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
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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):

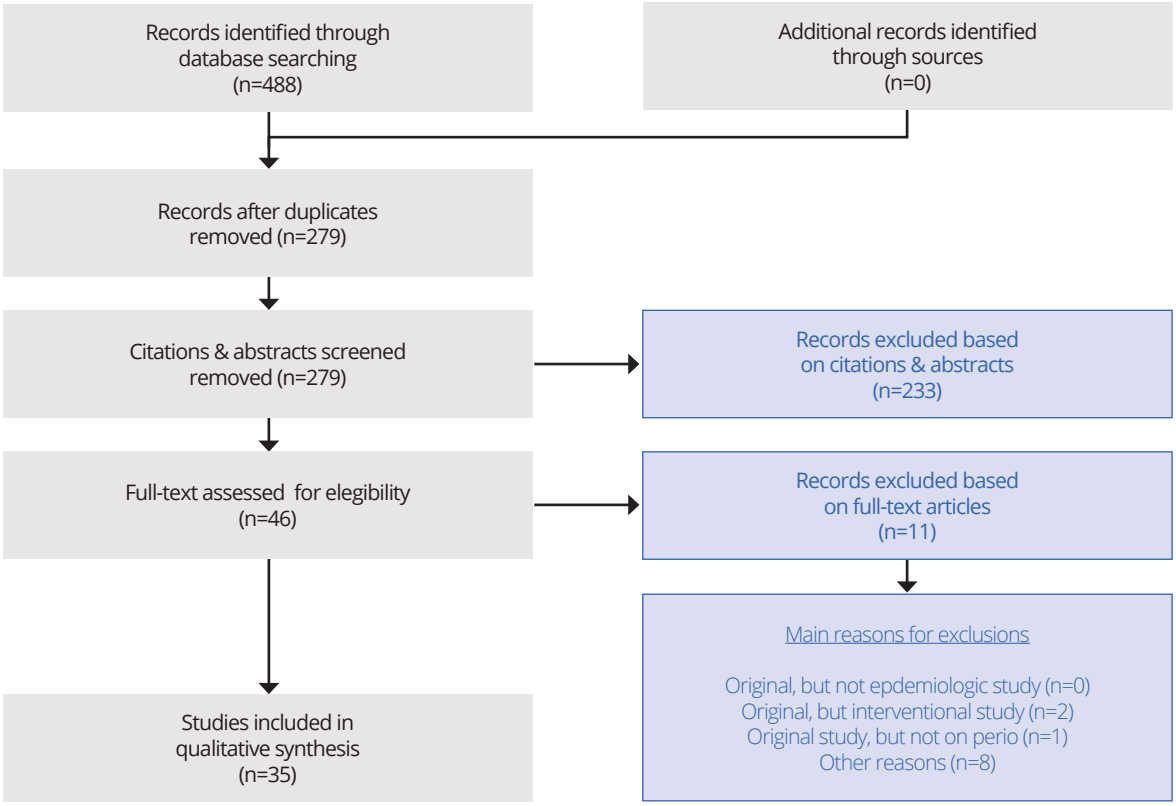
E1. Low birth weight (LBW)=15
- Prospective (COH)=5
- Case-control (CC)=6
- Cross-sectional (CS)=4

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

Figure 1. Flow of studies during review



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 (Abati *et al*., 2013; Haerian-Ardakani *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

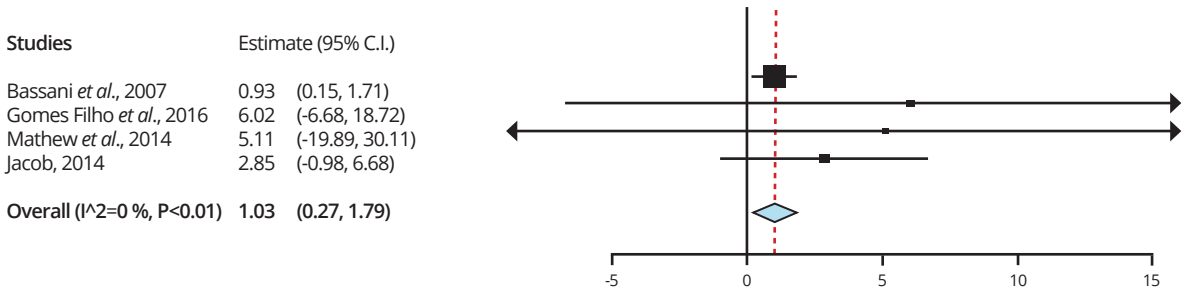
The total evidence is based on 11 case-control studies, spread across the globe, and 3,718 participants: three of these found no differences between cases and controls (1,946 participants), while eight studies found periodontitis to be significantly associated with LBW (1,722 participants). Overall,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

Meta-analysis was performed on a total of four 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). The value of I2=0% confirms the wide homogeneity.

Table 1.
Selected case control studies of maternal periodontitis and low birth weight

Author	Year, location	Characteristics of population	Sample size	Periodontitis definition	Categorical or continuous analysis of perio-data	Type of recording	Newcastle-Ottawa quality rating	Finding, OR
Reza Karimi	2015, Iran	Unspecified	264	CPITN (at least 1 sextant with at least 1 site with PPD >4)	Categorical	Full recording	Selection** Compar-ability* Exposure**	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-primigravida
Gomes-Filho	2016, Brazil	Women were seen postpartum. The mean ± SD age of the participants was 23.86 ± 6.6 years	372	≥ 4 teeth with ≥ 1 site with PD±4 mm, attachment loss ±3mm, and BOP at the same site	Categorical	Full recording	Selection*** Compar-ability* Exposure***	Yes, there was a statistically significant association between periodontitis and LBW (ORunadjusted=4.51, 95% CI=2.63 to7.74) (ORadjusted=6.02,95% CI=2.47 to 15.17)
Mathew	2014, India	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)	160	PPD ≥ 4mm and CAL ≥ 2mm at a given site	Categorical	Full recording	Selection*** Compar-ability* Exposure***	Yes, there was a statistically significant association. Women with PD were nearly 5 times likely to deliver a LBW infant in comparison to mothers without PD (OR 5,1 CI 1-26)
Jacob & Nath	2014, India	Women were seen postpartum	340	PPD of ≥4 mm in at least one site	Categorical	Full recording	Selection *** Compar-ability* Exposure***	Yes, periodontal disease is a significantly associated independent risk factor for LBW, with an adjusted odds ratio (aOR) of 2.85 (95% [CI], 1.62–5.5)
Abati	2013, Italy	Women were seen postpartum within three days of deliveryy	750	"healthy":all sites with CAL < 4 mm. "moderate": at least one site with CAL from 4 to 6 mm. "high":at least ≥1 site site with CAL ≥ 6 mm	Categorical	Full recording	Selection *** Compar-ability* Exposure***	No, there was no significant association after adjusting for confounding factors. OR are not reported for single pregnancy outcome
Haerian-Ardakani	2013, Iran	Women were seen up to three days after delivery	88	CPITN (at least 1 sextant with at least 1 site with PPD >4)	Categorical	Full recording	Selection*** Compar-ability* Exposure**	Yes, there was a statistically significant association (p=0.0006)

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.

