dentifrice (0.03% triclosan-copolymer) versus placebo with a very similar study design (RCT), in 180 women at three months of pregnancy. After five months (third term of pregnancy), the test group reported reductions of 40.5% in plaque, 22.5% in gingivitis, and 35.3% in bleeding levels ($p<0.05$). No adverse effects relative to the use of the dentifrice were reported.

The efficacy of professional oral-hygiene and fluoride-varnish applications once in each term in conjunction with 0.12% chlorhexidine mouth rinses (three periods of 10 days, followed by a break of six weeks) versus no treatment has been tested in 180 pregnant women (Vasiliauskiene *et al*., 2007). Plaque and gingival inflammation scores increased significantly in the control group, from moderate gingivitis at the beginning of pregnancy to severe gingivitis at the end. By contrast, in the test group, the mean gingival inflammation and the plaque levels decreased significantly when compared to the first-term visit. The difference in gingival inflammation between groups was 1.58 (standard error=0.07).

Finally, research has been conducted on the efficacy of probiotic *Lactobacillus reuteri* lozenges (Bio-Gaia AB, Lund, Sweden) – twice daily over seven weeks, until delivery – versus placebo, in 45 women at the beginning of their third term of pregnancy who showed signs of gingival inflammation (GI>1) (Schlagenhauf *et al*., 2016). Significant differences between test and control groups were found in terms of gingival inflammation and plaque levels ($p<0.001$).

With a different study design, another plaque-control regimen was implemented in Geishinger *et al*. (2014) and Kaur *et al*. (2014), in a prospective case series to evaluate an intensive oral-hygiene protocol designed to reduce gingival inflammation in pregnant women. One-hundred and twenty participants (16-24 weeks of pregnancy) with GI≥2 scores at ≥50% teeth were included. The protocol consisted of:

- An initial intervention (a DVD to explain the potential link between pregnancy gingivitis and prematurity and a detailed approach to using the home-care aids).
- Baseline examination involved the taking of pictures to show participants the state of their gingiva.
- One-to-one intervention: dental prophylaxis followed by individually tailored intensive one-on-one oral-hygiene counselling, providing feedback regarding both positive and negative aspects of oral-hygiene performance, coupled with demonstration and instructions for using oral-hygiene products.

- An oral-health home-care kit was dispensed that was adequate for approximately six weeks of use as prescribed. Each kit included: one powered toothbrush (Oral B Triumph; Procter & Gamble, Cincinnati, USA); 0.454% Stannous fluoride toothpaste (Crest Pro Health; Procter & Gamble); Dental floss (and interproximal brushes and/or floss-threaders if needed); Cetyl pyridinium chloride (CPC) 0.07% mouth rinse (Crest Pro Health).

Eight weeks after the plaque-control regimen, statistically significant reductions in plaque, gingival inflammation, PPD, and CAL levels ($p<0.001$) (Geisinger *et al*., 2014), and in the levels of TNF-α and IL-1b ($p<0.01$) (Kaur *et al*., 2014) were reported.

As a summary from plaque-control regimens in pregnancy gingivitis, it can be concluded that:

(1) There are not many well-designed long-term follow-up (nine months) RCTs within this research line;

(2) The existing evidence based on RCTs suggest the efficacy on clinical parameters on pregnancy gingivitis of: chlorhexidine rinses adjunctive to supra- and subgingival scaling and maintenance therapy each two to three weeks after 30 weeks of gestation (Lopez *et al*., 2005); triclosan-copolymer dentifrice after five to nine months (Kraivaphan *et al*., 2006, 2007); professional prophylaxis and chlorhexidine rinses (three periods of 10 days and six weeks break) (Vasiliauskiene *et al*., 2007); and probiotics (Lactobacillus reuteri) during seven weeks (Schlagenhauf *et al*., 2016).

(3) There are promising results on intensive oral-hygiene regimens based on a powered-toothbrush, a stannous fluoride dentifrice, and a CPC mouth rinse during eight weeks in a prospective case-series (Geisinger *et al*., 2014);

(4) No evidence of adverse side effects of any of these protocols has been reported.

In the case of *granuloma gravidarium*, lesions that do not cause significant functional or aesthetic problems should not be excised during pregnancy, because they may recur and can ultimately resolve spontaneously after delivery (Daley *et al*., 1991). During pregnancy, careful oral hygiene, removal of dental plaque, and the use of soft toothbrushes are very important to avoid occurrence and recurrence of a pregnancy tumour (Gondivkar *et al*., 2010; Wang *et al*., 1997). Ideally, any existing periodontal inflammation should be treated before pregnancy (Lindenmüller *et al*., 2010; Manegold-Brauer & Brauer, 2014)

Table 1a.
Material and methods from the included cohort studies: sample size, age, maximum follow-up, number of visits, inclusion criteria for pregnant group, periodontal status defined at baseline; country, setting and source of funding.

