Biological mechanisms between periodontal diseases and pregnancy complications

A systematic review and meta-analysis of epidemiological association between adverse pregnancy outcomes and periodontitis: an update of the review by Ide & Papapanou (2013)

Report co-authored by Dr Morena Petrini, Dr Mervi Gürsoy, Dr Stefano Gennai, Prof Filippo Graziani

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Biological mechanisms between periodontal diseases and pregnancy complications: a systematic review and meta-analysis of epidemiological association between adverse pregnancy outcomes and periodontitis - an update of the review by Ide & Papapanou (2013)

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Running title: Effect of periodontal disease on adverse pregnancy outcomes

Key words: Periodontal disease, pregnancy, epidemiology

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Clinical Relevance
Scientific rationale for the study: To test the epidemiological association between maternal periodontitis and adverse pregnancy outcomes (APOs).

Principal findings: The great heterogeneity of the included literature does not allow the drawing of robust and definitive conclusions. There might be some association between APOs and periodontitis as indicated by the meta-analysis performed.

Practical implications: Despite the need for further structured research, it may be stated cautiously that it would be advisable to diagnose and treat maternal periodontitis, as a possible effect on APOs cannot be excluded.
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Abstract

Aim: To update the available evidence on the impact of periodontal disease on adverse pregnancy outcomes (APOs).

Material and methods: Observational studies (cross-sectional, case-control, and cohort design) on the effect of periodontitis on pregnancy outcome, published after May 2012, were identified through electronic databases and hand-searched journals. Findings were summarised by evidence tables, using the PRISMA statement. Quality of the included studies was evaluated through the Newcastle-Ottawa scale. Meta-analysis was performed with a random approach when feasible.

Results: Results were divided for the following pregnancy outcomes: low birth weight (LBW), preterm birth (PTB), preterm low birth weight (PTLBW), and pre-eclampsia (PE). A total of 35 studies have been included in the update, although some of these have been included in more than one category. The overall synthesis, drawn from 108 studies, indicated that there might be some association between APOs and periodontitis. However, the strength of this association is extremely limited and hampered by the wide heterogeneity in terms of methods, design, and result interpretation. In fact, a nearly equal number of manuscripts that did not indicate association was found in each of the sub-sets analysed.

Conclusions: There is still no clear evidence to support the association between maternal periodontal disease and adverse pregnancy outcomes.
Introduction

Adverse pregnancy outcomes (APOs) are serious events that every year cause the death or disability of many newly born infants worldwide (Sanz & Kornman, 2013). The most common adverse pregnancy outcomes are represented by low birth weight (LBW), preterm birth (PTB), and pre-eclampsia (PE). LBW is defined as weight <2.5 kg and is categorised as “very low” if new-born weight is <1.5 kg (World Health Organization & Brämer, 1992). PTB or very PTB, representing respectively birth at <37 and <32 weeks of gestation, is the second most common cause of death in children less than years old worldwide and is responsible every year for the death of 1.1 million babies and disabilities in many survivors (World Health Organization & Brämer, 1992; Sanz & Kornman, 2013). PE is defined as maternal hypertension and proteinuria after the 20th gestational week and it occurs in about 10% of women (World Health Organization & Brämer, 1992; Duley, 2009; World Health Organization, 2011; Ide & Papapanou, 2013).

Adverse pregnancy outcomes represent an important health issue which affects not only the infant but also the mother; indeed more than half a million women die each year from related causes (Duley, 2009). About 10-15% of maternal death during pregnancy is associated with PE and eclampsia, which could affect liver, kidneys, brain, and the clotting system. PE may determine a higher risk of PTB and LBW for the newly born infant (Duley, 2009).

There is evidence that adverse pregnancy outcomes are correlated with intra-uterine infections and increased local and systemic inflammatory markers, and a double relationship with periodontitis has been hypothesised (Armitage, 2013; Sanz & Kornman, 2013). Periodontitis is also a chronic inflammation, caused by the persistence of bacterial infection, and for this reason is a potential source of circulating inflammatory biomarkers (Slade et al., 2000; Noack et al., 2001; Hingorani & D’Aiuto, 2008) which may also be related to possible APOs (Gürsoy & Graziani, 2017).

However, clear evidence in literature about the relationship between maternal periodontitis and APOs is lacking, as contradictory findings are reported (Sanz & Kornman, 2013; Ide & Papapanou, 2013). The broad heterogeneity found may possibly affect an overall synthesis of the data. Indeed, it has been shown that APOs are particularly associated with certain risk factors – such as environmental, behavioural, psychosocial, medical, biological, and genetics – that, in selected population, could be combined, thereby causing an increased risk.

Thus, the objective of this systematic review was to assess and update the available evidence relating APOs with periodontitis.

Materials and methods

Protocol development and eligibility criteria

The structure of the study was designed as an update of the review on the same topic published in 2013 by Ide & Papapanou (Ide & Papapanou, 2013).

A detailed protocol was designed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (Moher et al., 2009; Liberati et al., 2009). The systematic review was designed to answer the following focused questions:

1. Do pregnant women who have poorer periodontal health have greater risk for low birth weight?
2. Do pregnant women who have poorer periodontal health have greater risk for preterm birth?
3. Do pregnant women who have poorer periodontal health have greater risk for preterm low birth weight?
4. Do pregnant women who have poorer periodontal health have greater risk for pre-eclampsia?

**Information sources and search**

We conducted a search on electronic databases (Medline, Embase, Web of Science, and Cochrane Central), using the same MeSH terms, key words, and free terms, from June 2012 to April 2017. The words searched were:

((Periodontitis) or (periodontal disease) or (gingivitis)) and ((adverse pregnancy outcome) or (birth weight) or (preterm) or (preterm) or (pre-eclampsia) or (pre-eclampsia) or (stillbirth) or (miscarriage)). Filters used were: Humans. Hand searching of relevant periodontal journals was also conducted (Journal of Periodontology, Journal of Clinical Periodontology, Journal of Periodontal Research) and further publications were searched by using bibliographies and reference lists, and by reviewing lists of later papers which had cited the publication of interest where these papers were available online.

The presence of duplicates was assessed through Mendeley software.

**Study selection and data collection**

Eligibility assessment was performed through title-and-abstract analysis and full-text analysis. Titles and abstracts of the search results were initially screened by the reviewer Morena Petrini for possible inclusion in the review. Each round of calibration consisted of a duplicate, independent validity assessment of 20 titles and abstracts from the search. After two rounds of calibration, a consistent level of agreement was found.

In order to avoid excluding potentially relevant articles, abstracts providing unclear results were included in the full-text analysis. The full texts of all studies of possible relevance were then obtained for independent assessment against the stated inclusion criteria. Any disagreement was resolved by discussion among the reviewers.

**Eligibility criteria**

Studies to be included had to be non-intervention, observational studies such as cohort, case-control or cross-sectional in design evaluating periodontal status (measures of inflammation, signs of disease such as pocketing and attachment level excluding tooth loss/edentulism) of the included subjects, and one parameter related to pregnancy-related complications.

Excluded articles were classified according to a hierarchical scale according to the main reasons for exclusion: N1, not original study (review, guidelines, comment); N2, original, but not epidemiologic study; N3, original, but interventional study; N4, original study, but not on effect of periodontal disease on adverse pregnancy outcome; N5, other reasons (Borgnakke et al., 2013).

Manuscripts not to be excluded were categorised into the following groups: E1, low birth weight (LBW); E2, preterm birth (PTB); E3, preterm low birth weight (PTLBW); E4, pre-eclampsia.

Data of the included articles were extrapolated through an ad hoc extraction sheet.
**Data items**

Risk of bias across studies
Heterogeneity among the studies was tested when feasible and evaluated through an I2 test. Data were considered heterogeneous for I2 value higher than 40%.

Risk of bias in individual studies
The quality of each cohort and case-control study according to NOS for Assessing the Quality of Non-randomised Studies (Wells et al., 2011). Evaluation of cross-sectional studies was made according to scale suggested by Borgnakke and co-workers (Borgnakke et al., 2013). Using these forms, we rated each report at both the study and outcome levels.

Summary measures and synthesis of the results
Outcomes considered were odds ratios (OR), hazard ratios (HR), and hazard-rate ratios (HRR), risk ratios, rate ratios, and relative risks (RR). Results were presented as the manuscript by Needleman and co-workers at a recent EFP workshop, highlighting results of the previous evidence, summary of the new evidence, and overall synthesis (Needleman et al., 2015). Data were collected in evidence tables and results of the meta-analysis were summarised with Forest plots.

Additional analysis
Meta-analysis was performed when outcome data (adjusted OR of developing APOs) were homogenous and available from at least two studies.