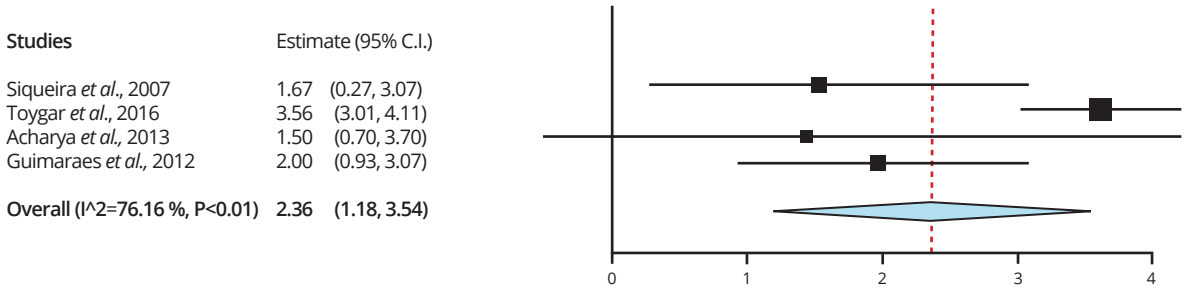
Author	Year, location	Characteristics of population	Sample size	Periodontitis definition	Categorical or continuous analysis of perio-data	Type of recording	Newcastle-Ottawa quality rating	Finding, OR
Muwazi	2014, Uganda	Postpartum mothers	400	Community periodontal index Advanced periodontitis: pocket depth ≥ 6mm	Categorical	Partial recording	Selection** Compar-ability* Exposure***	No, there was no statistically significant association between PPD and birth weight ($p > 0.05$).
Acharya	2013, India	Unspecified	316	Unspecified	Categorical and linear	Full recording	Selection** Compar-ability* Exposure**	No, there was no significant association between periodontal disease and LBW, adjusted OR: PPD>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 (*)
Guimarães	2012, Brazil	Women with single pregnancy	1686	>4 Sites PPD>4mm and CAL>3mm; PD and CAL>4mm	Categorical	Full recording	Selection*** Compar-ability* Exposure***	Yes, there was a statistically significant association between periodontal disease and LBW. Non-adjusted OR 1.58 (95% CI 1.14–2.21); Multivariate-adjusted OR 2.00 (95% CI 1.39–2.90)
Kothiwale	2014, India	Mothers within the age group of 18–35 years with a singleton pregnancy	770	According to the WHO criteria	Categorical	Partial recording	Selection* Compar-ability* Exposure**	Yes, PPD was > 6 mm, the prevalence of low birth weight was significantly higher (P = 0.032) than in the healthy group (PPD < 5 mm).

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.

Figure 3.
Meta-analysis plot of cross-sectional of low birth weight, reporting periodontitis as a categorical variable (odds ratio).



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.

Table 3.
Selected cohort studies of maternal periodontitis and low birth weight

Author	Year, location	Characteristics of population	Sample size	Periodontitis definition	Categorical or continuous analysis of perio-data	Type of recording	Newcastle-Ottawa quality rating	Finding, OR
Lohana	2017, India	Pregnant women between 20-24 weeks	300	Slight: 1-2 mm CAL Moderate: 3-4 mm Severe >5 mm	Categorical	Full recording	Selection*** Compar-ability* Exposure****	Yes, there was a statistical association between the level of periodontal disease severity and LBW (p< 0.001)
Tellapragada	2016, India	Pregnant women with a gestational age of 8-24 weeks	726	Community Periodontal Index (CPI): A pathological pocket depth of at least 4 mm (CPI score ≥3) among any one of the six index teeth	Categorical	Partial recording	Selection** Compar-ability* Exposure****	Yes, there was a statistical significant difference for LBW in people affected from periodontitis (p=0.003) Adjusted RR, 3.38; 95% (CI, 1.6 to 6.9)
Wang	2013, Taiwan	Pregnant women prior to 26 weeks of gestation	211	Periodontitis >5% gingival bleeding, with CAL > 6 mm in two or more sites and with one or more sites with PD of 5 mm	Categorical	Full recording	Selection** Compar-ability* Exposure****	Yes, there was a significant correlation between maternal periodontal disease and LBW (p=0.009; after Bonferroni correction p<0.0167) The rate of LBW was 7.3% (6/82) for healthy women and 14.5% (9/62) for women with periodontitis and the difference was significant (x2 15.345; p = 0.005).
Kumar	2013, India	Primigravidas at 14–20 weeks of gestation	340	Periodontitis: CAL and PPD >4 mm in one or more sites	Categorical	Full recording		Yes, periodontitis was significantly associated with LBW OR=3.03 (1.53–5.97) in univariate analysis and still remained associated in a multivariate analysis.
Santa Cruz	2013, Spain	Pregnant women examined before 26th week of gestation, and divided in two groups: non-periodontitis and periodontitis	170	Generalized moderate to severe periodontitis: ≥ 15 sites or more with 3 mm or more CAL loss (PPD > 3 mm)	Categorical	Full recording	Selection **** Compar-ability* Exposure**	No, there was no statistically significant association. The presence of Capnocytophaga spp. was related to LBW (p = 0.008)

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; 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).

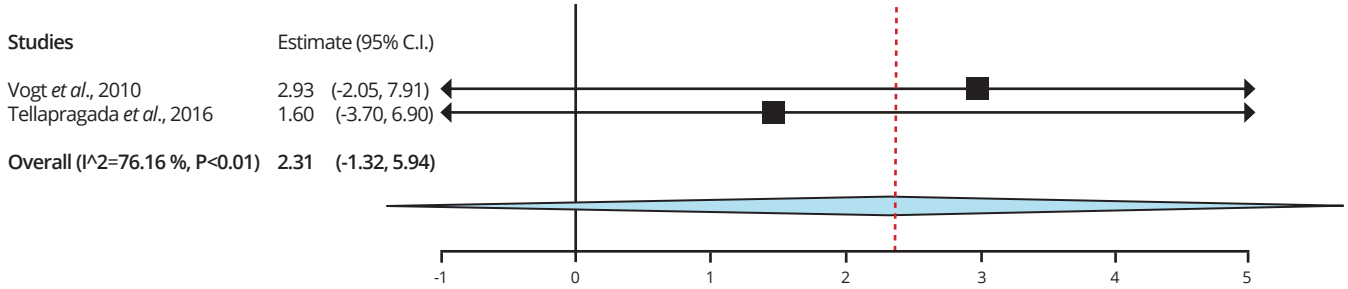
Kumar *et al.* (2013) conducted a study of 340 primigravida women aged 20-35 years, with single live pregnancy, recruited at 14-20 weeks; full periodontal examination was performed and periodontitis was defined as CAL and PPD >4 mm in one or more sites. The study reported significant association (OR = 2.72, 95% CI:1.30, 5.68) for LBW in periodontitis-affected subjects. 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 two studies (pooled RR = 2.31, 95% CI: -1.32, 5.94). Results were highly heterogeneus: I2=76.16% but statistically significant (p<0.01).

Figure 4.
Meta-analysis plot of prospective studies of low birth weight, reporting periodontitis as a categorical variable (Relative risk).



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.