First author (year)	Final sample size	Mean age	Follow-up	No. of visits	Inclusion criteria (pregnant)	Periodontal status at baseline	Site, setting & funding
Cohen *et al.* (1969, 1971)	P: 15 NP: 15	P: 24 (SD = 4.72)/ NP: NR (Age matched)	P & NP: 21 m	P & NP: 4 (1st, 2nd, 3rd terms, 3 and 15 m postpartum)	<12 w of pregnancy	NR	Pennsylvania Hospital Funding NR
O'Neil; (1979a, 1979b)	P: 30 NP: 30	P & NP: NR	P: 8 m NP: 1 m	P: 3 (14th, 30th w of pregnancy, 8 w postpartum) NP: 2 (28 d apart)	18-32 y; good health, adequate number of teeth, no pockets > 3 mm	Adequate number of teeth; no pockets > 3 mm	England University Grants
Kornman & Loesche (1980)	P: 20 NP: 11	P & NP: NR	P: ≥6 m NP: 0 m	P: from 13th w of pregnancy, weekly until postpartum NP: 1	No loss of periodontal attachment; moderate to good oral hygiene, no dental prophylaxis 6 m prior	No loss of periodontal attachment; moderate to good oral hygiene, no dental prophylaxis 6 m prior	USA Hospital Grants
Tilakaratne *et al.* (2000)	P: 47 NP: 47	P: 24 (17-36) NP: 25 (17-36)	P & NP: 9 m	P & NP: 4 (1st, 2nd, 3rd terms, 3 m postpartum)	1st pregnancy, 1st term	NR	Sri-Lanka NR NR
Gürsoy *et al.* (2008, 2009, 2010a, 2010b, 2013, 2014, 2016)	P: 24 NP: 22	P: 29.3 (SD = 2.8) NP: 30.4 (SD = 3.1)	P: 7 m NP: 3 m	P: 4 (1st, 2nd, 3rd terms, 4-6 w postpartum, postlactation NP: 3 (once per month)	10 w of pregnancy, periodontally healthy, nonsmoker or former smoker	Periodontally healthy	Finland Health Center Grants
Akalin *et al.* (2009)	P: 72 NP: 52	NR	P: 6 m NP: 0 m	P: 2 (1st & 2nd terms) NP: 1	No smoking, no periodontal treatment	P: 33 chronic periodontitis; 18 gingivitis, 21 healthy	Turkey University Grant
Figuero *et al.* (2010); Carrillo-de-Albornoz *et al.* (2010, 2012)	P: 42 (26) NP: 20	P: 30.15 NP: 24.38	P: 9 m NP: 6 m	P: 4 (1st, 2nd, & 3rd terms and 3 m postpartum). NP: 2 (6 m apart)	12-14 w of pregnancy, non-periodontitis	Non-periodontitis	Spain Hospital Grants

Table 1a.

First author (year)	Final sample size	Mean age	Follow-up	No. of visits	Inclusion criteria (pregnant)	Periodontal status at baseline	Site, setting & funding
Wu *et al.* (2016)	P: 30 NP: 20	P: 29.24 (SD=2.31) NP: 28.33 (SD=1.97)	P: 6m NP: 2m	P: 3 (1st, 2nd, 3rd terms); NP: 2 (1/m)	12-14w of pregnancy; no smoking	Periodontal health & excellent oral hygiene (plaque)	China Hospital Project
Kinnby *et al.* (1996)	P: 14	P: 27-40	P: 4m	P: 2 (31-37th w of pregnancy, 3m postpartum)	NR	No GI or PI above 2	Sweden NR Grants
Yalcin *et al.* (2002b)	P: 61	P: 23.62 (SD = 4.01)	P: 6 m	P: 3 (1st, 2nd, & 3rd terms)	NR	NR	Turkey NR NR
Lieff *et al.* (2004)	P: 903	P: 28.3 (SD = 6.5)	P: 4m	P: 2 (26 w of pregnancy and 48 h postpartum)	<26 w of pregnancy	Periodontal health, mild and moderate / severe periodontal disease	USA Hospital and Private obstetric clinics OCAP study
Adriaens *et al.* (2009); Bieri *et al* (2013)	P: 20	P: 31.5 (SD = 4)	P: 7 m	P: 4 (1st, 2nd, & 3rd terms and 4-6 w postpartum)	Consecutive consenting singleton pregnant women <12 w of pregnancy	NR	Switzerland Hospital Grant
Buduneli *et al.* (2010)	P: 43	P: 26.2 (SD = 4.8)	P: 8 m	P: 2 (2nd term and postpartum)	NR	NR	Turkey Maternity Clinic Grant
Gumus *et al.* (2015)	P: 47	P: 27-31.5 (median)	P: 15 m	P (2nd or 3rd term) & PP (6m)	2nd or 3rd terms	PP: 14 healthy, 21 gingivitis, 12 periodontitis	Turkey University Research Foundation

Table 1b.
Material and methods from the included cross-sectional studies: sample size, distribution of women throughout pregnancy, age, inclusion criteria for pregnant group, Periodontal status defined before entering the study, Country, setting and source of funding.