The patient was the unit of the analysis. Analyses were performed with OpenMeta[Analyst] (http://www.cebm.brown.edu/open_meta/open_meta/open_meta). Hazard ratios (HR) were expressed as mean effect size and 95% CI for dichotomous data using a random model and were calculated with Meta-Essentials: Workbooks for meta-analysis (Version 1.1) (http://www.erim.eur.nl/research-support/meta-essentials/downloads/).

**Results**

**Study selection**

A total of 488 studies were identified for inclusion in the review, all selected electronically as hand-searching did not identify further articles for the full-text analysis (Figure 1). Screening of duplicates, titles, and abstracts led to the rejection of 442 articles and the full text of the remaining 46 articles was obtained. After full-text analysis and the exclusion of a further 10 articles, the remaining 35 articles were analysed for methodological quality and availability of data for systematic review.

Articles included in the qualitative synthesis (taking into account that some studies have been included in more than one category):

E1. Low birth weight (LBW)=15
   - Prospective (COH)=5
   - Case-control (CC)=6
   - Cross-sectional (CS)=4

E2. Preterm birth (PTB)=18
   - Prospective (COH)=6
   - Case-control (CC)=7
   - Cross-sectional (CS)=5
E3. Preterm low birth weight (PTLBW)=6
- Prospective (COH)=1
- Case-control (CC)=4
- Cross-sectional (CS)=1

E4. Pre-eclampsia (PE)=8
- Prospective (COH)=3
- Case-control (CC)=4
- Cross-sectional (CS)=1

Studies investigating maternal periodontitis and low birth weight (LBW), E1:

Case-control studies of maternal periodontitis and low birth weight

Summary of previous evidence

Previous evidence was based on five papers and 1,744 participants (Moore et al., 2005; Gomes-Filho et al., 2006; Bassani et al., 2007, Cruz et al., 2009; Vettore et al., 2008a,b), four studies of Brazilian populations and one in the UK. Three of these studies found no statistically significant differences among cases (LBW) and controls, while Vettore et al. (2008a,b), found slightly deeper
periodontal pocket depth (PPD) in controls but no differences for other parameters. The only paper that found a significant OR for LBW and maternal periodontitis was Cruz et al. (2009), which analysed a subpopulation of Bassani et al. (2007), reporting a significant odds ratio (OR=1.74, 95% CI: 1.19,2.54) for LBW in the presence of periodontitis. Meta-analysis of such studies reported periodontitis as a continuous variable (OR = 1.35, 95% CI: 1.08, 1.68) of being associated with LBW.

New evidence

New evidence is based on six manuscripts (Martinez de Tejada et al., 2012; Abati et al., 2013; Haerian-Ardakani et al., 2013; Santa Cruz et al., 2013; Mathew et al., 2014; Jacob & Nath, 2014; Reza Karimi et al., 2015; Gomes-Filho et al., 2016) comprising a total of 1,974 participants (Table 1).

All studies performed full-mouth periodontal examination although the periodontitis definition varied significantly among the studies. With the exception of the work of Abati et al. (2013) – which examined 750 women in Italy three days after delivery and found no statistically significant differences between cases and controls in terms of periodontal status – all other studies found significant correlation between LBW and maternal periodontitis. Abati et al. (2013) reported OR of having APOs, irrespective of the type, showing no correlation after adjustment for confounders.

Two Iranian studies (Reza Karimi et al., 2015; Haerian-Ardakani et al., 2013) conducted on 352 women three days after delivery, concluded that cases were more frequently afflicted by periodontal diseases. In particular, Reza Karimi et al. (2015) concluded that the frequency of LBW in primary pregnancies was 2.3 times greater in cases of maternal periodontitis. Adjusted ORs were presented only in three manuscripts (Jacob & Nath, 2014; Mathew et al., 2014; Gomes Filho et al., 2016), all indicating a higher risk of LBW infants if the mother is affected by periodontitis.

In a Brazilian study conducted by Gomes-Filho et al. (2016) on 372 women seen postpartum, the frequency of LBW in cases of maternal periodontitis was 4.5 times greater than that observed among mothers without periodontitis (OR adjusted=6.02, 95% CI: 2.47, 15.17). Mathew et al. (2014) conducted a study in India with more than 160 women who delivered during the study, finding a significant association between periodontal disease (PD) and LBW. In particular, cases were three times more likely to have PPD≥4mm (p=0.017) and twice as likely to have clinical attachment loss (CAL)≥2mm (p=0.007) when compared to controls. The presence of periodontitis determines a higher risk of LBW (OR = 5.11, 95% CI: 1.00, 26.00) (p=0.04). Jacob & Nath (2014) examined the periodontal status of 340 women postpartum in India, defining periodontal disease according to WHO criteria. PD was considered a significant risk factor for LBW (adjusted OR = 2.85 , 95% CI: 1.62, 5.5).

Evidence synthesis

The total evidence is based on 11 case-control studies, spread across the globe, and 3,718 participants: three of these found no differences between cases and controls (1,946 participants), while eight studies found periodontitis to be significantly associated with LBW (1,722 participants). Overall, data are conflicting and highly heterogeneous in terms of methods, populations, and definitions.

Meta-analysis was performed on a total of five studies (Figure 2) reporting adjusted OR (Bassani et al., 2007; Mathew et al., 2014; Jacob & Nath, 2014; Gomes-Filho et al., 2016) (pooled OR = 1.03, 95% CI: 0.27, 1.79). Results were statistically significant (p<0.01). Nonetheless, the value of I²=0% further confirms the wide heterogeneity.
Table 1. Selected case control studies of maternal periodontitis and low birth weight

<table>
<thead>
<tr>
<th>Author</th>
<th>Year, Location</th>
<th>Characteristics of population</th>
<th>Sample size</th>
<th>Periodontitis definition</th>
<th>Categorical or continuous analysis of perio-data</th>
<th>Type of recording</th>
<th>Newcastle Ottawa quality rating</th>
<th>Finding, OR</th>
</tr>
</thead>
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<tr>
<td>Reza Karimi</td>
<td>2015, Iran</td>
<td>Unspecified</td>
<td>264</td>
<td>CPITN (at least 1 sextant with at least 1 site with PPD &gt;4)</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection** Comparability* Exposure**</td>
<td>Yes, the frequency of low birth weight in newborns of women affected with periodontal diseases were 2.3 times higher in primigravida and 6 times higher in non-primeigravida</td>
</tr>
<tr>
<td>Gomes-Filho</td>
<td>2016, Brazil</td>
<td>Women were seen postpartum. The mean ± SD age of the participants was 23.86 ± 6.6 years</td>
<td>372</td>
<td>≥ 4 teeth with ≥ 1 site with PD&gt;4 mm, attachment loss &gt; 3mm, and BOP at the same site</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparability* Exposure***</td>
<td>Yes, there was a statistically significant association between periodontitis and LBW (ORUnadjusted=4.51, 95% CI=2.63 to 7.76) (ORAdjusted=6.02,95% CI=2.47 to 15.17)</td>
</tr>
<tr>
<td>Mathew</td>
<td>2014, India</td>
<td>Women between 18 and 35 years of age with at least 18 teeth, who delivered singleton, live infants during study period. The mean age of the cases was 23.50 years (SD 3.37) and controls was 23.30 years (SD 3.46)</td>
<td>160</td>
<td>PPD ≥ 4mm and CAL ≥ 2mm at a given site</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparability* Exposure***</td>
<td>Yes, there was a statistically significant association between mothers with PD were nearly 5 times likely to deliver a LBW infant in comparison to mothers without PD (OR 5.1, CI 1-26)</td>
</tr>
<tr>
<td>Jacob &amp; Nath</td>
<td>2014, India</td>
<td>Women were seen postpartum</td>
<td>340</td>
<td>PPD of &gt;4 mm in at least one site</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection *** Comparability* Exposure***</td>
<td>Yes, periodontal disease is a significantly associated independent risk factor for LBW, with an adjusted odds ratio [OR] of 2.85 (95% CI), 1.62-5.5</td>
</tr>
<tr>
<td>Abati</td>
<td>2013, Italy</td>
<td>Women were seen postpartum with three days of delivery</td>
<td>750</td>
<td>“healthy”: all sites with CAL &lt; 4 mm. “moderate”: at least one site with CAL from 4 to 6 mm. “severe”: at least ≥1 site with CAL ≥ 6 mm</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection *** Comparability* Exposure***</td>
<td>No, there was no significant association after adjusting for confounding factors. OR are not reported for single pregnancy outcome</td>
</tr>
<tr>
<td>Haerian-Ardakani</td>
<td>2013, Iran</td>
<td>Women were seen up to three days after delivery</td>
<td>88</td>
<td>CPITN (at least 1 sextant with at least 1 site with PPD &gt;4)</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparability* Exposure***</td>
<td>Yes, there was a statistically significant association (p=0.0006)</td>
</tr>
</tbody>
</table>

Figure 2. Meta-analysis plot of case-control studies of low birth weight, reporting periodontitis as a categorical variable (odds ratio).
Cross-sectional studies of maternal periodontitis and low birth weight:

Summary of previous evidence

Previous evidence was based on three studies (Lunardelli & Peres, 2005; Toygar et al., 2007; Siqueira et al., 2007), two Brazilian and one Turkish; however, one of these studies reported only data about LBW associated with PTB. Siqueira (2007) used the criteria of Lopez (2002) to define periodontitis in 1,277 women seen postpartum and found a significant OR (OR = 1.67, 95% CI: 1.11, 2.51). Toygar et al. (2007) used the CPITN partial periodontal examination on 3,576 women seen postpartum (OR = 3.56, 95% CI: 1.74, 7.25) for LBW between those with a CPITN score of 4 and those with CPITN<1. No meta-analysis was deemed possible.

