Effect of periodontal disease treatment during pregnancy on preterm birth incidence: a metaanalysis of randomized trials

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We conducted a metaanalysis of randomized controlled trials to determine whether periodontal disease treatment with scaling and/or root planing during pregnancy may reduce preterm birth (PTB) or low birthweight (LBW) infant incidence. Treatment resulted in significantly lower PTB (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.35-0.86; $P = .008$) and borderline significantly lower LBW (OR, 0.48; 95% CI, 0.23-1.00; $P = .049$), whereas no difference was found for spontaneous abortion/stillbirth (OR, 0.73; 95% CI, 0.41-1.31; $P = .292$). Subgroup analysis suggested significant effect of treatment in the absence of history of PTB or LBW (OR, 0.48; 95% CI, 0.29-0.77; $P = .003$) and less severe periodontal disease as defined by probing depth (OR, 0.49; 95% CI, 0.28-0.87; $P = .014$) or bleeding on probing site (OR, 0.37; 95% CI, 0.14-0.95; $P = .04$). If ongoing large and well-designed randomized trials support our results, we might need to reassess current practice or at least be cautious prior to rejecting treatment of periodontal disease with scaling and/or root planing during pregnancy.

Key words: gingivitis, low birthweight, metaanalysis, periodontitis, pregnancy, preterm birth

Background and objective

Preterm birth (PTB) rate affects almost 12-13% of pregnancies in the United States and 5-9% in Europe and developed countries.[1] PTB is the number 1 cause of neonatal morbidity and mortality and causes 75% of neonatal deaths that are not a result of congenital anomalies. Although most preterm babies survive, they are at increased risk of neurodevelopmental, respiratory, and gastrointestinal complications.[2]

Approximately 70% of cases of PTB are spontaneous and no specific cause can be identified.[3] Infection has been associated with preterm delivery and low birth weight (LBW) of the infant. Microbiological studies suggest that intrauterine infection might account for 25-40% of PTBs,[4] whereas others claim that this can be the minimum estimate because conventional culture techniques cannot detect all cases with intrauterine infections.[5]

Microorganisms may result in chorioamnionitis mainly either ascending from the vagina and the cervix or by retrograde spread through the fallopian tubes. Nonetheless, other causes of pathogens access in the chorionic cavity are accidental introduction at the time of invasive procedures and hematogenous dissemination through the placenta.

Remote site infections, such as periodontitis, may cause PTB through hematogenous transportation of specific pathogens, organisms, or inflammatory cytokines in the amniotic fluid or chorioamniotic membranes.[6] Periodontal disease during pregnancy has been postulated to be 1 of the causes of PTB and LBW infants. Several case-control studies suggested that periodontitis is an increased risk factor independent of other factors. A recent metaanalysis of 17 observational studies[7] and a previous 1 of 2 case controls and 3 prospective cohorts[8] indicated an association between periodontal disease and PTB or LBW infants.

Several randomized trials have been published comparing nonsurgical treatment vs no treatment in pregnant women with periodontal disease regarding PTB and LBW infant rates. However, its effect remains unclear. Although early and latest data showed a beneficial effect of treatment, one of the largest randomized trials revealed no benefit.[9] Surprisingly, this randomized trial has found a higher rate of stillbirths/spontaneous abortions in the control, nontreatment group.

To shed light on this discrepancy and determine whether treatment of periodontal disease during pregnancy has the potential of reducing PTB or LBW incidence, we conducted a metaanalysis of all up-to-date randomized controlled trials.

Materials and methods

Identification of randomized studies

Two independent investigators (D. M. and S. T.) searched the Cochrane Central Trials Registry, Web of Science, and Medline without year and language restriction. The last search was updated in January 2008. Results were compared and a consensus was reached with the involvement of a third investigator (I. P. P.). We used the following searching algorithm: (periodontal disease or periodontitis or gingivitis) and (preterm labor or PTB or premature rupture of membranes or PROM or LBW). In addition, we tried to identify any previous systematic reviews of randomized trials

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TABLE 1
Maternal baseline characteristics from trials included in the analysis

