

# Periodontitis and risk for preeclampsia — a systematic review

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## ABSTRACT

**Objectives:** The aim of the study is to review systematic cohort and randomized trials on the relationship between periodontitis and preeclampsia. Periodontitis is an independent risk factor for preeclampsia (PE), and periodontal treatment could play a significant role in the prevention of this pregnancy complication.

**Material and methods:** A total of 821 items (published until March 2019), thematically related to the relationship between periodontitis, its treatment and the incidence of preeclampsia, were collected from the databases of PubMed, Scopus, Google Scholar and the Polish Database of Medical Bibliography and analyzed. In the end, 6 cohort studies and 3 randomized controlled trials (from the years 2003–2016) were deemed eligible for the review. The main exclusion criteria were as follows: case-control and cross-sectional studies, medical and dental conditions.

**Results:** A significant relationship between periodontitis and the risk for developing preeclampsia was demonstrated in 5 cohort trials, which was not confirmed by only 1 study. A total of 2724 pregnant women, including 195 (7.16%) with PE, were analyzed. In 3 randomized trials which assessed the impact of non-surgical treatment (scaling and root planing = SRP) on the occurrence of preeclampsia, the preventive effects of the implemented treatment was not confirmed. A total of 116 women from the group of 1825 pregnant subjects undergoing the non-surgical treatment (SRP) and 116 women from the control group of 1827 pregnant women were subsequently diagnosed with PE, which amounted to 6.30% and 6.35%, respectively.

**Conclusions:** The cohort studies indicated that periodontitis may result in an increased risk for developing PE. A more detailed analysis regarding the impact of potential risk factors and modification of further studies (clarification of how periodontitis and preeclampsia should be defined in observations, consideration of disease severity, earlier at 12–16 weeks of gestation — implementation of the non-surgical treatment, modification and extension of the classical protocol of the non-surgical treatment of periodontal diseases, as well as conducting European studies), are necessary due to considerable discrepancies in the available literature sources (cohort and randomized observations).

**Key words:** periodontitis; periodontal therapy; adverse obstetric outcomes; preeclampsia; systematic review

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## INTRODUCTION

Periodontitis is a chronic and multifactorial inflammatory disease associated with advanced dysbiosis of the pathogenic bacterial biofilm in periodontal pockets, which leads to a progressive destruction of the periodontal attachment apparatus. Periodontal pathological processes include high biomass of periopathogens (*Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Aggregatibacter actinomycetemcomitans*, *Filifactor alocis* and *Catonella morbi*) in the biofilm on the root surface, progressive character of the inflammatory process in the connective tissue and bone resorption of the alveolar ridge, as well as excessive reactivity

of the host immunological-inflammatory response to the bacterial biofilm. Periodontitis is a social disease — the most recent nationwide epidemiological study has demonstrated that it occurs in approximately 30% of the Polish population between the ages of 34 and 45 years [1]. Confirmed risk factors include the non-modifiable (age, sex, race and genotype) and the modifiable (smoking, poorly controlled diabetes, presence of perio-pathogens in the subgingival biofilm, poor oral hygiene, obesity and the metabolic syndrome, osteoporosis, low social and economic status, stress, and poor-quality diet) causes [2]. According to the Polish epidemiological reports, periodontitis is diagnosed in 11–12%

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of all pregnant women [3, 4]. Periodontitis is a risk factor for diabetes and a likely risk factor (evidence from case-control and cohort studies; no evidence from interventional studies) for cardiovascular diseases and their endpoints — myocardial infarction, stroke, CVD mortality, low birth weight and/or preterm birth, and chronic renal failure [5, 6].