New evidence

New evidence is based on four studies (Guimaraes et al., 2012; Acharya et al., 2013, Kothiwale et al., 2014, Muwazi et al., 2014) and 3,172 participants (Table 2). Kothiwale et al. (2014) have conducted the study on 770 mothers, undergoing partial periodontal examination. When PPD was >6 mm, the prevalence of low birth weight was significantly higher than in the healthy group (PPD < 5 mm). Muwazi and co-workers (2014) performed partial CPI periodontal examinations on 400 Ugandan mothers: periodontal parameters of gingival bleeding, PPD of 4-5 mm, and calculus with plaque deposits were not significantly associated with birth weight (p > 0.05); the only significant association was between LBW and gingival recession (p < 0.017). Acharya and co-workers (2013) performed full periodontal examinations on 316 pregnant women in India: severe gingivitis was significantly associated with LBW, but there was not a significant association between periodontitis and LBW. Periodontitis was found to be associated with a decrease of birth weight in 1,686 women with single pregnancy in Brazil. Periodontitis was measured with full-mouth examination and two different definitions of the disease were given. According to the type of definition, periodontitis showed adjusted OR of LBW varying from 1.65 to 2.

Table 2. Selected cross-sectional studies of maternal periodontitis and low birth weight.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year, location</th>
<th>Characteristics of population</th>
<th>Sample size</th>
<th>Periodontitis definition</th>
<th>Categorical or continuous analysis of peri-data</th>
<th>Type of recording</th>
<th>Newcastle-Ottawa quality rating</th>
<th>Finding, OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muwazi</td>
<td>2014, Uganda</td>
<td>Postpartum mothers</td>
<td>400</td>
<td>Community periodontal index Advanced periodontitis pocket depth ≥ 6mm</td>
<td>Categorical</td>
<td>Partial recording</td>
<td>Selection** Comparability* Exposure***</td>
<td>No, there was no statistically significant association between PPD and birth weight (p &gt; 0.05)</td>
</tr>
<tr>
<td>Acharya</td>
<td>2013, India</td>
<td>Unspecified</td>
<td>316</td>
<td>Unspecified</td>
<td>Categorical and linear</td>
<td>Full recording</td>
<td>Selection** Comparability* Exposure**</td>
<td>No, there was no significant association between periodontal disease and LBW, adjusted OR: PPD&gt;4 OR=1.5 (0.7, 2.9), p=0.34. Only severe gingivitis was associated OR=0.8 (0.2-1.4), p=0.04(*)</td>
</tr>
<tr>
<td>Guimarães</td>
<td>2012, Brazil</td>
<td>Women with single pregnancy</td>
<td>1686</td>
<td>&gt;4 Sites PPD&gt;4mm and CAL&gt;3mm; PD and CAL&gt;4mm</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparability* Exposure***</td>
<td>Yes, there was a statistically significant association between periodontal disease and LBW: non-adjusted OR=1.58 (95% CI 1.1-1.921) Multivariate-adjusted OR=2.00 (95% CI 1.39-2.90)</td>
</tr>
<tr>
<td>Kothiwale</td>
<td>2014, India</td>
<td>Mothers within the age group of 18-35 years with a singleton pregnancy</td>
<td>770</td>
<td>According to the WHO criteria</td>
<td>Categorical</td>
<td>Partial recording</td>
<td>Selection* Comparability* Exposure**</td>
<td>Yes, PPD was &gt; 6 mm, the prevalence of low birth weight was significantly higher (p = 0.032) than in the healthy group (PPD &lt; 5 mm).</td>
</tr>
</tbody>
</table>
Evidence synthesis

Total evidence is based on seven articles and 8,025 patients: four studies on a total of 7,309 patients have found an association between periodontal disease and LBW. In particular, Siqueira et al. (2007) found a significant OR (OR = 1.67, 95% CI: 1.11, 2.51), Toygar et al. (2007) also found a significant OR (OR = 3.56, 95% CI: 1.74, 7.25) for CPITN > 4, Guimarães et al. (2012) found a non-adjusted significant association (OR= 1.58, 95% CI: 1.14,2.21) and Kothiwale et al. (2014) have found a positive association (OR = 2.21, 95% CI: 1.07, 4.55), (p = 0.032) for probing pocket depth (PPD) > 6 mm to have LBW. The other two, based on 716 patients, found a not-significant correlation between periodontitis and LBW, but Muwazi et al. (2014) found a significant correlation between LBW and gingival recession, while Acharya et al. (2013) found a significant correlation between LBW and severe gingivitis, confirming that all studies agree that LBW and maternal periodontal status are associated. Considering that the number of patients included in the studies that found a significant association between LBW and periodontal disease is almost 10 times the size of that of those that did not find any statistical significant differences, there is enough evidence to support the first hypothesis.

Meta-analysis was performed on a total of four studies (Figure 3) and the pooled OR was 2.36, (95% CI 1.18-3.54). Results were statistically significant (p<0.01), although the large value of I²=76.16% confirms the great heterogeneity among studies.

Prospective studies of maternal periodontitis and low birth weight:

Summary of previous evidence

Previous data were based on nine heterogeneous papers and a total of 6,324 participants. Five studies on 4,354 patients (Marin et al., 2005; Farrell et al., 2006; Agueda et al., 2007; Srinivas et al., 2009; Vogt et al., 2010) did not find a significant association between LBW and periodontitis. Nevertheless, some degree of association was highlighted. Marin et al. (2005) and Srinivas et al. (2009) did find, in a sub-group analysis, a significant association for women of more than 25 years of age. Agueda et al. (2007) found a higher incidence of periodontitis cases in the LBW group but not significant results on multivariate regression. Vogt et al. (2010) found statistically significant association only in a multivariate analysis (RR = 2.93, 95% CI: 1.36, 6.34) in women with periodontitis. The four studies that found a significant association between LBW and periodontal disease were based on 1,970 participants. Al-Habashneh et al. (2013) found a significant association between LBW and CAL, but not with increased PPD. Other prospective studies (Saddki et al., 2008; Rakoto-Alson et al., 2010; Boggess et al., 2013) (RR = 2.3, 95% CI: 1.1, 4.5), Saddki et al. (2008) risk factor for LBW (adjusted OR = 3.84, 95%, CI: 1.34, 11.05).
Meta-analysis indicated a significant overall risk ratio (RR = 1.75, 95% CI: 1.41, 2.16) in subjects with periodontitis when the disease was categorised. Meta-analysis on continuous data indicated conflicting results as no differences in mean PPD between women with or without LBW were noted. On the other hand, when CAL level was considered, a difference of 1.12 mm was noted between the two groups.

