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# Effect of pregnancy on gingival inflammation in systemically healthy women: a systematic review

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***Abstract***

**Aim:** To obtain an overall quantitative estimate of the association between pregnancy and gingival inflammation.

**Material and Methods:** Medline and EMBASE databases were searched through August 2011. Prospective cohort or cross-sectional studies assessing the effect of pregnancy on gingival inflammation evaluated by the gingival index (GI) and/or bleeding on probing were included. Meta-analyses were performed if possible.

**Results:** Forty-four articles representing 33 studies (14 cohort and 19 cross-sectional) were included. Meta-analyses, performed whenever possible, revealed (1) a significantly lower GI in pregnant women in the first term compared with those in their second or third term of pregnancy; (2) a lower mean GI score in post-partum women compared with women in their second [WMD = 0.143; 95% 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, when considering cohort studies; (3) Non-pregnant women had lower mean GI values than women in their second or third term of pregnancy. Small changes in plaque levels were reported.

**Conclusion:** Despite the limited number of studies included in the meta-analyses, the present systematic review confirms the existence of a significant increase in GI throughout pregnancy and between pregnant *versus* post-partum or non-pregnant women, without a concomitant increase in plaque levels.

Key words: bleeding on probing; gingival inflammation; periodontal diseases; pregnancy; pregnancy gingivitis

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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 target areas involved in these changes (Amar & Chung 1994). Pregnancy gingivitis, defined as gingival inflammation initiated by plaque and exacerbated by endogenous sex steroid hormones (Mariotti 1994), affects 36%–100% of pregnant women (Maier & Orban 1949, Loe & Silness 1963, Jensen et al. 1981). Clinical studies have reported an increase in the extent and severity of gingival inflammation during pregnancy, which abates post-partum with the fall in hormone production (Cohen et al. 1971, Tilakaratne et al. 2000, Yalcin et al. 2002a, Gursoy et al. 2008).

The gingival inflammatory pattern during pregnancy is controversial, and studies have reported varying severities and timings of the peak inflammation. Most studies have reported that gingival inflammation peaks in the third trimester (Loe & Silness 1963, Cohen et al. 1969, Hugoson 1971, Kornman & Loesche 1980, Zaki et al. 1984,

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Tilakaratne et al. 2000, Taani et al. 2003), although others have observed the greatest inflammation during the second trimester (Arafat 1974a, Samant et al. 1976, Muramatsu & Takaesu 1994, Gursoy et al. 2008). Reported gingival severity ranges from mild inflammation to severe hyperplasia, pain and profuse bleeding (Samant et al. 1976, Thomson & Pack 1982). Most of these articles 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 in the gingival index (GI) during pregnancy.

Other articles have considered pregnancy gingivitis from a microbiological or immunological perspective, because hormonal variations during pregnancy may affect the physiology of host–parasite interactions in the oral cavity. It has been postulated that pregnancy-related hormonal influences on the immune system (O'Neil 1979a, Raber-Durlacher et al. 1991, 1993) or subgingival biofilm (Kornman & Loesche 1980, Jensen et al. 1981, Jonsson et al. 1988, Muramatsu & Takaesu 1994, Raber-Durlacher et al. 1994, Adriaens et al. 2009) may contribute to the aetiology and pathogenesis of pregnancy gingivitis. However, the results have been inconclusive and this issue remains controversial.

The source of the conflicting information about pregnancy gingivitis may be attributed to methodological differences among the studies, including variations in the measured periodontal indices, gingivitis severity and study designs. Given that pregnancy gingivitis seems to be an important problem facing women, there is strong interest in evaluating the actual effect of pregnancy on gingival inflammation. In addition, the association between periodontal diseases and adverse pregnancy outcomes gives even more relevance to this topic (for review, see Chambrone et al. 2011a,b).

The primary objective of this systematic review was to obtain an overall quantitative estimate of the association between pregnancy and gingival inflammation. The secondary objectives were (1) to evaluate whether there is any quantitative or qualitative difference in the subgingival microbiological profile (biofilm) during pregnancy compared with post-partum; (2) to assess if there is any quantitative or qualitative alteration in the local maternal immune system during pregnancy compared with post-partum; and (3) to analyse patient-centred outcomes during pregnancy.

## Materials and Methods

### Protocol development and eligibility criteria

A detailed protocol was designed according to Needleman (2002) to answer the following question*: What is the effect of pregnancy on systemically healthy women in terms of gingival inflammation*?

To be considered for inclusion, studies needed to be prospective cohort or cross-sectional studies assessing the effect of pregnancy on periodontal health. Only publications in English were considered. In addition, the following P.E.C.O. definitions were considered:

- *Population*. Studies should include systemically healthy post-pubertal women, including only pregnant women or pregnant and non-pregnant women.
- *Exposure*. Pregnancy was the exposure considered for evaluation.
- *Comparison*. The specific comparisons investigated were either differences throughout pregnancy or differences between pregnant *versus* non-pregnant post-pubertal fertile women. Studies including only non-pregnant women, only post-partum women or pregnant women without specific comparisons throughout pregnancy were excluded.
- *Outcome measures*. The primary outcome variable was gingival inflammation, evaluated by GI or bleeding on probing (BOP). As secondary outcomes, probing pocket depth (PPD), clinical attachment level (CAL), plaque index (PI), microbiological status (total flora, presence of certain bacterial pathogens and percentage and proportions of flora of certain bacterial pathogens), changes in local maternal immune system (presence of inflammatory mediators in gingival crevicular fluid) and patient-centred outcomes (self-reported pain, gingival bleeding and gingival hypertrophy) were considered.

### Search strategy

Electronic databases were searched up to and including August 2011. The MEDLINE database was searched via Pubmed, and Embase was searched via Ovid. The search was restricted to articles with human subjects and included a combination of controlled vocabulary and free text terms:

Exposure:

- "pregnancy" OR "pregnant" OR "pregnant women" OR "pregnan*"

Outcomes:

- "periodontal" OR "periodontal diseases" OR "periodontal disease" OR "periodont*" OR "gingival" OR "gingivitis" OR "gingiv*" OR "gingival hyperplasia" OR "gingival overgrowth" OR "pregnancy gingivitis" OR "gingival inflammation" OR "gingival bleeding".

[Exposure AND Intervention]

Hand searching was performed on the *Journal of Periodontology*, *Journal of Periodontal Research* and *Journal of Clinical Periodontology*. Bibliographies of all retrieved article were also checked.

### Screening

Titles and abstracts of all identified reports were screened independently by two reviewers (DH, CM). Inter-observer agreement was assessed by kappa scores.

For studies that appeared to meet the inclusion criteria or for which there were insufficient data in the title or abstract to make a clear decision, the full report was obtained and independently assessed by two reviewers (DH, CM). Disagreement was checked by an independent reviewer (EF) and resolved through discussion. Special attention was

paid to avoid the inclusion of duplicate data in the global result.

#### Quality assessment

The Newcastle–Ottawa scale (NOS) for cohort studies and a modification of NOS for cross-sectional studies was used for the assessment of risk of bias in individual studies (Wells et al. 2011). It includes three main categories: selection of the participants, comparability of the groups and ascertainment of the outcome of interest. Studies with five or more points were considered as high quality (Aldabe et al. 2012). A full explanation of the NOS can be found in Appendix S1 and S2.

