Periodontitis, female fertility and conception (Review)

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Abstract. Periodontal disease (PD) has been shown to increase the risk of preterm birth, preeclampsia and low birth weight. These observations have suggested that PD may also affect the early phase of pregnancy, including conception. The present study aimed to evaluate whether an association exists between oral health status and the chance of clinical pregnancy, according to the currently published literature, by performing a systematic review. The PubMed and EMBASE databases were searched from their start dates to October 2021 using the following keywords: 'Infertility' OR 'conception' OR 'pre-pregnancy' OR 'time-to-pregnancy' AND 'periodontitis' OR 'periodontal disease' OR 'dental infection' OR 'gingivitis' OR 'odontogenic infection' (limits: Full article, English, Human). A total of 6 papers reporting observational information on PD and spontaneous (4 studies) or medically induced conception (2 studies) were retrieved. As such, there were limited studies with different designs (randomized controlled trials and observational studies) and different settings. Moreover, in the selected studies, the ethnicity of the women was heterogeneous. According to the limited published literature, oral health might affect fertility in women. However, only results from prospective randomized trials, comparing PD treatment vs. no treatment in women seeking pregnancy, may clarify the real effectiveness of treatment in improving the conception rate.

Contents

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1. Introduction

During the last decades, observational studies have suggested a possible link between chronic periodontitis and adverse pregnancy outcomes (1-3). Periodontal disease (PD) is associated with the risk of pregnancy complications and adverse outcomes, such as preterm birth, preeclampsia and low birth weight, in a bidirectional relationship (4). The published data, however, are not totally consistent: systematic reviews and meta-analyses showed different conclusions that were not robust (3,5-7). Furthermore, these findings were also challenged by the fact that systematic reviews, evaluating the effectiveness of therapeutic interventions to treat PD during pregnancy, showed inconsistent results with regard to the risk of adverse pregnancy outcomes (8-10).

Along this line, a recent review underlined the fact that PD is associated with conditions associated with fertility, such as polycystic ovary syndrome, endometriosis and bacterial vaginosis (11). These observations suggested that PD may also affect the early phases of pregnancy, including conception. Furthermore, PD was associated with impaired semen parameters, suggesting a potential positive association between male factor infertility and dental health status (12).

Several studies have analyzed the association between PD and clinical pregnancy. The present review revised the available data on the association between oral health status and the chance of spontaneous and medically induced pregnancy.

2. Literature search

This review was registered in the PROSPERO database (registration number: CRD42021273066). The PubMed and EMBASE databases were searched from their initial start dates to October 2021 using the following keywords as both a free text and index terms search: 'Infertility' OR 'conception' OR

Table I. Patient, intervention, comparator, outcome, study design criteria for the inclusion and exclusion of studies.

Parameter	Inclusion criteria	Data extraction
Patient	Women seeking pregnancy	Location, age, type of patients
Intervention	Assessment of dental health	Type of assessment
Comparator	Absence of periodontitis	Group definition
Outcome	Clinical pregnancy (yes/no)	Details of conception
Study	Cross-sectional, cohort and case-control studies	Type of study design

'pre-pregnancy' OR 'time-to-pregnancy' AND 'periodontitis' OR 'periodontal disease' OR 'dental infection' OR 'gingivitis' OR 'odontogenic infection'. Only studies published in English and conducted on humans were included. Letters to the editor, commentaries, historic reviews and laboratory studies were excluded. The reference lists of identified articles were also checked to search for other pertinent studies. Two authors reviewed the papers and independently selected the articles eligible for the systematic review. Studies were selected for the review if they met all the following criteria: Cross-sectional, cohort and case-control design, studies reporting original data, studies reporting the diagnosis of PD and studies reporting the number of conceptions.

Data extraction. A patient, intervention, comparator, outcome, study design structure was used to define the study aims and the inclusion and exclusion criteria (13). The review aimed to assess whether there is an association between periodontitis and conception in women seeking pregnancy, spontaneously or by *in vitro* fertilization (IVF) (Table I).

