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## **PERIODONTITIS IN PREGNANCY AS RISK FACTORS OF PREECLAMPSIA : A LITERATURE REVIEW**

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### **ABSTRACT**

**Background:** Periodontitis may indicate the presence of chronic endotoxin inflammatory disease and cytokines, which are considered as risk factors for systemic diseases such as cardiovascular disease, atherosclerosis, and cerebrovascular ischemia. Maternal periodontitis substitutes a potential microorganism that can penetrate the circulation, directly or indirectly has the capacity to affect the health of the mother and fetus. Preeclampsia is associated with an abnormal maternal cytokine response, such as elevated tumor necrosis tumor (TNF)- $\alpha$ , interleukin (IL)-1 and 6 levels that cause endothelial damage to the placenta.

**Aims:** Reviewing epidemiological associations between periodontitis and preeclampsia

**Methods:** The method used in this paper is literature review. Literature searches were conducted using the electronic databases Science Direct and Google Scholar.

**Results:** Many studies showed that periodontitis is a risk factor for the occurrence of preeclampsia. Periodontal disease is known to cause systemic inflammation early in pregnancy through increased IL-6 mechanism and increased systemic CRP, during pregnancy the increased progesterone hormone causes greater vascular permeability, stimulates the production of prostaglandins that can cause inflammation, and can decrease the regulation of interleukin-6 production that is less resistant to bacterial inflammation.

**Conclusion:** The guidance of maintaining the dental and oral health of pregnant and under-five mothers published by the government can be developed into a strategic and innovative program to increase community interest to regularly check the health of teeth to health facilities.

**Keywords:** Preeclampsia, periodontitis, pregnant Women

### **INTRODUCTION**

During the period of pregnancy, many of the changes that occur in the mouth associated with periodontal disease include gingivitis and periodontitis. Research shows there is a relationship between elevated levels of pregnancy hormones in plasma levels and decreased periodontal health status[1]. Periodontitis is one of the most common chronic inflammatory diseases. Periodontitis may indicate the presence of chronic endotoxin inflammatory disease and cytokines, which are considered as risk factors for systemic diseases such as cardiovascular disease, atherosclerosis, and cerebrovascular ischemia[2]. Periodontitis is a disease that damages tooth support tissue, caused by dental plaque and Gram-negative anaerobic organisms is the main character of this chronic inflammation[3]. Maternal periodontitis substitutes a potential

microorganism that can penetrate the circulation, directly or indirectly has the capacity to affect the health of the mother and fetus[4].

In general, periodontal disease has a prevalence of about 40% associated with gingivitis and periodontitis that occurs in pregnant women[5]. During the period of pregnancy, the hormone progesterone increases to 10-fold and estrogen hormone increase as much as 30-fold when compared at the time of menstruation. Increased progesterone hormones cause greater vascular permeability, stimulate prostaglandin production that can cause inflammation, and may decrease regulation of interleukin-6 production that is less resistant to bacteria-induced inflammation[6].

Periodontal tissue increases the immuno-inflammatory response to bacteria by activating hosted cytokines such as interleukin (IL-6), IL-1, and tumor necrosis factor (TNF- $\alpha$ ). The mechanism by activating the production of prostaglandins that cause damage to connective tissue and causes bone loss. Just as periodontal tissue can trigger an immunoglobulin response, which can also lead to a vascular response in pregnant women that may be linked to various complications of pregnancy such as preeclampsia, premature birth and low birth weight. Periodontal disease may be a source of endotoxin, inflammatory cytokines like TNF- $\alpha$ , and oxidative stressors in maternal-fetal[7].