New evidence

New evidence is based on five studies (Table 3) including a population of 1,747 participants (Kumar et al., 2013, Santa Cruz et al., 2013, Wang et al., 2013; Kothiwale et al., 2014; Tellapragada et al., 2016; Lohana et al., 2017). Three of these were conducted in India, and the others in Taiwan and Spain. Except for Santa Cruz et al. (2013), all manuscripts reported a statistically significant association between LBW and periodontitis, despite the large degree of heterogeneity present among the studies (in terms of periodontitis definition, periodontal recording, timing of inclusion, and NOS values). Lohana et al. (2017) conducted a cohort study of 300 pregnant women (gestational age, 20-24 weeks), categorising the disease and showing a statistical association between severity of periodontitis and LBW. Tellapragada et al. (2016), in a study of 790 pregnant woman (gestational age, 8-24 weeks) who underwent partial periodontal examination, found statistically significant differences for LBW between people affected by...
periodontitis and those not affected (p<0.001). Kumar et al. (2013) conducted a study of 340 primigravida women aged 20-35 years, with single live pregnancy, recruited at 14-20 weeks; full periodontal examination was performed and periodontitis was defined as CAL and PPD >4 mm in one or more sites. The study reported significant association (OR = 2.72, 95% CI:1.30, 5.68) for LBW in periodontitis-affected subjects. Kothiwale et al. (2014) conducted a study of 770 mothers, who underwent partial periodontal examination. When PPD was >6 mm, the prevalence of low birth weight was significantly higher than in the healthy group (PPD <5 mm). Wang et al. (2013) performed a full periodontal examination of 211 pregnant women (<26 weeks of gestation) in Taiwan: after delivery a significant correlation between maternal periodontitis and LBW was found, indicating a rate of LBW of 7.3% (6/82) in the periodontally healthy group compared to 14.5% (9/62) in the periodontitis-affected group. This difference was significant (p = 0.005).

Evidence synthesis

Total evidence is based on 14 papers and 8,071 participants: seven studies on 3,066 patients found a statistically significant correlation between LBW and maternal disease. One additional study found the association significant only between LBW and CAL levels. Conversely, six studies on 5,005 patients did not report significant results, although in two of these studies (Marin et al., 2005; Srinivas et al., 2009) the correlation becomes statistically significant if only women older than 25 years are considered.

Meta-analysis (Figure 4) was performed on a total of seven studies (pooled RR = 2.31, 95% CI: 2.32, 4.97). Results were highly heterogeneous (I²=0%) but not statistically significant (p=0.21).

**Studies investigating maternal periodontitis and preterm birth (PTB), E2:**

**Case-control studies of maternal periodontitis and preterm birth**

Summary of previous evidence

Previous evidence was based on 19 papers and 9,528 participants. Of these, eight studies found no statistically significant differences between preterm birth and controls (Moore et al., 2005; Lunardelli & Peres, 2005; Wood et al., 2006; Vettore et al., 2008a, 2008b; Heimonen et al., 2009; Nabet et al., 2010; Iwanaga et al., 2011), which was found in the remaining 11 manuscripts (López et al., 2002; Jarjoura et al., 2005; Bosnjak et al., 2006; Radnai et al., 2006; Le et al., 2007; Santos-Pereira et al., 2007; Toygar et al., 2007; Siqueira et al., 2007; Guimarães et al., 2010; Giannella et al., 2011; Piscoya et al., 2012). Eleven studies (Jarjoura et al., 2005; Lunardelli &
Peres, 2005; Radnai et al., 2006; Le et al., 2007; Santos-Pereira et al., 2007; Siqueira et al., 2007; Guimarães et al., 2010; Nabet et al., 2010; Giannella et al., 2011; Iwanaga et al., 2011), including 7,575 participants (2,721 cases and 4,854 controls), reporting periodontitis as a categorical variable were included in a meta-analysis (pooled OR = 2.47, 95% CI: 2.19, 2.77) and significant heterogeneity. Periodontal outcomes were correlated but the differences were clinically limited and the data highly heterogeneous.

Table 4.
Selected case-control studies of maternal periodontitis and preterm birth.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year, location</th>
<th>Characteristics of population</th>
<th>Sample size</th>
<th>Periodontitis definition</th>
<th>Categorical or continuous analysis of perio-data</th>
<th>Type of recording</th>
<th>Newcastle-Ottawa quality rating</th>
<th>Finding, OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jain</td>
<td>2016, India</td>
<td>Women between 18 and 35 yrs were seen within 72 hours of delivery</td>
<td>200</td>
<td>PD&gt;1, according to the Periodontal disease Index; teeth: 16,21,24,30,41,44</td>
<td>Categorical</td>
<td>Partial recording</td>
<td>Selection** Comparator* Exposure**</td>
<td>No, there was no association. Periodontal disease was higher in cases than in the controls, but the difference is not statistically significant (p=0.062)</td>
</tr>
<tr>
<td>Bulut</td>
<td>2014, Turkey</td>
<td>Women aged 18-40 were examined postpartum</td>
<td>100</td>
<td>4 teeth with ≥1 site with a PPD≥4 mm and CAL≥3 mm at the same site</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparator* Exposure***</td>
<td>No, there was no statistically significant difference (OR=1.48; 95% CI=0.54–4.06)</td>
</tr>
<tr>
<td>Macedo</td>
<td>2014, Brazil</td>
<td>Women aged 18-40 were examined within 48h postpartum</td>
<td>296</td>
<td>Definition n°1: ≥4 teeth with ≥1 site showing a PPD≥4 mm and CAL≥3 mm; Definition n°2: ≥1 site with PPD&lt;4 mm and CAL&lt;3 mm</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparator* Exposure***</td>
<td>Yes, a significant association was found if using definition No. 2 (ORadjusted = 1.98; 95% CI = 1.14–3.43; p = 0.015)</td>
</tr>
<tr>
<td>Ye</td>
<td>2013, Japan</td>
<td>Women between 23 and 44 yrs old were seen during the second trimester</td>
<td>95</td>
<td>PD≤5 mm</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparator* Exposure***</td>
<td>No, there was no statistically significant association although the percentage of sites with PD C5 mm was significantly higher in the PB group than in the TB group</td>
</tr>
<tr>
<td>Pattanasheeti</td>
<td>2013, India</td>
<td>Women aged 20-30 years seen at 6 months of pregnancy and after 48h postpartum</td>
<td>200</td>
<td>Mild periodontitis: ≥1 site with PPD≥2mm and positive BOP; Severe periodontitis: ≥15 sites with PPD≥4 mm</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparator* Exposure***</td>
<td>No, the incidence of preterm birth in relation to periodontal status in non-preeclamptic patients is not significant, but in the same population the worsening of periodontal status is significantly associated with PTB (p&lt;0.01)</td>
</tr>
<tr>
<td>Abati</td>
<td>2013, Italy</td>
<td>Women were seen postpartum within five days of delivery</td>
<td>750</td>
<td>Mild periodontitis: ≥1 site with CAL≥4mm; Severe periodontitis: ≥1 site with CAL≥6</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparator* Exposure***</td>
<td>No, there was no statistically significant difference between the groups. Odds ratio are not reported for single pregnancy outcome</td>
</tr>
<tr>
<td>Martinez de Tejada</td>
<td>2012, Switzerland</td>
<td>Cases were women delivering between 22 and 34 weeks of gestation and controls were women delivering at term (≥37 weeks)</td>
<td>429</td>
<td>≥2 interproximal sites with attachment loss ≥4 mm, not on the same tooth, or ≥2 two interproximal sites with PD≥5 mm, not on the same tooth</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparator* Exposure***</td>
<td>Yes, there was still a significant association after adjusting for confounders (OR 2.38; 95% CI: 1.36–4.14)</td>
</tr>
</tbody>
</table>
New evidence

New evidence is based on seven publications (Martínez de Tejada et al., 2012; Abati et al., 2013; Ye et al., 2013; Pattanashetti et al., 2013; Macedo et al., 2014; Bulut et al., 2014; Jain et al., 2016) and 2,070 participants. Except for the study conducted by Jain et al. (2016), all the studies had a full recording performed, but the definition of periodontitis was very heterogeneous. Five studies for a total of 1,345 women – comprising 750 women from Italy (Abati et al., 2013), 400 women from India (Pattanashetti et al., 2013; Jain et al., 2016), 95 women from Japan (Ye et al., 2013), and 100 women from Turkey (Bulut et al., 2014) – did not find any statistically significant difference between cases and controls. The remaining two studies found a significant correlation between maternal periodontitis and preterm birth and include 296 women from Brazil (Macedo et al., 2014) and 429 from Switzerland (Martínez de Tejada et al., 2012), for a total of 989 women. The article by Macedo et al. (2014) was the only new study, correlating positively maternal periodontitis and premature birth.

The authors considered two different definitions of periodontitis: ≥4 teeth with ≥1 site showing a PPD ≥4 mm and CAL ≥3 mm (definition 1) or ≥1 site with PPD and CAL ≥4 mm (definition 2). According to the first definition, periodontitis was not associated with PTB (OR=1.62; 95% CI: 0.80, 3.29) (p = 0.178); however, a significant association was found with the second definition (OR=1.98, 95% CI: 1.14, 3.43) (p = 0.015). In the study of Martínez de Tejada et al. (2012) 429 women, analysed with full-mouth periodontal examination, indicated a significant association between PTB and maternal periodontitis (adjusted OR = 2.38, 95% CI: 1.36, 4.14).

