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Factors Associated With Preeclampsia: A Systematic Review

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ABSTRACT
Preeclampsia remains a significant public health threat in developed and developing countries, contributing to maternal and perinatal morbidity and mortality globally. The prevalence of preeclampsia in developed countries is 1.3% - 6%, while in other developing countries it is 1.8% - 18%. Preeclampsia is a pregnancy complication characterized by an increase in blood pressure (hypertension) that usually appears after 20 weeks of gestation, accompanied by damage to organs such as the kidneys, which can be seen from the presence of protein in the urine (proteinuria). The goal is to find out what are the factors that cause preeclampsia in mothers. This study uses the Systematic Review method in accordance with the PRISMA Guidelines. The focus of the review is determined by keywords, inclusion and exclusion criteria, article search strategies with relevant databases (PubMed, Scince Direct, and Wiley), the article selection process is described in the PRISMA flowchart, Critical Appraisal using CEBM, then data extraction, and presenting the results. There are 106 articles that are removed duplicates which are then selected from titles, abstra to full text. Finally, 11 selected articles that met the inclusion criteria, Nine themes were found in this study, namely Demographic factors, Obstetric History, Health Conditions, Family Health History, ANC Visits, PAPP-P and β hCG, P53 Gene Changes, Based on Sex, Nonproteinuric and Placenta Location. In this review, an article related to the factors that cause preeclampsia in mothers was obtained, so it is recommended that researchers conduct further research related to preeclampsia management based on the causative factors. This is so that the problem of preeclampsia in mothers can be solved.

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INTRODUCTION

Currently, maternal mortality is a problem in various parts of the world, including Indonesia. In general, there was a decrease in maternal mortality during the period 1991-2020 from 390 to 189 per 100,000 live births. This figure has almost reached the 2024 RPJMN target of 183 per 100,000 live births. Despite the tendency to decrease maternal mortality rates, efforts are still needed to accelerate the reduction of AKI to achieve the SGDs target of 70 per 100,000 live births by 2030 (Ministry of Health, 2023). The most common causes of maternal mortality in 2023 are hypertension in pregnancy with 412 cases, obstetric

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hemorrhage with 360 cases and other obstetric complications with 204 cases (Ministry of Health, 2023).

According to WHO data, the maternal mortality rate was around 287,000 during and after pregnancy and childbirth in 2020. The main complications that cause almost 75% of all maternal deaths are Heavy bleeding, Infections, High blood pressure during pregnancy (Preeclampsia and Eclampsia), Complications due to childbirth, and unsafe abortions (WHO, 2024).

Preeclampsia remains a significant public health threat in developed and developing countries, contributing to maternal and perinatal morbidity and mortality globally. The prevalence of preeclampsia in developed countries is 1.3% - 6%, while in other developing countries it is 1.8% - 18%. The incidence rate of preeclampsia in Indonesia itself is 128,273/year or around 5.3%. Globally, 10% of pregnant women worldwide experience preeclampsia and are responsible for 76,000 maternal deaths and 500,000 infant deaths, each year (POGI, 2016).

According to the Indonesian Ministry of Health, 2023, Preeclampsia is a health problem that arises after more than 20 weeks of gestation, characterized by the appearance of hypertension and proteinuria. Meanwhile, according to WHO, 2024, Preeclampsia is a pregnancy complication characterized by an increase in blood pressure (hypertension) that usually appears after 20 weeks of gestation, accompanied by damage to organs such as the kidneys, which can be seen from the presence of protein in the urine (proteinuria).

Preeclampsia is a complication in pregnancy that has three main symptoms, namely gestational hypertension >140/90 mmHg, edema, and protein in >3 grams of urine and often appears during pregnancy, childbirth, and even in postpartum mothers. This manifestation occurs in pregnant women with a gestational age of more than 20 weeks (Dewi *et al.*, 2022)

Recent evidence suggests that preeclampsia is a two-stage disease. The first stage is the early stage of asymptomatic pregnancy, which is caused by poor placenta due to abnormal invasion of trophoblasts and remodeling of the spiral artery. This results in the second stage of the disease, which is characterized by ischemia/placental reperfusion injury and a maternal immune-mediated response. As a result, there is a release of antiangiogenic factors and placental debris into the maternal circulation and an inadequate release of proangiogenic factors. So that the consequences of the whole are clinical manifestations such as high blood pressure, proteinuria, and acute kidney injury, liver dysfunction, hemolysis, thrombocytopenia, and less often liver rupture, seizures (eclampsia), stroke, and death (Yuanwei Fan, Graham M., 2016).