#### Data extraction

Data were extracted by two reviewers independently (AC, EF) with specially designed data extraction forms. Any disagreement was discussed, and a third reviewer (DH) was consulted when necessary. Authors were consulted to obtain any further information not available in the article. When the study results were published more than once or results were detailed in multiple publications, the most complete data set from all sources was identified, and the data were included only once.

#### Heterogeneity assessment

Heterogeneity between studies was assessed using the Cochran's Q-test for homogeneity (Cochran 1954), jointly with the $I^2$ index (Higgins et al. 2003) to know the percentage of variation in the global estimate that could be attributed to heterogeneity (<25%: low heterogeneity; 25% –50%: moderate; 50%–75%: high, >75% very high).

#### Data synthesis

To summarize and compare studies, mean values of primary and secondary outcomes were directly pooled and analysed with weighted mean differences (WMDs) and 95% confidence intervals (CIs), considering independently each study design (cohort and cross-sectional). Study-specific estimates were pooled with both the fixed- and random- (Dersimonian & Laird 1986) effect models. If a significant and large heterogeneity was found, then the random-effect model results were presented. Publication bias was evaluated using the Egger's test (Egger & Smith 1998).

All analyses were done using Stata 11 (StataCorp LP, College Station, TX, USA, 2011). Statistical significance was defined as a p-value <0.05.

## Results

#### Description of studies

*Search results*

A total of 431 articles were identified. Screening of the titles and abstracts led to rejection of 336 articles (85.9% inter-observer agreement; kappa = 0.72). After full-text analysis and exclusion of 51 articles, data were extracted from 44 articles, reporting 33 different studies (Figure 1). Results were most frequently reported in only one article, but some studies were reported in two (Loe & Silness 1963, Silness & Loe 1964, Cohen et al. 1969, 1971, El-Ashiry et al. 1970, 1971, Arafat 1974a,b, O'Neil 1979a, b), three (Carrillo-De-Albornoz et al. 2010, 2012, Figuero et al. 2010) or four articles (Gursoy et al. 2008, 2009, 2010a,b). Among the 33 studies, 14 were prospective cohort studies that included both pregnant and non-pregnant groups or included only pregnant women (Table 1a). Nineteen were cross-sectional studies comparing pregnancy trimester groups, pregnant and non-pregnant groups or pregnant and post-partum groups (Table 1b).

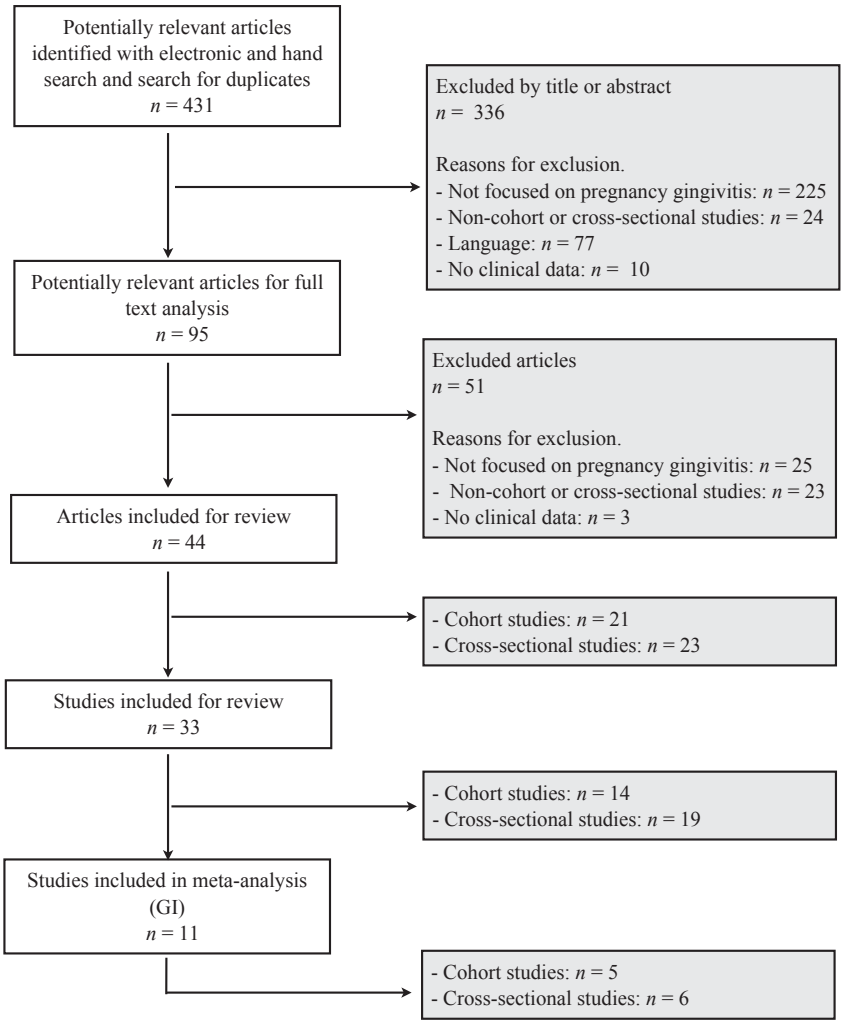


*Fig. 1.* Flow of the study. GI, Gingival inflammation.