First author (year)	Sample size	Distribution throughout pregnancy	Mean age	Inclusion criteria (pregnant)	Periodontal status at baseline	Site, setting & funding
Ringsdorf *et al.* (1962)	P: 330 PP: 36	15 (1st); 120 (2nd); 195 (3rd term)	NR	NR	NR	USA Obstetric clinics Grants
Löe & Silness (1963); Silness & Löe (1964)	P: 121 PP: 61	10 (2 m), 11 (3 m), 13 (4 m); 14 (5m); 20 (6 m); 21 (7 m); 17 (8 m); 15 (9 m)	P: 25.3 (18-34) PP: 25.7 (18-38)	2-9 m of pregnancy	NR	Norway Hospital NR
Katz *et al.* (1969)	P: 111 NP: 22	17 (3 & 4 m); 27 (5 m); 18 (6 m); 13 (7 m); 7 (8 m); 29 (9 m)	NR	3-9 m of pregnancy	NR	Israel NR NR
El-Ashiry *et al.* (1970, 1971)	P: 120 NP: 50	40 (1st); 40 (2nd); 40 (3rd term)	18-39 y	Pregnant women in the 1st, 2nd or 3rd term	NR	Egypt NR NR
Adams *et al.* (1974)	P: 100 NP: 100	NR	P: 16-39 y NP: 17-45 y	All women 3-9 m attending the hospital during 4 w	NR	United Kingdom Hospital NR
Arafat (1974a, 1974b)	P: 477 NP: 233	NR	NR	NR	NR	USA Hospital NR
Samant *et al.* (1976)	P: 120 NP: 40	40 (1st); 40 (2nd); 40 (3rd term)	NR	NR	NR	India or USA? NR NR

P=pregnant; NP=non-pregnant; PP=postpartum; m=months; y=years

Table 1b.

First author (year)	Sample size	Distribution throughout pregnancy	Mean age	Inclusion criteria (pregnant)	Periodontal status at baseline	Site, setting & funding
Jensen *et al.* (1981)	P: 54 NP: 50	NR	NR	18-40 years, no dental prophylaxis within 6 m, no previous periodontal therapy, no medication	No previous periodontal therapy	USA University Grants
Saleh *et al.* (1983)	P: 20 NP: 20	10 (12-14 w); 10 (28-32 w)	20-40 y	Free from systemic disease	NR	Egypt NR NR
Zaki *et al.* (1984)	P: 30 NP: 10	10 (1st term); 10 (2nd term); 10 (3rd term)	20-40 y	NR	NR	Egypt Hospital NR
Jonsson *et al.* (1988)	P: 30 NP: 30	NR	P: 28.8 (SD = 4.6 NP: 30.7 (SD = 4.4))	Not received dental treatment in the previous 6 m	Not received dental treatment in the previous 6 m	Canada NR NR
Miyazaki *et al.* (1991)	P: 2424 NP: 1565	28 (2 m); 437 (3 m); 1054 (4 m); 553 (5 m); 143 (6 m); 81 (7 m); 59 (8 m); 33 (9 m); 36 (10 m)	P: 22.75 (16-46)	NR	NR	Japan Health centres NR
Malisa *et al.* (1993)	P: 100 PP: 100	50 (2nd term); 50 (3rd term)	18-45 y	Women in the 2nd & 3rd terms	NR	Tanzania Hospital Public
Muramatsu & Takaesu (1994)	P: 19 PP: 8 NP: 12	NR	P: 28.5 (23-36) PP: 27.1 (22-31) NP: 22.9 (18-37)	All women with 2-10 m of pregnancy	NR	Japan Hospital NR
Nuamah & Annan (1998)	P: 100 NP: 100	50 (2nd term); 50 (3rd term)	15-45 y	All women in the 2nd & 3rd terms of pregnancy	NR	Ghana Hospital NR

P=pregnant; NP=non-pregnant; PP=postpartum; m=months; y=years

Table 1b.

First author (year)	Sample size	Distribution throughout pregnancy	Mean age	Inclusion criteria (pregnant)	Periodontal status at baseline	Site, setting & funding
Taani *et al.* (2003)	P: 200 NP: 200	29 (1st term); 61 (2nd term); 110 (3rd term)	P: 30 (SD = 0.05) NP: 32 (SD = 0.05)	At random from gynaecology clinics	NR	Jordan Gynaecology clinics Grants
Diaz-Guzman & Castellanos-Suarez (2004)	P: 93 NP: 5537	NR	P: 30.03 (SD=6.6) NP: 33.2 (SD=15.3)	All women >15years requesting dental care	NR	Mexico University NR
Yokoyama *et al.* (2008)	P: 22 NP: 15	NR	P: 31.9 (SD = 4.4) NP: 31.6 (SD = 5.4)	No periodontal treatment or antibiotics in the previous 3 m	No periodontal treatment in the previous 3 m	Japan University Grants
Acharya & Bhat (2009)	P: 259 NP: 237	NR	P: 26 (SD = 5.5) NP: 27.8 (SD = 6.9)	All women reporting for antenatal checkup during 3 m in a hospital with a lower-middle class population	NR	India Hospital NR
Rakchanok *et al.* (2010)	P: 94 NP: 103	NR	15-35 years or more	3-6 m of pregnancy	NR	Thailand Hospital Private

P=pregnant; NP=non-pregnant; PP=postpartum; m=months; y=years

Table 2a.
Outcome variables and main conclusion from the cohort studies.