Evidence synthesis (existing and new evidence)

The overall evidence is based on 25 publications: 13 of these (3,320 participants) did not indicate any relevant differences between cases and controls. On the other hand, 11 studies significantly related periodontitis and preterm birth (8,298 participants). Meta-analysis was performed on a total of 10 studies (Figure 5) (OR: 1.38, 95% CI: 0.95, 1.82). Results were statistically significant (p<0.01) and homogenous (I²=0 %).

Figure 5.
Meta-analysis plot of case-control studies of preterm birth, reporting periodontitis as a categorical variable (odds ratio).
Cross-sectional studies of maternal periodontitis and preterm birth:

In the review by Ide and Papapanou (2013) no cross-sectional studies were found.

New evidence

New evidence is based on five studies (Acharya et al., 2013, Kothiwale et al., 2014, Muwazi et al., 2014; Perunovic et al., 2016; Martínez-Martínez et al. 2016) with 1,676 participants (Table 5). Two of the studies did not give a definition of periodontitis (Acharya et al., 2012; Perunovic et al., 2016), one used the CPITN, and the remaining one used five different definitions (Armitage, 1999; Jeffcoat et al., 2001; Radnai et al., 2004; Bassani et al., 2007; Macedo et al., 2014). Four of these manuscripts did not find any statistically significant association between maternal periodontitis and preterm birth, including 316 women from India (Acharya et al., 2013), 400 women from Uganda (Muwazi et al., 2014), and 70 women from Mexico (Martínez-Martínez et al., 2016). Only one study showed a correlation between PTB and periodontitis: Perunovic et al. (2016) reported data from 120 women from Serbia and concluded that women with PTB had a higher percentage of periodontitis (FTB 14.3% vs PTB 64.3% (p<0.01).

Table 5.
Selected cross-sectional studies of maternal periodontitis and preterm birth.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year, location</th>
<th>Characteristics of population</th>
<th>Sample size</th>
<th>Periodontitis definition</th>
<th>Type of recording</th>
<th>Newcastle-Ottawa quality rating</th>
<th>Finding, OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martínez-Martínez</td>
<td>2016, Mexico</td>
<td>Women of 20-35 years with a single live pregnancy</td>
<td>70</td>
<td>Numerous definitions; Armitage; Jeffcoat et al.; Radnai et al; Bassani et al; Macedo et al OMS</td>
<td>Full recording</td>
<td>Selection*** Comparability* Exposure***</td>
<td>No, due to the broad spectrum of definition used, there were no statistical differences between the groups, confirming the fact that there was no association between periodontitis and preterm birth</td>
</tr>
<tr>
<td>Perunovic</td>
<td>2016, Serbia</td>
<td>Women aged 18-35 with a single live pregnancy</td>
<td>120</td>
<td>≥1 site with PPD&gt;5 mm</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Yes, this study shows that women with PTB had higher % of periodontitis (FTB 14.3% vs PTB 64.3% (p&lt;0.01)</td>
</tr>
<tr>
<td>Muwazi</td>
<td>2014, Uganda</td>
<td>Postpartum mothers of single live pregnancy</td>
<td>400</td>
<td>Community periodontal index: Moderate periodontits: PPD&gt;4 mm, Advanced periodontitis - PPD &gt; 6 mm, Index teeth: 16, 11, 26, 36, 31, 46</td>
<td>Partial recording</td>
<td>Selection*** Comparability* Exposure***</td>
<td>No, gingival bleeding, periodontal pocket depth of ≥5 mm, calculus with plaque deposits, and gingival recession were not significantly associated with gestation age (p &gt; 0.05)</td>
</tr>
<tr>
<td>Acharya</td>
<td>2013, India</td>
<td>Women aged 18-42 were visited 1 day after delivery</td>
<td>316</td>
<td>≥1 site with PPD&gt;4 mm</td>
<td>Categorical</td>
<td>Full recording</td>
<td>No, there was not a significant association between periodontal disease and PTB (adjusted OR=1.8 (95% CI 0.9-3.5), p=0.12)</td>
</tr>
<tr>
<td>Kothiwale</td>
<td>2014, India</td>
<td>Mothers within the age group of 18–35 years with a single live pregnancy</td>
<td>770</td>
<td>According to the WHO criteria</td>
<td>Categorical</td>
<td>Partial recording</td>
<td>PTB showed only a greater prevalence of higher CPI scores (27.5% had PPD &gt; 6 mm and 9.3% had PPD ≤ 5 mm) as compared to term delivery (24.2% had PPD &gt; 6, 8.5% had PPD ≤ 5 mm)</td>
</tr>
</tbody>
</table>
Biological mechanisms between periodontal diseases and pregnancy complications

Prospective studies of maternal periodontitis and preterm birth

Summary of previous evidence

Previous evidence was based on seven studies and 7,648 participants (Offenbacher et al., 2006; Agueda et al., 2008; Rakoto-Alson et al., 2010; Vogt et al., 2010; Moore et al., 2004; Srinivas et al., 2009; Al Habashneh et al., 2012). Of these, four found a statistically significant difference between preterm birth and controls (Offenbacher et al., 2006; Agueda et al., 2008; Rakoto-Alson et al., 2010; Vogt et al., 2010). Three studies, including 2,468 participants, reported periodontitis as a categorical variable (pooled RR = 1.15, 95% CI: 0.89, 1.49). A high degree of heterogeneity was found when relating PTB to periodontal measures.

New evidence

New evidence is based on six studies (Kumar et al., 2013; Wang et al., 2013; Santa Cruz et al., 2013; Kothiwale et al., 2014; Tellapragada et al., 2016; Hassan et al., 2016; Lohana et al., 2017) and 4,905 participants (Table 6). The definition of periodontitis varied among the studies (CPITN, WHO, not specified, etc) and one study (Tellapragada et al., 2016) did not register a full recording. Two studies did not show any significant association between PTB and maternal periodontitis (Santa Cruz et al., 2013, Wang et al., 2014). Santa Cruz et al. (2013) reported data from 170 women recruited from different community clinics in Spain, who were examined before the 26th week of gestation and – according to their periodontal status – were divided in non-periodontitis group (n=116) and periodontitis group (n=54).

The results indicate that there was no significant association between PTB and maternal periodontitis (OR=1.325), but the presence of Eikenella corrodens was significantly related to PTB (p=0.022). Kothiwale et al. (2014) included 770 mothers aged 18-35 with a single live pregnancy in India. Periodontitis was defined using the WHO criteria and the results indicate that, although there was an increase in PTB with the increase of the severity of PD, the relationship between PTB and maternal periodontal disease was not significant (p=0.051). Wang et al. (2014) reported data from a cohort of 211 women (22 PTB and 189 full-term birth) visited before the 26th week of gestation, which did not indicate any difference in PTB (p=0.080).

On the other hand, four studies found some differences among the cohorts. Kumar et al. (2014) recruited 340 primigravida aged 18-35 from an antenatal clinic in India during the 14th-20th weeks of pregnancy of a singleton. Periodontitis was found to be significantly associated with PTB (OR = 2.72, 95% CI: 1.30, 5.68). Hassan et al. (2016) reported data from a study in Saudi Arabia including 94 women (22 PB and 72 full term) evaluated during the second trimester of pregnancy. Results showed that women with an outcome of PTB had more severe periodontal conditions than those with full-term birth (p<0.0001). Tellapragada et al. (2016) reported findings from 726 pregnant Indian women aged 18-35 who were examined during 8-24 weeks of gestation. Periodontitis was defined with a partial recording using the Community Periodontal Index as ≥1 PPD≥4 mm among at least one of the six index teeth evaluated. The authors reported a statistically significant association (OR=2.39, 95% CI: 1.1, 4.9) (p=0.02) between PTB and periodontitis. Lohana et al. (2017) examined 300 Indian women between 20 and 24 weeks of gestation (248 TB and 51 PTB). The authors defined slight periodontitis as CAL 1-2 mm, moderate periodontitis as CAL 3-4 mm, and severe periodontitis as CAL >5 mm. The results show a statistical association between gestational age and the level of PD (p<0.001).
Evidence synthesis

The overall evidence is based on 13 publications: seven of these (6,722 participants) did not find any relevant differences between the groups, whereas eight studies (4,307 participants) have significantly related periodontitis and PTB.