*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<br>NP: 15 | P: 24 (SD = 4.72)/<br>NP: NR<br>(Age matched) | P & NP:21 month | P & NP: 4 (1st, 2nd, 3rd terms, 3 and 15 months post-partum) | < 12 weeks of pregnancy | NR | Pennsylvania<br>Hospital<br>Funding NR |
| O'Neil (1979a,b) | P: 30<br>NP: 30 | P & NP: NR | P: 8 month<br>NP: 1 month | P: 3 (14th, 30th week of pregnancy, 8 weeks post-partum)NP: 2 (28 days apart) | 18–32 years; good health, adequate number of teeth, No pockets > 3 mm | Adequate number of teeth; No pockets > 3 mm | England<br>University<br>Grants |
| Kornman & Loesche (1980) | P: 20<br>NP: 11 | P & NP: NR | P: $\geq$ 6 month<br>NP: 0 month | P: from 13th week of pregnancy, weekly until post-partum<br>NP: 1 | No loss of periodontal attachment; moderate to good oral hygiene, no dental prophylaxis 6 months prior | No loss of periodontal attachment; moderate to good oral hygiene, no dental prophylaxis 6 months prior | USA<br>Hospital<br>Grants |
| Tilakaratne et al. (2000) | P: 47<br>NP: 47 | P: 24 (17-36)<br>NP: 25 (17–36) | P & NP: 9 month | P & NP: 4 (1st, 2nd, 3rd terms, 3 months post-partum) | 1st pregnancy, 1st term | NR | Sri Lanka<br>NR<br>NR |
| Gursoy et al. (2008, 2009, 2010a,b) | P: 21<br>NP: 22 | P: 29.3 (SD = 2.8)<br>NP: 30.4<br>(SD = 3.1) | P: 7 month<br>NP: 3 month | P: 4 (1st, 2nd, 3rd terms, 4–6 weeks post-partum, post-lactation<br>NP: 3 (once per month) | 10 weeks of pregnancy, periodontally healthy, non-smoker or former smoker | Periodontally healthy | Finland<br>Health Center<br>Grants |
| Akalin et al. (2009) | P: 72<br>NP: 52 | NR | P: 6 month<br>NP: 0 month | P: 2 (1st & 2nd terms)<br>NP: 1 | No smoking, no periodontal treatment | P: 33 chronic periodontitis; 18 gingivitis, 21 healthy | Turkey<br>University<br>Grant |
| Figuero et al. (2010), Carrillo-De-Albornoz et al. (2010, 2012) | P: 42 (26)<br>NP: 20 | P: 30.15<br>NP: 24.38 | P: 9 month<br>NP: 6 month | P: 4 (1st, 2nd, & 3rd terms and 3 months post-partum).<br>NP: 2 (6 months apart) | 12–14 weeks of pregnancy, non-periodontitis | Non-periodontitis | Spain<br>Hospital<br>Grants |
| Hugoson (1971) | P: 26 | P: 24.88 | P: 10 month | P: 9 (12th, 18th, 24th, 30th, 34th, 38th week of pregnancy, 1–3 days, 8 and 20 weeks post-partum | NR | NR | Sweden<br>Hospital<br>Grants |
| Cerna et al. (1990) | P: 39 | NR | P: 6 month | P: from 8–12 week, every second week, until delivery | Good general health | NR | Czechoslovakia<br>Hospital<br>Funding NR |
| Kinnby et al. (1996) | P: 14 | P: 27–40 | P: 4 month | P: 2 (31–37th week of pregnancy, 3 months post-partum) | NR | No GI or PI above 2 | Sweden<br>NR<br>Grants |
| Yalcin et al. (2002b) | P: 61 | P: 23.62 (SD = 4.01) | P: 6 month | P: 3 (1st, 2nd & 3rd terms) | NR | NR | Turkey<br>NR<br>NR |
| Lieff et al. (2004) | P: 903 | P: 28.3 (SD = 6.5) | P: 4 month | P: 2 (26 weeks of pregnancy and 48 h post-partum) | <26 weeks of pregnancy | Periodontal health, mild and moderate/ severe periodontal disease | USA<br>Hospital and Private obstetric clinics<br>OCAP study |
| Adriaens et al. (2009) | P: 20 | P: 31.5 (SD = 4) | P: 7 month | P: 4 (1st, 2nd & 3rd terms and 4–6 week post-partum) | Consecutive consenting singleton pregnant women < 12 weeks of pregnancy | NR | Switzerland<br>Hospital<br>Grant |
| Buduneli et al. (2010) | P: 43 | P: 26.2 (SD = 4.8) | P: 8 month | P: 2 (2nd term and post-partum) | NR | NR | Turkey<br>Maternity Clinic<br>Grant |

P, Pregnant; NP, Non-pregnant; GI, gingival index; PI, plaque index.

*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 | Site, setting & funding |
|---|---|---|---|---|---|---|
| Ringsdorf et al. (1962) | P: 330<br>PP: 36 | 15 (1st); 120 (2nd); 195 (3rd term) | NR | NR | NR | USA<br>Obstetric clinics<br>Grants |
| Loe & Silness (1963),<br>Silness & Loe (1964) | P: 121<br>PP: 61 | 10 (2 months), 11 (3 months), 13 (4 months); 14 (5 months); 20 (6 months); 21 (7 months); 17 (8 months); 15 (9 months) | P: 25.3 (18–34)<br>PP: 25.7 (18–38) | 2–9 months of pregnancy | NR | Norway<br>Hospital<br>NR |
| Katz et al. (1969) | P: 111<br>NP: 22 | 17 (3 & 4 months); 27 (5 months); 18 (6 months); 13 (7 months); 7 (8 months); 29 (9 months) | NR | 3–9 months of pregnancy | NR | Israel<br>NR<br>NR |
| El-Ashiry et al. (1970, 1971) | P: 120<br>NP: 50 | 40 (1st); 40 (2nd); 40 (3rd term) | 18–39 years | Pregnant women in the 1st, 2nd or 3rd term | NR | Egypt<br>NR<br>NR |
| Adams et al. (1974) | P: 100<br>NP: 100 | NR | P: 16–39 years<br>NP: 17–45 years | All women 3–9 months pregnant attending the hospital during 4 week | NR | United Kingdom<br>Hospital<br>NR |
| Arafat (1974a,b) | P: 477<br>NP: 233 | NR | NR | NR | NR | USA<br>Hospital<br>NR |
| Samant et al. (1976) | P: 120<br>NP: 40 | 40 (1st); 40 (2nd); 40 (3rd term) | NR | NR | NR | India or USA?<br>NR<br>NR |
| Jensen et al. (1981) | P: 54<br>NP: 50 | NR | NR | 18–40 years, no dental prophylaxis within 6 months, no previous periodontal therapy, no medication | No previous periodontal therapy | USA<br>University<br>Grants |
| Saleh et al. (1983) | P: 20<br>NP: 20 | 10 (12–14 weeks); 10 (28–32 weeks) | 20–30 years | Free from systemic disease | NR | Egypt<br>NR<br>NR |
| Zaki et al. (1984) | P: 30<br>NP: 10 | 10 (1st term); 10 (2nd term); 10 (3rd term) | 20–40 years | NR | NR | Egypt<br>Hospital<br>NR |
| Jonsson et al. (1988) | P: 30<br>NP: 30 | NR | P: 28.8 (SD = 4.6)<br>NP: 30.7 (SD = 4.4) | Not received dental treatment in the previous 6 months | Not received dental treatment in the previous 6 months | Canada<br>NR<br>NR |
| Miyazaki et al. (1991) | P: 2424<br>NP: 1565 | 28 (2 months); 437 (3 months); 1054 (4 months); 553 (5 months); 143 (6 months); 81 (7 months); 59 (8 months); 33 (9 months); 36 (10 months) | P: 22.75 (16–46)<br>NP: 27.78 (18–42) | NR | NR | Japan<br>Health Centers<br>NR |
| Malisa et al. (1993) | P: 100<br>PP: 100 | 50 (2nd term); 50 (3rd term) | 18–45 years | Women in the 2nd & 3rd terms | NR | Tanzania<br>Hospital<br>Public |
| Muramatsu & Takaesu (1994) | P: 19PP: 8<br>NP: 12 | NR | P: 28.5 (23–36)<br>PP: 27.1 (22–31)<br>NP: 22.9 (18–37) | All women with 2–10 months of pregnancy | NR | Japan<br>Hospital<br>NR |
| Nuamah & Annan (1998) | P: 100<br>NP: 100 | 50 (2nd term); 50 (3rd term) | 15–45 years | All women in the 2nd & 3rd terms of pregnancy | NR | Ghana<br>Hospital<br>NR |
| Taani et al. (2003) | P: 200<br>NP: 200 | 29 (1st term); 61 (2nd term); 110 (3rd term) | P: 30 (SD = 0.05)<br>NP: 32 (SD = 0.05) | At random from gynaecology clinics | NR | Jordan<br>Gynaecology clinics<br>NR |
| Diaz-Guzman &<br>Castellanos-Suarez (2004) | P: 93<br>NP: 5537 | NR | P: 30.03 (SD=6.6)<br>NP: 33.2 (SD=15.3) | All women >15 years requesting dental care | NR | Mexico<br>University<br>NR |