First author (year)	Probe	Gingival inflammation/ bleeding	Plaque index	PPD/CAL	Other outcomes	Periodontal treatment	Periodontal treatment
Cohen *et al.* (1969, 1971)	Modified Michigan	Periodontal screening exam. O´Leary; full-mouth	PI (0-2); all teeth; 2 loc/tooth	NR/NR	NR	No	Gingival periodontal index was higher in the pregnant group. Increased periodontal disease during pregnancy did not result in increased periodontal disease at 15 m postpartum.
O´Neil (1979a, 1979b)	NR	GI_L&S (6 teeth)	PI_S&L (6 teeth)	NR/NR	Lymphocyte blood response	Scaling & OHI in patients with gingival inflammation (14th-30th w of pregnancy)	Preexisting chronic gingivitis gradually worsened during pregnancy, even in the presence of reduced amounts of bacterial plaque.
Kornman & Loesche (1980)	NR	GI_L&S (2 teeth; 1 loc/ tooth) interdental bleeding score (all sites mesial to 1st molars)	PI_S&L (2 teeth; 1 loc/tooth)	NR/NR	Microbiological analyses (GCF)	No	Gingivitis increased significantly between 13-28 w of pregnancy and then decreased. Subgingival flora changed to a more anaerobic flora as pregnancy progressed.
Gürsoy *et al.* (2008, 2009, 2010a, 2010b, 2013, 2014)	WHO	BoP (0-2; full-mouth; 6 loc/tooth)	VPI (pres/abs; full-mouth; 6 loc/tooth)	Full-mouth; 6 loc/tooth	Questionnaire; microbiological & immunological analyses (GCF; & saliva); estrogen level (saliva); in silico complex network model; antimicrobial defensins (saliva)	Initial SRP + OHI when needed to reduce gingival inflammation	Pregnancy resulted in reversible gingivitis without loss of attachment. Increased *P. nigrescens* levels were associated with pregnancy gingivitis. Pregnancy gingivitis mainly affected GCF PMN elastase; changes in MMP-8, MPO, and TIMP-1 levels were not observed. Salivary MMPs, MPO, and TIMP-1 were significantly reduced during pregnancy. Simultaneous enhanced oestrogen levels and plaque scores during 2nd and 3rd terms brought an additional risk of developing gingivitis compared to high plaque index alone.Pregnancy has a suppressive effect on salivary concentrations of hBD-1, hBD-2 and HNP-1, while hBD-3 remains unaffected. .
Akalin *et al.* (2009)	Michigan with Williams markings	GI_L&S (5 non-molar teeth; 4 loc/ tooth). BoP (Muhleman index; 5 nonmolar teeth; 4 loc/teeth)	PI_S&L (5 nonmolar teeth; 4 loc/tooth)	5 nonmolar teeth; 6 loc/tooth	Immunological analyses in GCF	OHI + supragingival scaling in 1st, 2nd, 3rd terms	Systemic and local GCF AO levels decreased in pregnancy and periodontitis. Antioxidants reached their lowest levels in the late phase of pregnancy.

VPI: visible plaque index; SRP: scaling and root planing; OHI: oral hygiene instructions; GCF: gingival crevicular fluid; PMN: polymorphonuclear neutrophils; MMP: metalloproteinases; MPO: myeloperoxidase; TIMP: metalloproteinase inhibitor; BOP: Bleeding on probing (presence/absence); GI-L&S: Gingival index described by Löe & Silness (1963); PI-S&L: Plaque index describe by Silness & Löe (1964); pres/abs, presence/absence; PAI-2: plasminogen activator inhibitor type 2.

Table 2a.

First author (year)	Probe	Gingival inflammation/ bleeding	Plaque index	PPD/CAL	Other outcomes	Periodontal treatment	Periodontal treatment
Figuero *et al.* (2010) Carrillo-de-Albornoz *et al.* (2010, 2012)	CPC-12	GI_L&S (full-mouth; 4 loc/tooth)	PI_S&L; full-mouth; 4 loc/ tooth)	NR	Questionnaire; microbiological & immunological analyses in GCF; hormonal levels in saliva	OHI in each visit	Gingival inflammation was exacerbated during pregnancy, but this exacerbation was not associated with hormonal or immunological changes. Bacterial challenge to the gingival tissues, both quantitatively (PI) and qualitatively (presence of P. gingivalis), affected the gingival inflammation level during pregnancy.
Wu *et al.* (2016)	Kangqiao	GI_L&S & BoP (0-2) (full-mouth; 3 loc/tooth)	PI_S&L (full-mouth; 3loc/ tooth)	PPD & CAL: full-mouth; 3 loc/ tooth	Immunological analyses (GCF); hormone levels (blood)	OHI at each visiti	Estradiol and progesterone levels in bloos confirm this would influence the inflammatory status of gingivia even under good oral hygiene control, independent of GCF levels of IL-1b and TNF_a.
Hugoson (1971)	NR	GI_L&S (6 teeth, 4 loc/tooth)	PI_S&L (6 teeth; 4 loc/tooth)	PPD: 6 teeth; 4 loc/tooth CAL: NR	GCF volume	In 11 women, 8 w after delivery (SRP + OHI)	Independently of its degree of inflammation at the first examination, existing gingivitis gradually increased in severity throughout pregnancy.
Cerna *et al.* (1990)	NR	GI_L&S (lower frontal teeth) BOP (SBI; lower frontal teeth)	PI (Green & Vermillion; lower frontal teeth)	NR/NR	Rusell periodontal index; self-reported bleeding; vitamin levels in blood	Treatment of caries lesions	Maximum inflammatory levels were seen in the 8th m of pregnancy, with amelioration shortly after delivery.
Kinnby *et al.* (1996)	NR	GI_L&S (mesial to 1st molars, 2loc/teeth)	PI_S&L (mesial to 1st molars, 2loc/ teeth)	PPD (mesial to 1st molars, 2loc/ teeth)	Immunological analyses (GCF)	No	Pregnancy gingivitis might be explained by a lower PAI-2 response in women with higher gingival inflammatory reaction during pregnancy
Yalcin *et al.* (2002b)	Williams	GI_L&S (full-mouth; 4 loc/tooth)	PI_S&L (Full-mouth; 4 loc/tooth)	PPD: full-mouth; 4 loc/tooth CAL: NR	Questionnaire	No	Gingival inflammation during pregnancy was related to the educational level of the population.
Lieff *et al.* (2004)	UNC-15	GI_L&S (full-mouth; 2 loc/tooth) BoP (full-mouth; 6 loc/tooth)	PI (modified from S&L; full-mouth, vestibular)	Full-mouth; 6 loc/tooth	Microbiological analyses (GCF), immunological analyses (GCF)	No	No significant change in mean attachment loss, GI, or bleeding scores was found during pregnancy.