For each study, the following information was extracted: Last name of the first author, year of publication, country where the study was conducted, number and characteristics of included subjects, design of the study, criteria for the diagnosis of periodontitis and clinical pregnancy (spontaneous or induced), and potentially confounding variables.

Quality assessment. The Newcastle-Ottawa Scale was used to evaluate the quality of the studies (14). This scale includes items for cohort and case-control studies: Selection (max 4 points) and comparability (max 2 points) of study groups, assessment of outcome (cohort studies; max 3 points) or ascertainment of exposure (case-control studies; max 3 points). For cohort and case-control studies, 8 or 9 points indicated a high-quality study, 6 or 7 points indicated a medium-quality study, and ≤5 points indicated a low-quality study. For cross-sectional studies, items for selection (max 3 points), comparability (max 2 points) and outcome (max 3 points) were included (15). A score of 7 or 8 points indicated a high-quality study, 6 points indicated a medium-quality study and ≤5 points indicated a low-quality study.

3. Spontaneous pregnancy and pregnancy after IVF

Search results. In PubMed/MEDLINE, the initial search retrieved 161 papers, and after inclusion criteria were applied, such as the requirements to be written in English (n=35) and be a human study (n=40), 86 published studies were screened. The same search, performed in EMBASE, retrieved 48 studies, with 15 duplicates of those studies retrieved in PubMed/MEDLINE. Overall, 119 studies were screened.

Of these 119 studies, 28 (27 in PubMed/MEDLINE + 1 in EMBASE) were reviews or editorials or commentaries, 17 (13+4) were regarding pregnancy outcome, 7 (6+1) were on male fertility, 6 (4+2) discussed the association between dental disease and presence of infertility or infertility-related factors, 4 were on gestational diabetes, 3 were on body mass index (BMI) and PD in pregnancy, 3 reported on oral health during IVF treatment, 2 reported on Chinese traditional medicine, 1 was a case report, 1 was a study protocol and 41 were animal or laboratory studies, or did not regard female fertility. Overall, 6 studies (16-21) were included in the present systematic review.

Of the 6 studies, 4 included healthy women seeking pregnancy (16,18,19,21) and 2 studies enrolled patients attending fertility clinics (17,20). Table II reports the main methodological characteristics of the studies. A total of 4 studies were prospective cohorts (17,19-21), 1 was a cross-sectional study (18) and 1 was a sub-analysis of a randomized controlled trial (RCT) of treatment for PD in mid-pregnancy (16).

In all but a single study (21), the patients received a comprehensive oral examination to diagnose caries, periodontal status and/or other possible dental infection sources. Only 1 study evaluated the presence of major periodontal pathogens in the saliva and the presence of antibodies in the serum and saliva (19).

Of the 6 studies, 2 studies (17,20) did not assess confounding variables. The study by Nwhator *et al* (18) adjusted the data for age, and the study by Hart *et al* (16) adjusted the data for BMI, ethnicity and smoking. Finally, the studies by Paju *et al* (19) and Bond *et al* (21) assessed several confounders such as age, current smoking, socioeconomic status, bacterial vaginosis, previous deliveries and clinical periodontal attachment loss.

Regarding study quality, all retrieved studies scored at least 4 out of 9 [out of 8 for the cross-sectional study (18)] (Table III). No study may be considered truly representative of the general population, but only of the specified target population (healthy women and women from fertility clinics).

Studies on spontaneous pregnancy. Hart *et al* (16) conducted a sub-analysis of the SMILE study (22), a multi-center RCT of treatment for PD in mid-pregnancy. Planned pregnancies accounted for 1,956 of the 3,416 pregnancies available for study: 1,439 pregnancies in women without PD and 517 pregnancies in women with PD. Women with planned pregnancies were asked about the time taken to conceive (TTC).

Table II. Characteristics of selected studies.