ID	Study	Treatment	Total no. of patients	Patients followed up	Live births	Gestational age (wks)	Age mean (y)	Nulliparous (%)	Previous PTB/LBW (%)	< 12 y education (%)	Smoking (%)	Vaginosis (%)	Country
1	López et al[17]	Yes	200	176	168	< 21	28	21.47	4.3	33.4	25.7	25.1	Chile
	2002	No	200	196	190		27	25	7.4	40.8	23.4	17	
2	Jeffcoat et al[13]	Yes	123	123	123	< 25	22.8	19.1	4.1[a]	NA	13	24.4	US
	2003	No	123	123	123		22.2	19.4	4.9[a]	NA	12.2	23.6	
3	López et al[18]	Yes	580	570	563	< 22	25.54	35.80	3.44	77.76	14.47	17.18	Chile
	2005	No	290	286	282		24.98	33.45	7.47	80.78	17.44	18.15	
4	Michalowicz et al[9]	Yes	413	407	402	< 21	26.1	25.9	12.5	76.3	13	12	US
	2006	No	410	405	391		25.9	25.6	16.5	77.6	13	12	
5	Offenbacher et al[15]	Yes	40	35	35	< 22	26.8	NA	75	62.2	7.5	12.5	US
	2006	No	34	32	32		25.7	NA	88.2	76.5	11.8	23.5	
6	Sadatmansouri et al[16]	Yes	15	15	15	< 20	29.1	NA	0	6.7	NA	6.7	Iran
	2006	No	15	15	15		28.4	NA	13.3	6.7	NA	20	
7	Tarannum and Faizuddin[14]	Yes	120	101	99	< 21	23	42	NA	NA	0	NA	India
	2007	No	100	91	89		22.9	41	NA	NA	0	NA	

ID, study number; *LBW*, low birthweight infants; *NA*, nonapplicable; *PTB*, preterm birth.

[a] History of preterm birth < 35 weeks.

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in this field. We reviewed the references of all eligible trials. Cross-searches were performed in Medline using the names of investigators who were lead authors in at least 1 eligible trial.

Finally, the last 5-year volumes of 3 journals were hand-searched for potentially eligible articles.

Eligibility criteria

We considered eligible all randomized controlled studies comparing periodontal treatment with scaling and/or root planing vs no treatment or prophylaxis in pregnant women with periodontal disease. Trials were considered eligible if they included pregnant women with documented periodontal disease (periodontitis or gingivitis) as defined by the International Workshop for a Classification of Periodontal Diseases and Conditions in 1999.[10] Trials were considered eligible regardless of the depth and severity of periodontal disease.

For trials that, according to their protocol, had included arms with patients receiving concomitant treatment (eg, antibiotics), we focused on the eligible patient subgroups.

We finally excluded single-arm studies, nonrandomized and pseudorandomized trials, and trials published in meeting abstracts.

Data extraction and outcomes

Data were extracted by N. P. P. and I. P. P. From each eligible trial we recorded for both arms the following items: authors' names, journal and year of publication, country of origin, gestational age at enrollment, number of patients randomized and eligible per arm, number of live births, and patients' inclusion criteria. Baseline characteristics at enrollment that could affect PTB rates included mean age, parity, education level, smoking and history of vaginosis during ongoing pregnancy, and history of PTB (< 37 weeks; Table 1). Periodontal status was determined prior to treatment by recording the number of natural teeth, bleeding on probing site (BOP), probing depth (PD), and clinical attachment loss (CAL; Table 2).

Birth-related outcome measures were recorded for women in both arms: number of spontaneous abortions/stillbirths, number of PTBs (< 37 weeks), and LBW infants (< 2500 g), whereas periodontal outcomes included BOP, PD, and CAL (Table 3).

We finally recorded study design items, including whether there was a description of the mode of randomization, allocation concealment, withdrawals per arm, and blinding.[11]

Statistical analysis

The 2-by-2 tables were constructed and odds ratio (OR) was calculated for each primary study to estimate the relative risk of spontaneous abortion/stillbirth,

TABLE 2
Periodontal status baseline characteristics from trials included in the analysis