*Table 1b. (Continued)*

| First author (year) | Sample size | Distribution throughout pregnancy | Mean age | Inclusion criteria (Pregnant) | Periodontal status | Site, setting & funding |
|---|---|---|---|---|---|---|
| Yokoyama et al. (2008) | P: 22<br>NP: 15 | NR | P: 31.9 (SD = 4.4)<br>NP: 31.6 (SD = 5.4) | No periodontal treatment or antibiotics in the previous 3 months | No periodontal treatment in the previous 3 months | Japan<br>University<br>Grants |
| Acharya & Bhat (2009) | P: 259<br>NP: 237 | NR | P: 26 (SD = 5.5)<br>NP: 27.8 (SD = 6.9) | All women reporting for antenatal check-up during 3 months in a hospital with a lower middle-class population | NR | India<br>Hospital<br>NR |
| Rakchanok et al. (2010) | P: 94<br>NP: 103 | NR | 15–35 years or more | 3–6 months of pregnancy | NR | Thailand<br>Hospital<br>Private |

P, Pregnant; NP, Non-pregnant; PP, Post-partum.

*Table 2a.* Outcome variables and main conclusion from the cohort studies included in the systematic review

| First author (year) | Probe | Gingival inflammation/ bleeding | Plaque index | PPD/CAL | Other outcomes | Periodontal treatment | Author's conclusions |
|---|---|---|---|---|---|---|---|
| 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 months post-partum. |
| O'Neil (1979a,b) | 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 week of pregnancy) | Pre-existing 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 and 28 weeks of pregnancy and then decreased. Subgingival flora changed to a more anaerobic flora as pregnancy progressed. |
| Tilakaratne et al. (2000) | Brodontic | GI_L&S (full-mouth; 4 loc/tooth) | PI_S&L (full-mouth; 4 loc/tooth) | PPD: NRCAL: all teeth; 2 loc/tooth | NR | No | Pregnancy had an effect only on the gingiva and not on periodontal attachment levels. |
| Gursoy et al. (2008, 2009, 2010a,b) | 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) | 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. |

*Table 2a. (Continued)*

| First author (year) | Probe | Gingival inflammation/ bleeding | Plaque index | PPD/CAL | Other outcomes | Periodontal treatment | Author's conclusions |
|---|---|---|---|---|---|---|---|
| Akalin et al. (2009) | Michigan with Williams markings | GI_L&S (5 non-molar teeth; 4 loc/ tooth)BoP (Muhleman index; 5 non-molar teeth; 4 loc/teeth) | PI_S&L (5 non-molar teeth; 4 loc/tooth) | 5 non-molar 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. |
| 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. |
| 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 weeks 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 (Greene & Vermillion, 1964; 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 month of pregnancy, with amelioration shortly after delivery. |
| Kinnby et al. (1996) | NR | GI_L&S (mesial to 1st molars, 2 loc/teeth) | PI_S&L (mesial to 1st molars, 2 loc/teeth) | PPD (mesial to 1st molars, 2 loc/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. |
| Adriaens et al. (2009) | Florida | BOP (pres/abs; full-mouth; 6 loc/tooth) & in micro locations | NR | Full-mouth; 6 loc/tooth | Microbiological analyses | No | Decreased levels of 17/37 species were observed during pregnancy. Elevated *P. gingivalis* and *T. forythia* levels were associated with BOP at 12 weeks. |
| 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. |

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 Loe & Silness (1963); PI-S&L, Plaque index describe by Silness & Loe (1964); pres/abs, presence/absence; PAI-2, plasminogen activator inhibitor type 2.

*Table 2b*. Outcome variables and main conclusion from the cross-sectional studies included in the systematic review

| First author (year) | Probe | Gingival inflammation/bleeding | Plaque index | PPD/CAL | Other outcomes | Authors' conclusions |
|---|---|---|---|---|---|---|
| Ringsdorf et al. (1962) | NR | PMA | NR | NR/NR | NR | The average PMA index was essentially the same for pregnant and non-pregnant patients. |
| Loe & Silness (1963), Silness & Loe (1964) | NR | GI_L&S (6 teeth; 4 loc/tooth) | PI_S&L (6 teeth; 4 loc/tooth) | PPD: 6 teeth; 4 loc/tooth | PerI (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 | PerI (Rusell 1956) | Plaque, gingival and periodontal indexes increased during the whole pregnancy. |
| El-Ashiry et al. (1970, 1971) | NR | Own(0–3) | NR | NR/NR | Calculus: Greene & Vermillion, 1964 | 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,b) | NR | GI (PerI Rusell 1956) (full-mouth, 2 loc/tooth) | PI (Greene & Vermillion, 1964; 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 et al. (1976) | NR | GI_L&S | PI (Greene, 1967; NR; NR) | NR/NR | PerI (Rusell 1956) | Gingivitis significantly increased during pregnancy. |
| Jensen et al. (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 et al. (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 interproximal 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. |

*Table 2b. (Continued)*

| First author (year) | Probe | Gingival inflammation/bleeding | Plaque index | PPD/CAL | Other outcomes | Authors' conclusions |
|---|---|---|---|---|---|---|
| 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 & Takaesu (1994) | WHO probe | GI (pres/abs; full-mouth; 6 loc/tooth) BOP (pres/abs; all teeth; 6 loc/tooth) | Oral Hygiene Index (Greene & Vermillion 1964) | PPD: all teeth; 6 loc/tooth CAL: NR | Microbiological analyses (GCF) | From the 3–5 month of pregnancy, the number of sites with BoP increased concomitantly with increasing percentages of *P. intermedia.* |
| Nuamah & Annan (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. |
| Diaz-Guzman & Castellanos-Suarez (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 & Bhat (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 et al. 1962); DMFT, tooth decay, missing teeth, fillings; PerI, periodontal index; pres/abs: presence/absence.

*Table 3a.* Descriptive results from the main outcome, gingival inflammation from cohort studies included in the systematic review

| Reference | Index | Cohort | Pregnant women | | | | | | | | | | Non-pregnant | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1st term (13–14 weeks) | | | 2nd term (26–27 weeks) | | | 3rd term (39–40 weeks) | | | Post-partum | 1st visit (baseline) | | | Last visit | | |
| | | | n | mean | SD | n | Mean | SD | n | Mean | SD | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| Cohen et al. (1969, 1971) | 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,b) | 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 | | | |
| 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 |
| Gursoy et al. (2008, 2009, 2010a,b) | 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 | Periodontitis | 33 | 1.26 | 0.46 | | | | 33 | 1.84 | 0.56 | | | | 27 | 1.15 | 0.58 | | | |
| | | Gingivitis | 18 | 0.93 | 0.47 | | | | 18 | 1.39 | 0.57 | | | | | | | | | |
| | | Health | 21 | 0.1 | 0.1 | | | | 21 | 0.97 | 0.36 | | | | 25 | 0.08 | 0.09 | | | |
| Figuero et al. (2010), Carrillo-De-Albornoz et al. (2010, 2012) | 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 |
| Hugoson (1971) | GI-L&S | | 26 | 0.92 | 0.2 | 26 | 1.12 | NR | 26 | 1.34 | 0.31 | 26 | NR | NR | | | | | | |
| Cerna et al. (1990) | GI-L&S | | frequency distribution | | | | | | | | | | | | | | | | | |
| Kinnby et al. (1996) | GI-L&S | | | | | | | | | | | | | | | | | | | |
| 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% | | | | | | |

GI-L&S, Gingival index described by Loe & Silness (1963); BOP, Bleeding on probing; NR, not reported; SD, standard deviation.