First author, year	Country	Type of study	Sample size	Criteria of diagnosis of PD	Confounders	Study quality	Outcome-results	(Refs.)
Spontaneous conception								
Hart *et al*, 2012	Australia	Sub-analysis of a RCT of treatment for PD in mid-pregnancy	1,956 planned pregnancies; 1,439 pregnancies without PD; 517 pregnancies with PD	Presence of pockets ≥4-mm deep at ≥12 probing sites in fully erupted teeth	BMI, ethnicity, smoking	9/9	TTC >12 months Reference: Caucasian women without PD. Non-Caucasian women with PD: 13.9 vs. 6.2%; OR, 2.88 (95% CI, 1.62-5.12); P<0.001. Caucasian women with PD: 8.6 vs. 6.2%; OR, 1.15 (95% CI, 0.74-1.79); P=0.534	(16)
Nwhator *et al*, 2014	Nigeria	Cross sectional study	70 women	Oral hygiene index score, commu nity periodontal index and periodontitis risk score using matrix metalloproteinase-8 (neutrophil collagenase-2)	Age	4/8	TTC, <12 months. Periodontitis risk score associ ated with odds of TTC: OR, 0.157; 95% CI, 0.041-0.600; P<0.01	(18)
Paju *et al*, 2017	Finland	Observational prospective study	256 women	Major periodontal pathogens in the saliva and serum, and saliva antibodies against major periodontal pathogens	Age, current smoking, socioeconomic status, bacterial vaginosis, previous deliv eries, and clinical periodontal attachment loss	8/9	Not becoming pregnant within a year. Women positive for *P. gingivalis* by polymerase chain reaction and with high salivary antibodies: HR, 3.75 (95% CI, 1.01-13.9; P=0.048). Women with high levels of serum *P. gingivalis* IgA and signs of periodontal infection: HR, 1.62 (95% CI, 1.03-2.54; P=0.035)	(19)
Bond *et al*, 2021	USA	Prospective cohort study	2,764 pregnancy planners; 1,506 pregnancies in women; 2,499 women without PD diagnosis; 152 pregnancies in 265 women with PD diagnosis	Self-reported diagnosis of PD	Ethnicity, history of bacterial vaginosis, diabetes, endometriosis, polycystic ovarian syndrome, age, education, annual income, BMI in kg/m^2, insurance coverage, weekly servings of sugar-sweetened soft drinks, marital status, current employment, partner's education level, maternal and paternal education level, use of a prenatal or multi-vitamin at baseline, use of folic acid supplementation at baseline, use of vitamin D supplementation at baseline, frequency of intercourse at baseline, doing anything to improve conception chances at baseline, healthy eating index score, parity, smoking	6/9	Time to pregnancy. Reference: Women without self-reported PD diagnosis. Women with self- reported PD diagnosis: aFR, 0.89 (95% CI, 0.75-1.06). Reference: Women without self-reported PD treatment. Women with self-reported PD treatment: aFR, 0.79 (95% CI, 0.67-0.94)	(21)
In vitro fertilization								
Pavlatou *et al*, 2013	Greece	Cohort study	20 women with healthy periodontium; 19 women with gingivitis; 21 women with periodontitis	Gingivitis was defined as >10% of surfaces bleeding after light mechan ical stimulation by the periodontal probe with no evidence of periodontal pockets. Adult periodontitis was defined when two or more sites exhib ited a probing depth of ≥4 mm	Not reported	7/9	Number of follicles, number of embryos, attainment of pregnancy. Trend for negative correlation between the number of follicles, transferred embryos, attainment of pregnancy and the gingival index was recorded in all women	(17)

Table II. Continued.

First author, year (Refs.)	Country	Type of study	Sample size	Criteria of diagnosis of PD	Confounders	Study quality	Outcome-results	
Khalife *et al*, 2019	Jordan	Cohort study	17 women with mild/moderate gingivitis; 7 women with severe gingivitis (PD)	Women were classified as having gingivitis if no pocketing (≤3 mm) and no bleeding on probing were observed; chronic periodontitis was defined as pockets (≥4 mm) in two or more sites and bleeding on probing	Not reported	6/9	No difference between women with mild and severe gingivitis	(20)

RCT, randomized controlled trial; PD, periodontal disease; TTC, time taken to conceive; OR, odds ratio; CI, confidence interval; HR, hazard ratio; BMI, body mass index; aFR, adjusted fecundability ratio.

