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Periodontitis as a Risk Factor of Preeclampsia in Pregnancy: A Scoping Review

Fiki Muhammad Ridho[1*], Avina Oktaviani Algifnita[2], Naurah Nabilah Pramaztri[1], Eko Puji Laksono[3], Bella Pardian Nur Allifiah[4], Mahesa Ahmad[5]

[1]Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Master Program in Health Policy and Management, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[3]Department of Intensive Care Unit Nursing, Tarakan General Hospital, Jakarta, Indonesia
[4]Faculty of Dental Medicine, Universitas Muhammadiyah Yogyakarta, Yogyakarta, Indonesia
[5]East Java Provincial Education Office, Surabaya, Indonesia
*Corresponding Author: fikimuhammadridho@gmail.com
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ABSTRACT

Introduction: Preeclampsia (PE) is a pregnancy complication characterized by hypertension and proteinuria after 20 weeks of gestation. Although the causes of PE are still unclear, some factors play an important role in increasing the incidence of PE, namely periodontitis which has an impact on the systemic spread of pathogens and inflammatory mediators, causing adverse pregnancy outcomes. This scoping review aims to evaluate, identify, and provide a deeper understanding of the relationship and possible mechanisms between periodontitis and increased PE in pregnant women. A literature search following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted in PubMed, ScienceDirect, Scopus, and Google Scholar until July 2023. In the end, 14 articles were included for review.
Results: All of the included studies stated that periodontitis mostly affects pregnant women with PE, and periodontitis is believed to play a role in increasing the risk of PE through the mechanism of bacteremia due to periodontal pathogens translocating from the oral cavity to the placenta and through cytokines and inflammatory mediators produced by inflamed periodontal tissue, resulting in disruption of the placenta, further increasing the risk of PE in pregnant women.
Conclusions: In conclusion, there is a significant increase in the incidence of PE in pregnant women who experience periodontitis. Future research to review the mechanisms by which periodontitis increases the risk of PE and to examine whether periodontitis treatment before and during pregnancy can prevent PE may be warranted.

Introduction

Periodontitis is a multifactorial chronic inflammation of the periodontal tissue caused by specific pathogens found in plaque biofilms, which leads to progressive destruction of the periodontal ligament and alveolar bone (Tonetti et al., 2018). Periodontitis commonly presents with several clinical signs, including gingival inflammation, clinical attachment loss (CAL), bleeding on probing (BOP), deep probing depth (PD), mobility, and pathological migration (Papapanou et al., 2018).

It is believed that almost 19% of adults globally are affected by severe periodontal disease (World Health Organization, 2023). In Indonesia, 74.1% of Indonesian people have periodontitis (Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan RI, 2018). This makes periodontitis a global public health problem because there has been a significant increase in the last few decades and there is some evidence to suggest that there is an association between periodontitis and systemic disease (Smyrlis et al., 2019), such as diabetes mellitus (Liccardo et al., 2019), cardiovascular disease (Rahimi & Afshari, 2021), cognitive impairment (Guo et al., 2021), renal disease (Baciu et al., 2023), rheumatoid arthritis (Krutyhołowa et al., 2022), respiratory disease (Dong et al., 2022), cancer (Tuominen & Rautava, 2021), metabolic syndrome (Pirih et al., 2021), pregnancy complications such as premature birth (Uwambaye et al., 2021), low birth weight (Bhavsar et al., 2023), and preeclampsia (PE).

PE is a complication that occurs after 20 weeks of gestation and affects around 6.7% of pregnant women (95% CI=5.8-7.6) (Macedo et al., 2020), with symptoms of blood pressure ≥140/90 mmHg followed by one or more other conditions, such as proteinuria (≥300 mg/24h), acute renal failure (creatinine ≥90 mmol/L), thrombocytopenia, liver complications, neurological complications, and uteroplacental abnormalities (Fox et al., 2019; Phipps et al., 2019; Rana et al., 2019).

The etiology of PE is multifactorial, some of these risk factors include placental oxygen imbalance, abnormal alterations in the spiral arteries, pathological placentation, fetomaternal oxidative stress, inflammation, and maternal blood circulation disturbances (Ahmadian et al., 2020). Other factors include age ≥35 years, multiple pregnancies, nullipara, chronic hypertension, obesity, pre-gestational diabetes mellitus, irregular antenatal check-ups, primigravida, family history of PE, chronic kidney disease, antiphospholipid syndrome, trisomy 13, and systemic lupus erythematosus (Rana et al., 2019; Syahfirda et al., 2023). In addition, other clinical factors significantly increase the risk of PE, including polycystic ovary syndrome (Fornes et al., 2022), sleep-related breathing disorders (Carnelio et al., 2016), periodontal disease, urinary tract infections (Yan et al., 2018), and *Helicobacter pylori* (Elkhouly et al., 2016).