*Population description*

*Cohort studies*. The population description of selected cohort studies is reported in Table 1a. The overall study population ranged from 14 to 903 women, including 1353 pregnant women and 197 non-pregnant women. The mean age for pregnant women varied from 24 to 31.5 years, but it was not reported in four studies (O'Neil 1979a,b, Kornman & Loesche 1980, Cerna et al. 1990, Akalin et al. 2009).

Baseline diagnosis of periodontal status was not established in seven studies (Cohen et al. 1969, 1971, Hugoson 1971, Cerna et al. 1990, Tilakaratne et al. 2000, Yalcin et al. 2002b, Adriaens et al. 2009, Buduneli et al. 2010). Two studies referred only to the absence of periodontal attachment loss or PPD > 3 mm (O'Neil 1979a,b, Kornman & Loesche 1980). One study included only periodontally healthy women (Gursoy et al. 2008, 2009, 2010a,b), one included only women without periodontitis (Carrillo-De-Albornoz et al. 2010, 2012, Figuero et al. 2010) and one included both women who were periodontally healthy and those with periodontal disease (Lieff et al. 2004). Only one study clearly identified subgroups according to periodontal status (chronic periodontitis, gingivitis and periodontally healthy) (Akalin et al. 2009). Follow-up ranged from 4 to 21 months. Some studies performed periodontal treatment [supragingival scaling or oral hygiene instructions (OHI)]; however, this aspect was not clearly explained in the articles (Table 2a).

*Cross-sectional studies*. Data from the cross-sectional studies are described in Table 1b. The whole study population ranged from 37 to 5537 women, including a total of 4824 pregnant women, 205 post-partum women and 8324 non-pregnant women. Eleven studies gave information about the exact term or month in which pregnant women were assessed, whereas eight studies did not provide this information and considered pregnant women as a whole group. The mean age of pregnant women varied between 18 and 45 years. However, five studies did not give information about this aspect. None of the included studies

*Table 3b.* Descriptive results from the main outcome, gingival inflammation from cross-sectional studies included in the systematic review

| Reference | Index | tooth | Pregnant women | | | | | | | | | | Non-pregnant | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1st term (13–14 weeks) | | | 2nd term (26–27 weeks) | | | 3rd term (39–40 weeks) | | | Post-partum | | | | | |
| | | | n | mean | SD | n | Mean | SD | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| Ringsdorf et al. (1962) | PMA | | frequency distribution | | | | | | | | | | | | | | |
| Loe & Silness (1963), Silness & Loe (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 et al. (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,b) | GI (Russell) | | 477 | 1.34 | NR | 477 | 0.77 | NR | 477 | 0.94 | NR | 477 | 0.72 | NR | 233 | 0.768 | NR |
| Samant et al. (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 et al. (1981) | GI-L&S | 16 | 54 | 1.2 | NR | | | | | | | | | | 27 | 0.48 | NR |
| | | 26 | 54 | 0.93 | NR | | | | | | | | | | 27 | 0.63 | NR |
| Saleh et al. (1983) | GI-L&S | | | | | 10 | 1.784 | 0.363 | | | | 10 | 1.829 | 0.28 | 20 | 1.438 | 0.23 |
| Zaki et al. 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 | 0.27 | | | | | | | | | | 30 | 0.78 | 0.19 |
| Miyazaki et al. (1991) | CPITN | | frequency distribution | | | | | | | | | | | | | | |
| Malisa et al. (1993) | CPITN | | frequency distribution | | | | | | | | | | | | | | |
| Muramatsu & Takaesu (1994) | GI dichotomous | | frequency distribution | | | | | | | | | | | | | | |
| Nuamah & Annan 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 |
| Diaz-Guzman & Castellanos-Suarez (2004) | SPI | | frequency distribution | | | | | | | | | | | | | | |
| Yokoyama et al. (2008) | BOP | | 22 | 69.5% | 29.2% | | | | | | | | | | 15 | 53.8% | 28.8% |
| Acharya & Bhat (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 et al. 1962); GI-L&S, Gingival index described by Loe & Silness (1963); MPBI, Modified periodontal bleeding index; CPITN, Community periodontal index of treatment needs; SPI, Simplified periodontal index; BOP, bleeding on probing; NR, not reported; SD, standard deviation.

considered the periodontal diagnosis at baseline, although two of them excluded women with previous dental/periodontal treatment (Jensen et al. 1981, Yokoyama et al. 2008).

#### Effect of exposure

*Main outcome: gingival inflammation*

Descriptive results from all included studies are given in Tables 2 and 3. In an overview, it was observed that most studies reported that gingival inflammation peaks in the third trimester (Loe & Silness 1963, Cohen et al. 1969, Hugoson 1971, Kornman & Loesche 1980, Zaki et al. 1984, Tilakaratne et al. 2000, Taani et al. 2003), although others have observed the greatest level of inflammation during the second trimester (Arafat 1974a, Samant et al. 1976, Muramatsu & Takaesu 1994, Gursoy et al. 2008, Carrillo-De-Albornoz et al. 2010, 2012, Figuero et al. 2010) of pregnancy. In addition, pregnant women in the third or second term reported higher GI or BOP when compared with post-partum-women. This difference was even greater when pregnant women were compared with non-pregnant women.

Of the 33 included studies, 24 assessed gingival inflammation in terms of GI (Tables 3a and 3b). Twelve of the 24 studies assessing gingival inflammation could not be included in the meta-analyses because they were missing data (El-Ashiry et al. 1970, 1971, Adams et al. 1974, O'Neil 1979a,b, Kornman & Loesche 1980, Cerna et al. 1990, Muramatsu & Takaesu 1994, Lieff et al. 2004); they only gave data on the prevalence of gingivitis (Kinnby et al. 1996, Diaz-Guzman & Castellanos-Suarez 2004); or they did not use the Loe & Silness (1963) GI (GI_L&S) and could not be grouped (Ringsdorf et al. 1962, Cohen et al. 1969, 1971, Arafat 1974b).

Differences were observed in the number of teeth assessed, including full-mouth, Ramfjord teeth or not reported (Tables 2a and 2b). Jensen et al. (1981) only reported data on two individual teeth, and these data were excluded from the meta-analyses.