Author	Year, location	Characteristics of population	Sample size	Periodontitis definition	Categorical or continuous analysis of perio-data	Type of recording	Newcastle-Ottawa quality rating	Finding, OR
Jain	2016, India	Women between 18 and 35 yrs were seen within 72 hours of delivery	200	PDI≥1 , according to the Periodontal disease Index Index teeth: 16,21,24,36,41,44	Categorical	Partial recording	Selection** Compar-ability* Exposure**	No, there was no association. Periodontal disease was higher in cases than in the controls, but the difference is not statistically significant (p=0.892)
Bulut	2014, Turkey	Women aged 18-40 were examined postpartum	100	4 teeth with ≥1site with a PPD≥4 mm and CAL≥3 mm at the same site	Categorical	Full recording	Selection*** Compar-ability* Exposure***	No, there was no statistically significant difference (OR=1.48; 95%CI=0.54–4.06)
Macedo	2014, Brazil	Women aged 18-40 were examined within 48h postpartum	296	Definition n°1: ≥4 teeth with ≥1site showing a PPD≥4 mm and CAL ≥3 mm Definition n°2: ≥1 site with PPD and CAL ≥4 mm	Categorical	Full recording	Selection***- Compar-ability* Exposure**	Yes, a significant association was found if using definition No. 2 (ORadjusted = 1.98; 95% CI = 1.14–3.43; p = 0.015)
Ye	2013, Japan	Women between 23 and 44 years old were seen during the second trimester	95	PD≥5 mm	Categorical	Full recording	Selection*** Compar-ability* Exposure**	No, there was no statistically relevant association although the percentage of sites with PD C5 mm was significantly higher in the PB group than in the TB group
Pattanashetti	2013, India	Women aged 20-30 years seen at 6 months of pregnancy and after 48h postpartum.	200	Mild periodontitis: ≥1 site with PPD≥3mm and positive BoP Severe periodontitis: ≥15 sites with PPD≥4 mm	Categorical	Full recording	Selection***- Compar-ability* Exposure**	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<0,01)
Abati	2013, Italy	Women were seen postpartum within five days of delivery	750	Mild periodontitis: ≥1 site with CAL 4-6mm Severe periodontitis: ≥1 site with CAL≥6	Categorical	Full recording	Selection*** Compar-ability* Exposure***	No, there was no statistically significant difference between the groups. Odds ratio are not reported for single pregnancy outcome
Martínez de Tejada	2012, Switzer-land	Cases were women delivering between 22 and 34 weeks of gestation and controls were women delivering at term (≥37 weeks)	429	≥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	Categorical	Full recording	Selection***- Compar-ability* Exposure**	Yes, there was still a significant association after adjusting for confunders (OR: 2.38; 95% CI: 1.36–4.14

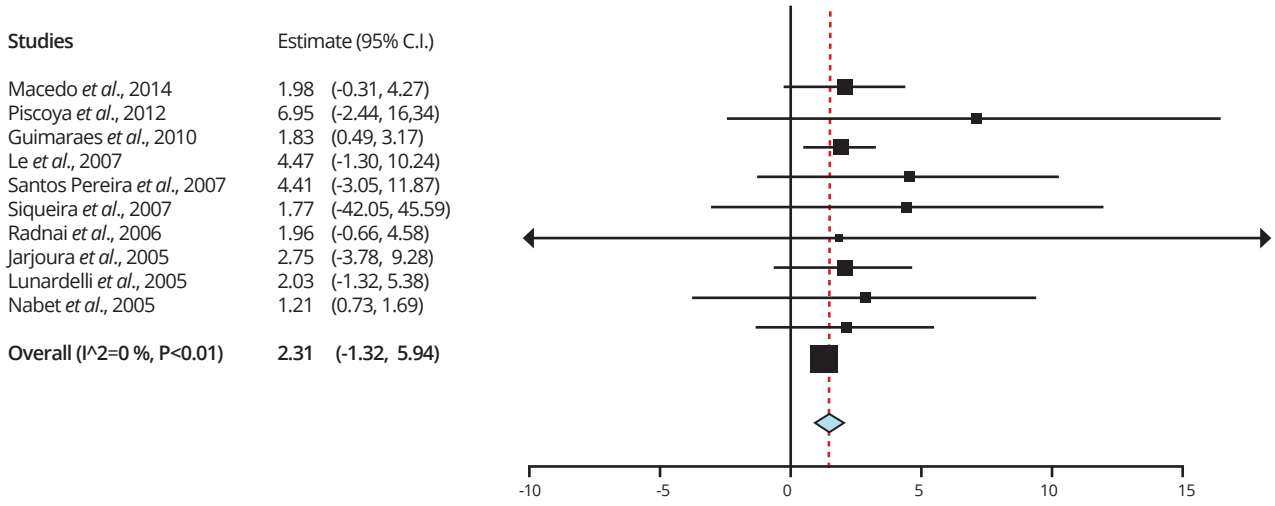
New evidence is based on seven publications (Martínez de Tejada *et al.,* 2012; Abati *et al.,* 2013; Ye *et al.,* 2013; Pattanashetti *et al.,* 2013; Macedo *et al.,*2014; Bulut *et al.,* 2014; Jain *et al.,* 2016) and 2,070 participants. Except for the study conducted by Jain *et al.* (2016), all the 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) (0R = 2.31, 95% CI: -1.32, 5.94). 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). 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). 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.

Author	Year, location	Characteristics of population	Sample size	Periodontitis definition	Categorical or continuous analysis of perio-data	Type of recording	Newcastle-Ottawa quality rating	Finding, OR
Martínez-Martínez	2016, Mexico	Women of 20-35 years with a single live pregnancy	70	Numerous definitions: Armitage; Jeffcoat *et al*.; Rdanai *et al*; Bassani *et al*; Macedo *et al*; OMS	Variables	Full recording	Selection** Compar-ability* Exposure***	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
Perunovic	2016, Serbia	Women aged 18-35 with a single live pregnancy	120	≥1 site with PPD≥5 mm	Categorical	Full recording	Selection*** Compar-ability* Exposure**	Yes, this study shows that women with PTB had higher % of periodontitis (FTB 14.3% vs PTB 64.3% (p<0.01)
Muwazi	2014, Uganda	Postpartum mothers of single live preg-nancy	400	Community periodontal index: Moderate periodontitis - PD ≥4 mm Advanced periodontitis - PD ≥ 6 mm Index teeth: 16, 11,26, 36, 31, 46	Categorical	Partial recording	Selection** Compar-ability* Exposure***	No, gingival bleeding, periodontal pocket depth of 4–5 mm, calculus with plaque deposits, and gingival recessions were not significantly associated with gestation age (p > 0.05).
Acharya	2013, India	Women aged 18-42 were visited 1 day after delivery	316	≥1 site with PPD≥4 mm	Categorical	Full recording	Selection* Compar-ability* Exposure**	No, there was not a significant association between periodontal disease and PTB (adjusted OR=1.8 (CI0.9-3.5) p=0.12)
Kothiwale	2014, India	Mothers within the age group of 18–35 years with a single live pregnancy	770	According to the WHO criteria	Categorical	Partial recording	Selection*** Compar-ability* Exposure**	No, there was no statistically significant association (X2 = 9.436, DF = 4, P = 0.051). PTB showed only a greater prevalence of higher CPI scores (27.5% had PPD ≥ 6 mm and 9.3% had PPD ≤ 5 mm) as compared to term delivery (24.2% had PPD ≥ 6, 8.5% had PPD ≤ 5 mm)

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; 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 *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). 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

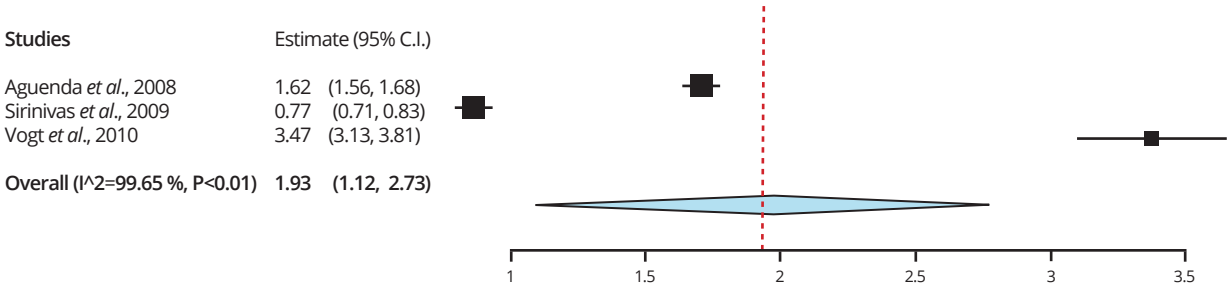
The overall evidence is based on 13 publications: five of these (6,722 participants) did not find any relevant differences between the groups, whereas eight studies (4,307 participants) have significantly related periodontitis and PTB.