Periodontal disease is a chronic inflammatory condition that affects many pregnant women. Many events have been reported regarding the relationship between periodontal disease and other systemic conditions, including cardiovascular disease and diabetes mellitus. However, the role of periodontitis in pregnant women as a potential stress that has a negative impact is a relatively new area of investigation. Nevertheless, recent studies have shown an association between maternal periodontal disease and some adverse pregnancy outcomes, including premature birth, low birth weight, fetal growth restriction, and perinatal mortality[8]

Preeclampsia is one of the complications of pregnancy and remains a major cause of maternal and infant death[9], 5-10% of preeclampsia can affect pregnancy. Preeclampsia is the third most common cause of maternal death in the UK and causes up to 40,000 pregnancy-related deaths per year in developing countries, which can lead to morbidity, and which contribute to 25% of preterm labor[10]. Preeclampsia occurs usually after 20 weeks' gestation[7, 11], and is characterized by a normal vascular response to placentation that manifests as general vasospasm, coagulation system activation, decreased organ perfusion that affects the kidneys, liver and brain. Preeclampsia is characterized by blood pressure exceeding 140/90 mmHg, and urine protein exceeding 300mg in 24 hours. This condition occurs in about 3% -10% of pregnant women and is currently the leading cause of maternal and infant death perinatal[7].

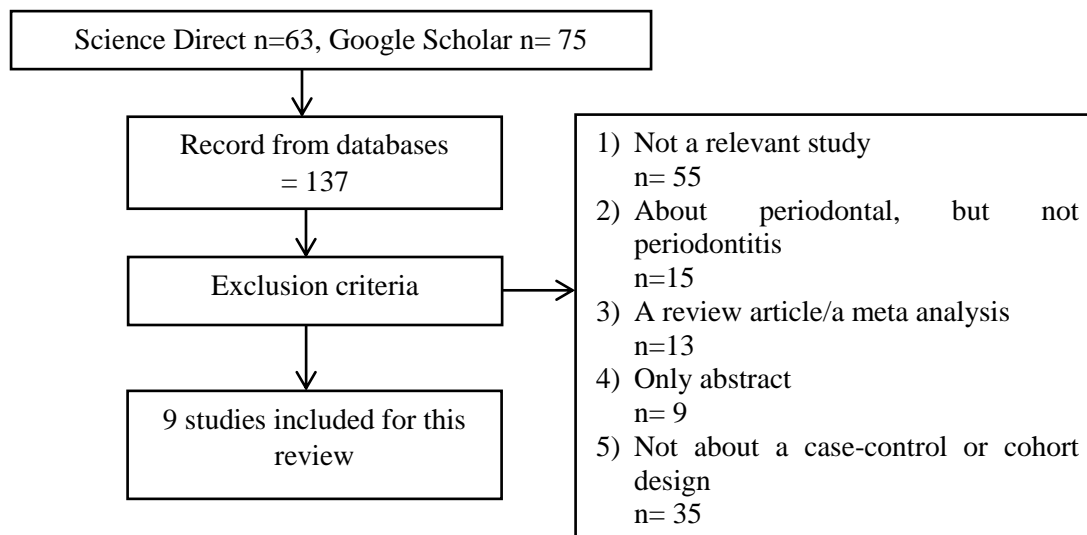
According to the data of the SDKI, maternal mortality rate has decreased, in 2007 was 228/100.000 live births, by 2012, Maternal Mortality Rate increases again to 359/100,000 live births. And by 2015, based on data SUPAS 2015 AKI showed a decrease of AKI 305/100.000 live births [12]. The five biggest causes of maternal death are bleeding, hypertension in pregnancy (HDK), infection, old / stuck particles, and abortion. Maternal mortality in Indonesia is still marked by three major causes of death: bleeding, hypertension in pregnancy (HDK), and infection. But the proportions have changed, where bleeding and infection have a tendency to decrease while hypertension in pregnancy (HDK) proportion is increasing. Preeclampsia occurs in approximately 5% of all pregnancies, 10% in first-child pregnancies and 20-25% of pregnant women with a history of hypertension before pregnancy[13]. In 2010 the incidence of Hypertension in Pregnancy was 21.5%, in 2011 of 24.7%, in 2013 by 26.9% and in 2014 increased to 27.1%[14].