Although many studies have been carried out but Preeclampsia until now the exact cause is unknown, the pathogenic process of Preeclampsia begins during the first trimester, long before clinical signs appear. Therefore, it is difficult to identify early biomarkers. The main reason for this may be ethical, as it is difficult to conduct research on early pregnancy, as this can harm the mother and fetus (Gathiram and Moodley, 2016). However, there are several factors that contribute to the occurrence of preeclampsia in pregnant women. Some of the factors that cause preeclampsia are primigravida, early gestational period (<34

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weeks), obesity or maternal nutritional status, history of hypertension, age, genetic factors, diabetes mellitus, pregnancy pregnancy, and culture related to food consumption patterns (Dewi *et al.*, 2022)

Symptoms such as high blood pressure, cardiovascular, cerebrovascular involvement, renal, disseminated intravascular coagulation (DIC) and HELLP syndrome (hemolysis, increased liver enzymes, low platelet count) in the mother, neonate and fetus. complications such as premature birth, low birth weight, and intrapartum death. Cerebral hemorrhage is the most common cause of death in patients with eclampsia (Faiza, et al., 2023). From the description of the facts and phenomena above, the researcher is interested in making a Systematic Review proposal regarding the Factors of Preeclampsia in Pregnant Women.

METHODS

This study uses the Systematic review method. This Systematic Review process is carried out in accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). PRISMA provides a systematic framework for researchers to report on the objectives, methods, outcomes, and conclusions of the Systematic Review. This review includes several steps, namely:

Eligibility Criteria

To identify Systematic Review questions and develop a search strategy, the PICO framework is used. This is outlined in Table 1. To identify relevant articles in this Systematic Review, the first step taken is to determine the inclusion and exclusion criteria of the framework that has been created so that the data sought is not widened and focuses on the context sought. The inclusion and exclusion criteria in this study can be seen in Table 2.

Tabel 1. Framework Research Question.

P (Population, Patient, Problem)	I (Intervension, Prognostics factor, Exposure)	C (Comparison or Intervention/if appropriate)	O Outcomes
Pregnant Mother	Factor	-	Preeklampsia

Table 2. Inclusion and Exclusion Criteria

No	Aspects	Inclusion Criteria	Exclusion Criteria
1	Article Characteristics	a. *Original Research/Peer Reviewed* b. Articles published in English and Indonesian c. Articles published in the period from 2014 to 2023 d. All *design studies*	a. *Grey literature* includes *conference papers, conference proceedings,* theses/dissertations, books, *guidelines* and other *papers* that are considered grey *literature* b. Articles published in predator journals *c. Reviewed Article*

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No	Aspects	Inclusion Criteria	Exclusion Criteria
2	Participants	Population : pregnant women	
3	Study Focus	a. Articles about the incidence of preeclampsia b. Articles on the factors that contribute to the occurrence of preeclampsia	

Search Strategy

To identify the relevant articles in this review, the first step for a search strategy will start with developing keywords that focus on "Determinant" and "Preeclampsia". The list of keywords that will be used as the basis for a broader literature search will be written in detail in Table 3. The search uses three databases: PubMed, Scince Direct, and Wiley. Boolean operators (AND and OR) will be used to combine or exclude keywords in the search.