Although the cause of PE is still unknown with certainty, some evidence has reported a significant association between infections, including periodontitis, and PE. In addition, periodontitis is an oral infection that has a negative impact on systemic health, while PE has an impact on adverse pregnancy outcomes. Therefore, the

objective of this scoping review of the published literature is to evaluate, identify, and provide a deeper understanding of the relationship and possible mechanisms between periodontitis and increased PE in pregnant women.

Methods

Review Methodology

This scoping review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The Population (P), Intervention (I), Comparison (C), and Outcome (O) questions used to answer this research were do pregnant women (P) who experience periodontitis (I) compared to pregnant women with healthy periodontal conditions (C) have an increased risk of PE (O)?

Information Sources

A comprehensive literature search was conducted until July 2023 on the following databases: PubMed, ScienceDirect, Scopus, and Google Scholar.

Search Strategy

In the search, several keywords were used such as [(periodontitis) OR (periodontal disease) OR (maternal periodontitis)] AND [(preeclampsia) OR (pre-eclampsia) OR (pregnancy outcomes)]. Search results were limited to articles written in English, published within the last 10 years, and studies conducted on humans.

Selection Process

All search results that matched the keywords used were then grouped and duplicates, if any, were removed. Studies were then screened according to the predetermined inclusion criteria, if they did not match, they were excluded. In the final stage of the study selection process, all fully accessible articles were extracted. The article documentation process was carried out in Microsoft Excel for Windows. The entire study selection process was conducted by independent researchers: FMR, AOA, NNP, EPL, and BPNA.

Results

A total of 5,867 articles were identified from initial searches through databases. After the removal of duplicates, 4,871 articles were filtered based on inclusion criteria, resulting in 482 remaining articles. The findings were then screened based on the title and abstract and irrelevant articles were excluded, leaving 58 full-text articles which were then assessed for eligibility. In this final stage, 14 articles were included for review, including 10 case-control studies, 3 prospective cohort studies, and 1 cross-sectional study. The entire study selection process is presented in **Figure 1**.