Pre-eclampsia (PE) is a hypertensive disorder characterized by signs of damage to another organ system, which typically develops after 20 weeks of gestation. PE has been estimated to occur in 2–8% of all pregnant women and is currently considered to be the second main cause of maternal and perinatal mortality [7, 8]. The most common maternal PE- and hypertension-related complications include a generalized tonic-clonic convulsion, disseminated intravascular coagulation, liver failure and acute renal failure with proteinuria, bleeding to the central nervous system and retina, HELLP syndrome, congestive heart failure, pulmonary edema, placental abruption and cesarean delivery [9]. Fetal PE- and hypertension-related complications include the risk for admission to the neonatal intensive care unit, intrauterine growth restriction, low birth weight, prematurity, intrauterine fetal demise, and early infant mortality [9]. Risk factors for PE include: age (> 35 years), race (African-American), (family) history of PE, multiple gestation, intrauterine growth restriction, obesity, chronic hypertension, pharmacological interventions for the induction of the ovulation, pregestational diabetes mellitus type I or II, gestational diabetes mellitus, systemic lupus, and the antiphospholipid syndrome [9, 10]. Chronic maternal infections (e.g. urinary tract infections) are indicators of PE-related risk. In 2002, Riché et al. [11], were the first to publish the results of a cohort study at Chapel Hill, North Carolina, on the relationship between periodontitis and the development of preeclampsia.

### Objectives

The aim of this systematic review is to present cohort and randomized trials on the relationship between periodontitis and preeclampsia. A confirmed role of periodontitis as an independent PE-related risk factor would play a vital role in the prevention of this obstetrical syndrome.

## MATERIAL AND METHODS

A systematic review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12].

Questions for the review:

1. Do the adjusted odds ratio values indicate an independent influence of periodontitis on the occurrence of PE in cohort studies about the relationship between periodontitis and preeclampsia?
2. Does periodontal treatment significantly reduce the incidence of PE?

These questions concerned population-based and non-experimental cohort and randomized control trials (CCTs or RCTs).

The review covered all publications in English, German, Polish and Russian about the relationship between periodontal diseases and preeclampsia, as well as the influence of periodontal treatment on PE-related morbidity.

The inclusion criteria were as follows: pregnancy with no PE symptoms before 20 weeks of gestation (blood pressure > 140/90 mm Hg and proteinuria). The exclusion criteria included (family) history of PE, incidence of PE in multiparous women, intrauterine growth restriction, pharmacologically treated hypertension, pharmacologically stimulated ovulation, pregestational diabetes mellitus type I or II, gestational diabetes mellitus, systemic lupus, antiphospholipid syndrome, and fewer than 10 teeth.

All information was obtained from electronic databases. Electronic searches were conducted in PubMed, Scopus, Google Scholar and the Polish Medical Bibliography Databases. All texts were published until the end of March 2019 were figured in. When searching potential papers, the following keywords were used: periodontitis or periodontal disease or periodontal treatment in combination with at least one of the following terms: preeclampsia, pre-eclampsia, pregnancy outcomes, pregnancy complications. The obtained articles were subsequently checked independently by both authors (TK, AZ) against the inclusion and the exclusion criteria.

The first selection eliminated all the abstracts, case descriptions, reviews, animal studies, *in vitro* studies and repeated publications. Subsequently, the texts of the original works were verified against the inclusion criteria (inter alia, with the above definitions of preeclampsia and periodontitis only in accordance with the clinical probing depth and/or clinical attachment loss) and the exclusion criteria (case-control and cross-sectional studies were excluded). If the trial was repeated in the same center, the subsequent study was taken into consideration. The relationship between periodontitis and PE (Odds Ratios — ORs) as well as the effect of periodontal treatment on the risk for developing PE (Risk Ratios — RRs) had to be determined in the studies qualified for the review. The decisions of the authors were compared at the end of the review and the text was included in the analysis only when mutual consensus was reached.

Each study-related entry, independently obtained by both authors (TK, AZ), included the name of the author(s), year of publication, country of study, sample size, age of the examined women, definition of periodontitis, time of study, and in case of the periodontal treatment — time of treatment and its type, OR (RR) as well as 95% confidence interval (CI) values and statistical adjustments for the confounding factors.