Table 6. Prospective studies of maternal periodontitis and preterm birth weight.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year, location</th>
<th>Characteristics of population</th>
<th>Sample size</th>
<th>Periodontitis definition</th>
<th>Categorical or continuous analysis of peri-data</th>
<th>Type of recording</th>
<th>Newcastle-Ottawa quality rating</th>
<th>Finding, OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lohana</td>
<td>2017, India</td>
<td>Pregnant women between 20 and 24 weeks</td>
<td>300</td>
<td>Periodontitis: slight 1-2 mm CAL • moderate 3-4 mm • severe &gt;5 mm</td>
<td>Categorical</td>
<td>Full recording</td>
<td>**</td>
<td>Yes, there was a statistical association between the level of periodontal disease severity and gestational age, P&lt;0.001</td>
</tr>
<tr>
<td>Tellapragada</td>
<td>2016, India</td>
<td>Pregnant women with a gestational age of 8-24 weeks</td>
<td>726</td>
<td>CPI ≥1, PPD&gt;4 mm (CPI score ≥3) among any one of the six index teeth examined</td>
<td>Categorical and linear</td>
<td>Partial recording</td>
<td>***</td>
<td>Yes, there were some statistical significant differences for PTB in relation to periodontitis (p=0.001)</td>
</tr>
<tr>
<td>Hassan</td>
<td>2016, Saudi Arabia</td>
<td>Women were seen during the second trimester and after delivery</td>
<td>94</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>****</td>
<td>Yes, women with PTB had more severe periodontal disease than those with FTB (p=0.001)</td>
</tr>
<tr>
<td>Wang</td>
<td>2014, Taiwan</td>
<td>Pregnant women prior to 26 weeks of gestation</td>
<td>211</td>
<td>Periodontitis: &gt;5% gingival bleeding, with CAL &gt; 6 mm ≥2 sites and with ≥1 sites with PD of 5 mm</td>
<td>Categorical</td>
<td>Full recording</td>
<td>****</td>
<td>No, the differences in PTB incidence among the groups was not clinically significant (p=0.080)</td>
</tr>
<tr>
<td>Kumar</td>
<td>2013, India</td>
<td>Primigravida women aged 20-35 years with single live pregnancy recruited at 14-20 weeks</td>
<td>340</td>
<td>Periodontitis: CAL and PPD &gt;4 mm in one or more sites</td>
<td>Categorical</td>
<td>Full recording</td>
<td>****</td>
<td>Yes, periodontitis was found to be significantly associated with preterm delivery with OR (95% CI) of 2.72 (1.30-5.68)</td>
</tr>
<tr>
<td>Santa Cruz</td>
<td>2013, Spain</td>
<td>Pregnant women examined before 26th week of gestation and divided in two groups: non-periodontitis and periodontitis</td>
<td>170</td>
<td>≥15 sites with CAL ≥3 mm or more CAL loss</td>
<td>Categorical</td>
<td>Full recording</td>
<td>****</td>
<td>No, there was no significant association between PTB and maternal periodontitis (OR=1.325). The presence of Eikenella Corrodens was significantly related to PTB (p=0.022)</td>
</tr>
</tbody>
</table>
Meta-analysis was performed on a total of three studies (Figure 6) (pooled adjusted RR = 1.93, 95% CI: 1.12, 2.73). Results were statistically significant (p<0.01), although the value of I²=99.65% represented wide heterogeneity among studies.

Figure 6.
Meta-analysis plot of prospective studies of preterm birth, reporting periodontitis as a categorical variable (relative risk).

Studies investigating maternal periodontitis and preterm low birth weight (PTLBW), E3:

Case-control studies of maternal periodontitis and preterm low birth weight:

Summary of previous evidence

Previous evidence is based on nine case-control studies including 6,442 participants. Three of four publications (Offenbacher et al., 1996; Gomes-Filho et al., 2007; Toygar et al., 2007) that reported periodontitis as a categorical value found a statistically significant correlation between periodontitis and PTLBW, with an OR of between 2.10 and 7.5 (results based on 4002 participants).

Figure 7.
Meta-analysis plot of case-control studies of pre-eclampsia reporting periodontitis as a categorical variable (odds ratio).
Khader and co-workers (Khader et al., 2009) found a significant association for PTBW and periodontitis (evaluated as a linear variable) (OR = 2.04, 95% CI 1.58, 2.61) for each millimetre of PD increment on 586 non-smoking postpartum women. In contrast, four of five studies that reported periodontitis as a linear variable (1,481 participants) found no statistically significant differences (Davenport et al., 2002; Buduneli et al., 2005; Noack et al., 2005; Vettore et al., 2008b). Overall, meta-analysis indicated a higher OR for PTBW in subjects with periodontitis (OR = 2.06, 95% CI: 1.34, 3.16). On the other hand, when considering periodontitis as continuous variable, no differences were noted in terms of CAL or gingival bleeding.

New evidence

New evidence was based on four case-controls (Table 7) including 588 participants (Mesa et al., 2013, 2016; Blanc et al., 2015; Kayar et al., 2015). Three studies were conducted in Spain (Blanc et al., 2015; Mesa et al., 2013 and 2016). Although they all used the same periodontal-disease definition – ≥4 teeth with ≥1 site with PPD ≥4 mm and CAL≥3 mm at the same site – their conclusions varied. Blanc et al. (2015) and Mesa et al. (2016) found no statistically significant association. On the other hand, Mesa et al. (2013) found significantly worse periodontal parameters in cases with PTBW (p<0.01). Another study (Kayar et al., 2015), conducted in Turkey with 156 mothers who delivered within 24 hours, found a significantly greater PPD and CAL (p<0.05) in cases compared to controls: in particular, CAL increased the risk of PLBW (OR=1.39, 95% CI: 1.04, 1.85).

Table 7. Selected case-control studies of maternal periodontitis and preterm low birth weight.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year, location</th>
<th>Characteristics of population</th>
<th>Sample size</th>
<th>Periodontitis definition</th>
<th>Type of recording</th>
<th>Newcastle-Ottawa quality rating</th>
<th>Finding, OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kayar</td>
<td>2015, Turkey</td>
<td>Women were seen within 24h of delivery</td>
<td>156</td>
<td>moderate to severe periodontitis: PD&gt;5 mm and CAL&gt;2 mm</td>
<td>Categorical and linear</td>
<td>Full recording</td>
<td>Selection*** Comparability* Exposure***</td>
</tr>
<tr>
<td>Blanc</td>
<td>2015, Spain</td>
<td>Women of age ≥18 were seen postpartum</td>
<td>57</td>
<td>≥4 teeth showed ≥1 sites with PPD ≥4 mm and CA loss ≥3 mm</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection** Comparability* Exposure***</td>
</tr>
<tr>
<td>Mesa</td>
<td>2013, Spain</td>
<td>women of age ≥18 were seen postpartum</td>
<td>244</td>
<td>Definition n°1: ≥4 teeth with ≥1 site showing a PPD≥4 mm and CAL≥3 mm Definition n°2: ≥1 site with PPD and CAL≥4 mm</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparability* Exposure**</td>
</tr>
<tr>
<td>Mesa</td>
<td>2016, Spain</td>
<td>Pregnant women &lt;37 weeks of gestation</td>
<td>131</td>
<td>≥4 teeth showed ≥1 site with PD ≥4 mm and AL≥3 mm at the same site</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparability* Exposure**</td>
</tr>
</tbody>
</table>
Evidence synthesis (existing and new evidence)

Total evidence is based on 13 studies: six of these (with a total of 4,988 participants) found a statistically significant association between periodontal disease and PTLBW, while seven studies (with a total of 2,042 participants) found no significant differences between cases and controls. Meta-analysis was not performed because of the absence of adjusted data.

**Cross-sectional studies of maternal periodontitis and preterm low birth weight:**

In the review by Ide and Papapanou (2013) no cross-sectional studies were found.

**Summary of previous evidence**

No cross-sectional studies were reported in the previous review.

**New evidence**

Only one study (Table 8) has been included in this category (Acharya et al., 2013). Full-mouth periodontal examination at six sites per tooth was performed on 316 pregnant woman in India. Adjusted (educational and socio-economic status, age) OR was significant (OR = 1.7, 95% CI: 0.7, 4.3) for PPD>4 mm and for severe CAL (OR = 1.1, 95% CI: 0.4, 3.54). However, results were not statistically significant.