Overall, preeclampsia is divided into 2 types: early-stage preeclampsia and slow type preeclampsia. Early Preeclampsia occurs at <34 weeks 'gestation and late-stage preeclampsia occur at 34 weeks' gestation.

There are very different causes between early and late types. Primary types are caused by abnormalities in the placenta whereas slow-type preeclampsia is caused by additional factors other than the placenta such as body mass index or infection[15]. In Indonesia, research on periodontitis against the risk of preeclampsia at Dr. Soetomo hospital found a slow rate of type of preeclampsia incidence of 72% of total preeclampsia / eclampsia[16]. Although the cause of preeclampsia is still not known for certain, but periodontitis is considered as one of the triggers of preeclampsia. The objective of this study was to determine whether there was a relationship between periodontitis with preeclampsia. Hypothesis: there is a relationship between periodontitis with preeclampsia.

## METHODS

The research articles were reviewed from electronic databases including Science Direct and Google Scholar. The number of keywords were used, including "periodontitis in pregnant women" and "periodontitis is risk preeclampsia. A total of journals 137 international journals of publications range from 2008 to 2017, but only . Table 1. shows the characteristics of the exclusion study



## RESULTS

Table 2. shows the quality of the included studies with case-control and prospective cohort design.

Table 2. Overview of Periodontitis Research with Risk of Preeclampsia

Authors	Tittle	Design	Variable	Result
Shetty., M, Shetty., PK, Ramesh., A.,Thomas., B, Prabhu., S, Rao., A (2010)	Periodontal disease in pregnancy is a risk factor for preeclampsia	Cohort study	BP $\geq$ 140/90 mmHg, $\geq$ 1+ proteinuria and CAL $\geq$ 3 mm and PD $\geq$ 4mm	Pregnant women who had periodontitis, and 48 h after delivery with significant periodontitis had preeclampsia (Before delivery: 5.78 (2.41-13.89) After delivery: 20.15 (4.55–89.29))
Moura da Silva G, Coutinho SB, Piscoya MD,	Periodontitis as a Risk Factor for Preeclampsia	Case control study	BP>140/90 mmHg and $\geq$ 300 mg/24 h or 2+ proteinuria and Four or more	Periodontitis remained an independent risk factor for



Authors	Title	Design	Variable	Result
Ximenes RA, Jamelli SR (2012)			teeth with one or more sites with PD $\geq$ 4 mm and CAL $\geq$ 3 mm in the same site	preeclampsia (8.60 (3.92-18.88))
Chaparro A, Sanz A, Quintero A, Inostroza C, Ramirez V, Carrion F, et al. (2013)	Increased inflammatory biomarkers in early pregnancy is associated with the development of pre-eclampsia in patients with periodontitis	Case control study	BP $>$ 140/90 $\pm$ 300 mg protein urine and pregnant women who did not exhibit PPD greater or equal to 4 mm and an attachment loss 3 mm	There was an association between preeclampsia and plasmatic levels and associated with IL-6 levels in GCF samples in early pregnancy (1.06 (1.007–1.117))
Ruma., M, Bogges., K, Moss., K, Jared., H, Murtha., A, Beck.,J et al. (2008)	Maternal periodontal disease, systemic inflammation, and risk for preeclampsia	Cohort study	BP $>$ 140/90 mmHg and at least 1 proteinuria. Periodontal disease was defined as 1 or more tooth sites with greater than or equal to 4-mm pocket depth or 1 or more tooth pockets greater than 3 mm that bled on probing.	Women with periodontal disease and CRP $\geq$ 75th percentile were at increased risk for preeclampsia (5.8 (1.2-26.9))
Shah, Sujay B. Shah, Nilesh Mehta, Rupal (2015)	Evaluation of Relationship between Maternal Periodontal Status and Preeclampsia	Case-Control Study	BP $\geq$ 140/90 mm Hg, protein urine $\pm$ 300 mg. PD $\geq$ 4mm and CAL $\geq$ 3mm	Maternal periodontitis was associated with preeclampsia (9.333 (2.847-30.602))
Ha, Oh, Yang, Jun, Jin, Paik (2011)	Oral Health Behaviors, Periodontal Disease, and Pathogens in Preeclampsia	Case-control study	BP $>$ 140/90 mm Hg, $\geq$ 1+ proteinuria. Localized: CAL $\geq$ 3.5 mm on two or three sites in the different tooth Generalized: CAL $\geq$ 3.5 mm on four or more sites in the different teeth	Women who have a habit of taking care of teeth, are more likely to get preeclampsia than women who rarely take care of teeth. (Localized: 4.79 (1.02–29.72) Generalized: 6.60 (1.25–41.61)))
Siqueira, Cota., L O M, Costa.,J, Haddad, Lana, Costa[17] (2008)	Maternal Periodontitis as a Potential Risk Variable for Preeclampsia	Case-control study	BP $>$ 140/90 mmHg, $\geq$ 1+proteinuria. Four or more teeth with PD $\geq$ 4 mm and CAL $\geq$ 3 mm at the same site	Preeclampsia were associated with an increase in the number of sites with BOP, and PD and CAL $\pm$ 4 mm (1.52 (1.01–2.29))