## RESULTS

The initial review of the literature identified 821 items thematically related to the relationship between periodontitis, its treatment and the development of preeclampsia. After careful analysis, 16 articles, meeting the inclusion and the exclusion criteria, were selected. The last scrutiny excluded 2 cohort studies conducted previously in the same center [11, 13], 3 studies with endpoints which differed from the accepted ones [14–16], and 1 study with inadequate methodology [17]. In the end, 6 cohort studies [18–23] and 3 randomized control trials (RCTs) [24–26] were deemed eligible for the review. The process of selecting works for the systematic review is presented in Figure 1.

Table 1 summarizes the eligible cohort studies conducted between 2003 and 2016. A significant relationship

between periodontitis and PE was confirmed by 5 sources [18, 20–23] and not verified by only 1 [19]. A total of 2724 pregnant women were assessed, with 195 (7.16%) diagnosed with PE. These observations were conducted in the USA, India, Korea and Canada. The diversified pool of confounding factors, which were being regarded in the multi-factor analysis of the modelling process, was strongly emphasized.

Table 2 presents 3 randomized studies which assessed the impact of non-surgical treatment (scaling and root planing — SRP) on the morbidity of mothers with PE. None of them confirmed the protective effect of the periodontal treatment on developing PE. Non-surgical periodontal treatment (removal of subgingival deposits with scaling and root planing along with the application of an antiseptic in the