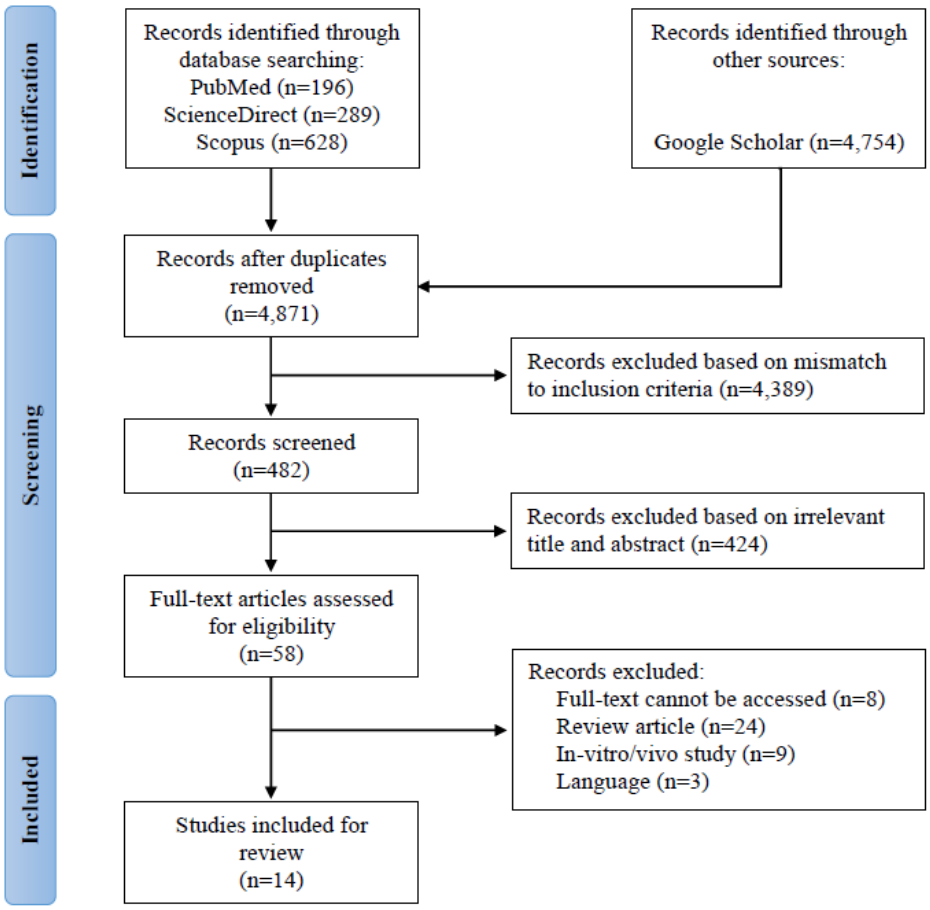

Figure 1. PRISMA flowchart.

Table 1. Summary of the included studies.

References	Country	Design	Participant	Result
Afshari et al. (2013)	Iran	Case-control study	180 cases, 180 controls	Pregnant women who have poor periodontal conditions have a higher risk of PE. The results of the study concluded that the progression and severity of periodontitis increased the risk of PE and adverse pregnancy outcomes.
Chaparro et al. (2013)	Chile	Case-control study	11 cases, 43 controls	There was a relationship between PE and plasma CRP levels. PE was correlated with IL-6 levels elevation in GCF samples in early pregnancy, resulting in increasing the risk of PE.
Pralhad et al. (2013)	India	Case-control study	100 cases, 100 controls	The study results showed that the prevalence of periodontal disease was

				65.5% and was significantly higher in women with hypertension (p<0.0001).
Ha et al. (2014)	Korea	Prospective cohort study	283 pregnant women	Periodontitis enhanced the risk of PE among pregnant women who had never smoked. Periodontitis has been linked to a higher risk of developing PE.
Jahromi et al. (2014)	Iran	Case-control study	100 cases, 100 controls	A significant relationship existed between PE and periodontal disease. Gingivitis occurred more frequently in mild PE cases (56.8%) compared to severe PE cases (31.6%). Periodontitis occurred more often in cases with severe PE.
Aly et al. (2015)	Egypt	Case-control study	40 cases, 40 controls	The PE group had a greater number of anaerobes in both blood and placental samples in comparison to the control group. A notable difference was observed between the two groups in terms of TNF-α levels as measured by the ELISA assay in serum.
Desai et al. (2015)	India	Case-control study	120 cases, 1120 controls	Maternal periodontitis was associated with PE. After primiparity matching, maternal periodontitis was still associated with the incidence of PE.
Lee et al. (2016)	Korea	Prospective cohort study	328 pregnant women	Periodontitis had a 5.56-fold increased risk of experience preterm birth with PE in pregnant women, in comparison to pregnant women without periodontitis.
Mahendra et al. (2016)	India	Case-control study	25 cases, 25 controls	Pregnant women with PE showed significantly higher BOP and CAL in comparison to normotensive pregnant women. The PPAR-γ expression was decreased and NF-κB was significantly increased in pregnant women with PE in comparison to normotensive pregnant women.
Soucy-Giguère et al. (2016)	Canada	Prospective cohort study	258 pregnant women	Periodontal disease diagnosed early in pregnancy was correlated with a significantly increased risk of developing PE.

Khalighinejad et al. (2017)	USA	Case-control study	50 cases, 50 controls	Apical periodontitis was significantly more common in the case group. Maternal apical periodontitis can significantly predict the incidence of PE.
Jaiman et al., (2018)	India	Case-control study	15 cases, 15 controls	The periodontal condition of pregnant women with PE was statistically worse in comparison to those who were normotensive.
Sumathy et al., (2018)	India	Case-control study	100 cases; 100 controls	46% of all patients suffer from periodontitis. Of the 46% of patients, 67 patients experienced PE.
Chitra et al., (2019)	India	Cross sectional study	60 preeclamptic pregnant women	88.3% of PE patients were found to have mild periodontal disease and 11.7% had moderate periodontal disease. A correlation existed between elevated CRP levels caused by periodontal disease and a higher incidence of PE.