Authors	Title	Design	Variable	Result
Politano, Passini, Nomura, Velloso, Morari, Couto[18] (2011)	Correlation between periodontal disease, inflammatory alterations and pre-eclampsia	A case-control	BP $\geq$ 140/90 mmHg of and proteinuria $\pm$ 300 mg. Two or more sites showed pocket formation ( $\pm$ 4 mm), clinical attachment level ( $\pm$ 4 mm)	There was an association between periodontitis and pre-eclampsia 3.73( 1.32–10.58)
J. E. Ha, Jun JK, Ko HJ, D. I. Paik, K. H.Bae (2014)	Association between periodontitis and preeclampsia in never-smokers	Cohort study	BP $\geq$ 140/90 mmHg and 1+ proteinuria. CAL $\geq$ 4.0 mm	There was a significant relationship between periodontitis and the occurrence of preeclampsia among never-smokers 5.56 (1.49–20.71).

*Case-control studies of maternal periodontitis and periodontitis*

In this study there are 6 journals used to analyze the influence of periodontitis on the incidence of preeclampsia. Moura DA Silva G, Coutinho SB, Piscoya MD, Ximenes RA, Jamelli SR (2012), reported that 574 respondents showed that respondents with periodontitis were more likely to have preeclampsia than those with a healthy periodontium. Chaparro A, Sanz A, Quintero A, Inostroza C, Ramirez V, Carrion F, et al (2013) reported data from women in Santiago, Chile that pregnant women who had periodontitis who later developed preeclampsia showed an elevated level of IL-6 in plasma GCF and CRP during early pregnancy. Periodontal disease is known to cause systemic inflammation early in pregnancy through increased IL-6 mechanism and systemic CRP enhancement. Therefore, the two inflammatory agents are considered a trigger in the relationship between periodontal disease and preeclampsia. Subsequently, Shah, Sujay B. Shah, Nilesh Mehta, Rupal (2015) reported that 310 respondents who had periodontitis but neither preeclampsia nor those with preeclampsia were found to have a relationship. Subsequently, Shah, Sujay B. Shah, Nilesh Mehta, Rupal (2015) reported that 310 respondents who had periodontitis but neither preeclampsia nor those with preeclampsia were found to have a relationship. Ha, Oh, Yang, Jun, Jin, Paik (2011), Conducted a study looking at hygiene and oral hygiene status as measured by a periodontal AL  $\geq$ 3.5 mm tool on two or three teeth (as localized periodontitis) or  $\geq$  4 teeth (as a generalized periodontitis) associated with an increased risk of preeclampsia. Patients with generalized periodontitis were almost six times more likely to have preeclampsia, and patients with localized periodontitis were nearly five times more likely to have preeclampsia. Politano, Passini, Nomura, Velloso, Morari, Couto (2011) reported maternal periodontitis is a risk factor associated with preeclampsia. Siqueira, Cota.L O M, Costa.J, Haddad, Lana, Costa (2008) Reported that clinically periodontitis was associated with preeclampsia; However, the researchers were unable to prove a systemic inflammatory process involving TNF $\alpha$  and IL-6 cytokines as the cause of preeclampsia.