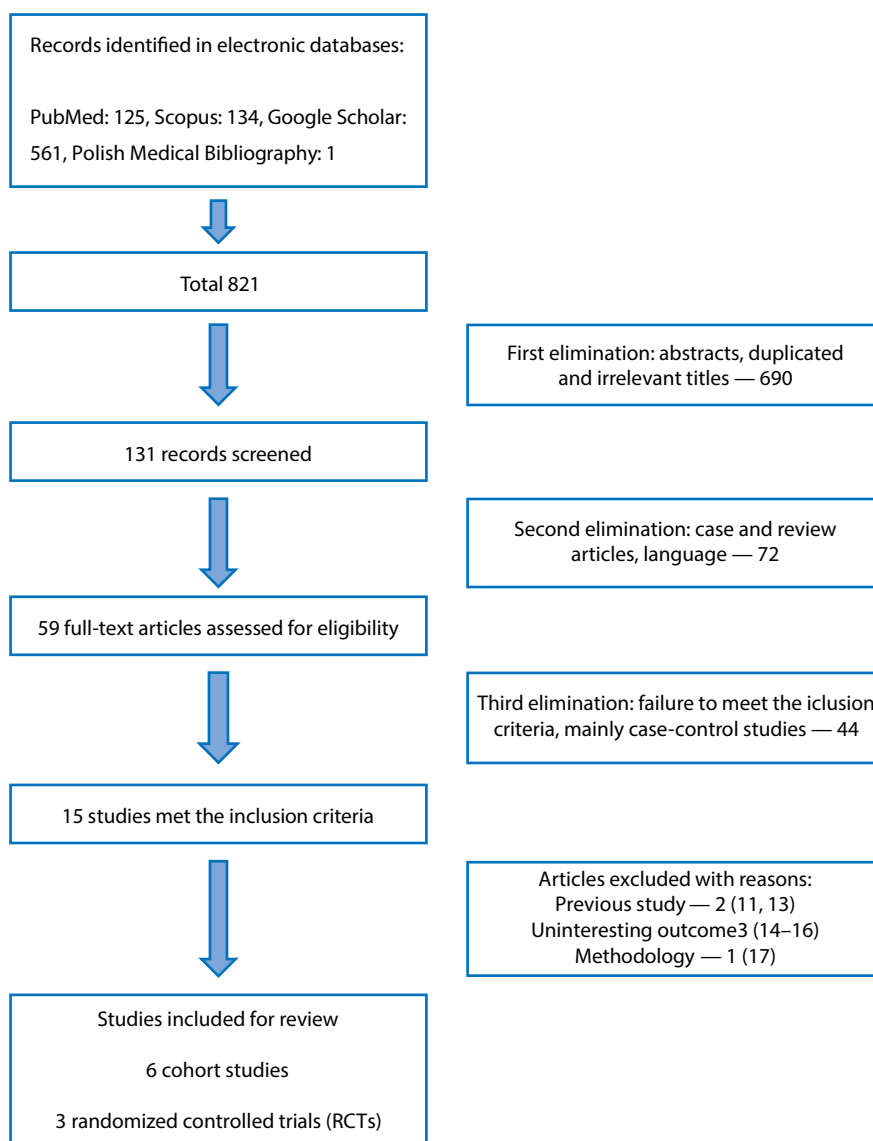


Figure 1. Flow chart of the study selection process for the systemic review

**Table 1. Summary of cohort studies included in the present review**

Study/Year	Country, city	Sample size, maternal age	Definition of periodontitis	Time of examination	OR (95% CI)	Adjustment of factors
Boggess et al. [18] 2003	USA Chapel Hill	763 women, 39 with PE Age 18–35	PD with BoP > 3 mm	1st visit < 26 weeks, next 26–36 weeks	<b>2.4</b> (1.1–5.3) For heavy P	Maternal age, race, insurance, smoking
Srinivas et al. [19] 2009	USA Philadelphia	786 women, 48 with PE Mean age 23.9	PD and CAL ≥ 3 mm	PD and CAL ≥ 3 mm	0.71 (0.37–1.36)	Maternal age, race, smoking, obesity
Shetty et al. [20] 2010	India Mangalore	130 women, 30 with PE Mean age 26.8	PD ≥ 4 mm CAL ≥ 3 mm	1st visit < 26 weeks, next 26–36 weeks and within 2 days after delivery	<b>5.78</b> (2.41–13.89)	Maternal age, education, income
Kumar et al. [21] 2014	India New Delhi	504 women, 51 with PE Age 20–35	PD and CAL ≥ 4 mm	1st visit 14–18 weeks, next after 20 weeks	<b>2.66</b> (1.32–5.73)	Maternal age, education, BMI, income
Ha et al. [22] 2014	Korea Seoul	283 women, 13 with PE Mean age 32.8 (25–40)	CAL ≥ 3 mm	1st visit 21–24 weeks, next after 26 weeks	<b>4.51</b> (1.13–17.98)	Maternal age, BMI, health & oral health behaviors
Soucy-Giguère et al. [23] 2016	Canada Quebec	258 women, 14 with PE Mean age 35 (19–45)	PD with BoP > 4 mm	1st visit 15–24 weeks, next after 26 weeks and after delivery	<b>5.89</b> (1.24–28.05)	BMI, smoking

**Table 2. Summary of intervention studies included in the present systematic review**

Study/Year	Country, city	Sample size of the study and control groups, maternal age	Definition of periodontitis	Kind of intervention	Periodontal treatment time	RR (95% CI)
Michalowicz et al. [24] 2006	USA Minneapolis	IG: 407 (31 PE) CG: 405 (20 PE) Mean age 26	PD ≥ 4 mm CAL ≥ 2 mm	IG: Hand and ultrasonic SRP	Before 21 weeks of gestation, monthly control	1.54 (0.89–2.66)
Offenbacher et al. [25] 2009	USA San Antonio Tuscaloosa	IG: 880 (67 PE) CG: 882 (74 PE) Mean age 25.4	CAL ≥ 3 mm	IG: Hand and ultrasonic SRP	Before 23 weeks of gestation, no follow-up visits during pregnancy	0.9 (0.66–1.24)
Newnham et al. [26] 2009	Australia Perth	IG: 538 (18 PE) CG: 540 (22 PE) Mean age 30.5	PD ≥ 4 mm	IG: SRP and rinsing with 0.12% chlorhexidine mouthwash	20–24 weeks of gestation, 28–31 weeks and control visit 32–36 weeks	0.82 (0.44–1.56)