**Table 8.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year, location</th>
<th>Characteristics of population</th>
<th>Sample size</th>
<th>Periodontitis definition</th>
<th>Categorical or continuous analysis of periodontal data</th>
<th>Type of recording</th>
<th>Newcastle-Ottawa quality rating</th>
<th>Finding, OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acharya</td>
<td>2013, India</td>
<td>Unspecified</td>
<td>316</td>
<td>Unspecified</td>
<td>Linear</td>
<td>Full recording</td>
<td>Selection+ Comparability* Exposure**</td>
<td>No, there was no significant association between periodontal disease and PTLBW (adjusted OR: PPD&gt;4 mm OR=1.7 (0.7-4.3), p=0.24)</td>
</tr>
</tbody>
</table>

**Prospective studies of maternal periodontitis and preterm low birth weight**

**Summary of previous evidence**

Previous evidence was based on two studies and 1,346 participants (Agueda et al., 2007; Ercan et al., 2013). Meta-analysis indicated, on one hand, a higher PPD in subjects with PTLBW and, on the other hand, no differences in CAL. Results were highly heterogeneous.

**New evidence**

Only one study has been included in this category (Tellapragada et al., 2016), which carried out a partial periodontal examination of 726 pregnant women (gestational age, 8-24 weeks) in India. In this population, a statistically significant association between maternal periodontitis and PTLBW was found (p=0.001) and an adjusted RR (adjusted for age, level of education, parity, monthly household income, and maternal body mass index) for PTLBW of 3.29 (CI 95% 1.8, 5.7).
Evidence synthesis

Overall, consistency among the literature indicated that women with PTLBW showed a worse periodontal condition compared to controls. Nevertheless, only the data from Tellapragada et al. (2016) were significant. It was not possible to perform any meta-analysis.

Studies investigating maternal periodontitis and pre-eclampsia (PE), E4:

Case-control studies of maternal periodontitis and pre-eclampsia:

Summary of previous evidence

Previous evidence was based on seven papers (Canakci et al., 2004; Contreras et al., 2006; Cota et al., 2006; Siqueira et al., 2008; Nabet et al., 2010; Taghzouti et al., 2011; Khader et al., 2006) and 3,406 participants. Of these, five studies (Canakci et al., 2004; Contreras et al., 2006; Siqueira et al., 2008; Nabet et al., 2010; Taghzouti et al., 2011) found a statistically significant difference between cases and controls. Five studies, reporting periodontitis as a categorical variable, were adequate for meta-analysis (pooled OR: 1.61, 95% CI: 1.36, 1.92). Statistical significant differences were also noted in terms of periodontal parameters indicating lower periodontal health in cases.

Table 9. Selected case-control studies of maternal periodontitis and pre-eclampsia.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year, location</th>
<th>Characteristics of population</th>
<th>Sample size</th>
<th>Periodontitis definition</th>
<th>Categorical or continuous analysis of peri-data</th>
<th>Type of recording</th>
<th>Newcastle Ottawa quality rating</th>
<th>Finding, OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tellapragada</td>
<td>2016, India</td>
<td>Pregnant women with a gestational age of 6–24 weeks</td>
<td>790 (765 follow-up)</td>
<td>Community Periodontal Index (CPI) scoring system at the time of recruitment: A pathological pocket depth of at least 4 mm (CPI score ≥3) in any one of the six index teeth examined was diagnostic for periodontitis</td>
<td>Categorical analysis of periodontal data</td>
<td>Partial recording</td>
<td>Selection*** Comparability* Exposure****</td>
<td>Yes, there was statistical significant differences for PTLBW in people affected and not by periodontitis (p&lt;0.001); aRR=3.29 (1.8, 5.7)</td>
</tr>
</tbody>
</table>

New evidence

New evidence is based on four publications (Tab. 9) (Abati et al., 2013; Moura da Silva et al., 2012; Chaparro et al., 2013; Pattanashetti et al., 2013) which investigated 1,554 participants. Moura da Silva et al. (2012) reported data from a study of 574 women (284 cases with pre-eclampsia and 290 controls without pre-eclampsia) and, after adjusting for confounders, periodontitis still remained an independent risk factor for pre-eclampsia (OR=8.60, 95%). The study reported by Pattanashetti et al. (2013) involved 200 women aged 20 to 30 years and before the 26th week of gestation, recruited in a hospital in India. The authors identified as mild periodontitis the presence of ≥1 site with PPD≥3mm and positive BoP, and as severe periodontitis the presence of ≥15 sites with PPD≥4 mm.

The results indicate that 30% of cases (pre-eclamptic patients) were characterised by moderate/severe periodontitis, against 20% of controls. Two of these studies did not find any statistically significant difference between cases and controls. Abati et al. (2013) examined a large population, consisting of 750 mothers (230 cases and 520 controls), recruited in three different hospitals throughout Italy who were visited within five days of delivery and examined for several outcomes. Periodontitis was not related to pre-eclampsia or other pregnancy outcomes in general (OR adjusted = 1.0, 95%) for
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Chaparro et al. (2016) studied a small sample (n=30) of women from Chile (10 cases and 20 controls). There was no significant difference between the groups, but it was also a very limited sample and the primary objective of the study was to identify whether patients with pre-eclampsia had a higher level of placental biomarkers and angiogenic factors in oral fluids.

Evidence synthesis

The overall evidence is based on 11 publications: four of these (with a total of 1,462 participants) did not find any relevant differences between cases and controls, whereas the remaining seven studies (with 3,497 participants) significantly related periodontitis and pre-eclampsia. Meta-analysis was performed over a total of six studies (Figure 7) (pooled OR = 2.85, 95% CI: 0.57, 5.12). Results were statistically significant (p<0.01), although the value of I^2=94.02% represented heterogeneity among studies.

Cross-sectional studies of maternal periodontitis and pre-eclampsia

Summary of previous evidence

In the review by Ide and Papapanou (2013) no cross-sectional studies had been found related to preterm birth and maternal periodontitis.

New evidence

New evidence is based on one study (Hirano et al., 2012) (Table 10). Hirano et al. (2012) reported findings from 127 (18 pre-eclamptic, 109 non-preeclamptic) women from a university hospital in Japan, evaluated within five days after labour. The women received a full periodontal examination and were considered affected by periodontitis if they had ≥60% of sites with CAL ≥3mm. The results indicate no statistically relevant association between pre-eclampsia and any of the periodontal clinical parameters evaluated.

Table 10. Selected case-control studies of maternal periodontitis and pre-eclampsia.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year, location</th>
<th>Characteristics of population</th>
<th>Sample size</th>
<th>Periodontitis definition</th>
<th>Categorical or continuous analysis of periodontal data</th>
<th>Type of recording</th>
<th>Newcastle-Ottawa quality rating</th>
<th>Finding, OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaparro</td>
<td>2016, Chile</td>
<td>Women with at least 18 teeth</td>
<td>30</td>
<td>≥4 teeth with ≥1 site with PPD≥4 and CAL≥3 and positive BoP</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection**, Comparability* Exposure***</td>
<td>No, there was no statistically significant difference between the groups</td>
</tr>
<tr>
<td>Pattanashetti</td>
<td>2013, India</td>
<td>Women aged 20-30 years seen at 6 months of pregnancy and after 48h postpartum</td>
<td>200</td>
<td>Mild periodontitis: ≥1 site with PPD≥3mm and positive BoP Severe periodontitis: ≥15 sites with PPD≥4 mm</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparability* Exposure**</td>
<td>The 30% of cases (pre-eclamptic patients) were characterized by moderate/severe periodontitis, against the 20% of controls</td>
</tr>
<tr>
<td>Abati</td>
<td>2013, Italy</td>
<td>Women were seen postpartum within five days of delivery</td>
<td>750</td>
<td>Moderate periodontitis: ≥1 site with CAL 4-6 mm Severe periodontitis: ≥1 site with CAL≥6</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparability* Exposure***</td>
<td>No, there was no statistically significant difference between the groups</td>
</tr>
<tr>
<td>Moura Da Silva</td>
<td>2012, Brazil</td>
<td>Puerperae with pre-eclampsia and puerperae without pre-eclampsia visited during the 48-hour postpartum period</td>
<td>574</td>
<td>≥4 teeth with ≥1 site with PPD≥4mm and CAL ≥3mm in the same site</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparability* Exposure***</td>
<td>Yes, there was a significant difference (OR=8.60, 95% CI 3.92-18.88)</td>
</tr>
</tbody>
</table>
Prospective studies of maternal periodontitis and pre-eclampsia

Summary of previous evidence

Previous data were based on three papers (Table 11) reporting different data of the same study (Riche et al., 2002; Boggess et al., 2003; Horton et al., 2010) of 850 participants. The results reported a statistically significant association between severe periodontitis and pre-eclampsia (OR = 2.4, 95% CI: 1.1, 5.3).