Table 3. Keywords used in search

No	Keywords
1	Determinant
2	Reason
3	Factor
4	Element
5	Cause
6	OR 1-5
7	Preeclampsia
8	6 AND 8

Table 4. Search Strings in the Database

Keywords	Search String
Determinant	(((((Determinant) OR (Reason) OR (Factor) OR (Element) OR (Cause)
Preeclampsia	(Peeclampsia)
Combining Keywords Using Boolean AND, Time Range and Abstract	(((((Determinant) OR (Reason) OR (Factor) OR (Element) OR (Cause) AND (Peeclampsia)

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Article Selection

It found 106 articles from searches of the three databases which were then stored and filtered in Zotero's reference management software. The screening process began by removing duplicates, and 3 duplicate articles were found. A total of 33 articles were screened through titles and abstracts. Furthermore, 33 articles were screened in fulltext and the last 10 years. and 24 articles were found that did not meet the eligibility criteria and were in the EXKLUD for several reasons. So that the articles included in this study are as many as 11 articles. The finding of the number of articles and the filtering process will be described in figure 1. PRISMA Flowchart below.

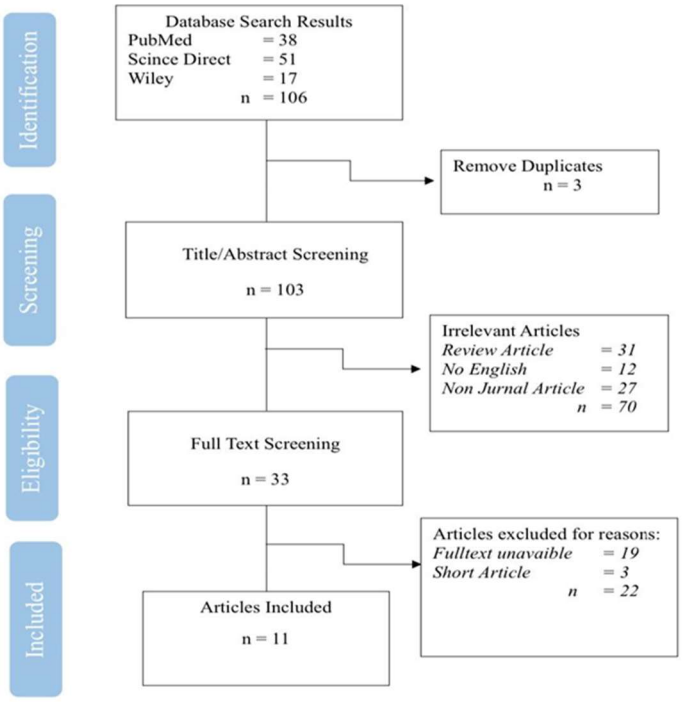

Figure 1. PRISMA Flowchart

Critical Appraisal

The tools selected to assess the quality in this Systematic Review are the Center for Evidence-Based Management (CEBM) and the Mixed Methods Appraisal Tool (MMAT). The article is given a code to facilitate review with the number A1-A11.

Data Charting and Extraction

After being analyzed and evaluated from several points above, the results of data collection are extracted in accordance with the objectives of the Review.

RESULTS AND DISCUSION

Demographic Factors

Mother's Age

There are two articles that state that the mother's age factor is one of the causes of preeclampsia. Based on research conducted by (Faiza *et al.*, 2023), The results showed that

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the majority of patients were between 18-27 years old (72%). Based on research (Tesfahun *et al.*, 2023), instead stating that women over 35 years of age have a higher odds of developing preeclampsia compared to women under 35 years of age, with AOR = 2.1; 95% CI: 1.3, 3.4. Based on this, it can be known that the maternal age factor is one of the causes of preeclampsia. This is in line with research conducted by (Adwoa *et al.*, 2022) and (Otu-Nyarko *et al.*, 2022), the results of the study agreed that maternal age factors had an effect on the occurrence of preeclampsia, with the age group of 18-24 years, 25.5% in the age group of 25-29 years, and 26.1% in the age group of 30-34 years and the age category of 35-39 years (27.9%).