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

Author	Year, location	Characteristics of population	Sample size	Periodontitis definition	Categorical or continuous analysis of perio-data	Type of recording	Newcastle-Ottawa quality rating	Finding, OR
Lohana	2017, India	Pregnant women between 20 and 24 weeks	300	Periodontitis: • slight 1-2 mm CAL • moderate 3-4 mm • severe >5 mm	Categorical	Full recording	Selection**** Compar-ability* Exposure****	Yes, there was a statistical association between the level of periodontal disease severity and gestational age. P< 0.001
Tellapragada	2016, India	Pregnant women with a gestational age of 8-24 weeks	726	CPI: ≥1 PPD≥4 mm (CPI score ≥3) among any one of the six index teeth examined	Categorical and lineal	Partial recording	Selection*** Compar-ability* Exposure***	Yes, there were some statistical significant differences for PTB in relation to periodontitis (p<0.001)
Hassan	2016, Saudi Arabia	Women were seen during the second trimester and after delivery	94	Unspecified	Unspecified	Unspecified	Selection**** Compar-ability* Exposure**	Yes, women with PTB had more severe periodontal disease than those with FTB (probing pocket depth= 6.0 and 2.4, clinical attachment loss= 1.9 and 1.6, P<0.0001 and 0.003)
Wang	2014, Taiwan	Pregnant women prior to 26 weeks of gestation	211	Periodontitis: >5% gingival bleeding, with CAL > 6 mm ≥2 sites and with ≥1 sites with PD of 5 mm	Categorical	Full recording	Selection*** Compar-ability* Exposure****	No, the differences in PTB incidence among the groups was not clinically significant (p=0.080)
Kumar	2013, India	Primigravida women aged 20-35 years with single live pregnancy recruited at 14-20 weeks	340	Periodontitis: CAL and PPD >4 mm in one or more sites	Categorical	Full recording	Selection**** Compar-ability* Exposure***	Yes, periodontitis was found to be significantly associated with preterm delivery with OR (95% CI) of 2.72 (1.30–5.68)
Santa Cruz	2013, Spain	Pregnant women exami-ned before 26th week of gestation, and divided in two groups: non-periodontitis and periodontitis	170	≥ 15 sites with CAL ≥3 mm or more CAL loss	Categorical	Full recording	Selection**** Compar-ability* Exposure***	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)

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).

Khader and co-workers (Khader *et al*., 2009) found a significant association for PTLBW 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 PTLBW 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 ≥1site 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 PTLBW ($p<0.01$). 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.

Author	Year, location	Characteristics of population	Sample size	Periodontitis definition	Categorical or continuous analysis of perio-data	Type of recording	Newcastle-Ottawa quality rating	Finding, OR
Kayar	2015, Turkey	Women were seen within 24h of delivery	156	moderate to severe periodontitis: PD>5 mm and CAL > 2 mm	Categorical and linear	Full recording	Selection*** Compar-ability* Exposure***	Yes, The PD ($p < 0.05$) and CAL ($p < 0.05$) values were significantly higher in the cases (OR=1.39, 95% CI: 1.04–1.85)
Blanc	2015, Spain	Women of age ≥18 were seen postpartum	57	≥4 teeth showed ≥1sites with PD ≥4 mm and CA loss ≥3 mm	Categorical	Full recording	Selection** Compar-ability* Exposure***	No, there was no statistically significant association between periodontitis and PLBW
Mesa	2013, Spain	women of age ≥18 were seen postpartum	244	Definition n°1: ≥4 teeth with ≥site showing a PPD≥4 mm and CAL ≥3 mm Definition n°2: ≥1 site with PPD and CAL ≥4 mm	Categorical	Full recording	Selection*** Compar-ability* Exposure**	Yes, there is a significant association; periodontal values were significantly worse in cases versus controls ($p<0.01$)
Mesa	2016, Spain	Pregnant women <37 weeks of gestation	131	≥4 teeth showed ≥1site with PD ≥4 mm and AL≥3 mm at the same site	Categorical	Full recording	Selection*** Compar-ability* Exposure**	No, there was no statistically significant difference, although periodontal parameters are worse in cases

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

Author	Year, location	Characteristics of population	Sample size	Periodontitis definition	Categorical or continuous analysis of perio-data	Type of recording	Newcastle-Ottawa quality rating	Finding, OR
Acharya	2013, India	Unspecified	316	Unspecified	Linear	Full recording	Selection* Compar-ability* Exposure**	No, there was no significant association between periodontal disease and PLBW (adjusted OR: PPD>4 OR=1.7 (0.7-4.3), p=0.24)

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 (Table 9) 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.

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

Author	Year, location	Characteristics of population	Sample size	Periodontitis definition	Categorical or continuous analysis of perio-data	Type of recording	Newcastle-Ottawa quality rating	Finding, OR
Tellapragada	2016, India	Pregnant women with a gestational age of 8-24 weeks	790 (726 follow up)	Community Periodontal Index (CPI) scoring system at the time of recruitment. A pathological pocket depth of at least 4 mm (CPI score ≥3) among any one of the six index teeth examined was diagnostic for periodontitis	categorical	Partial recording	Selection*** Compar-ability* Exposure****	Yes, there was statistical significant differences for PLBW in people affected and not by periodontitis (p=0.001); aRR=3.29 (1.8, 5.7)

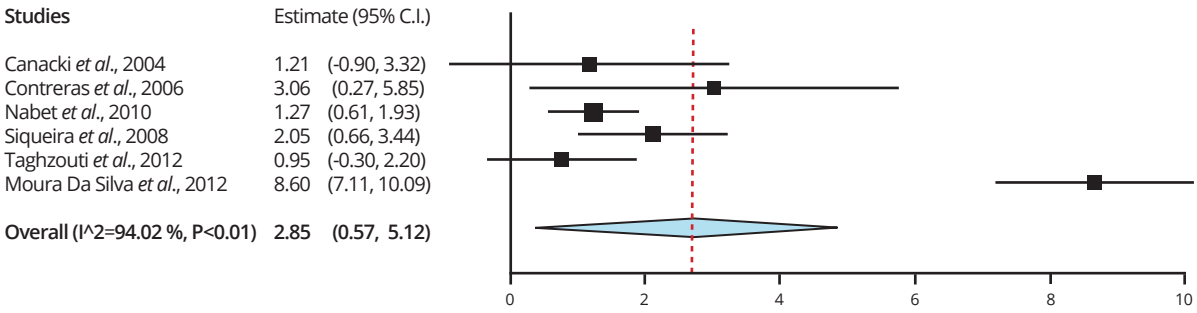
Studies investigating maternal periodontitis and pre-eclampsia (PE), E4:

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*., 2012) 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.

Figure 7.
Meta-analysis plot of case-control studies of pre-eclampsia reporting periodontitis as a categorical variable (odds ratio).



New evidence

New evidence is based on four publications (Table 10) (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 moderate periodontitis (≥1 site with CAL 4-6mm) and 1.2 for severe periodontitis (≥1 site with CAL≥6). 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.