*Table 4*. Meta-analyses of the comparisons (a) throughout pregnancy; (b) pregnancy *versus* post-partum; and (c) pregnant *versus* non-pregnant women for gingival index (Loe & Silness 1963), expressed as WMD with 95% confidence intervals (CI) and evaluation of heterogeneity

| Comparison | WMD | 95% IC | *p*-value | I-squared | $\chi^2$ *p*-value |
|---|---|---|---|---|---|
| *(a) Changes throughout pregnancy* | | | | | |
| 1st *versus* 2nd term | | | | | |
| Cohort ($n = 3$) | −0.140 | −0.224; −0.057 | **0.001** | 0.0% | 0.924 |
| Cross-sectional ($n = 4$) | −0.320 | −0.433; −0.206 | **0.000** | 87.8% | **0.000** |
| 2nd *versus* 3rd term | | | | | |
| Cohort ($n = 3$) | −0.074 | −0.160; 0.012 | 0.092 | 0.0% | 0.406 |
| Cross-sectional ($n = 4$) | 0.014 | −0.142; 0.171 | 0.857 | 95.9% | **0.000** |
| 1st *versus* 3rd term | | | | | |
| Cohort ($n = 7$) | −0.415 | −0.610; −0.220 | **0.000** | 89.4% | **0.000** |
| Cross-sectional ($n = 5$) | −0.242 | −0.460; −0.024 | **0.030** | 97.0% | **0.000** |
| *(b) Pregnancy versus post-partum* | | | | | |
| 1st term *versus* post-partum | | | | | |
| Cohort ($n = 2$) | 0.015 | −0.086; 0.116 | 0.767 | 0.0% | 0.865 |
| Cross-sectional ($n = 1$) | 0.170 | −0.035; 0.375 | 0.105 | – | – |
| 2nd term *versus* post-partum | | | | | |
| Cohort ($n = 2$) | 0.143 | 0.031; 0.255 | **0.012** | 0.0% | 0.936 |
| Cross-sectional ($n = 1$) | 0.180 | 0.026; 0.334 | **0.022** | – | – |
| 3rd term *versus* post-partum ($n = 3$) | | | | | |
| Cohort ($n = 2$) | 0.256 | 0.151; 0.360 | **0.000** | 13.5% | 0.282 |
| Cross-sectional ($n = 1$) | 0.040 | −0.156; 0.236 | 0.688 | – | – |
| *(c) Pregnant versus non-pregnant* | | | | | |
| 1st term *versus* non-pregnant | | | | | |
| Cohort ($n = 4$) | 0.537 | 0.176; 0.898 | **0.004** | 93.4% | **0.000** |
| Cross-sectional ($n = 4$) | 0.365 | −0.079; 0.808 | 0.107 | 99.5% | **0.000** |
| 2nd term *versus* non-pregnant | | | | | |
| Cohort ($n = 2$) | 0.385 | 0.264; 0.507 | **0.000** | 0.0% | 0.350 |
| Cross-sectional ($n = 3$) | 0.741 | 0.128; 1.354 | **0.018** | 99.8% | **0.000** |
| 3rd term *versus* non-pregnant | | | | | |
| Cohort ($n = 4$) | 0.643 | 0.426; 0.861 | **0.000** | 81.0% | **0.001** |
| Cross-sectional ($n = 4$) | 0.679 | 0.012; 1.347 | **0.046** | 99.9% | **0.000** |

Bold text indicates statistically significant differences. WMD, weighted mean differences.

Results from meta-analyses are presented in Table 4. Meta-analyses revealed a lower GI_L&S in pregnant women in the first term compared with those in their second or third term of pregnancy in both cohort ($p = 0.001$; $p = 0.000$) and cross-sectional ($p = 0.000$; $p = 0.030$) studies. However, a high and statistically significant heterogeneity was found in nearly all groups. Post-partum women had lower mean GI_L&S scores than women in their second [WMD = 0.143; 95% 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, when considering cohort studies. Non-pregnant women had lower mean GI_L&S values than women in their second or third term of pregnancy, in both cohort and cross-sectional studies.

No meta-analyses could be performed with BOP data, because the studies used different indices that could not be properly compared (Tables 3a and 3b).

### *Secondary outcomes*

*Plaque index*. Of the 33 included studies, 26 assessed PI. Some studies could not be included in the meta-analyses due to missing data (Katz et al. 1969, Hugoson 1971, Adams et al. 1974, O'Neil 1979a,b, Kornman & Loesche 1980, Cerna et al. 1990, Muramatsu & Takaesu 1994, Kinnby et al. 1996, Lieff et al. 2004, Gursoy et al. 2008, 2009, 2010a,b) or due to the use of non-standardized PI (Ringsdorf et al. 1962, Miyazaki et al. 1991, Malisa et al. 1993). Of the remaining 14 studies, eight used the PI described by Silness & Loe (1964) (PI_S&L) and were included in the meta-analyses, together with a study that used a modified index (Lieff et al. 2004). Other investigations used the PI described by Greene & Vermillion (1964) (Arafat 1974a,b, Samant et al. 1976), a dichotomous index (Jonsson et al. 1988, Gursoy et al. 2008, 2009, 2010a,b, Buduneli et al. 2010) or a self-proposed index (Cohen et al. 1969, 1971).

The number of teeth used to determine the index varied, including full-mouth, Ramfjord teeth or not reported (Tables 2a and 2b). All studies using the PI_S&L assessed it in four sites per tooth, except Lieff et al. (2004), which only assessed the buccal surfaces.

Results from meta-analyses are presented in Table 5. The comparisons throughout pregnancy revealed non-significant differences in PI_S&L when considering cohort studies ($p > 0.05$), and significant differences, although of low magnitude (0.109–0.048), when considering cross-sectional studies. No significant differences were found when comparing pregnant and post-partum women.

*Probing pocket depth*. Eighteen studies assessed PPD, but some could not be included in the meta-analyses because they had missing data (Hugoson 1971, Gursoy et al. 2008, 2009, 2010a,b); only reported data as frequencies (Kinnby et al. 1996, Yokoyama et al. 2008, Adriaens et al. 2009, Buduneli et al. 2010) or as graphics (Muramatsu & Takaesu 1994); or used indices that could not be pooled (Ringsdorf et al. 1962, Miyazaki et al. 1991, Malisa et al. 1993, Nuamah & Annan 1998). Data from eight studies were pooled in the meta-analyses, with one study (Akalin et al. 2009) providing three sets of data according to periodontal status (chronic periodontitis, gingivitis or health).

The number of teeth assessed varied among studies, including full-mouth, Ramfjord teeth or not reported (Tables 2a and 2b). Most studies evaluated six sites per tooth, whereas Hugoson (1971), Jonsson et al. (1988), Yalcin et al. (2002b), Loe & Silness 1963), assessed four sites. Jensen et al. (1981) only reported data on two teeth (16, 26), and these data were excluded from the meta-analyses.