a. Residence

One article states that living in the countryside is also a factor in the occurrence of preeclusion. This was conveyed by, The results of the study (Sk, 2023), show that women living in rural areas have a higher risk of experiencing eclampsia-related deaths, with the majority (85%) of women who die from eclampsia living in rural areas. Many women are referred to three or more hospitals before they die, indicating delays in treatment. Based on the above, it can be seen that living in the countryside is also a factor in the occurrence of preeklasia. Based on a research study conducted by (Das and Biswas, 2015), this result states that living in rural areas is associated with an increased risk of eclampsia. However, research conducted by (Agrawal, 2014), showed that almost one-third of respondents who reported symptoms indicating preeclampsia were slightly higher in urban India.

b. Economy and Low Education

One article conveyed that Economics and Education are factors that cause preeclampsia. This was conveyed by, (Aabidha *et al.*, 2015), which states that out of 1900 women screened, 93 women were detected to have pre-eclampsia. 30.1% came from socioeconomic class 4, the study also showed that women with low levels of education were more likely to have pre-eclampsia. Based on this, it can be seen that Economics and Education are factors that cause preeclampsia. According to research conducted by (Anto *et al.*, 2024), (Kiondo *et al.*, 2012), (Boachie-Ansah *et al.*, 2023), and (Njelita *et al.*, 2021)This is in line with research showing that lower education is associated with an increase in preeclampsia, economic class status figures are also included as a factor in the occurrence of preeclampsia.

Obstetric History

a. Primigravida

There are five articles that state that primigravida is a factor that has a great influence on the occurrence of preeclampsia. research conducted by (Anto *et al.*, 2023), primigravida is independently associated with preeclampsia. Thus, primigravida mothers have a 1.95 times increased risk of preeclampsia compared to multigravida pregnant women.

This is in line with the research conducted (Aabidha *et al.*, 2015), stated that of the 1900 women screened, 93 women were detected to have pre-eclampsia, 46.23% were primigravida. According to (Asres *et al.*, 2022) Being a first-time mother or primigravida is also a risk factor for preeclampsia because women who get pregnant for the first time may

not be able to adapt to the physiological changes that occur during pregnancy. During early pregnancy, new blood vessels develop to flow blood to the placenta, and the inability to adapt to these changes can increase the risk of preeclampsia.

According to (Haile *et al.*, 2021), The results showed that primigravida mothers had a 5.41 times higher risk of developing preeclampsia compared to multigravida mothers. Research conducted by (Sk, 2023), also states that primigravida or nullipara status has a higher risk of developing eclampsia. Based on this, it can be known that primigravida is a factor that has a great influence on the occurrence of preeclampsia.

b. SC History

One research article said that the previous history of SC was a factor in the occurrence of preeclampsia. This can be seen from the citation of research conducted by (Anto *et al.*, 2023), having had a previous cesarean delivery was also associated with an increased risk of preeclampsia by 4.66 times. Various uterine changes due to cesarean delivery can inhibit the invasion of trophoblasts and alter the blood flow of the uteroplacenta in subsequent pregnancies, resulting in preeclampsia in subsequent pregnancies. Based on this, it can be seen that the Previous SC History is a factor in the occurrence of preeclampsia.

This is agreed by the research conducted (Cho *et al.*, 2015), It is caused by changes in the uterus resulting from surgical procedures or manipulations during cesarean section, which can interfere with the normal invasion of trophoblasts and the subsequent uterine and placental blood flow, potentially leading to preeclampsia.

c. History of Preeclampsia

There are four articles stating that the Previous History of Preeclampsia is a factor. This was conveyed by (Aabidha *et al.*, 2015), stating that out of 1900 women screened, 93 women were detected to have pre-eclampsia. Mothers with a previous history of pre-eclampsia 7.52% had preeclampsia, A previous history of preeclampsia is a factor associated with an increased risk of preeclampsia in subsequent pregnancies. Women who experience pre-eclampsia in the first pregnancy have a seven-fold risk of developing pre-eclampsia in the second pregnancy.

According to (Tesfahun *et al.*, 2023), also stated the same where Women who had a history of preeclampsia in previous pregnancies had a higher risk of developing the same condition in subsequent pregnancies, with AOR = 8; 95% CI: 1.2, 10.3. Based on research (Asres *et al.*, 2022)The results of this study show that women with a history of preeclampsia are 49.5 times more likely to experience this condition. (Haile *et al.*, 2021), History of preeclampsia in previous pregnancy increases the risk by 5.55 times. Based on this, it can be known that the Previous History of Preeclampsia is a factor in the occurrence of preeclampsia.