ID	Study	Treatment	Disease type	Definition of periodontal disease	Natural teeth (N)	BOP (%)	PD > 4 mm (%)	CAL > 3 mm (%)	PD (mm)	CAL (mm)
1	López et al[17]	Yes	Mild-moderate	≥ 4 teeth with >1 site with PD > 4 mm and CAL > 3 mm	25.6	49.9	20.9	7.8	2.71	1.86
	2002	No			24.57	55.4	23.9	6.4	2.94	1.75
2	Jeffcoat et al[13]	Yes	Mild-moderate	3 sites with CAL > 3 mm	NA	NA	NA	68.6	NA	NA
	2003	No			NA	NA	NA	69	NA	NA
3	López et al[18]	Yes	Gingivitis	BOP > 25% of sites and no sites with CAL > 2 mm	25	55.09	9.24	NA	2.26	1.12
	2005	No			24.8	51.42	12.23	NA	2.22	1.17
4	Michalowicz et al[9]	Yes	Mild-moderate	≥ 4 teeth with >1 site with PD > 4 mm and CAL > 2 mm and BOP > 35% of sites	26.7	69.6	26.5	NA	NA	NA
	2006	No			26.8	69	24.8	NA	NA	NA
5	Offenbacher et al[15]	Yes	Mild-moderate	> 2 sites with PD > 5 mm and CAL 1-2 mm at ≥ 1 site with PD > 5 mm	> 20	43.9	7.86	NA	2.27	0.55
	2006	No			> 20	47.7	6.35	NA	1.98	0.54
6	Sadatmansouri et al[16]	Yes	Mild-moderate	≥ 4 teeth with > 1 site with PD > 4 mm and CAL > 3 mm	NA	16.6	72.2	69.8	2.3	2.3
	2006	No			NA	13.4	57.1	54.7	2.3	2.2
7	Tarannum and Faizuddin[14]	Yes	Mild-moderate	CAL > 2 mm at > 50% of examined sites	> 20	NA	NA	NA	NA	1.99
	2007	No			> 20	NA	NA	NA	NA	1.99

BOP, bleeding on probing site; *CAL*, clinical attachment loss; *ID*, study number, *NA*, nonapplicable; *PD*, probing depth.

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PTB, and LBW infants among treatment group compared with no-treatment group. Statistical significance was defined as $P < .05$.

Analyses for spontaneous abortion/stillbirth were based on all patients randomized except patients lost in follow-up.

Analyses for PTB and LBW infants were based on live births, including all randomized pregnancies except patients lost in follow-up and pregnancies leading to spontaneous abortions or stillbirths. PTBs and indicated preterm deliveries caused by coexisting conditions such as preeclampsia, placenta previa, or placenta abruption were included in our final analysis.

Studies with zero events in both groups (treatment and no treatment) were excluded from analysis.

The χ^2 statistic test was used to test the homogeneity of the estimates of OR between studies, with a level of significance of .1. In case of homogeneity, pooled OR and 95% confidence interval (CI) were calculated according to the Mantel-Haenszel method.[12] In case of heterogeneity DerSimonian and Laird random effects model was used to pool ORs and to calculate CIs.

Prespecified subgroup analyses were performed to explain the possible sources of clinical heterogeneity between studies on the basis of some baseline characteristics of the trials regarding potential risk factors; for lower rate of previous PTB/LBW infants we considered studies with less than 10% patients with history of PT/LBW whereas for low level

TABLE 3
Pregnancy- and periodontal-related parameters after treatment

ID	Study	Treatment	PTB (N)	Stillbirth/ abortion (N)	LBW (N)	BOP (%)	PD > 4 mm (%)	CAL > 3 mm (%)	PD (mm)	CAL (mm)
1	López et al[17]	Yes	7	8	1	14.9	2.9	1.3	2.1	1.04
	2002	No	14	6	7	62.5	27	6.38	2.98	1.84
2	Jeffcoat et al[13]	Yes	5	0	NA	NA	NA	NA	NA	NA
	2003	No	11	0	NA	NA	NA	NA	NA	NA
3	López et al[18]	Yes	18	7	4	15.09	1.8	NA	1.93	0.93
	2005	No	17	4	3	56.62	14.5	NA	2.33	1.18
4	Michalowicz et al[9]	Yes	44	5	40	3.8	NA	9.72	NA	NA
	2006	No	38	14	43	22.7	NA	0.84	NA	NA
5	Offenbacher et al[15]	Yes	9	NA	NA	11.5	0.84	NA	1.46	0.45
	2006	No	14	NA	NA	39.5	15.7	NA	2.39	0.58
6	Sadatmansouri et al[16]	Yes	0	0	0	0.7	53.31	41.4	2.1	2
	2006	No	3	0	1	17.2	68.6	67.1	2.5	2.3
7	Tarannum and Faizuddin[14]	Yes	53	2	26	NA	NA	NA	NA	NA
	2007	No	68	2	48	NA	NA	NA	NA	NA

BOP, bleeding on probing site; *CAL*, clinical attachment loss; *ID*, study number; *LBW*, low birthweight infants; *NA*, nonapplicable; *PD*, probing depth; *PTB*, preterm birth.