In the group of 146 women with a TTC >12 months, the cases of PD were more frequent (34.9 vs. 25.7%; P=0.015) than in the group with TTC ≤12 months. Patients with a diagnosis of PD took an average of 7 months (95% CI, 5.7-8.6) to conceive compared with 5 months (95% CI, 4.4-5.5) in healthy controls (P=0.019).

The cross-sectional study by Nwhator *et al* (18) included 70 pregnant women. The diagnosis and the risk of PD were based on the oral hygiene index score (23), community periodontal index (CPI) (24) and matrix metalloproteinase-8 immunoassay (25). The odds ratio (OR) for TTC <12 months decreased with increasing CPI [OR, 0.48; 95% confidence interval (CI), 0.26-0.90] and periodontitis (OR, 0.16; 95% CI, 0.04-0.60), suggesting that chronic periodontitis was positively associated with a lower chance of pregnancy.

The study by Paju *et al* (19) evaluated 256 non-pregnant women who underwent clinical oral and gynecological examinations. The major periodontal pathogens in the saliva were detected, and serum and saliva antibodies against major periodontal pathogens were analyzed. The follow-up period for becoming pregnant was 12 months. *Porphyromonas gingivalis* was detected in the saliva of 8.3% of women who did not become pregnant and in 2.1% of those who became pregnant (P=0.032), resulting in a hazard ratio for not becoming pregnant of 3.8 (95% CI, 1.0-13.9) in the women with polymerase chain reaction results positive for *P. gingivalis*, and high salivary antibodies, and a hazard ratio for not becoming pregnant of 1.6 (95% CI, 1.0-2.5) in subjects with elevated levels of serum *P. gingivalis* IgA and a clinical diagnosis of periodontal infection.

The prospective cohort study by Bond *et al* (21) involved 2,764 women who had been attempting to become pregnant for six or fewer menstrual cycles at enrollment and were not using fertility treatment. Oral health was self-reported by the woman. Fecundability ratios were 0.89 (95% CI, 0.75-1.06) comparing women with and without a previous periodontitis diagnosis, 0.79 (95% CI, 0.67-0.94) comparing women with and without previous periodontitis treatment, and 0.71 (95% CI, 0.44-1.16) comparing women with and without a tooth that became loose. Among the limitations of the study, the fact that PD diagnosis was self-reported and that the disease severity could not be measured was highlighted.

Studies on pregnancy after IVF. The study by Pavlatou *et al* (17) considered 60 women eligible for IVF: 20 with healthy periodontium, 21 with PD and 19 with gingivitis. No association with the number of follicles, the number of embryos and dental health was found among the three groups. No statistically significant difference emerged when comparing between IVF success and oral diseases.

The study by Khalife *et al* (20) included 34 women who underwent IVF. PD was classified according to the American Academy of Periodontology criteria (26). The outcomes of 28 women were analyzed: 17 had a positive pregnancy test (60.7%), with a total of 13 live births (46.4%) and 4 pregnancy losses (14.3%). All women had different degrees of gingivitis (mild, 47.1%; mild-to-moderate, 8.8%; and severe, 23.5%). No statistically significant associations emerged between the severity of gingivitis and clinical pregnancy.

Table III. Study quality evaluation according to the Newcastle-Ottawa Scale.

First author, year	Type of study	Selection		Comparability		Outcome (CS)/ exposure (CC)		Study quality[a]	(Refs.)
Healthy women									
Hart *et al*, 2012	Cohort	1	*	1	*	1	*	9/9	(16)
		2	*	2	*	2	*		
		3	*			3	*		
		4	*						
Nwhator *et al*, 2014	Cross-sectional	1	*	1	*	1	*	4/8	(18)
		2		2		2	*		
		3				3			
Paju *et al*, 2017	Cohort	1		1	*	1	*	8/9	(19)
		2	*	2	*	2	*		
		3	*			3	*		
		4	*						
Bond *et al*, 2021	Cohort	1		1	*	1		6/9	(21)
		2	*	2	*	2	*		
		3				3	*		
		4	*						
Women from Fertility Clinics									
Pavlatou A *et al*, 2013	Cohort	1	*	1		1	*	7/9	(17)
		2	*	2		2	*		
		3	*			3	*		
		4	*						
Khalife *et al*, 2019	Cohort	1	*	1		1	*	6/9	(20)
		2	*	2		2	*		
		3	*			3			
		4	*						

[a]The Newcastle-Ottawa quality assessment scale was used for CC and CS, with a maximum score of 9 (14). For the assessment of cross-sectional studies, an adapted version was used with a maximum score of 8 (15). CC, case-control; CS, cohort studies.