Based on research conducted by (Grum *et al.*, 2017) and (Mou *et al.*, 2021), the risk is 14.7% in the second pregnancy for women who have had preeclampsia in the first pregnancy and 31.9% in women who have had preeclampsia in the previous two pregnancies. The risk in multipara women without a history of preeclampsia is about 1%.

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d. Multiple Pregnancy

Two articles stated that multiple pregnancies also affect the occurrence of preeclampsia. This was conveyed (Aabidha *et al.*, 2015), twin pregnancies (4.3%), (Aabidha *et al.*, 2015), Women with multiple pregnancies have a 6.41 times higher chance of developing preeclampsia compared to women with single pregnancies. Based on this, it can be seen that multiple pregnancies also affect the occurrence of preeclampsia.

e. Parity

There is one article that states that parity is one of the factors that trigger the occurrence of preeclampsia, taken in a research citation (Aabidha *et al.*, 2015)The results of this study showed that the number of previous pregnancies (five or more) also contributed to an increased risk of preeclampsia with an odds ratio suggesting that women who were pregnant five times or more had a higher risk. Based on this, it can be seen that the Gravida History is one of the factors that trigger the occurrence of preeclampsia.

According to research (Otu-Nyarko *et al.*, 2022), (Agrawal, 2014), (Boachie-Ansah *et al.*, 2023), (Kiondo *et al.*, 2012), Women who had five or more children had an OR of 3.71 (95% CI: 1.84–7.45), suggesting that high multiparity was also associated with an increased risk of pre-eclampsia.

Health Conditions

a. Anemia

There are two studies that state that anemia is a factor in the current medical condition of the mother that can cause preeclampsia. This was conveyed by (Aabidha *et al.*, 2015), this study stated that Anemia was related to pre-eclampsia in 55.91% of cases. According to (Haile *et al.*, 2021), Anemia is also associated with a higher risk of 3.23 times. Based on this, it can be known that anemia is a factor in the mother's current medical condition that can cause preeclampsia. This is also found in the research studies conducted (Ali *et al.*(2011), The study found that women with severe anemia had a 3.6 times higher risk of developing preeclampsia.

b. Diabetes

Two Articles state that Diabetes is a factor in the mother's current medical condition that can cause preeclampsia. Based on research (Aabidha *et al.*, 2015), and diabetes related in 3.22% of cases. According to (Haile *et al.*, 2021)The results showed that eight variables were identified as determinants of preeclampsia among women attending childbirth services. Women who had a history of diabetes mellitus (DM) had a 4.31 times higher risk of developing preeclampsia compared to women who did not have a history of DM. Based on this, it can be known that Diabetes is a factor in the mother's current medical condition that can cause preeclampsia. Based on research conducted (Belay and Wudad, 2019), the study is in line with diabetes stating that women with a history of diabetes mellitus have a higher risk of developing preeclampsia (AOR = .058, 95% CI = [.007 – .465]).

c. Body Mass Index

Two articles state that a high BMI (Body Mass Index) or BMI (BMI) is a factor in the mother's current medical condition that can cause preeclampsia. (Aabidha *et al.*, 2015), Women who have a BMI between 26-30 by 48.8%. Research (Faiza *et al.*, 2023), Body

Mass Index (BMI) As many as 86 (64%) patients have a BMI of >27 kg/m2. Overweight/obesity can be a risk factor for eclampsia. Pregnant women with these characteristics have a higher risk of developing complications of preeclampsia and eclampsia. Other factors such as a previous history of eclampsia, a high body mass index (BMI), high blood pressure at the initial visit, and age over 40 years were also mentioned, however, no specific data or evidence was provided in the citation regarding how much each of these factors affected preeclampsia.