Table 11. Selected cross-sectional studies of maternal periodontitis and pre-eclampsia.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year, location</th>
<th>Characteristics of population</th>
<th>Sample size</th>
<th>Periodontitis definition</th>
<th>Categorical or continuous analysis of peri-data</th>
<th>Type of recording</th>
<th>Newcastle Ottawa quality rating</th>
<th>Finding, OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirano</td>
<td>2012, Japan</td>
<td>Women were examined 5 days after labour</td>
<td>127</td>
<td>≥ 60% of sites with CAL &gt;3 mm</td>
<td>Categorical and linear</td>
<td>Full recording</td>
<td>Selection** Comparability* Exposure***</td>
<td>No, there was no a statistically significant association</td>
</tr>
</tbody>
</table>

New evidence

New evidence is based on three studies (Kumar et al., 2013, 2014; Ha et al. 2014) and a total of 1,127 participants. The definition of periodontitis was homogeneous, the characteristics of the samples were similar, and all the studies found a statistically relevant association between periodontitis and pre-eclampsia. Kumar et al. (2013) examined 340 Indian women (adjusted OR=5.160, 95%). Kumar et al. (2014) reported data from 504 Indian women (OR = 2.66) for pre-eclampsia. The study reported by Ha et al. (2014) involved 283 Korean women (67 cases, 216 controls) and the results show that, after adjusting for confounding factors, there was still a significant association (OR=5.56).

Evidence synthesis

The overall evidence is based on six studies and 1,977 participants. All studies found a significant correlation between mothers’ periodontitis and pre-eclampsia. Meta-analysis could not be performed as the RR presented in the original manuscripts were not adjusted.

Discussion

Overall, the updated evidence confirmed the previous findings reported by Ide & Papapanou (2013): contradictory findings and the broad heterogeneity of the available literature prevent the drawing of solid and definitive conclusions. Manuscripts varied in terms of definition of periodontitis, types and extension of periodontal examination, inclusion criteria, sample size, and adjustment of possible confounding factors. The noted differences should be taken in account when evaluating the overall scenario.

Overall evidence on low birth weight would suggest that there might be an association with periodontitis. The data on prospective studies would suggest a higher risk of this APO in subjects with a lower periodontal condition. Data gathered from case-control and cross-sectional studies
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would further confirm this finding. However, one should take in account that the data from prospective studies were not significant and that gathered from cross-sectional studies were highly heterogeneous.

The evidence on preterm birth would suggest a higher tendency for periodontitis in women who deliver preterm. Prospective studies would confirm these finding with a high relative risk; however, the data are hampered by the extreme heterogeneity. Pre-eclampsia appeared to be associated with periodontitis. In fact, a higher consensus (all prospective studies indicated a higher risk in periodontitis-affected women) could be drawn despite the usual significant heterogeneity.

Studies on adverse pregnancy outcomes and periodontitis indicate that there might be some association. However, the strength of this association is extremely limited and hampered by the significant heterogeneity. In fact, an equal number of manuscripts not indicating association was found nearly in each of the sub-sets analysed. Further co-ordinated research is strongly needed.

Table 12. Prospective studies of maternal periodontitis and pre-eclampsia.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year, location</th>
<th>Characteristics of population</th>
<th>Sample size</th>
<th>Periodontitis definition</th>
<th>Categorical or continuous analysis of perio-data</th>
<th>Type of recording</th>
<th>Newcastle-Ottawa quality rating</th>
<th>Finding, OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ha</td>
<td>2014, Korea</td>
<td>Women aged 25-40 with a single live pregnancy during the 21st-24th week of gestation</td>
<td>283</td>
<td>CAL ≥4mm on ≥2 sites not on the same tooth</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparability* Exposure***</td>
<td>Yes, there was a significant association (OR=5.56, 1.49–20.71)</td>
</tr>
<tr>
<td>Kumar</td>
<td>2014, India</td>
<td>Primigravida women aged 20-35 with single live pregnancy between 14 and 18 weeks</td>
<td>504</td>
<td>As ≥1 site with CAL and PPD&gt;4mm</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparability* Exposure**</td>
<td>Yes, there was a significant association (OR=2.66, 1.32–5.73)</td>
</tr>
<tr>
<td>Kumar</td>
<td>2013, India</td>
<td>Primigravidas at 14-20 weeks of gestation</td>
<td>340</td>
<td>CAL and PPD &gt;4 mm in ≥1 site</td>
<td>Categorical</td>
<td>Full recording</td>
<td>Selection*** Comparability* Exposure**</td>
<td>Yes, pre-eclampsia was significantly higher in the periodontitis group (OR=5.160, 1.942–13.707)</td>
</tr>
</tbody>
</table>
References


Biological mechanisms between periodontal diseases and pregnancy complications


Biological mechanisms between periodontal diseases and pregnancy complications


Martinez de Tejada, B., Gayet-Ageron, A., Combescure, C., Irion, O. & Baehni, P. (2012) Association between early preterm birth and periodontitis according to USA and European consensus


Biological mechanisms between periodontal diseases and pregnancy complications


Mervi Gürsoy is an associate professor in periodontology at the University of Turku (Finland). She was awarded her DDS degree by the University of Helsinki (1999), and then her PhD in periodontology (2012) and her qualification as a specialist in periodontology (2013) from the University of Turku.

Her doctoral thesis was “Pregnancy and periodontium – A clinical, microbiological, and enzymological approach via a longitudinal study” and she has subsequently co-authored various research articles relating to periodontology and pregnancy, the most recent of which was “Salivary antimicrobial defensins in pregnancy” published in the *Journal of Clinical Periodontology* (October 2016).

Dr Gürsoy has received the Young Researcher award from the Scandinavian Society of Periodontology (2011), the Hatton award (clinical research, senior category) from the IADR/Scandinavian division (NOF) (2011), the second prize of the Unilever/IADR Hatton award (2012), and the IADR/Philips Oral Healthcare Young Investigator Research grant (2013).

She reviews articles for numerous scientific publications in the field of periodontology and oral microbiology.

She has been a junior officer on the European Federation of Periodontology’s undergraduate committee (2015-2017) and a board member of the Finnish Society of Periodontology.
Authors

Morena Petrini

Morena Petrini is a postdoctoral researcher in periodontology at the University of Pisa (Italy). Graduated (cum laude) as a doctor in dentistry in 2008, she was awarded her PhD in Basic and Applied Medical Science with the mention of “Doctor Europeus” in 2013, and she obtained her speciality (cum laude) in oral surgery in 2017, at the University of Chieti, Italy.

Dr Petrini is the author of more than 20 articles in international journals and co-author of two books on dental materials.

Stefano Gennai

Stefano Gennai, a post-doctoral research assistant in periodontology at the University of Pisa (Italy), graduated with honours in Dentistry in 2009, and then obtained his master in Oral Surgery in 2011 at the University of Pisa. He was awarded a PhD in “Clinical Physiopathology” at the University of Pisa with a thesis on the acute inflammation after periodontal treatment.

Dr Gennai has received the Robinson Award from the American Academy of Periodontology (2013), the Jaccard Prize for Clinical Research from the European Federation of Periodontology (2015), and the HM Goldman Prize from the Italian society of periodontology (SIdP, 2017).

He is co-author of a number of publications in several international journals.
Biological mechanisms between periodontal diseases and pregnancy complications

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His research activities are focused on periodontal surgical treatment and periodontal medicine. He is the author of more than 60 articles in international journals, a member of the editorial board of the Journal of Clinical Periodontology, associate editor of Minerva Stomatologica, and a reviewer for numerous scientific journals.

He is the co-ordinator of the Periodontology, Halitosis, and Periodontal Medicine unit of the University Hospital of Pisa (www.periomed.org), and the founder of the Centre of Dental Hygiene and Periodontology, also in Pisa, where he runs his private practice in periodontology (www.cidep.it).

Prof Graziani has received the second prize for graduate research from the European Federation of Periodontology (2005), the Robinson Award from the American Academy of Periodontology (2013), the Jaccard Prize for Clinical Research from the European Federation of Periodontology (2015), and the HM Goldman Prize from the Italian Society of Periodontology (2017).

He is a member of the executive committee of the European Federation of Periodontology (EFP), and is due to become its president in 2019. He is the EFP delegate of the Italian Society of Periodontology and Implantology (SidP), of which he is a former secretary general. Prof Graziani was the co-ordinator of European Gum Health Day 2017.
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 which 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

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.

www.efp.org

Oral-B is the worldwide leader in the over $5 billion tooth-brush market. Part of the Procter & Gamble Company, the brand includes manual and electric toothbrushes for children and adults, oral irrigators, interdental products such as dental floss, together with toothpastes and mouth rinses. Oral-B manual toothbrushes are used by more dentists than any other brand in the USA and many international markets.

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.

www.dentalcare.com
The EFP thanks Oral-B for its support and its unrestricted grant.