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

Author	Year, location	Characteristics of population	Sample size	Periodontitis definition	Categorical or continuous analysis of perio-data	Type of recording	Newcastle-Ottawa quality rating	Finding, OR
Chaparro	2016, Chile	Women with at least 18 teeth	30	As ≥4 teeth with ≥1 site with PPD≥4 and CAL≥3 and positive BoP	Categorical	Full recording	Selection**- Compar-ability* Exposure**	No, there was no statistically significant difference between the groups
Pattanashetti	2013, India	Women aged 20-30 years seen at 6 months of pregnancy and after 48h postpartum	200	Mild periodontitis: ≥1 site with PPD≥3mm and positive BoP Severe periodontitis: ≥15 sites with PPD≥4 mm	Categorical	Full recording	Selection*** Compar-ability* Exposure**	The 30% of cases (pre-eclamptic patients) were characterized by moderate/severe periodontitis, against the 20% of controls.
Abati	2013, Italy	Women were seen postpartum within five days of delivery	750	Moderate periodontitis: ≥1 site with CAL 4-6 mm Severe periodontitis: ≥1 site with CAL≥6	Categorical	Full recording	Selection*** Compar-ability* Exposure***	No, there was no statistically significant difference between the groups.
Moura Da Silva	2012, Brazil	Puerperae with pre-eclampsia and puerperae without pre-eclampsia visited during the 48-hour postpartum period	574	≥4 teeth with ≥1 site with PPD≥4mm and CAL ≥3mm in the same site	Categorical	Full recording	Selection*** Compar-ability* Exposure***	Yes, there was a significant difference (OR=8.60, 3,92-18,88)

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 I2=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 11). 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 11.
Selected cross-sectional studies of maternal periodontitis and pre-eclampsia.

Author	Year, location	Characteristics of population	Sample size	Periodontitis definition	Categorical or continuous analysis of perio-data	Type of recording	Newcastle-Ottawa quality rating	Finding, OR
Hirano	2012, Japan	Women were examined 5 days after labour	127	≥ 60% of sites with CAL >3 mm	Categorical and linear	Full recording	Selection** Compar-ability* Exposure***	No, there was no a statistically significant association

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).

New evidence

New evidence (Table 12) 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).

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

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

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 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.

References

Abati, S., Villa, A., Cetin, I., Dessole, S., Luglie, P. F., Strohmenger, L., Ottolenghi, L. & Campus, G. G. (2013) Lack of association between maternal periodontal status and adverse pregnancy outcomes: a multicentric epidemiologic study. *The Journal Of Maternal-fetal & Neonatal Medicine : The Official Journal Of The European Association Of Perinatal Medicine, The Federation Of Asia And Oceania Perinatal Societies, The International Society Of Perinatal Obstetricians* 26, 369–372.

Acharya, S., Pentapati, K.C. & Bhat, P. V. (2013) Dental neglect and adverse birth outcomes: a validation and observational study. *International Journal Of Dental Hygiene* 11, 91–98.

Agueda, A., Ramón, J. M., Manau, C., Guerrero, A. & Echeverría, J. J. (2007) Periodontal disease as a risk factor for adverse pregnancy outcomes: a prospective cohort study. *Journal Of Clinical Periodontology* 35 (1), 16-22.

Armitage, G. C. (1999) Development of a Classification System for Periodontal Diseases and Conditions. *Annals Of Periodontology* 4, 1-6.

Armitage, G. C. (2013) Bi-directional relationship between pregnancy and periodontal disease. *Periodontology 2000* 61, 160-176.

Bassani, D. G., Olinto, M. T. A. & Kreiger, N. (2007) Periodontal disease and perinatal outcomes: a case-control study. *Journal Of Clinical Periodontology* 34, 31-39.

Blanc, V., O'Valle, F., Pozo, E., Puertas, A., Leon, R. & Mesa, F. (2015) Oral bacteria in placental tissues: increased molecular detection in pregnant periodontitis patients. *Oral Diseases* 21, 905-912.

Boggess, K. A., Berggren, E. K., Koskenoja, V., Urlaub, D. & Lorenz, C. (2013) Severe pre-eclampsia and maternal self-report of oral health, hygiene, and dental care. *Journal Of Periodontology* 84, 143-151.

Boggess, K. A., Lieff, S., Murtha, A. P., Moss, K., Beck, J. & Offenbacher, S. (2003) Maternal periodontal disease is associated with an increased risk for pre-eclampsia. *Obstetrics And Gynecology* 101, 227-231.

Borgnakke, W. S., Ylöstalo, P. V., Taylor, G.W. & Genco, R. J. (2013) Effect of periodontal disease on diabetes: Systematic review of epidemiologic observational evidence. *Journal Of Clinical Periodontology* 40, S135-S152.

Bosnjak, A., Relja, T., Vucićević-Boras, V., Plasaj, H. & Plancak, D. (2006) Preterm delivery and periodontal disease: a case-control study from Croatia. *Journal Of Clinical Periodontology* 33, 710-716.

Buduneli, N., Baylas, H., Buduneli, E., Turkoglu, O., Kose, T. & Dahlen, G. (2005) Periodontal infections and preterm low birth weight: a case-control study. *Journal Of Clinical Periodontology* 32, 174-181.

Bulut, G., Olukman, O. & Calkavur, S. (2014) Is there a relationship between maternal periodontitis and preterm birth? A prospective hospital-based case-control study. *Acta Odontologica Scandinavica* 72, 866-873.

Canakci, V., Canakci, C. F., Canakci, H., Canakci, E., Cicek, Y., Ingec, M., Ozgoz, M., Demir, T., Dilsiz, A. & Yagiz, H. (2004) Periodontal disease as a risk factor for pre-eclampsia: A case control study. *The Australian & New Zealand Journal Of Obstetrics & Gynaecology* 44, 1-6.

Chaparro, A., Sanz, A., Quintero, A., Inostroza, C., Ramirez, V., Carrion, F., Figueroa, F., Serra, R. & Illanes, S.E. (2013) Increased inflammatory biomarkers in early pregnancy is associated with the development of pre-eclampsia in patients with periodontitis: a case control study. *Journal Of Periodontal Research* 48, 302-307.

Contreras, A., Herrera, J. A., Soto, J. E., Arce, R. M., Jaramillo, A. & Botero, J. E. (2006) Periodontitis is associated with pre-eclampsia in pregnant women. *Journal Of Periodontology* 77, 182-188.

Cruz, S. S., Costa, M. da C. N., Gomes-Filho, I. S., Rezende, E. J. C., Barreto, M.L., Dos Santos, C.A.S.T., Vianna, M.I.P., Passos, J. S. & Cerqueira, E. M. M. (2009) Contribution of periodontal disease in pregnant women as a risk factor for low birth weight. *Community Dentistry And Oral Epidemiology* 37, 527-533.

Davenport, E. S., Williams, C. E. C. S., Sterne, J. A. C., Murad, S., Sivapathasundram, V. & Curtis, M. A. (2002) Maternal Periodontal Disease and Preterm Low Birthweight: Case-Control Study. *Journal Of Dental Research* 81, 313-318.

Duley, L. (2009) The global impact of pre-eclampsia and eclampsia. *Seminars In Perinatology* 33, 130–137.

Ercan, E., Eratalay, K., Deren, O., Gur, D., Ozyuncu, O., Altun, B., Kanli, C., Ozdemir, P. & Akincibay, H. (2013) Evaluation of periodontal pathogens in amniotic fluid and the role of periodontal disease in preterm birth and low birth weight. *Acta Odontologica Scandinavica* 71, 553-559.

Farrell, S., Ide, M. & Wilson, R. F. (2006) The relationship between maternal periodontitis, adverse pregnancy outcome and miscarriage in never smokers. *Journal Of Clinical Periodontology* 33, 115-120.