Based on this, it can be known that a high BMI (Body Mass Index) or BMI (BMI) is a factor in the mother's current medical condition that can cause preeclampsia. This is according to studies (Agrawal, 2014), and (Young, Twedt and Catov, 2016), Women with the lowest BMI have a relatively lower prevalence of preeclampsia In the studies analyzed, women with obesity were more likely to develop preeclampsia compared to women without obesity.

d. History of Hypertension

One article stated that having a history of hypertension was also one of the factors in the occurrence of preeclampsia. Where this was researched by (Haile *et al.*, 2021), states that Women who have a history of hypertension have a higher risk of developing preeclampsia, with AOR = 2.9; 95% CI: 3.0, 7.3. Based on this, it can be seen that having a history of hypertension is also one of the factors that cause preeclampsia. Women with a history of chronic hypertension had an OR of 2.29 (95% CI: 1.12–4.66), suggesting that pre-existing hypertension increased the risk of pre-eclampsia. This was conveyed by (Kiondo *et al.*, 2012).

e. Gestational Age Less than 34 Weeks

One article states that the frequency of young gestational age also affects the occurrence of preeclampsia. Research (Faiza *et al.*, 2023), the results of the study stated that gestational age plays an important role in the occurrence of preeclampsia where most patients (61%) have a gestational age of ≤34 weeks when eclampsia occurs so that younger gestational age increases the risk of eclampsia. Based on this, it can be known that the frequency of young gestational age also affects the occurrence of preeclampsia.

Based on research conducted by (Melese, Badi and Aynalem, 2019), this study is in line with the gestational age of less than 34 weeks with the incidence of preeclampsia, The results of the study regarding gestational age in weeks show that the median gestational age is 38 weeks, with a range from 21 to 43 weeks. A total of 225 (49.4%) respondents had a gestational age between 37 to 40 weeks. In addition, discontinued pregnancies at 20-27 weeks and 28-36 weeks had higher unfavorable perinatal outcomes compared to discontinued pregnancies at 37-40 weeks, with odds ratios (AOR) of 9.6 (95% CI 2.00, 18.65) for 20-27 weeks of age.

Family Health History

a. History of Hypertension

Three Articles state that it is true that a family history of hypertension is a factor in the occurrence of preeclampsia. Research (Asres *et al.*, 2022)The results of this study showed that some significant factors that increased the risk of preeclampsia in pregnant women

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were that women with a family history of hypertension were 7.2 times more likely to develop preeclampsia.

The results of research conducted by (Haile *et al.*, 2021), Stated Family history of hypertension Increased the risk of preeclampsia by 2.60 times. This is not much different from the research conducted (Tesfahun *et al.*, 2023), Women with a family history of hypertension have about twice the odds of developing preeclampsia compared to those who do not have such a history. Based on this, it can be known that a family history of hypertension is a factor in the occurrence of preeclampsia.

This is in line with the research conducted (Melese, Badi and Aynalem, 2019), (Tessema, Tekeste and Ayele, 2015), the family history of hypertension has a significant value with an odds ratio (AOR) of 7.19 (95% CI 3.4 – 15.2), which shows that pregnant women with a family history of hypertension are about seven times more likely to develop preeclampsia.

b. History of Diabetes

One research article said that a family history of diabetes was also a factor in the occurrence of preeclampsia. (Asres *et al.*, 2022), A family history of diabetes mellitus (DM) also contributes to an increased risk of preeclampsia. Based on this, it can be known that a family history of diabetes is also a factor in the occurrence of preeclampsia.

This is in line with research conducted by (Belay and Wudad, 2019), (Tessema, Tekeste and Ayele, 2015), Family history of diabetes mellitus is a significant factor related to the occurrence of preeclampsia. The data suggest that women with a family history of diabetes mellitus have a higher risk of developing preeclampsia, although no specific figures were given in the study. This suggests that genetic or environmental factors related to diabetes mellitus may contribute to the risk of preeclampsia.

c. History of Preeclampsia

One article said that women who have a family history of preeclampsia also contribute to triggering the onset of preeclampsia. The results of research conducted by (Honarjoo *et al.*, 2019), Family history of preeclampsia increases the likelihood of preeclampsia by 5.24 times. Based on this, it can be seen that the family history of Preeclampsia also contributes to triggering the onset of preeclampsia. This is in line with research conducted by (Grum *et al.*, 2017), the results of the study stated that the previous history of pre-eclampsia significantly increased the risk of preeclampsia (AOR = 4.28; $p < 0.05$).