Results from meta-analyses are presented in Table 6. Significantly higher mean PPD values were observed in the

*Table 5.* Meta-analyses of the comparisons (a) throughout pregnancy; (b) pregnancy *versus* post-partum; and (c) pregnant *versus* non-pregnant women for plaque index (Silness & Loe 1964), expressed as WMD with 95% confidence intervals (CI) and evaluation of heterogeneity

| Comparison | WMD | 95% IC | *p*-value | I-squared | $\chi^2$ *p*-value |
|---|---|---|---|---|---|
| *(a) Changes throughout pregnancy* | | | | | |
| 1st *versus* 2nd term | | | | | |
| Cohort ($n = 2$) | 0.001 | −0.124; 0.125 | 0.989 | 15.5% | 0.277 |
| Cross-sectional ($n = 3$) | −0.048 | −0.085; −0.012 | **0.010** | 0.0% | 0.491 |
| 2nd *versus* 3rd term | | | | | |
| Cohort ($n = 2$) | −0.027 | −0.138; 0.084 | 0.636 | 0.0% | 0.934 |
| Cross-sectional ($n = 3$) | −0.067 | −0.085; −0.050 | **0.000** | 42.7% | 0.175 |
| 1st *versus* 3rd term | | | | | |
| Cohort ($n = 7$) | 0.004 | −0.043; 0.052 | 0.774 | 28.8% | 0.208 |
| Cross-sectional ($n = 4$) | −0.109 | −0.144; −0.073 | **0.000** | 0.0% | 0.658 |
| *(b) Pregnancy versus post-partum* | | | | | |
| 1st term *versus* post-partum | | | | | |
| Cohort ($n = 3$) | −0.003 | −0.078; 0.07 | 0.931 | 0.0% | 0.893 |
| Cross-sectional ($n = 1$) | −0.150 | −0.276; −0.024 | **0.020** | – | – |
| 2nd term *versus* post-partum ($n = 2$) | | | | | |
| Cohort ($n = 1$) | −0.070 | −0.217; 0.077 | 0.350 | – | – |
| Cross-sectional ($n = 1$) | −0.040 | −0.158; 0.078 | 0.508 | – | – |
| 3rd term *versus* post-partum ($n = 4$) | | | | | |
| Cohort ($n = 3$) | −0.144 | −0.415; 0.127 | 0.297 | 0.0% | 0.658 |
| Cross-sectional ($n = 1$) | −0.199 | −0.765; 0.366 | 0.490 | – | – |
| *(c) Pregnant versus non-pregnant* | | | | | |
| 1st term *versus* non-pregnant | | | | | |
| Cohort ($n = 4$) | 0.060 | 0.006; 0.114 | **0.030** | 0.0% | 0.397 |
| Cross-sectional ($n = 2$) | −0.151 | −0.356; 0.054 | 0.150 | 0.0% | 0.358 |
| 2nd term *versus* non-pregnant ($n = 2$) | | | | | |
| Cohort ($n = 1$) | 0.120 | −0.049; 0.289 | 0.163 | – | – |
| Cross-sectional ($n = 1$) | 0.016 | −0.243; 0.275 | 0.904 | – | – |
| 3rd term *versus* non-pregnant | | | | | |
| Cohort ($n = 4$) | 0.073 | 0.023; 0.122 | **0.004** | 0.0% | 0.454 |
| Cross-sectional ($n = 2$) | −0.001 | −0.212; 0.210 | 0.993 | 0.0% | 0.706 |

Bold text indicates statistically significant differences. WMD, weighted mean differences.

third term of pregnancy as compared with non-pregnant women (WMD = 0.699 mm; 95% CI 0.473; 0.924]; $p < 0.001$) in cohort studies, although a high heterogeneity between them was observed.

*Clinical attachment level*. Only three comparisons were available for meta-analyses of CAL. Results are reported in Table 6. Only two cohort studies could be included in meta-analyses. Statistically significant differences were found when comparing first and second terms of pregnancy, and between the third term of pregnancy and non-pregnant women ($p < 0.001$).

### *Other study outcomes*

Microbiological, immunological and patient-centred outcomes were reported in a few of the included studies (Tables 2a and 2b). Five cohort and four cross-sectional studies reported data on microbiological outcomes on gingival crevicular fluid or in saliva. Immunological data was reported in six cohort studies, including levels or concentrations of interleukin-1$\beta$ (IL-1$\beta$), IL-6, prostaglandin $E_2$, tumour necrosis factor-$\alpha$ (Carrillo-De-Albornoz et al. 2010, 2012, Figuero et al. 2010), tissue-type plasminogen activator inhibitor-2 (Kinnby et al. 1996, Buduneli et al. 2010), total antioxidant capacity and superoxide dismutase activity (Akalin et al. 2009). Only two studies reported information on patient-centred outcomes (Cerna et al. 1990, Acharya & Bhat 2009). Due to the scarcity of data and discrepancies among the selected outcomes, no meta-analyses with any of these outcomes could be performed.

### Quality assessment and publication bias

The evaluation of risk of bias in individual studies is given in Appendix 1 and 2. All included cohort studies, except Buduneli et al. (2010), Lieff et al. (2004), Kinnby et al. (1996) and Yalcin et al. (2002b), were considered as having high quality. In the case of cross-sectional studies, only Taani et al. (2003) and Acharya & Bhat (2009) were given a score higher than 5.

No publication bias was detected for changes in GI either throughout pregnancy or when comparing pregnant to post-partum or non-pregnant women (data not shown).

## Discussion

This systematic review was designed with the main outcome of obtaining an overall quantitative estimate of the association between pregnancy and gingival inflammation. Fourteen prospective cohort studies and 19 cross-sectional studies assessing gingival inflammation either by GI or by BOP index were included. They revealed: (1) an increase in gingival inflammation throughout pregnancy with a peak in the second or third terms of pregnancy, depending on the publication or when comparing pregnant women to post-partum or non-pregnant women; (2) PPD and PI did not undergo great variation throughout pregnancy or post-partum, although tended to be lower in non-pregnant women than in pregnant or post-partum 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 aspect.

Meta-analyses on the primary outcome were conducted in only a few studies and revealed: (1) a lower GI_L&S in pregnant women in the first term compared with those in their second or third term of pregnancy in both cohort (WMD 0.140–0.415) and cross-sectional (WMD 0.242–0.320) studies; (2) reduced GI_L&S scores in post-partum women when compared with women in their second (WMD = 0.143; 95% 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_L&S when comparing non-pregnant women with women in any term of pregnancy in both cohort

*Table 6*. Meta-analyses of the available comparisons for probing pocket depth (PPD) and clinical attachment level (CAL), expressed as WMD with 95% confidence intervals (CI) and evaluation of heterogeneity

| Comparisons | WMD | 95% IC | *p*-value | I-squared | $\chi^2$ *p*-value |
|---|---|---|---|---|---|
| *(a) PPD: Changes throughout pregnancy* | | | | | |
| 1st *versus* 2nd term | | | | | |
| Cohort ($n = 1$) | −0.120 | −0.193; −0.047 | **0.001** | – | – |
| Cross-sectional ($n = 2$) | −0.248 | −0.664; 0.168 | 0.243 | 84.0% | **0.012** |
| 2nd *versus* 3rd term | | | | | |
| Cohort ($n = 1$) | −0.060 | −0.136; 0.016 | 0.123 | – | – |
| Cross-sectional ($n = 2$) | −0.087 | −0.115; −0.059 | **0.002** | 13.3% | 0.283 |
| 1st *versus* 3rd term | | | | | |
| Cohort ($n = 5$) | −0.453 | −0.781; −0.126 | **0.007** | 97.6% | **0.000** |
| Cross-sectional ($n = 2$) | −0.293 | −0.799; 0.212 | 0.256 | 86.9% | **0.006** |
| *(b) PPD: Pregnant versus non-pregnant* | | | | | |
| 1st term *versus* non-pregnant | | | | | |
| Cohort ($n = 2$) | −0.007 | −0.203; 0.188 | 0.942 | 85.0% | **0.01** |
| Cross-sectional ($n = 1$) | 0.940 | 0.899; 0.981 | **0.000** | – | – |
| 3rd term *versus* non-pregnant | | | | | |
| Cohort ($n = 2$) | 0.699 | 0.473; 0.924 | **0.000** | 85.5% | **0.009** |
| Cross-sectional ($n = 1$) | 1.460 | 1.445; 1.475 | **0.000** | – | – |
| *(c) CAL* | | | | | |
| 1st *versus* 3rd term | | | | | |
| Cohort ($n = 2$) | −0.609 | −0.936; −0.283 | **0.000** | 93.6% | **0.000** |
| Cross-sectional ($n = 1$) | 0.170 | 0.142; 0.198 | **0.000** | – | – |
| 1st term *versus* non-pregnant | | | | | |
| Cohort ($n = 2$) | −0.031 | −0.413; 0.351 | 0.875 | 93.4% | **0.000** |
| Cross-sectional ($n = 1$) | 0.220 | 0.194; 0.246 | **0.000** | – | – |
| 3rd term *versus* non-pregnant | | | | | |
| Cohort ($n = 2$) | 0.674 | 0.574; 0.773 | **0.000** | 0.0% | 0.697 |
| Cross-sectional ($n = 1$) | 0.050 | 0.037; 0.063 | **0.000** | – | – |