VPI: visible plaque index; SRP: scaling and root planing; OHI: oral hygiene instructions; GCF: gingival crevicular fluid; PMN: polymorphonuclear neutrophils; MMP: metalloproteinases; MPO: myeloperoxidase; TIMP: metalloproteinase inhibitor; BOP: Bleeding on probing (presence/absence); GI-L&S: Gingival index described by Löe & Silness (1963); PI-S&L: Plaque index describe by Silness & Löe (1964); pres/abs, presence/absence; PAI-2: plasminogen activator inhibitor type 2.

Table 2a.

First author (year)	Probe	Gingival inflammation/ bleeding	Plaque index	PPD/CAL	Other outcomes	Periodontal treatment	Periodontal treatment
Adriaens *et al.* (2009); Bieri *et al.* (2013)	Florida	BOP (pres/abs; full-mouth; 6 loc/tooth) & in micro locations	NR	Full-mouth; 6 loc/tooth	Microbiological analyses (GCF), immunological analyses (GCF)	No	Moderate gingivitis during pregancy may partially resolved without any active treatment. Specifically decreasing expression of proinflammatory cytokines and levels of some bacteria appears to be explanatory to clinical periodontal improvemnst 4-6 weeks postpartum
Buduneli *et al.* (2010)	NR	BoP (pres/abs; full-mouth; 6 loc/tooth)	Pres/abs (full-mouth; 6 loc/tooth)	PPD: Full-mouth; 6 loc/tooth CAL: NR	Immunological analyses in GCF	No	Previous findings of pregnancy-related gingival hyperreactivity were confirmed. Involvement of the plasminogen activating system in the pathogenesis of pregnancy-related periodontal problems was not supported.
Gumus *et al.* (2015)	Williams	BoP (pres/abs; full-mouth; 6 loc/tooth)	Pres/abs (full-mouth; 6 loc/tooth)	PPD & CAL: Full-mouth; 6 loc/tooth	Immunological analyses (saliva)	No	Pregnancy has an effect (exacerbation) on biochemical paramaters in saliva related to periodontal diseases
Raga *et al.* (2016)	UNC-15	BoP (pres/abs; full-mouth; 6 loc/tooth)	Pres/abs (full-mouth; 4 loc/tooth)	PPD & CAL: Full-mouth; 6 loc/tooth	CRP and progesterone levels (blood)	No	Postpartum there is a dramatic reduction in progesterone and CRP, together with an improvement in BOP, PPD and CAL in the absence of periodontal treatment. The reduction of CRP is related to an improvement in gingival bleeding
Machado *et al.* (2016)	UNC-15	BoP (pres/abs; full-mouth; 6 loc/tooth)	NR	PPD & CAL: Full-mouth; 6 loc/tooth	Microbiological analyses (GCF	No	Greater number of teeth with PPD: 4-5mm during preganancy. A change in subgingival microbiota from 2nd term of pregnancy to postpartum, mainly for *P. Nigrescens*

VPI: visible plaque index; SRP: scaling and root planing; OHI: oral hygiene instructions; GCF: gingival crevicular fluid; PMN: polymorphonuclear neutrophils; MMP: metalloproteinases; MPO: myeloperoxidase; TIMP: metalloproteinase inhibitor; BOP: Bleeding on probing (presence/absence); GI-L&S: Gingival index described by Löe & Silness (1963); PI-S&L: Plaque index describe by Silness & Löe (1964); pres/abs, presence/absence; PAI-2: plasminogen activator inhibitor type 2.

Table 2b.
Outcome variables and main conclusion from the cross-sectional studies.