ANC Visit

Dua Sang said that the lack of ANC or irregular ANC can also increase the risk of preeclampsia. According to research conducted by (Sk, 2023), the absence of antenatal care (ANC) which causes a lack of antenatal care (ANC) is one of the factors in the occurrence of preeclampsia. However, specific data on the number of irregular mothers at ANC visits were not mentioned.

This was also stated in the study (Tesfahun *et al.*, 2023), ANC visit data showed that 45 participants (19.31%) had less than 3 ANC visits, while 188 participants (80.69%) had more than 3 ANC visits. Regularity in conducting ANC visits has an effect on the detection and management of preeclampsia, which suggests that lack of visits may increase the risk.

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Based on this, it can be known that the lack of ANC or irregular ANC can also increase the risk of preeclampsia. Based on research conducted by (Nobis and Hajong, 2016), stated that antenatal visits showed that 93.4% of women with eclampsia did not have antenatal visits, and only 6% did 3 antenatal visits.

PAPP-A dan β hCG

One article mentioned that PAPP-A and β hCG have a relationship that can cause preeclampsia. Based on research conducted by (Honarjoo *et al.*, 2019), indicating that PAPP-A and β hCG levels have a significant relationship with preeclampsia (PE). The mean MOM PAPP-A in the preeclampsia group was significantly lower (0.79) compared to the group without PE (1.19) with a $P < 0.001$. In addition, hCG β levels also showed significant differences between the two groups, where hCG β levels were higher in the PE group. Further evidence suggests that abnormal levels of PAPP-A (MOM < 0.4) and β hCG (MOM > 3) are associated with an increased risk of PE, with adjusted odds ratios for PAPP-A < 0.4 being 2.09 and for β hCG > 3 being 5.65. Based on this, it can be seen that PAPP-A and β hCG have a relationship that can cause preeclampsia.

This study is in accordance with (Ratna, jenni k, 2011), (Amélie Boutin, *et al.*, 2018), this study stated that the median maternal serum MOM of PAPP-A was significantly lower in women with PE, PD and SGA (0.79, 0.80 and 0.79 MOM, respectively) compared to the reference group (0.99 MOM) ($p<0.01$). The median maternal serum fβ-hCG MOM was also significantly lower in the SGA group (0.90 MOM) and in the PE and PD groups (0.86 and 0.92 MOM) compared to the reference group (0.99 MOM, $p=0.02$).

Changes in the p53 gene by sex

One article mentioned that the p53 level in maternal vein and umbilical cord samples has a relationship that can cause preeclampsia. It was researched by (Kharb *et al.*, 2022)The results of this study showed that p53 levels in maternal blood and cord blood were significantly higher in women with preeclampsia compared to normotensive pregnant women. In addition, p53 levels in the umbilical cord blood were higher in preeclampsia mothers who gave birth to a baby girl compared to those who gave birth to a baby boy. The birth weight of babies born to preeclampsia women was also lower compared to babies from normotensive mothers (2.63 ± 0.27 kg vs 2.86 ± 0.29 kg, $p=0.0029$, $p<0.05$). These findings indicate the role of apoptosis in the pathogenesis of preeclampsia and highlight the gender-based differences in p53 levels, which indicate the active contribution of the placenta to metabolism during pregnancy. Based on this, it can be seen that the p53 level in maternal vein and umbilical cord samples has a relationship that can cause preeclampsia.