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of education, we considered studies with < 50% of patients with education < 12 years. In addition, predefined subgroup analyses were also carried out to evaluate whether the effect of treatment differs according to severity of periodontitis; for less severe disease we considered studies with PD > 4 mm in lower or equal than 20% of examined sites and studies with BOP lower or equal to 50% of examined sites.

The data were analyzed using statistical software (STATA 8.0; Stata Corp, College Station, TX).

Results

Eligible trials characteristics

The electronic searches yielded 429 items; 246 from Medline, 173 from Web of Science, and 10 from Cochrane Central. Of those, 18 reports were scrutinized in full text. Eleven reports were considered ineligible. Seven randomized trials were recorded. There were 2663 patients: 1491 had been randomized to receive periodontal treatment and 1172 to no treatment (Figure 1).

Table 1 shows the key characteristics of the included trials.

Design and quality characteristics

Three trials reported an adequate randomization mode,[9,13,14] allocation concealment was ensured in 2 of 7 trials,[9,13] and 3 trials were blind.[9,13,15] Four of the trials were designed to assess PTBs as primary outcome[9,13,15,16] and 3 trials were designed to assess PTBs and LBW infants.[14,17,18]

Outcome measures

All of the trials reported PTBs. Cumulatively, 136 (9.7%) PTBs were observed in women receiving periodontal treatment and 165 (14.7%) in those who received no treatment. The number of events was higher in the no-treatment arm in all the trials except 2,[9,17] in which a similar number of PTBs was observed in both arms. Metaanalysis regarding PTB rate revealed strong statistically significant difference between compared arms. Pooled OR was 0.55 (95% CI, 0.35-0.86; $P = .008$), suggesting that treatment of periodontal disease during pregnancy reduces the incidence of PTB; moderate between-study heterogeneity was observed (Figure 2).

Data regarding LBW infants were reported in 5 of 7 trials.[9,14,16-18] A total of 71 (5.1%) LBW infants were reported in women receiving treatment and 102 (8.7%) in women who were not treated. When pooling the data from these trials, borderline statistically significant difference was observed in favor of the treatment arm. The OR was 0.48 (95% CI, 0.23-1.00; $P = .049$), suggesting that treatment of periodontal disease during

pregnancy might result in lower rate of LBW infants; moderate between-study heterogeneity was also observed for this outcome (Figure 2).

Data regarding spontaneous abortions/stillbirths were reported in 6 of 7 eligible trials.[9,13,14,16-18] Two trials reported no events in both arms and were excluded from our analysis.[13,16] A total of 22 events were reported in women receiving treatment and 26 in the control group. Although 1 of the trials described a borderline significantly higher rate of spontaneous abortions/stillbirths (P = .04) in the control arm,[9] when pooling the data we did not find any significant difference among the compared groups (OR, 0.73; 95% CI, 0.41-1.31; P = .292). No between-study heterogeneity was observed (Figure 2).