First author (year)	Probe	Gingival inflammation/ bleeding	Plaque index	PPD/CAL	Other outcomes	Authors' conclusions
Ringdorf (1962)	NR	PMA	NR	NR/NR	NR	The average PMA index was essentially the same for pregnant and non-pregnant patients.
Löe & Silness (1963, 1965); Silness & Löe (1964)	NR	GI_L&S (6 teeth; 4 loc/tooth)	PI_S&L (6 teeth; 4 loc/tooth)	PPD: 6 teeth; 4 loc/tooth	Perl (Rusell 1956)	The gingival condition was significantly different between pregnancy and after delivery.
Katz *et al.* (1969)	NR	GI_L&S (6 teeth)	PI_S&L (6 teeth; 4 loc/tooth)	NR/NR	Perl (Rusell 1956)	Plaque, gingival, and periodontal indexes increased during the whole pregnancy.
El-Ashiry (1970, 1971)	NR	Own (0-3)	NR	NR/NR	Calculus: Green & Vermillion	The greatest effect of pregnancy on the gingiva occurred during the 1st term, with further aggravation in the 3rd term.
Adams *et al.* (1974)	NR	GI (Modification GI_L&S, anterior teeth, only papilas)	Pres/abs (vestibular; anterior teeth)	NR/NR	NR	A factor other than debris served as a causative agent for gingivitis during pregnancy.
Arafat (1974a, 1974b)	NR	GI (Perl Rusell 1965) (full-mouth, 2 loc/tooth)	PI (Green & Vermi-llion; all teeth, 2 loc/tooth)	NR/NR	NR	Hormonal changes of pregnancy were a predisposing factor for periodontal changes. Dental plaque was the precipitating factor in the pathological changes.
Samant (1976)	NR	GI_L&S	PI (Greene, 1967; NR; NR)	NR/NR	Perl (Rusell 1956)	Gingivitis significantly increased during pregnancy.

PMA: periodontal scoring system (Ringsdorf 1962); DMFT: tooth decay, missing teeth, fillings; Perl: periodontal index; pres/abs: presence/ absence.

Table 2b.
Outcome variables and main conclusion from the cross-sectional studies.

First author (year)	Probe	Gingival inflammation/ bleeding	Plaque index	PPD/CAL	Other outcomes	Authors' conclusions
Jensen (1981)	Michigan probe with Williams markings	GI_L&S (7 teeth)	NR	PPD: 9 teeth; 6 loc/tooth CAL: NR	Microbiological analyses (GCF); GCF volume	GCF and gingival inflammation were increased during pregnancy. Increased fluid flow was associated with increased GI. The relative proportions of Bacteroides increased 55-fold in pregnant women over the control group.
Saleh *et al.* (1983)	NR	GI_L&S	PI_S&L	NR/NR	Gingival biopsies (oxygen consumption)	Gingivitis was aggravated and oxygen consumption was increased in the gingival tissue during pregnancy.
Zaki (1984)	NR	GI_L&S	PI_S&L	NR/NR	Hormones in saliva	Increased gingivitis severity during pregnancy was mediated by hormonal changes during this period.
Jonsson *et al.* (1988)	Michigan probe with Williams markings	Modified periodontal bleeding index (Van der Velden 1979) (all inter-proximal sites)	Pres/abs; all teeth; 4 loc/ tooth	PPD: All teeth; 4 loc/tooth CAL: NR	Microbiological analyses (GCF); Hormones in saliva	None of the clinical parameters differed significantly in pregnant and non-pregnant women. No correlation between clinical and bacteriological data was detected.
Miyazaki *et al.* (1991)	WHO probe	CPITN (10 teeth)	CPITN	CPITN	Profession	Pregnancy did not cause periodontal destruction. A special programme of periodontal disease prevention for pregnant women was not advised.
Malisa *et al.* (1993)	WHO probe	CPITN (10 teeth)	Pres/abs (10 teeth; NR)	CPITN	NR	Oral hygiene status of pregnant women was poor, and plaque elicited an irritating effect on the gingiva. Patients with clean mouths showed no gingival alterations.
Muramatsu *et al.* (1994)	WHO probe	GI (pres/abs; full-mouth; 6 loc/tooth) BOP (pres/abs; all teeth; 6 loc/tooth)	Oral Hygiene Index (Green & Vermi-llion, 1960)	PPD: all teeth; 6 loc/tooth CAL: NR	Microbiological analyses (GCF)	From the 3-5 m of pregnancy, the number of sites with BoP increased concomitantly with increasing percentages of P. intermedia.

PMA: periodontal scoring system (Ringsdorf 1962); DMFT: tooth decay, missing teeth, fillings; Perl: periodontal index; pres/abs: presence/ absence.

Table 2b.
Outcome variables and main conclusion from the cross-sectional studies.