This is in line with the research conducted (Vermeulen, Berneman and Van Bockstaele, 2003), (Muralimanoharan, 2013), The low rate of apoptosis in the placental villi and decided tissue is a normal physiological phenomenon. High levels of p53 expression can lead to an increase in the apoptosis process, leading to pathological changes in the placenta and abnormalities during pregnancy. Apoptosis is an orderly process of cell death and can be triggered by a variety of signals, including DNA damage, hypoxia, and other stress signals. P53 plays an important role in triggering apoptosis, especially in response to DNA damage and other stressful conditions. An increase in trophoblastic apoptosis is

observed in the placenta of preeclampsia, which is considered a causative factor in the pathogenesis of this condition. This apoptosis is more significant in the placenta of a male fetus compared to a female fetus.

Nonproteinuric

One article mentions that nonproteinurics have a relationship that can cause preeclampsia. Based on research conducted by (Owaraganise *et al.*, 2021), this study showed that the prevalence of nonproteinuric preeclampsia among pregnant women with hypertension was 24.6%. In addition, primigravida (first pregnancy) was found to be a significant risk factor for this condition. Because primigravida was found to be three times more likely to develop nonproteinuric preeclampsia compared to multipara. Multivariable logistic regression analysis showed that primigravida remained an independently associated factor with nonproteinuric preeclampsia (aOR = 2.70; 95% CI: 1.09–6.72, p = 0.032). The average age of patients was 26.9 (SD±7.1) years. 51.5% of patients were primigravida. Patients with non-proteinuric preeclampsia tend to be younger in age (23.7±6.8 years on average) and have more primigravids (72.7%) than patients with proteinuric preeclampsia. This study shows that non-proteinuric preeclampsia is quite common, especially in first-time pregnant women (primigravida).

This was also researched in studies conducted (Owaraganise *et al.*, 2021), where this study showed that the prevalence of non-proteinuric preeclampsia was 24.6% (95% CI: 17.9-32.7). Primigravidity (aOR 2.70 95%CI:1.09-6.72, p=0.032) is a factor that is independently associated with nonproteinuric preeclampsia. There was an insignificant difference in the frequency of end-organ dysfunction in women with non-proteinuric and proteinuric preeclampsia, p=0.309

Plasenta leaflet

One article states that the location of the Laterated Placenta has a relationship that can cause preeclampsia. Results of the study (Yousuf *et al.*, 2016), showing that out of a total of 201 women studied, 71 (24.5%) had a placenta located laterally. Of this group, 37 (52%) had uterine artery Doppler abnormalities. The study also found that subjects with lateral placenta and Doppler disorder had a higher risk of developing preeclampsia compared to those who had only lateral placenta alone ($p < 0.001$). After logistic regression analysis, the overall risk of developing preeclampsia in subjects with lateral placenta was 9.27 (odds ratio). Based on this, it can be known that Nonproteinuric has a relationship that can cause preeclampsia.

This is in line with research conducted by (Jani, Parul S. *et al.*, 2015), (Kakkar *et al.*, 2013), (Yousuf *et al.*, 2016), the location of the placenta is related to preeclampsia. Research shows that women with a lateral placenta have a five times greater risk of developing preeclampsia compared to those with a central placenta, with an odds ratio of 5.09 and a very significant p value.

The strength of *this Systematic Review* is that assessments are carried out using the PRISMA-SR checklist to assess the quality of *the review.* The limitation of the *Systematic Review* is that all the included articles are from developing countries, the researcher did not

find articles from developed countries so that they could not get an overview of the difference in the incidence of preeclampsia in developed and developing countries.

CONCLUSION

The results of *this review* found several studies that discussed the factors that cause preeclampsia in mothers. Factors related to preeclampsia are Demographic Factors, Obstetric History, Health Conditions, Family Health History, ANC Visits, PAPP-P and β hCG, Changes in the P53 Gene, Based on Sex in Preeclampsia, Nonproteinuric and Placental Location. Preeclampsia remains a significant public health threat in developed and developing countries, contributing to maternal and perinatal morbidity and mortality globally. It is hoped that better health care strategies, including specialized eclampsia units, increased screening and treatment protocols, and increased awareness of harmful signs during pregnancy to reduce maternal eclampsia-related deaths. In addition, the importance of better access to ANC and timely medical intervention is also emphasized to reduce maternal mortality due to eclampsia.

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