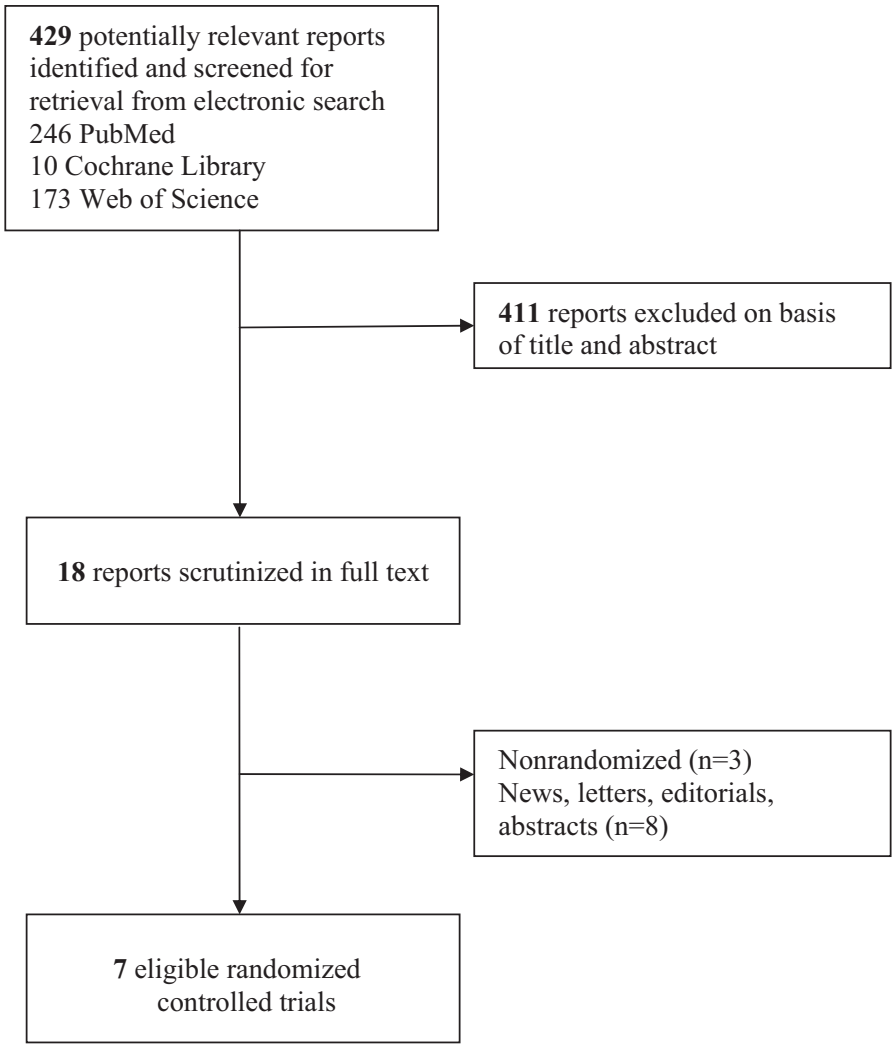
According to our protocol, we performed subgroup analysis regarding parameters that could be considered risk factors for PTB. Absence of a history of PTB was a strong determinant of treatment success. Subgroup analysis including studies with low rate of previous PTB or LBW infants (< 10% of included patients) resulted in OR of 0.48 (95% CI, 0.29-0.77; P = .003). However, no difference between compared groups was found when pooling the data for women with lower or higher educational level (Table 4).

A subgroup analysis was performed to determine different effect of treatment according to the level of periodontal disease. A significant effect of treatment was found in studies including women with less severe disease; subgroup analysis limited to studies with PD > 4 mm in lower or equal to 20% of patients' examined sites resulted in an OR of 0.49 (95% CI, 0.28-0.87; P = .014), whereas for studies with BOP lower or equal to 50% of examined patients' sites, OR was 0.37 (95% CI, 0.14-0.95; P = .040). When data from studies including women with more severe disease were pooled, no significant difference was observed among compared arms (Table 4).

Subgroup analysis for the outcome of LBW infants could only be performed for the parameter of history of PTB or LBW infants. Nonetheless, although no heterogeneity was found, no difference between treated and untreated patients was observed (OR, 0.34; 95% CI, 0.12-1.01; P = .052; Table 4).

Finally, periodontal outcomes were recorded both at baseline (Table 2) and after treatment (Table 3). For all the above outcomes, women receiving treatment with periodontal scaling and/or root planing had significantly improved periodontal disease status compared with women who did not receive treatment.

FIGURE 1
Flowchart diagram of study selection



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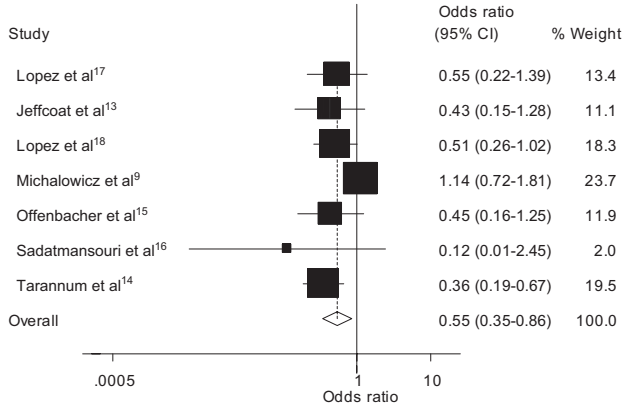
Comment