Discussion

Based on its prevalence, periodontitis is often found in pregnant women who experience PE, proven by several studies which report that the prevalence of the periodontal disease is quite high in pregnant women who experience PE, ranging from 72.8% to 93.3% (Afshari et al., 2013; Chaparro et al., 2013; Jaiman et al., 2018; Pralhad et al., 2013; Sumathy et al., 2018). Pregnant women with periodontitis are at increased risk of developing PE, as reported by the results of studies conducted by Pralhad et al. (OR=5.5; 95% CI=2.7-11.4), Desai et al. (OR=19.8; 95% CI=7.8-48.94), Ha et al. (OR=4.51; 95% CI=1.13-17.96), Lee et al. (OR=5.56; 95% CI=1.22-25.39), Soucy-Giguère et al. (RR=5.79; 95% CI=1.23-27.36), Khalighinejad et al. (OR=2.23; 95% CI=1.92-6.88), and Sumathy et al. (OR=6.03; 95% CI=3.28-11.31). Therefore, it can be concluded that there exists a significant correlation between periodontitis and the occurrence of PE.

Although there was a positive association between periodontitis and PE in these studies, there were differences in odds ratio (OR) values between studies, which may be due to ethnic factors in the study population, study sample size, control variables, and, most importantly, the definition of periodontitis used. We found several clinical indices used varied between studies to define periodontitis, such as PD ≥4 mm and BOP (Afshari et al., 2013;

Soucy-Giguère et al., 2016), PD ≥4 mm, CAL ≥3 mm, presence of inflammation and BOP (Aly et al., 2015; Chaparro et al., 2013; Desai et al., 2015; Mahendra et al., 2016; Sumathy et al., 2018), gingival index (GI) >1, oral hygiene index (OHI) >3, PD >4 mm, or CAL >3 mm (Pralhad et al., 2013), and several studies defined periodontitis using only one indicator, namely PD ≥4 mm (Chitra et al., 2019) and CAL ≥4 mm (Ha et al., 2014; Lee et al., 2016). This is believed to be one of the factors that causes significant differences in OR values between studies, however, periodontitis remains a risk factor for increasing the incidence of PE in pregnant women.

Several possible mechanisms link periodontitis with the increased incidence of PE in pregnant women, namely bacteremia from periodontitis and cytokines and mediators (Smyrlis et al., 2019). First, periodontitis causes the translocation of oral bacteria through bacteremia into the fetomaternal blood circulation (Jaiman et al., 2018), and then spreads the bacteria to the fetoplacental unit, leading to ectopic infection and/or triggering inflammatory reactions and increasing levels of cytokines and inflammatory mediators (Madianos et al., 2013). Second, cytokines and mediators produced by inflamed periodontal tissue cause the accumulation of mediators in large amounts or in the liver, causing an inflammatory response with the production of C-reactive protein (CRP) and fibrinogen (Chandy et al., 2017).

A large amount of several periodontal pathogens, such as *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, *Micromonas micros*, and *Eikenella corrodens*, are found in the placenta, chorionic trophoblastic, and several types of cells, such as amniotic epithelium, decidua, blood vessels, and amniotic fluid, and are associated with PE and gestational hypertension (Konopka & Zakrzewska, 2020; Le et al., 2022; Zi et al., 2015). Based on the results of several studies, there are significant similarities between the microorganisms found in the placenta and in the oral cavity of periodontitis patients (Curtis et al., 2020; Salminen et al., 2015).

Additionally, *P. gingivalis*, *Bergeyella sp.*, *T. forsythia*, *Capnocytophaga spp.*, *E. corrodens*, *Parvimonas micra*, and *T. denticola* are reported to be detected in women with preterm birth (Bobetsis et al., 2020; Mesa et al., 2013; Wang et al., 2013). Among these pathogens, *F. nucleatum* is known to cause adverse effects on pregnancy (Chitra et al., 2019), including PE, preterm birth, low birth weight with or without intrauterine infection, early neonatal sepsis, and stillbirth (Bobetsis et al., 2020). Another study added that *A.*

actinomycetemcomitans and *Prevotella intermedia* were also detected in placental samples from pregnant women with PE, where these bacteria would colonize in placenta through bacteremia (Fischer et al., 2019), which would impact adverse pregnancy outcomes, including PE.