Giannella, L., Giulini, S., Cerami, L. B., La Marca, A., Forabosco, A. & Volpe, A. (2011) Periodontal disease and nitric oxide levels in low risk women with preterm labor. *European Journal Of Obstetrics Gynecology And Reproductive Biology* 158, 47-51.

Gomes-Filho, I. S., Cruz, S.S., Rezende, E. J. C., dos Santos, C.A.S.T., Soledade, K. R., Magalhães, M. A., de Azevedo, A.C.O., Trindade, S. C., Vianna, M. I. P., Passos, J. de S. & Cerqueira, E.M.M. (2007) Exposure measurement in the association between periodontal disease and prematurity/low birth weight. *Journal Of Clinical Periodontology* 34, 957-963.

Gomes-Filho, I. S., Cruz, S.S., Rezende, E.J.C., Silveira, B. B. d. B., Trindade, S. C., Passos, J. S., Freitas, C.O.T., Cerqueira, E.M.M. & Santos, C. A. de S. T. (2006) Periodontal status as predictor of prematurity and low birth weight. *Journal Of Public Health Dentistry* 66, 295-298.

Gomes-Filho, I. S., Pereira, E. C., Cruz, S. S., Adan, L. F. F., Vianna, M. I. P., Passos-Soares, J. S., Trindade, S. C., Oliveira, E. P., Oliveira, M. T., Cerqueira, E. de M.M., Pereira, A. L., Barreto, M. L. & Seymour, G. J. (2016) Relationship among mothers' glycemic level, periodontitis, and birth weight. *Journal Of Periodontology* 87, 238-247.

Guimarães, A. N., Silva-Mato, A., Miranda Cota, L. O., Siqueira, F. M. & Costa, F. O. (2010) Maternal periodontal disease and preterm or extreme preterm birth: an ordinal logistic regression analysis. *Journal Of Periodontology* 81, 350-358.

Guimaraes, A. N., Silva-Mato, A., Siqueira, F. M., Cyrino, R. M., Cota, L.O.M. & Costa, F.O. (2012) Very low and low birth weight associated with maternal periodontitis. *Journal Of Clinical Periodontology* 39, 1024-1031.

Gürsoy, M. & Graziani, F. (2017) The biological mechanisms between periodontal diseases and pregnancy complications, unpublished data.

Ha, J. E., Jun, J. K., Ko, H. J., Paik, D. I. & Bae, K.H. (2014) Association between periodontitis and pre-eclampsia in never-smokers: a prospective study. *Journal Of Clinical Periodontology* 41, 869-874.

Al Habashneh, R., Khader, Y.S., Al Jabali, O. Al & Alchalabi, H. (2013) Prediction of preterm and low birth weight delivery by maternal periodontal parameters: receiver operating characteristic (ROC) curve analysis. *Maternal And Child Health Journal* 17, 299-306.

Haerian-Ardakani, A., Eslami, Z., Rashidi-Meibodi, F., Haerian, A., Dallalnejad, P., Shekari, M., Moein Taghavi, A. & Akbari, S. (2013) Relationship between maternal periodontal disease and low birth weight babies. *Iranian Journal Of Reproductive Medicine* 11, 625-630.

Hassan, K. S., El Tantawi, M. M., Alagl, A.S., Alnimr, A. M. & Haseeb, Y.A. (2016) Sensitivity and specificity of subgingival bacteria in predicting preterm birth – a pilot cohort study. *International Journal Of Health Sciences* 10, 532-541.

Heimonen, A., Janket, S.-J., Kaaja, R., Ackerson, L. K., Muthukrishnan, P. & Meurman, J. H. (2009) Oral inflammatory burden and preterm birth. *Journal Of Periodontology* 80, 884-891.

Hingorani, A.D. & D'Aiuto, F. (2008) Chronic inflammation, periodontitis and cardiovascular diseases. *Oral Diseases* 14, 102-104.

Hirano, E., Sugita, N., Kikuchi, A., Shimada, Y., Sasahara, J., Iwanaga, R., Tanaka, K. & Yoshie, H. (2012) The association of *Aggregatibacter actinomycetemcomitans* with pre-eclampsia in a subset of Japanese pregnant women. *Journal Of Clinical Periodontology* 39, 229-238.

Horton, A. L., Boggess, K. A., Moss, K.L., Beck, J. & Offenbacher, S. (2010) Periodontal disease, oxidative stress, and risk for pre-eclampsia. *Journal Of Periodontology* 81, 199-204.

Ide, M. & Papapanou, P. N. (2013) Epidemiology of association between maternal periodontal disease and adverse pregnancy outcomes – systematic review. *Journal Of Periodontology* 84, S181-S194.

Iwanaga, R., Sugita, N., Hirano, E., Sasahara, J., Kikuchi, A., Tanaka, K. & Yoshie, H. (2011) FcγRIIB polymorphisms, periodontitis and preterm birth in Japanese pregnant women. *Journal Of Periodontal Research* 46, 292-302.

Jacob, P. S. & Nath, S. (2014) Periodontitis among poor rural Indian mothers increases the risk of low birth weight babies: a hospital-based case control study. *Journal Of Periodontal & Implant Science* 44, 85-93.

Jain, S., Sharma, S., Chawla, S., Vaid, B.N., Kalra, N., Suneja, A., Guleria, K. & Kaur, L. (2016) Periodontal disease as a risk factor for preterm delivery in Indian women. *J. Evolution Med. Dent. Sci.* 5, 6565-6569.

Jarjoura, K., Devine, P. C., Perez-Delboy, A., Herrera-Abreu, M., D'Alton, M. & Papapanou, P.N. (2005) Markers of periodontal infection and preterm birth. *American Journal Of Obstetrics And Gynecology* 192, 513-519.

Jeffcoat, M. K., Geurs N. C., Reddy, M.S., Cliver, S. P., Goldenberg, R.L. & Hauth, J. C. (2001) Periodontal infection and preterm birth: Results of a prospective study. *The Journal Of The American Dental Association* 132, 875-880.

Kayar, N. A., Alptekin, N. O. & Erdal, M. E. (2015) Interleukin-1 receptor antagonist gene polymorphism, adverse pregnancy outcome and periodontitis in Turkish women. *Archives Of Oral Biology* 60, 1777-1783.

Khader, Y., Al-Shishani, L., Obeidat, B., Khassawneh, M., Burgan, S., Amarin, Z.O., Alomari, M. & Alkafajei, A. (2009) Maternal periodontal status and preterm low birth weight delivery: A case-control study. *Archives Of Gynecology And Obstetrics* 279, 165-169.

Kothiwale, S. V, Desai, B.R., Kothiwale, V. A., Gandhid, M. & Konin, S. (2014) Periodontal disease as a potential risk factor for low birth weight and reduced maternal haemoglobin levels. *Oral Health & Preventive Dentistry* 12, 83-90.

Kumar, A., Basra, M., Begum, N., Rani, V., Prasad, S., Lamba, A. K., Verma, M., Agarwal, S. & Sharma, S. (2013) Association of maternal periodontal health with adverse pregnancy outcome. *The Journal Of Obstetrics And Gynaecology Research* 39, 40-45.

Kumar, A., Begum, N., Prasad, S., Lamba, A. K., Verma, M., Agarwal, S. & Sharma, S. (2014) Role of cytokines in development of pre-eclampsia associated with periodontal disease – Cohort Study. *Journal Of Clinical Periodontology* 41, 357-365.