Bold text indicates statistically significant differences. WMD, weighted mean differences.

and cross-sectional studies (WMD 0.385–0.741). Regarding secondary outcomes, no significant differences could be found in the PI_S&L among pregnancy trimesters (WMD 0.001–0.027) and between the pregnancy and post-partum groups (WMD 0.003–0.144) in cohort studies. Small but significant changes in PI_S&L were observed among pregnancy trimesters in the case of cross-sectional studies (WMD 0.048–0.109). In the case of PPD or 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.

To our knowledge, this is the first systematic review, including meta-analyses, that has addressed the issue of increased gingival inflammation during pregnancy. Pregnancy gingivitis is a commonly recognized entity that is included in the most recent classification of periodontal diseases from the American Association of Periodontology. It is defined as "a gingival disease induced by plaque and modified by systemic factors" (Armitage 1999). However, until now, it has not been clearly tested by numerical data. Several narrative reviews of this topic have been published, all of which concluded that hormones might influence the development of gingival inflammation, but none of which considered the magnitude of the effect or the factors influencing them (Sooriyamoorthy & Gower 1989, Zachariasen 1993, Amar & Chung 1994, Laine 2002, Mascarenhas et al. 2003, Mealey & Moritz 2003).

Previous reviews have proposed various hypotheses for the factors involved in the pathogenesis of pregnancy gingival inflammation, such as depression of the maternal immune system, increased vascularity, cellular changes and changes in the oral biofilms. Although these potential hypotheses were assessed as secondary objectives in this study, no definitive results could be drawn. The absence of adequate information precluded us from performing meta-analyses on the data. Therefore, caution should be taken when proposing these factors as responsible for pregnancy gingivitis, because there is currently an absence of adequate data to support them.

Probably the most important limitation is that not all included studies could be grouped in the meta-analyses, because studies were missing data, presented data only in graphics or used different indices. An effort was made to contact the authors of the studies, but most of the articles were relatively old publications, and the information was not available. Missing data could neither be imputed, as some of the additional statistics required to do it also remained unavailable. This led to a small number of studies included in each comparison, determining that all conclusions derived from the quantitative analysis should be interpreted with caution, although, considering that they represent the "best available" evidence published regarding pregnant gingivitis. This reduced sample size in the conducted meta-analyses might have an impact also on the results from Egger′s test, which revealed no publication bias, as the test might have been underpowered due to sample size.

Another limitation of this systematic review was the inclusion of different study designs, with cross-sectional and cohort studies involving (a) pregnant and non-pregnant groups or (b) only pregnant women, and cross-sectional studies comparing (c) different terms of pregnancy, (d) pregnancy *versus* post-partum or (e) pregnant *versus* non-pregnant women. To overcome this problem, two approaches were adopted: (1) data were analysed according to the different aforementioned comparisons and were presented in the same way in tables; and (2) meta-analyses were performed to differentiate between cohort and cross-sectional studies. However, high levels of heterogeneity were found among studies in the GI_L&S meta-analyses. To further explore this high heterogeneity found, it would have been desirable to compare results from studies at low risk of bias with those at high/unclear risk of bias. The evaluation

of quality (modification of NOS) revealed that nearly all of the cross-sectional studies had low quality and nearly all cohort studies had high quality. Therefore, the scarce number of studies precludes this comparison.

Another important issue to consider regarding the study design is the lack of a periodontal criterion. As a result, patients with different periodontal statuses were grouped together. In the most recent articles, this problem was solved by excluding patients with periodontitis (Carrillo-De-Albornoz et al. 2010, 2012, Figuero et al. 2010), including only periodontally healthy patients (Gursoy et al. 2008, 2009, 2010a,b), or selecting groups of patients with different periodontal diagnoses (Akalin et al. 2009). This miscellaneous status could have lead to an overestimation of the effects of pregnancy on gingival inflammation, because hormones are well-known irritants over a previously inflamed gingiva (Guncu et al. 2005). Therefore, the exact role of pregnancy on a healthy gingiva remains unknown. Furthermore, periodontal treatment was included in some of the cohort studies during follow-up (Table 1a). However, the treatment used and the timing of treatment varied widely. For example, patients were treated by OHI (Carrillo-De-Albornoz et al. 2010, 2012, Figuero et al. 2010), with supragingival scaling at each term (Akalin et al. 2009), at baseline (Gursoy et al. 2008, 2009, 2010a,b) or after delivery (Hugoson 1971). In some cases, treatment was only performed in patients with gingival inflammation without a clearly defined criterion (O'Neil 1979a,b). This variability might have hampered the determination of the true magnitude of the effect of pregnancy on gingival inflammation.

The results of this systematic review confirm that gingival inflammation is significantly increased throughout pregnancy and when comparing pregnant *versus* postpartum or non-pregnant women, without a concomitant increase in plaque levels. However, this information should be considered with caution, due to the small number of studies included in the meta-analyses, the low quality of the included studies, differences in study design, absence of a periodontal diagnosis at baseline and performance of periodontal treatment in some cases. No conclusions could be drawn regarding secondary outcomes such as microbiological, immunological and patient-centred data, because no meta-analyses were possible for these factors. Future studies with higher quality should be designed to answer these questions.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** Risk of bias for cohort studies based on Newcastle-Ottawa scale. Total score calculated by the sum of the stars.

**Appendix S2.** Risk of bias for cross-sectional studies based on Newcastle-Ottawa scale. Total score calculated by the sum of the stars.

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**Clinical Relevance**

*Scientific rationale for the study*: Studies have found controversial results for the gingival inflammatory pattern during pregnancy, with varying severities and timings of peak inflammation.

*Principal findings:* A meta-analysis comparing pregnant *versus* post-partum and non-pregnant women revealed a significant increase in gingival inflammation throughout pregnancy, with a peak in the third trimester.

*Practical implications:* Pregnancy gingivitis is an important oral health issue facing women; therefore, special attention should be given in terms of prevention in dental practice.