Our metaanalysis provides evidence in favor of the treatment of periodontal disease during pregnancy. Despite moderate between-study heterogeneity we observed for 2 of the primary outcomes, treatment with scaling and root planing reduces the rate of PTB and may reduce the rate of LBW infants. Mechanisms by which surgical treatment of periodontal disease might reduce PTB risk remain unknown. It is likely that the benefit of treatment of periodontal disease is related to the decline of oral cavity pathogen concentration and the consequent reduction of transportation of organisms in the amniotic fluid and chorionic membranes.[15] In addition, a reduction in circulating inflammatory mediators produced in the oral crevice (and subse-

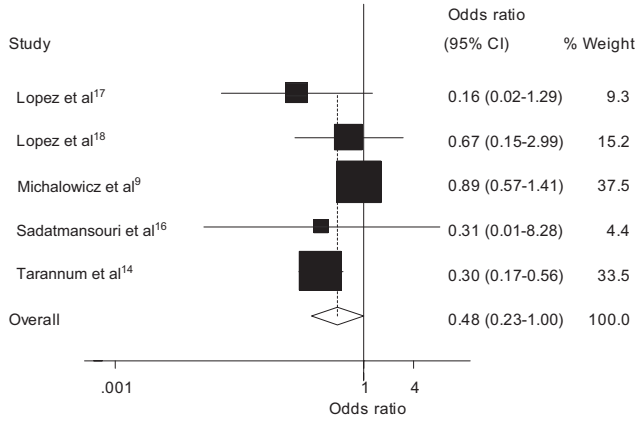
FIGURE 2
Metaanalysis plots for main outcome measures

PRETERM BIRTH
RANDOM EFFECTS ANALYSIS



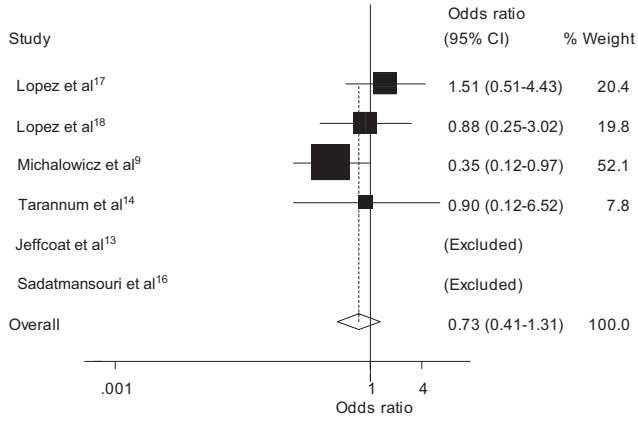
Heterogeneity chi-squared *= 12.16*
(d.f. = 6) P = .059
I-squared (variation in OR attributable to heterogeneity) = 50.7%
Estimate of between-study variance Tau-squared = 0.1676
Test of OR = 1: z = 2.64; P = .008

LOW BIRTHWEIGHT INFANTS
RANDOM EFFECTS ANALYSIS



Heterogeneity chi-squared *= 9.43*
(d.f. = 4) P = .051
I-squared (variation in OR attributable to heterogeneity) = 57.6%
Estimate of between-study variance Tau-squared = 0.3107
Test of OR = 1: z = 1.97; P = .049

ABORTION/ STILLBIRTH
FIXED EFFECTS ANALYSIS



Heterogeneity chi-squared *= 3.86*
(d.f. = 3) P = .277
I-squared (variation in OR attributable to heterogeneity) = 22.2%
Test of OR = 1: z = 1.05; P = .292

Jeffcoat et al[13] and Sadatmansouri et al[16] were excluded from abortion/stillbirth analysis because there were no events in both groups.

CI, confidence interval; *OR*, odds ratio.