*Cohort studies of maternal periodontitis and periodontitis*

3 studies used in the cohort design. Shetty., M, Shetty., PK, Ramesh., A.,Thomas., B, Prabhu., S, Rao., A (2010), a total of 130 pregnant women were enrolled between 26-32 weeks of gestation. The Oral health examination is performed on recruitment and again within 48 hours after delivery to determine the presence and / or progression of periodontitis in all subjects. There were significant differences (p <0.05) between the preeclampsia and normotensive groups in the distribution of periodontitis in both recruitment and postpartum. Some logistic regression showed that periodontitis at enrollment (OR = 5.78, 95% CI 2.41-13.89) and also within 48 hours after delivery (OR = 20.15, 95% CI 4.55-89 , 29), may be associated with an increased risk of preeclampsia. Ruma., M, Bogges., K, Moss., K, Jared., H, Murtha., A, Beck.,J et al. (2008) maternal periodontal disease with systemic inflammation as measured by C-reactive protein is associated with an increased risk for preeclampsia (5.8 ( 1.2-26.9). J. E. Ha, Jun JK, Ko HJ, D. I. Paik, K.

H.Bae (2014) there was a significant relationship between periodontitis and the occurrence of preeclampsia among never-smokers.[3].

#### *Summary for studies of periodontitis and preeclampsia*

The prospective cohort study is considered a good standard in assessing the effects of a particular disease as exposure to poor health outcomes. Prospective cohorts may provide strong evidence that pregnant women with periodontitis can lead to preeclampsia. The respondent's periodontal status is examined at different times during pregnancy or after delivery (at first recruitment and 48 hours after delivery).

### **DISCUSSION**

Based on the title of this review literature, the dependent variable is preeclampsia and the independent variable is periodontitis. Periodontitis is one of the most common diseases characterized by the destruction of connective tissue and bone tooth support following inflammation resulting from a secondary response to infection from periodontal bacteria[19]. The occurrence of inflammatory response of periodontal tissue to infection can be influenced by oral hygiene/bacterial plaque, smoking, stress, systemic factors (associated with either hematological disorders or certain genetic diseases)[20], alcohol, diabetes, obesity and metabolic syndrome, osteoporosis, dietary calcium and vitamin D, gender and genetic factor that may exacerbate the inflammatory pathology associated with periodontitis[19]. While the risk factor for preeclampsia since ancient times, the current understanding of the causes of preeclampsia has been still limited. Risk factors associated with pregnancy, pre-conceptional and pregnancy have been described, but preeclampsia remains a 'theoretical disease'[21]. Overall and regional of risk factors for preeclampsia are primiparity, nulipara and diabetes mellitus[22], previous preeclampsia, maternal pre-pregnancy body mass index[21, 23], Underlying medical conditions, smoking in pregnancy, pregnancy specific factors (multiple gestation), ethnicity, anemia, history of chronic hypertension [23] that are established risk factors. But, unresolved risk factors are maternal age, Previous miscarriages and induced abortions, candidate genes, chromosomal areas, twin studies, paternal genetic contribution, environmental risk factors (exercise, infections, socioeconomic)[21].