Le, H.T.T., Jareinpituk, S., Kaewkungwal, J. & Pitiphat, W. (2007) Increased risk of preterm birth among non- smoking, non- alcohol drinking women with maternal periodontitis. *Southeast Asian Journal Of Tropical Medicine And Public Health* 38, 586-593.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J.P.A., Clarke, M., Devereaux, P. J., Kleijnen, J. & Moher, D. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal Of Clinical Epidemiology* 62, e1-34.

Lohana, M. H., Suragimath, G., Patange, R. P., Varma, S. & Zope, S.A. (2017) A prospective cohort study to assess and correlate the maternal periodontal status with their pregnancy outcome. *Journal Of Obstetrics And Gynaecology Of India* 67, 27-32.

López, N. J., Smith, P. C. & Gutiérrez, J. (2002) Higher risk of preterm birth and low birth weight in women with periodontal disease. *Journal Of Dental Research* 81, 58-63.

Lunardelli, A. N. & Peres, M. A. (2005) Is there an association between periodontal disease, prematurity and low birth weight? A population-based study. *Journal Of Clinical Periodontology* 32, 938-946.

Macedo, J. F., Ribeiro, R. A., Machado, F. C., Assis, N.M.S.P., Alves, R. T., Oliveira, A.S. & Ribeiro, L. C. (2014) Periodontal disease and oral health-related behavior as factors associated with preterm birth: a case-control study in South-Eastern Brazil. *Journal Of Periodontal Research* 49, 458-464.

Marin, C., Segura-Egea, J. J., Martinez-Sahuquillo, A. & Bullon, P. (2005) Correlation between infant birth weight and mother's periodontal status. *Journal Of Clinical Periodontology* 32, 299-304.

Martínez-Martínez, R. E., Moreno-Castillo, D. F., Loyola-Rodríguez, J. P., Sánchez-Medrano, A. G., Miguel-Hernández, J.H.S., Olvera-Delgado, J. H. & Domínguez-Pérez, R. A. (2016) Association between periodontitis, periodontopathogens and preterm birth: is it real? *Archives Of Gynecology And Obstetrics* 294, 47-54.

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

definitions. *The Journal Of Maternal-fetal & Neonatal Medicine*: *The Official Journal Of The European Association Of Perinatal Medicine, The Federation Of Asia And Oceania Perinatal Societies, The International Society Of Perinatal Obstetricians* 25, 2160-2166.

Mathew, R. J., Bose, A., Prasad, J. H., Muliyil, J. P. & Singh, D. (2014) Maternal periodontal disease as a significant risk factor for low birth weight in pregnant women attending a secondary care hospital in South India: a case-control study. *Indian Journal Of Dental Research: Official Publication Of Indian Society For Dental Research* 25, 742-747.

Mesa, F., Pozo, E., Blanc, V., Puertas, A., Bravo, M. & O'Valle, F. (2013) Are periodontal bacterial profiles and placental inflammatory infiltrate in pregnancy related to birth outcomes? *Journal Of Periodontology* 84, 1327-1336.

Mesa, F., Pozo, E., O'Valle, F., Puertas, A., Magan-Fernandez, A., Rosel, E. & Bravo, M. (2016) Relationship between periodontal parameters and plasma cytokine profiles in pregnant woman with preterm birth or low birth weight. *Clinical Oral Investigations* 20, 669-674.

Moher, D., Liberati, A., Tetzlaff, J. & Altman, D. G., PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 339, b2535.

Moore, S., Randhawa, M. & Ide, M. (2005) A case-control study to investigate an association between adverse pregnancy outcome and periodontal disease. *Journal Of Clinical Periodontology* 32, 1-5.

Moura da Silva, G., Coutinho, S. B., Piscoya, M.D.B. V, Ximenes, R. A. A. & Jamelli, S.R. (2012) Periodontitis as a risk factor for pre-eclampsia. *Journal Of Periodontology* 83, 1388-1396.

Muwazi, L., Rwenyonyi, C. M., Nkamba, M., Kutesa, A., Kagawa, M., Mugyenyi, G., Kwizera, G. & Okullo, I. (2014) Periodontal conditions, low birth weight and preterm birth among postpartum mothers in two tertiary health facilities in Uganda. *BMC Oral Health* 14, 42.

Nabet, C., Lelong, N., Colombier, M. L., Sixou, M., Musset, A. M., Goffinet, F. & Kaminski, M. (2010) Maternal periodontitis and the causes of preterm birth: The case-control Epipap study. *Journal Of Clinical Periodontology* 37, 37-45.

Needleman, I., Nibali, L. & Di Iorio, A. (2015) Professional mechanical plaque removal for prevention of periodontal diseases in adults – Systematic review update. *Journal Of Clinical Periodontology* 42, S12-S35.

Noack, B., Genco, R. J., Trevisan, M., Grossi, S., Zambon, J. J. & Nardin, E. De. (2001) Periodontal infections contribute to elevated systemic c-reactive protein level. *Journal Of Periodontology* 72, 1221-1227.

Noack, B., Klingenberg, J., Weigelt, J. & Hoffmann, T. (2005) Periodontal status and preterm low birth weight: a case control study. *Journal Of Periodontal Research* 40, 339-345.

Offenbacher, S., Katz, V., Fertik, G., Collins, J., Boyd, D., Maynor, G., McKaig, R. & Beck, J. (1996) Periodontal infection as a possible risk factor for preterm low birth weight. *Journal Of Periodontology* 67, 1103-1113.

Pattanashetti, J. I., Nagathan, V. M. & Rao, S. M. (2013) Evaluation of periodontitis as a risk for preterm birth among preeclamptic and non-preeclamptic pregnant women – A case control study. *Journal Of Clinical And Diagnostic Research : JCDR* 7, 1776-1778.

Perunovic, N. D., Rakic, M. M., Nikolic, L. I., Jankovic, S. M., Aleksic, Z. M., Plecas, D. V, Madianos, P. N. & Cakic, S.S. (2016) The association between periodontal inflammation and labor triggers (elevated cytokine levels) in preterm birth: a cross-sectional study. *Journal Of Periodontology* 87, 248-256.

Piscoya, M.D.B. V, Ximenes, R.A.A., Silva, G. M., Jamelli, S. R. & Coutinho, S. B. (2012) Maternal periodontitis as a risk factor for prematurity. *Pediatrics International* 54, 68-75.

Radnai, M., Gorzó, I., Nagy, E., Urbán, E., Novák, T. & Pál, A. (2004) A possible association between preterm birth and early periodontitis: Pilot study. *Journal Of Clinical Periodontology* 31, 736-741.

Radnai, M., Gorzó, I., Urbán, E., Eller, J., Novák, T. & Pál, A. (2006) Possible association between mother's periodontal status and preterm delivery. *Journal Of Clinical Periodontology* 33, 791-796.

Rakoto-Alson, S., Tenenbaum, H. & Davideau, J.-L. (2010) Periodontal diseases, preterm births, and low birth weight: findings from a homogeneous cohort of women in Madagascar. *Journal Of Periodontology* 81, 205-213.

Reza Karimi, M., Hamissi, J. H., Naeini, S.R. & Karimi, M. (2015) The relationship between maternal periodontal status of and preterm and low birth weight infants in Iran: A case control study. *Global Journal Of Health Science* 8, 184-188.

Riche, E. L., Boggess, K. A., Lieff, S., Murtha, A. P., Auten, R. L., Beck, J. D. & Offenbacher, S. (2002) Periodontal disease increases the risk of preterm delivery among preeclamptic women. *Ann Periodontol* 7, 95-101.

Saddki, N., Bachok, N., Hussain, N.H.N., Zainudin, S.L.A. & Sosroseno, W. (2008) The association between maternal periodontitis and low birth weight infants among Malay women. *Community Dentistry And Oral Epidemiology* 36, 296-304.