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TABLE 4
Subgroup analysis performed for main outcomes

Subgroups	Included studies	OR (95% CI)	*P* value	Heterogeneity
PTB				
Analysis for low rate (< 10% of patients) of previous PTB or LBW	13,16-18	0.48 (0.29-0.77)	.003	No
Analysis according to level of education				
Low level (> 50% patients with education < 12y)	9,15,18	0.70 (0.37-1.33)	.279	Yes
High level (< 50% patients with education < 12 y)	16,17	0.46 (0.19-1.09)	.078	No
ANALYSIS ACCORDING TO THE LEVEL OF PERIODONTAL DISEASE				
PD > 4 mm in > 20% of examined sites	9,16,17	0.92 (0.62-1.38)	.696	No
PD > 4 mm in ≤ 20% of examined sites	15,18	0.49 (0.28-0.87)	.014	No
BOP > 50% of examined sites	9,17,18	0.74 (0.41-1.32)	.306	No
BOP ≤ 50% of examined sites	15,16	0.37 (0.14-0.95)	.040	No
LBW				
Analysis for low rate (< 10% of patients) of previous PTB or LBW < 10%	16-18	0.34 (0.12-1.01)	.052	No

BOP, bleeding on probing site; *CI*, confidence interval; *LBW*, low birthweight infants; *OR*, odds ratio; *PD*, probing depth; *PTB*, preterm birth.

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quently into the systemic circulation) of women with periodontal disease might result from surgical treatment leading to reduced exposure of genital tract tissues to these mediators.[19] Finally, the local inflammatory response in the crevice may lead to a systemic inflammatory immune response increasing the sensitivity of immune cells in the amnion (or other genital tract tissues) to an inflammatory stimulus such as ascending bacteria from the lower to the upper genital tract; therefore, surgical treatment of periodontal disease could be beneficial simply by reducing the periodontal driver of the systemic response.[19]

Although 1 trial included in our analysis has found a beneficial effect of treatment ($P = .04$) in reducing spontaneous abortion/stillbirth rate,[9] cumulative randomized evidence did not reveal any difference between compared arms.

Trials included in our analysis differ significantly in certain baseline characteristics of enrolled patients that could be considered potential risk factors for PTB. Because of low incidence of smoking (7.5-25.7%) and bacterial vaginosis (6.7-25.1%) the potential of gaining significant outcome differences from subgroup analysis would be limited; therefore, subgroup analysis for this parameters was omitted. Low level of education ranged from 6.7% to 80.78%, and previous PTB or LBW from 0% to 88.2% among compared studies.

According to our predefined subgroup analysis, benefit in PTB was particularly high among studies involving patients with a lower rate of previous PTB or LBW infants. History of a PTB is strongly associated with a subsequent PTB[20]; thus, the potential of experiencing a second PTB in this subgroup of women is higher than for the general population and may be irrelevant from coexisting conditions such as periodontitis. Therefore, although treatment of periodontal disease may actually have an effect in women without a history of PTB, this effect might be detrimental in women with a history of PTB.

Furthermore, the severity and degree of periodontal disease also differed among the trials included. One trial included patients with gingivitis[18] and 6 trials of patients with mild to moderate periodontitis.[9,13-17] According to our prespecified subgroup analysis, treatment was more effective in patients with less severe disease as defined by PD > 4 mm and BOP. A possible explanation is that scaling and root planning is associated with bacteremia from periodontopathic microorganisms in patients with severe periodontitis.[21] Moreover, after scaling, the incidence and magnitudes to bacteremia are significantly higher in patients with periodontitis than in patients with gingivitis.[22] Consequently, in less severe disease, treatment with scaling and/or root planing may result in reduced bacteremia, reduced systemic inflammatory response, and reduced exposure of genital tract tissues to bacteria and inflammation mediators compared with treatment in more severe disease. In this way, treatment in early stages of the disease might be more effective in the reduction of PTB incidence.

Several limitations exist in our metaanalysis. Our metaanalysis is based on data from trials that have published results in the literature and not on individual data. A metaanalysis of individual-level data might define treatment benefits in subgroups of patients who

have different risk of PTB or different stage of periodontal disease.[23] In addition, publication bias might exist in our analysis and might actually affect the observed outcomes.[24]

Allowing for these caveats, our data suggest that treatment with scaling and/or root planing during pregnancy significantly reduces the rate of PTB and may reduce the rate of LBW infants. Our results may indeed be premature and vulnerable to the conclusions drawn from ongoing large randomized controlled trials[25-27] that are going to shed light in this field. At the moment, the Obstetrics and Periodontal Therapy study[9] is the largest randomized trial to date and their results do not favor the use of periodontal disease treatment during pregnancy with scaling and root planning. Nonetheless, if ongoing large and well-designed randomized trials support our results, we might need to reassess current practice or at least be cautious prior to rejecting treatment of periodontal disease with scaling and/or root planing during pregnancy. ■

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