4. Discussion

Findings from this systematic review are based on a very limited number of studies, thus the results should be considered cautiously. Taking this aspect into account, the general results suggested that periodontitis is associated with conception.

In all the studies, the chance of conception was significantly lower in women with PD, except for that in a single study (20) that only included women with different grades of gingivitis.

The present systematic review was conducted to provide a summary of the evidence about the potential association between periodontitis and conception. As periodontitis is a modifiable risk factor, this association could be of clinical interest and have health policy consequences.

The limitations of the present review should be considered. Populations enrolled in the included studies were different: Hart *et al* (16) included women who were enrolled in an RCT, whereas the remaining studies reported on observational studies conducted in different settings. Moreover, in the selected studies, the ethnicity of the women was heterogeneous; it has been observed that PD was more common among non-Caucasian women, although in the study by Hart *et al* (16) PD did not affect TTC, which in turn did not differ among Caucasian and non-Caucasian women. Another major limitation was that the selected studies showed a difference in the ascertainment of PD. Lastly, the sample size was adequate in just 2 studies (16,21), and in 1 of these (21) the criteria for PD diagnosis did not rely on an objective evaluation, as oral health was self-reported by the women.

Despite these limitations, consistent results were observed among the studies. All the studies reported an inverse association between conception (spontaneous or induced) and the presence of PD. The findings regarding IVF, although not statistically significant (20), were of note also in consideration of the fact that ovulation induction exacerbates gingival inflammation (27).

The biological and clinical explanations of these findings are not clear. Smoking and diabetes (28,29) were shown to increase the risk of PD and they may also be associated with infertility and/or TTC (30,31). Smoking was considered as a confounding factor in 2 studies (16,19). Moreover, there is some evidence that PD is associated with endometriosis, which is in turn associated with fertility problems (32).

It is recognized that systemic inflammation may affect reproduction (33), and PD is associated with inflammation.

Thus, it is conceivable that the biological mechanism linking fertility to PD is inflammation. Otherwise, a recent review of the literature has clearly shown that PD reduces the quality of semen parameters (11). No information was reported in the considered studies on male semen parameters and the oral health of the men. It is at least partially conceivable that dental status may be in part similar among the partners of a couple who share similar risk factors (for example, socioeconomic status). Thus, factors in males may at least in part explain the observed association.

Periodontal therapy was reported to lower glycemic levels in diabetics (34), serum pro-inflammatory cytokines levels (11), white blood cell count, and fibrinogen and C-reactive protein (35) and increase sperm motility (36).

Overall, this review is preliminary as more articles would be necessary to draw a definite conclusion. However, the scope of a review is collecting all evidence (only published evidence in the present case) to evaluate if there are inconsistencies among findings, to determine if the evidence is sufficient to draw certain conclusions and to see if further studies are needed. Thus, reports from small-size studies are also important to add to the current knowledge.

Conclusion. This review suggests that PD may be associated with fertility, although there is a definite lack of studies on this issue. The disappointing outcomes with regard to the efficacy of PD treatment in pregnancy for lowering the risk of preeclampsia and a low birth weight, however, suggest that only the results from prospective RCTs, comparing PD treatment vs. no treatment in women seeking pregnancy, may clarify the real effectiveness of treatment in improving the conception rate.

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Availability of data and materials

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Authors' contributions

SCic, FP and MV designed the study; PAM, ERo and AF searched the literature and selected the papers; FF, SCip and GE extracted the data; FP, SG and ERi wrote the paper. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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