Santa Cruz, I., Herrera, D., Martin, C., Herrero, A. & Sanz, M. (2013) Association between periodontal status and preterm and/or low-birth weight in Spain: clinical and microbiological parameters. *Journal Of Periodontal Research* 48, 443-451.

Santos-Pereira, S.A., Giraldo, P. C., Saba-Chujfi, E., Amaral, R.L.G., Morais, S. S., Fachini, A. M. & Gonçalves, A.K.S. (2007) Chronic periodontitis and preterm labour in Brazilian pregnant women: An association to be analysed. *Journal Of Clinical Periodontology* 34, 208-213.

Sanz, M. & Kornman, K. (2013) Periodontitis and adverse pregnancy outcomes: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *Journal Of Clinical Periodontology 40 Suppl* 1, S164-S169.

Siqueira, F.M., Cota, L.O.M., Costa, J. E., Haddad, J.P.A., Lana, Â.M.Q. & Costa, F.O. (2007) Intrauterine Growth Restriction, Low Birth Weight, and Preterm Birth: Adverse Pregnancy Outcomes and Their Association With Maternal Periodontitis. *Journal Of Periodontology* 78, 2266–2276.

Siqueira, F. M., Cota, L.O.M., Costa, J. E., Haddad, J. P. A., Lana, Â.M.Q. & Costa, F.O. (2008) Maternal periodontitis as a potential risk variable for pre-eclampsia: A case-control study. *Journal Of Periodontology* 79, 207–215.

Slade, G. D., Offenbacher, S., Beck, J. D., Heiss, G. & Pankow, J. S. (2000) Acute-phase inflammatory response to periodontal disease in the US population. *Journal Of Dental Research* 79, 49–57.

Srinivas, S. K., Sammel, M. D., Stamilio, D. M., Clothier, B., Jeffcoat, M. K., Parry, S., Macones, G. A., Elovitz, M. A. & Metlay, J. (2009) Periodontal disease and adverse pregnancy outcomes: is there an association? *American Journal Of Obstetrics And Gynecology* 200, 497.e1-497.e8.

Taghzouti, N., Xiong, X., Gornitsky, M., Chandad, F., Voyer, R., Gagnon, G., Leduc, L., Xu, H., Tulandi, T., Wei, B., Senecal, J., Velly, A. M., Salah, M. H. & Fraser, W.D. (2012) Periodontal disease is not associated with pre-eclampsia in Canadian pregnant women. *Journal Of Periodontology* 83, 871-877.

Tellapragada, C., Eshwara, V. K., Bhat, P., Acharya, S., Kamath, A., Bhat, S., Rao, C., Nayak, S. & Mukhopadhyay, C. (2016) Risk factors for preterm birth and low birth weight among pregnant Indian women: A Hospital-based Prospective Study. *Journal Of Preventive Medicine And Public Health = Yebang Uihakhoe Chi* 49, 165-175.

Toygar, H. U., Seydaoglu, G., Kurklu, S., Guzeldemir, E. & Arpak, N. (2007) Periodontal Health and Adverse Pregnancy Outcome in 3,576 Turkish Women. *Journal Of Periodontology* 78, 2081-2094.

Vettore, M. V., Leão, A.T., Leal, M. do C., Feres, M. & Sheiham, A. (2008a) The relationship between periodontal disease and preterm low birth weight: clinical and microbiological results. *Journal Of Periodontal Research* 43, 615-626.

Vettore, M. V., Leal, M. do C., Leão, A. T., da Silva, A.M.M., Lamarca, G. A. & Sheiham, A. (2008b) The Relationship between Periodontitis and Preterm Low Birthweight. *Journal Of Dental Research* 87, 73-78.

Vogt, M., Sallum, A. W., Cecatti, J. G. & Morais, S. S. (2010) Periodontal disease and some adverse perinatal outcomes in a cohort of low risk pregnant women. *Reproductive Health* 7, 29.

Wang, Y. L., Liou, J. D. & Pan, W. L. (2013) Association between maternal periodontal disease and preterm delivery and low birth weight. *Taiwanese Journal Of Obstetrics & Gynecology* 52, 71-76.

Wood, S., Frydman, A., Cox, S., Brant, R., Needoba, S., Eley, B. & Sauve, R. (2006) Periodontal disease and spontaneous preterm birth: a case control study. *BMC Pregnancy Childbirth* 6, 24.

World Health Organization. (2011) *WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia*. Geneva: World Health Organization.

World Health Organization & Brämer, G.R. (1992) *International Statistical Classification of Diseases and Related Health Problems*. 10th Revision.

Ye, C., Katagiri, S., Miyasaka, N., Bharti, P., Kobayashi, H., Takeuchi, Y., Momohara, Y., Sekiguchi, M., Takamine, S., Nagasawa, T. & Izumi, Y. (2013) The anti-phospholipid antibody-dependent and independent effects of periodontopathic bacteria on threatened preterm labor and preterm birth. *Archives Of Gynecology And Obstetrics* 288, 65-72.

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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.

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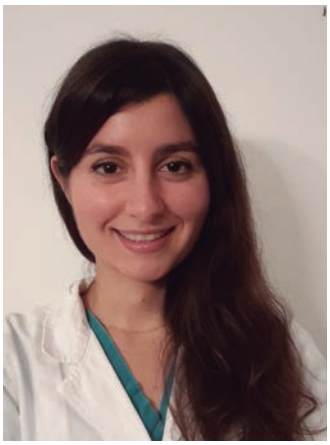

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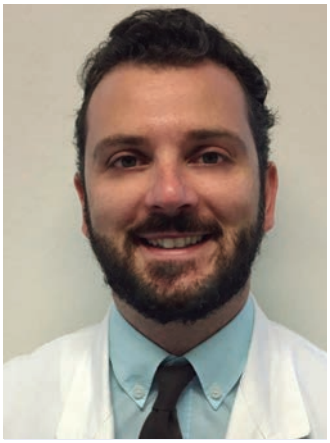
Morena Petrini is a postdoctoral researcher in periodontology at the University of Pisa (Italy). Graduated (cum laude) as a doctor in dentistry in 2008, she was awarded her PhD in Basic and Applied Medical Science with the mention of "Doctor Europeus" in 2013, and she obtained her speciality (cum laude)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

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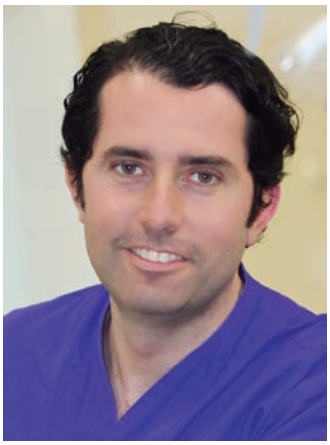

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Filippo Graziani is an associate professor of periodontology at the University of Pisa (Italy), an honorary professor at the University of Hong Kong, and an honorary senior lecturer in periodontology at University College London (UK). He graduated (cum laude) as a doctor in dentistry in 1998 at the University of Pisa, and was awarded his PhD in oral and maxillofacial surgery in 2001 by the University of Naples. He obtained his speciality in periodontology (distinction) from the Eastman Dental Institute at University College London in 2004. Further qualifications include a master's degree in clinical research (University of Pisa) and a speciality in oral surgery.

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.

Oral Health and **Pregnancy**: the project

Oral Health & Pregnancy

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

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

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

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

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

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

oralhealthandpregnancy.efp.org

A joint
EFP - Oral-B project

European Federation of Periodontology

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

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

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.

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

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