oral cavity) was performed in 1825 women, out of whom 116 (6.36%) were subsequently diagnosed with PE. In the control group (where only oral hygiene was performed and supra-gingival plaque was removed), 116 (6.35%) out of the 1827 examined women were diagnosed with PE. RCTs were carried out only in the USA and Australia.

## DISCUSSION

It is a well-known fact that cohort and randomized interventional controlled trials have the strongest evidential value in establishing a causal relationship between two pathologies. Therefore, clinical-control and cross-sectional studies were deliberately excluded from this review. The relatively high (over 7%) percentage of women with PE in the included studies resulted from the fact that the study populations comprised non-Caucasian subjects. The cohort trials clearly indicated that periodontitis may result in

an increased risk for developing PE in pregnancy (by 5-fold according to some sources). This relationship has also been confirmed by all three meta-analyses carried out in this field [27–29] so far. In all studies included in the meta-analyses, periodontitis was as an independent factor. Sgolastra et al. [27], after taking into account 12 clinical-control trials and 3 cohort studies from 2003–2012 in the random effects model, obtained the OR at the level of 2.17 (1.38–3.41), although with high and significant heterogeneity (only 8 studies confirmed the relevance of this relationship). Wei et al. [28], after including 13 clinical-control trials and 2 cohort studies from 2003–2012, using a random effects model, confirmed that the probability of developing PE among pregnant women with periodontitis was 3-fold higher with respect to gingivitis or healthy periodontium during pregnancy (OR — 2.79, CI — from 2.01 to 3.01). A significant heterogeneity among these studies has also been demonstrated (13 confirmed

the relevance of this association). Also, Huang et al. [29], by including 8 clinical-control and 3 cohort studies from 2003–2013, obtained in their model the OR at the level of 2.69 with a 95% confidence interval of 1.74–4.17. Nine studies reported a statistically significant relationship between periodontitis and PE. The subsequent meta-analysis demonstrated a significant impact of common risk factors (socio-economic status and obesity) on both pathologies, and sample size and the quality of the included studies on the strength of the relationship.

The etiopathological mechanisms providing an explanation for the link between periodontitis and PE remain to be fully elucidated. However, it seems that the destroyed attachment apparatus is the source of direct infection of the uteroplacental organ with perio-pathogens. The presence of *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia* and *Micromonas micros* in the placental-fetal unit, in chorionic trophoblasts, and in several types of cells such as amniotic epithelial, decidual, vascular and in the amniotic fluid was demonstrated [30]. Extremely significant similarities between the oral cavity microorganisms and the placenta were found [30]. On the other hand, inflammatory mediators, prooxidative factors, endo- and exotoxins and soluble forms of the adhesion molecules, which induce inflammation of the uteroplacental area, hypoxia, oxidative stress, endothelial dysfunctions leading to PE, penetrate into the cardiovascular bed as a result of periodontal inflammation [31].

From the clinical point of view, reduced incidence of PE by modifying the risk factor, in this case the periodontological treatment, is vital. That possibility has not been confirmed by previous studies, which seems to contradict the presented cohort observations or the aggregated results of the clinical-control and cohort studies in the meta-analysis. A meta-analysis of Kunnen et al. [32], based on the same three randomized interventional studies characterized in Table 2, demonstrates, in the randomized effects model, a lack of effect on PE — the overall RR 1.0 (0.78–1.28) with respect to no non-surgical treatment of periodontitis being conducted. This was also confirmed by the subsequent meta-analysis of Iheozor-Ejiofor et al. [33], which included the 2 described studies [24, 25] and the highly questionable study of 2000 — the overall RR was 1.1 (0.74–1.62). Additionally, very poor evidential quality of the combined studies, high risk of an error in a publication, and serious imprecision were emphasized by the authors. The fact that no protective effect of periodontal treatment on the development of PE is observed may be explained in two ways. First of all, it should be noted that the treatment of periodontitis was performed too late to affect the possible development of PE — by way of example, in the study by Newnham et al. [26] the treat-