Periodontitis during pregnancy has been linked to adverse pregnancy outcomes, including preterm birth, early miscarriage, low birth weight, and PE which is believed to be caused by an increased systemic inflammatory response (Jaiman et al., 2018). There was an increase in interleukin (IL)-6 in the gingival crevicular fluid (GCF) and an increase in CRP in early pregnancy that was 65% higher than in pregnant women without periodontitis (Chaparro et al., 2013; Jahromi et al., 2014), and an increase in matrix metalloproteinase (MMP)-9 (Desai et al., 2015). Furthermore, periodontitis induces an inflammatory response through increasing pro-inflammatory mediators such as IL-1β, prostaglandin (PG) E2, IL-6, tumor necrosis factor (TNF)-α (Mata et al., 2021), CRP, 8-isoprostane, soluble intercellular adhesion molecule (sICAM)-1, fibronectin, and α-fetoprotein in serum, umbilical cord blood, and amniotic fluid (Starzyńska et al., 2022).

Increased IL-6 and TNF-α impact endothelial cell function by increasing vascular permeability and inducing trophoblast cell apoptosis. Both cytokines stimulate and damage endothelial cells, causing complex inflammatory reactions in pregnant women, and contributing to the pathophysiology of PE (Aggarwal et al., 2019). This is corroborated by research conducted by Aly et al. (2015) and Chaparro et al. (2013) which confirmed that there were significant differences seen between the control group and the pregnant women in the PE group, regarding IL-6 and TNF-α in serum.

CRP functions as an indicator of inflammation and the level of damage to endothelial cells, which are factors that contribute to the development of PE (Renu et al., 2022). Elevated CRP levels in the blood are observed in cases of acute infections, cancer, and inflammatory disorders. CRP has the ability to attach to chromatin, which is liberated from necrotic or apoptotic cells, and small ribonucleoprotein nuclear particles. It suggests that CRP may contribute to the initiation of the inflammatory response that is characteristic of PE (Nasruddin et al., 2018). CRP is primarily formed in hepatocytes, although it is also produced by smooth muscle cells, endothelial cells, lymphocytes, macrophages, and adipocytes, under the influence of IL-6 and TNF-α (Sproston & Ashworth, 2018).

The aforementioned statement is in line with research conducted by Chitra et al. (2019) which stated that the mean of CRP

levels in individuals with mild and moderate periodontal disease were 1.155±1.8 mg/dL and 9.26±9.4 mg/dL, respectively, with a *p*-value of 0.001. This shows that the mean of CRP level in pregnant women with periodontitis is increased, possibly caused by periodontal pathogens, which not only trigger local inflammation but are also involved in increasing systemic inflammatory and immune responses.

The study carried out by Mahendra et al. (2016) concluded that there was a decrease in peroxisome proliferator-activated receptor gamma (PPAR-γ) expression ($p<0.05$) and an increase in nuclear factor kappa B (NF-κB) expression ($p<0.05$) significantly in pregnant women with PE in comparison to normotensive pregnant women. The results of the study are corroborated by evidence showing that the concentration of PPAR-γ activator in the bloodstream of pregnant women with PE is significantly reduced (Hu et al., 2022) while the NF-κB expression is increased, resulting in excessive inflammatory reactions, abnormal placentation, and consequently uteroplacental dysfunction, release of pro-inflammatory cytokines into the bloodstream, endothelial stress, and development of PE in pregnant women (Socha et al., 2021). This strengthens the evidence that pregnant women with periodontitis can increase NF-κB expression and decrease PPAR-γ expression which will increase the occurrence of PE.

Based on the results of the review conducted, there are limitations in the research reviewed, namely the population coverage of all the research studied, such as the absence of research from European and several Asian regions populations, thus it cannot reflect the results of the research from various populations and races. In addition, there are differences in the use of clinical indicators to define periodontitis which has an impact on varying OR values. However, the results of this scoping review can conclude that there is a relationship between periodontitis experienced by pregnant women and an increased incidence of PE as proven in studies with case-control study, prospective cohort study, and cross-sectional study designs which provide an overview for conducting research in the future regarding the mechanisms and prevention of PE through periodontitis treatment by dentists.

Conclusion

We concluded that there was a significant increase in the incidence of PE in pregnant women with periodontitis as indicated by the high prevalence of pregnant women with periodontitis who experience PE, in comparison to normotensive pregnant women. The

elevated prevalence of PE in pregnant women with periodontitis is caused by the translocation of periodontal pathogens to the fetoplacental unit through bacteremia and the activity of cytokines and inflammatory mediators that cause excessive inflammatory reactions in the placenta.

The results of our review require future research to investigate the mechanism of periodontitis in increasing the development of PE in pregnant women, as well as whether dental intervention aimed at preventing and treating periodontitis before or during pregnancy can have a positive impact on pregnancy outcomes, including reducing the occurrence of PE.

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