First author (year)	Probe	Gingival inflammation/ bleeding	Plaque index	PPD/CAL	Other outcomes	Authors' conclusions
Nuamah *et al.* (1998)	WHO probe	CPITN	CPITN	CPITN	NR	The number of sextants with BoP during the 2nd trimester of pregnancy was high, irrespective of the method of oral hygiene used.
Taani *et al.* (2003)	Michigan probe	GI_L&S	PI_S&L	PPD: 6 loc/tooth CAL: 6 loc/tooth	Educational level, profession	Pregnancy was associated with the inflammatory aspect of periodontal disease, rather than with attachment loss or plaque accumulation.
Díaz-Guzmán & Castellanos-Suárez (2004)	Michigan probe	Simplified periodontal index	NR	NR	NR	Pregnancy does not seems to be a risk factor for increased gingivitis or periodontitis
Yokoyama *et al.* (2008)	NR	BOP (full-mouth; 6 sites/tooth)	NR	PPD: All teeth; 6 loc/tooth CAL: NR	Microbiological analyses (saliva); Hormone levels (saliva)	*C. rectus* levels were higher in pregnant women, which may have been associated with increased salivary estradiol concentrations. This result may contribute to periodontal disease progression during pregnancy.
Acharya *et al.* (2009)	NR	GI_L&S	NR	CPITN	Questionnaire (14 items), DMFT	Oral health and perceived oral-health-related quality of life were poorer among pregnant women than non-pregnant women
Rakchanok *et al.* (2010)	NR	BOP	NR	NR; NR	Questionnaire; dental caries	Pregnant women were 2.2 times more likely to suffer from gingivitis than non-pregnant women (95% CI 1.1-4.7)

PMA: periodontal scoring system (Ringsdorf 1962); DMFT: tooth decay, missing teeth, fillings; Perl: periodontal index; pres/abs: presence/ absence.

Table 6a.
Descriptive results from the main outcome, gingival inflammation from cohort studies.

Reference	Index	Group	Pregnant women												Non-pregnant					
			1st term (13-14w)			2nd term (26-27w)			3rd term (39-40w)			Postpartum			1st visit (baseline)			Last visit		
			n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	
Cohen *et al.* (1969)	O´Leary		15	2.15	0.13	15	2.39	0.58	15	2.35	0.70	15	2.29	0.59	16	1.64	0.16	16	2.16	0.15
O´Neil (1979a)	GI-L&S		30	1.14		30	1.32													
Kornman & Loesche (1980)	GI-L&S		20	1.16	NR	20	1.44-1.61	NR	20	NR	NR	20	NR	NR	11	0.17	0.18	16	2.16	0.15
Tilakaratne *et al.* (2000)	GI-L&S		47	1.15	0.3	47	1.28	0.38	47	1.43	0.32	47	1.14	0.28	47	0.93	0.32	47	0.9	0.3
Gürsoy *et al.*	BOP		29	24.44	16.31	30	33.74	13.22	26	28.12	13.13	24.00	7.97	3,4	24	7.13	5.75	22	5.8	4.73
Akalin *et al.* (2009)	GI-L&S	P G H	33 18 21	1.26 0.93 0.1	0.46 0.7 0.1				33 18 21	1.84 1.39 0.97	0.56 0.57 0.36				27 25	1.15 0.08	0.58 0.09			
Figuero *et al.* (2010)	GI-L&S		42	1.01	0.41	42	1.13	0.43	42	1.14	0.44	26	0.98	0.4	20	0.65	0.44	20	0.58	0.2
Wu *et al.* (2016)	GI-L&S	PI<1	30	1.205	0.109	30	1.357	0.152	30	1.485	0.169	20	1.250	0.126	20	1.235	0.108	30		
Hugoson (1971)	GI-L&S		26	0.92	0.2	26	1.12	NR	26	1.34	0.31	26	NR	NR						
Kinnby *et al.* (1996)	GI-L&S		frequency distribution																	
Yalcin *et al.* (2002b)	GI-L&S		61	1.79	0.35	61	1.95	0.38	61	1.99	0.37									
Lieff *et al.* (2004)	GI-L&S		frequency distribution																	
Adriaens *et al.* (2009)	BOP		20	40.1%	18.2%							20	27.4	12.5						
Buduneli *et al.* (2010)	BOP		43	49.3%	37.7%							43	44.7%	36.6%						
Gumus *et al.* (2015)	BOP	P G H				17 25 17	100% 60% 10%					12 21 14	80% 50% 10%		15 28 27	90% 70% 5%				
Raga *et al.* (2016)	BOP								117	21.03	15.6	117	13.25%	12.85						

PMA: periodontal scoring system (Ringsdorf 1962); DMFT: tooth decay, missing teeth, fillings; Perl: periodontal index; pres/abs: presence/ absence.

Table 6b.
Descriptive results from the main outcome, gingival inflammation from cross-sectional studies.