This literature review shows a significant association between periodontitis and the incidence of preeclampsia arising from case-control research, and cohort design. Well designed cohort studies can provide strong results. In one case, an exposure is followed until the result is known. Because exposure was identified before the outcome, the cohort study has a temporal framework for assessing causality and thus has the potential to provide the strongest scientific evidence. The cohort study is very advantageous to check for rare exposures because subjects are selected by their exposure status. In addition, investigators can check multiple results simultaneously. Disadvantages include the need for large sample sizes and the duration of potentially long term follow-up studies that require time and cost. The case-control study identified subjects with yield status at the beginning of the investigation. Data on exposure to risk factors or some risk factors are collected retrospectively, usually through interviews, abstraction from records, or surveys[24]. The case-control study is unsuitable for research aimed at knowing the causal criteria.

Maternal periodontitis substitutes a potential microorganism that can penetrate the circulation, directly or indirectly has the capacity to affect the health of the mother and fetus[4]. During the period of pregnancy, the hormone progesterone increases to 10-fold and estrogen hormone increase as much as 30-fold when compared at the time of menstruation. Increased progesterone hormones cause greater vascular permeability, stimulate prostaglandin production that can cause inflammation, and may decrease regulation of interleukin-6 production that is less resistant to bacteria-induced inflammation[6]. Periodontal tissue increases the immuno-inflammatory response to bacteria by activating hosted cytokines such as interleukin (IL-6), IL-1, and tumor necrosis factor (TNF- $\alpha$ ). The mechanism by activating the production of

prostaglandins that cause damage to connective tissue and causes bone loss. Just as periodontal tissue can trigger an immunoglobulin response, which can also lead to a vascular response in pregnant women that may be linked to various complications of pregnancy such as preeclampsia, premature birth and low birth weight. Periodontal disease may be a source of endotoxin, inflammatory cytokines like TNF- $\alpha$ , and oxidative stressors in maternal-fetal[7].

The results of research on the relationship between periodontal disease and preeclampsia have been controversial. From a clinical point of view, the fundamental question is whether the treatment of periodontal disease in pregnant women can decrease the incidence of adverse events associated with preeclampsia. Research that has been done to determine the effects of the treatment of periodontal disease in women with preeclampsia showed negative results. Randomized clinical trials concluded that treatment of periodontal disease in pregnant women did not reduce the incidence of preeclampsia. The exact mechanism of periodontal disease associated with preeclampsia is not fully understood. Pregnant women with preeclampsia have a higher activation of inflammatory responses than do pregnant women without preeclampsia. The emergence and severity of periodontal disease are thought to increase the risk of development and severity of preeclampsia[11].

In other cases, several large randomized controlled clinical trials failed to find that standard periodontal therapy during pregnancy reduced the incidence of adverse pregnancy outcomes (e.g. premature birth and low birth weight). It is considered that treating periodontal disease during pregnancy may be too late to reduce inflammation. In addition, periodontal treatment during pregnancy may also cause bacteremia, which opens the pathway for poor pregnancy outcomes[25]. But, periodontal interventions before pregnancy will lower the risk of developing preeclampsia[11]. Pregnancy and oral hygiene are part of overall health care. Every health care worker can play an important role in encouraging pregnant women to check their dental and mouth conditions to dental health facilities[26]. Therefore, the government should maximize its role in appealing to the community, especially for women planning to become pregnant to perform dental and oral health checks, specifically focusing on periodontal disease, as well as optimizing health promotion related to oral and dental healthy.

## **CONCLUSION**

Periodontitis is one of the risk factors for the occurrence of preeclampsia, which can lead to a vascular response in pregnant women that may be linked to various complications of pregnancy such as preeclampsia. The mechanism by activating the production of prostaglandins that cause damage to connective tissue and causes bone loss. Just as periodontal tissue can trigger an immunoglobulin response. With the guidance of maintaining the dental and oral health of pregnant and under-five mothers published by the government is expected to reduce the impact of periodontal disease so that the community can maintain good hygiene and oral hygiene, and can avoid possible risk factors that can trigger the occurrence of periodontitis such as smoking and consuming alcohol. And can be developed into a strategic and innovative program to increase community interest to regularly check the health of teeth to health facilities

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