ment was started between 20 to 24 weeks of gestation. In the case of an early PE, there is no possibility that such treatment will have a preventive effect. Secondly, it remains unclear to what extent the classical protocol of non-surgical treatment of periodontitis (SRP) during pregnancy protects from the exposure to perio-pathogens and proinflammatory biomarkers. Such treatment significantly reduces the number of perio-pathogens in the periodontal pockets, but it does not eradicate them [34], thus failing to eliminate the source of maternal infection. Similarly, such treatment does not significantly reduce proinflammatory biomarkers in the serum and the umbilical cord blood [35] and, as it was indicated in one of the studies, a significant increase in serum TNF- $\alpha$ , IL-8 and MCP1 (monocyte chemotactic protein) was demonstrated after SRP had been performed in pregnant women [36]. If these two suggestions are true, then in the subsequent interventional studies, initiation of the non-surgical treatment between 12 to 16 weeks of pregnancy and improvement of its effectiveness (SRP in combination with supplemental antibiotic administration or antimicrobial photodynamic therapy) may have some effect on PE prevalence. However, methodologically improved interventional tests in pregnant women should certainly be continued, since it is difficult to exclude a positive influence of professional periodontal treatment on various complications of pregnancy.

The present review of the literature about the relationship between periodontitis and preeclampsia is not without limitations. Firstly, there are considerable discrepancies in the definitions of periodontitis, which also applies to Tables 1 and 2. However, if only one definition of periodontitis were to be selected, this would result in rejecting a majority of the analyzed studies. The epidemiological definition of CDC (Center for Disease Control and Prevention) and APP (American Academy of Periodontology) should be preferred, which suggests that at least 2 PD  $\geq$  4 mm pockets and at least 2 CAL  $\geq$  3 mm spaces on the contacting surfaces are required for such a diagnosis. Out of the 9 works analyzed in the review, this definition was applied only in one case [20]. Stratification of PE severity would also be of great significance. Secondly, the definition of preeclampsia should also be more precise and differentiated into the early and the late PE (with different risk factors), and it should reflect the degree of clinical advancement. Thirdly, to the best of our knowledge, there are no studies on the subject from Europe, including Poland. Extrapolating the research results of the racially, socio-economically and socio-demographically diverse populations to the Polish one is not prudent. This applies particularly to intervention studies, which have so far been carried out in only two highly developed countries — the USA and Australia. The mere diversity of health care systems between countries can create numerous barriers

for such observations. Next, it is necessary to rigorously monitor as many disruptive factors as possible, including, in particular, common risk factors for both pathologies: maternal age, obesity, socio-economic status and smoking. The development of clear recommendations on the inclusion of these variables in multifactorial analyses in this respect will certainly improve the evidence quality of the studies. Finally, exclusion of publications in Spanish, typically from South America, was a definite limitation.

## CONCLUSIONS

It needs to be emphasized that the relationship between periodontitis and preeclampsia remains controversial. The existing incompatibility between the cohort and randomized trials needs to be further clarified. It is necessary to conduct randomized control trials including Caucasian women, with an accurate effort and attempt to improve the methodology. As a result, periodontal treatment would not only have a beneficial effect on the quality of patient life in relation to oral health, but might also play a role in disease prevention, especially PE, which is associated with significant morbidity and mortality. PE constitutes a serious threat to the health and life of both, the mother and the fetus. Thus, any potential modifiable risk factor must be clearly established in terms of strength, dose-effect relationship and reversibility.

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