Reference	Index	Teeth	Pregnant women												Non-pregnant					
			1st term (13-14w)			2nd term (26-27w)			3rd term (39-40w)			Postpartum			1st visit (baseline)			Last visit		
			n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	
Ringdorf (1962)	PMA		frequency distribution																	
Löe & Silness (1963, 1965); Silness & Löe (1964)	GI-L&S		121	1.03	0.31	11	1.04	0.31	20	1.05	0.28	15	0.91	0.34	61	0.87	0.37			
Katz *et al.* (1969)	GI-L&S					22	0.32	NR	27	1.12	NR	29	0.89	NR				22	0.32	NR
El-Ashiry (1970, 1971)	Own					40	1.6	NR	40	1.6	NR	40	1.9	NR				50	0.6	NR
Adams *et al.* (1974)	GI-L&S		frequency distribution																	
Arafat (1974a, 1974b)	GI (Russell)		477	1.34	NR	477	0.77	NR	477	0.94	NR	477	0.72	NR				233	0.768	NR
Samant (1976)	GI-L&S					40	0.709	0.086	40	1.036	0.102	40	0.937	0.095				40	0.47	0.074
Jensen (1981)	GI-L&S	54 54	54 54	NR NR														27 27	0.48 0.63	NR NR
Saleh *et al.* (1983)	GI-L&S					10	1.784	0.363				10	1.829	0.28				20	1.438	0.23
Zaki (1984)	GI-L&S					10	1.39	0.22	10	1.731	0.32	10	1.836	0.44				10	1.418	0.252
Jonsson *et al.* (1988)	MPBI		30	0.71	0.71													30	0.78	0.19
Miyazaki *et al.* (1991)	CPITN		frequency distribution																	
Malisa *et al.* (1993)	CPITN		frequency distribution																	
Muramatsu *et al.* (1994)	GI dichoto-mous		frequency distribution																	
Nuamah *et al.* (1998)	CPITN		frequency distribution																	
Taani *et al.* (2003)	GI-L&S					29	2.06	0.11	61	2.5	0.06	110	2.6	0.05				200	1.18	0.041

PMA: periodontal scoring system (Ringsdorf 1962); GI-L&S: Gingival index described by Löe & Silness (1963); MPBI: Modifief periodontal bleeding indx; CPITN: Community periodontal index of treatment needs; SPI: Simplified periodon

Table 6b.
Descriptive results from the main outcome, gingival inflammation from cross-sectional studies.

Reference	Index	Teeth	Pregnant women												Non-pregnant					
			1st term (13-14w)			2nd term (26-27w)			3rd term (39-40w)			Postpartum			1st visit (baseline)			Last visit		
			n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	
Díaz-Guzmán & Castellanos-Suárez (2004)	SPI		frequency distribution																	
Yokoyama *et al.* (2008)	BOP		22	69.5%	29.2%													15	53.8%	28.8%
Acharya *et al.* (2009)	GI-L&S		250	1.25	0.9													237	0.98	0.3
Rakchanok *et al.* (2010)	BOP		94	86.2%	NR													103	72.8%	NR

PMA: periodontal scoring system (Ringsdorf 1962); GI-L&S: Gingival index described by Löe & Silness (1963); MPBI: Modifief periodontal bleeding indx; CPITN: Community periodontal index of treatment needs; SPI: Simplified periodon

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Oral Health and **Pregnancy**: the project

Oral Health & Pregnancy

The aim of the Oral Health and Pregnancy project, a collaboration between the European Federation of Periodontology (EFP) and Oral-B, is to promote women's oral health during pregnancy through guidelines for patients and for healthcare professionals.

The importance of oral health during pregnancy cannot be underestimated. Scientific studies have shown connections between gum disease and adverse pregnancy outcomes such as premature birth, low birth weight, and pre-eclampsia.

The Oral Health and Pregnancy project offers the site oralhealthandpregnancy.efp.org wich is full of advice – based on the latest scientific evidence – about the steps that need to be taken to ensure good oral health in pregnant women. The portal includes written, graphical, and video material in three areas:

- *The importance of women's oral health during pregnancy;*
- *The links between periodontal diseases and pregnancy;*
- *Preventing and treating periodontal disease during pregnancy.*

At the heart of the Oral Health and Pregnancy portal are sets of guidelines about oral health in pregnant women for dentists, dental hygienists, other health professionals, and for women themselves. These guidelines have been drawn up by some of the world's leading experts in periodontal science and are based on the results of numerous scientific studies.

The project will also provide a toolkit for the 30 national societies of periodontology which are members of the EFP to enable them to run their own campaigns on oral health and pregnancy, whether through similar portals or through the production and distribution of leaflets based on the guidelines. This toolkit will enable the important information contained in the guidelines to reach health professionals and women across Europe in local languages and adapted to local needs.

oralhealthandpregnancy.efp.org

A joint **EFP - Oral-B project**

EFP
European Federation of Periodontology

*The **European Federation of Periodontology** (EFP) is the leading global voice on gum health and gum disease and the driving force behind EuroPerio – the most important international periodontal congress – and Perio Workshop, a world-leading meeting on periodontal science. The EFP also edits the* Journal of Clinical Periodontology, *one of the most authoritative scientific publications in this field.*

The EFP comprises 30 national societies of periodontology in Europe, northern Africa, Caucasia, and the Middle East, which together represent about 14,000 periodontists, dentists, researchers, and other members of the dental team focused on improving periodontal science and practice.

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Oral B has been an EFP partner since 2009 and has participated in many EFP events, including EuroPerio7 (2012) and EuroPerio8 (2015) as a Diamond sponsor, the EFP Postgraduate Symposium in 2013 and 2015, and the European Workshop in Periodontology in 2014. The company will be a Diamond Sponsor of EuroPerio9, which takes place in Amsterdam in June 2018.

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