Meta Analysis Article

# Meta Analysis: The Relationship of Age, Parity and Antenatal Care Visits with Pre-Eclampsia

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**ABSTRACT**

Many mothers die due to complications during pregnancy and after delivery. The main complication, which is almost 75% of all maternal deaths, one of which is preeclampsia where the incidence of preeclampsia is estimated at 3-10% of all pregnancies. It is estimated that about 50,000 women die from preeclampsia each year. Factors causing preeclampsia were age, parity and ANC visits. This study examines studies that describe the relationship between age, parity and ANC visits with preeclampsia. This study uses a retrospective observational study, in the sense that the researcher makes a recapitulation of the factswithout performing experimental manipulation. The data source uses secondarydata obtained from previous online studies. The data collection procedure uses Google Scholar and Garuda Portal which have been involved in the last 10 years. Data were analyzed using Comprehensive Meta Analysis Version 3 (CMA 3). The results of data analysis showed that there was a relationship between Age (p value= 0.001), maternal parity (p value= 0.001), and ANC visits (p value < 0.001) with preeclampsia. The conclusion was there is a relationship between age, parity and ANC visits with preeclampsia through a meta-analysis study.

**Keywords** : Age, parity, ANC visit, preeclampsia

## INTRODUCTION

Preeclampsia is one of the leading causes of maternal mortality worldwide. It is estimated around 50.000 women die due to preeclampsia every year.[1] Preeclampsia also known as one of the problems that threatens the safety of mothers, especially in developing countries.[2] A tenth and a quarter of maternal deaths were counted in Asia and Africa, and in Latin America respectively.[3] Data from WHO shows that hypertension leads to 16% of maternal mortality rate in developing countries, 9% in Africa and Asia, and the highest one of 26% in Latin America and Caribbean.[4]

According to the data, the leading causes of maternal death in Indonesia from 2010-2018 are bleeding with 30.3% in 2013 and hypertension with 27.1% in 2018. According to Indonesia's Health Profile from 2018, hypertension is the second largest contributor to maternal mortality and has even shown an increase each year, whilst bleeding and infection shown decreased.[5]

Aside from bleeding, preeclampsia and eclampsia are the main cause of maternal mortality in Indonesia.[6] Several studies discussed the variables of age, parity and ANC visit and stated that these variables are risk factors for the incidence of preeclampsia. Osungbade & Ige (2011) explained that preeclampsia is more commonly found in high-risk maternal age groups.

Pregnant women aged <20 years old have a risk of developing preeclampsia 3.58 times greater than pregnant women aged 20-35 years old.[7]

High parity, defined as having more than 5 pregnancies, is vulnerable since it leads to many pathological obstetric events including mild preeclampsia. In terms of maternal mortality, 2 to 3 times parity is the safest parity. ANC visit is one of the risk factors of preeclampsia, in which antenatal care is considered very important in ensuring the safety of both mother and fetus

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during pregnancy and delivery.

The result on studies of age, parity and ANC factors are controversial, due to its related and unrelated results. There were 9 studies which stated that there was a relationship between maternal age and preeclampsia, and 4 studies which stated that there was no relationship were found. There were 9 studies which stated that there was a relationship between parity and preeclampsia, and 4 studies which stated that there was no relationship were found. While there were 8 studies which stated that there was a relationship between ANC visit and preeclampsia, and 5 studies which stated that there was no relationship were found.

From statements mentioned above, we conclude that there is research gap in the form of inconsistency of relation between age, parity, and ANC visit with preeclampsia. Thus, the authors are interested to analyze the previous studies about the relation of age, parity, and ANC visits of mothers with preeclampsia using meta-analysis method.

## METHOD

Study design used in this study is meta-analysis. The literature search and selection process in this study is described in the form of a Flow diagram Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). The process begins with identification, screening, eligibility, and inclusion. The database used consists of Google Scholar and Pubmed, which obtained a total of 1,002 articles found based on keywords. After a brief screening with exclusion criteria, 173 articles were obtained. Furthermore, in the eligibility stage by searching for full-text articles and testing their eligibility, 32 articles were obtained that met the requirements. And finally, 15 articles were obtained which were tested for meta-analysis according to the specified inclusion criteria.

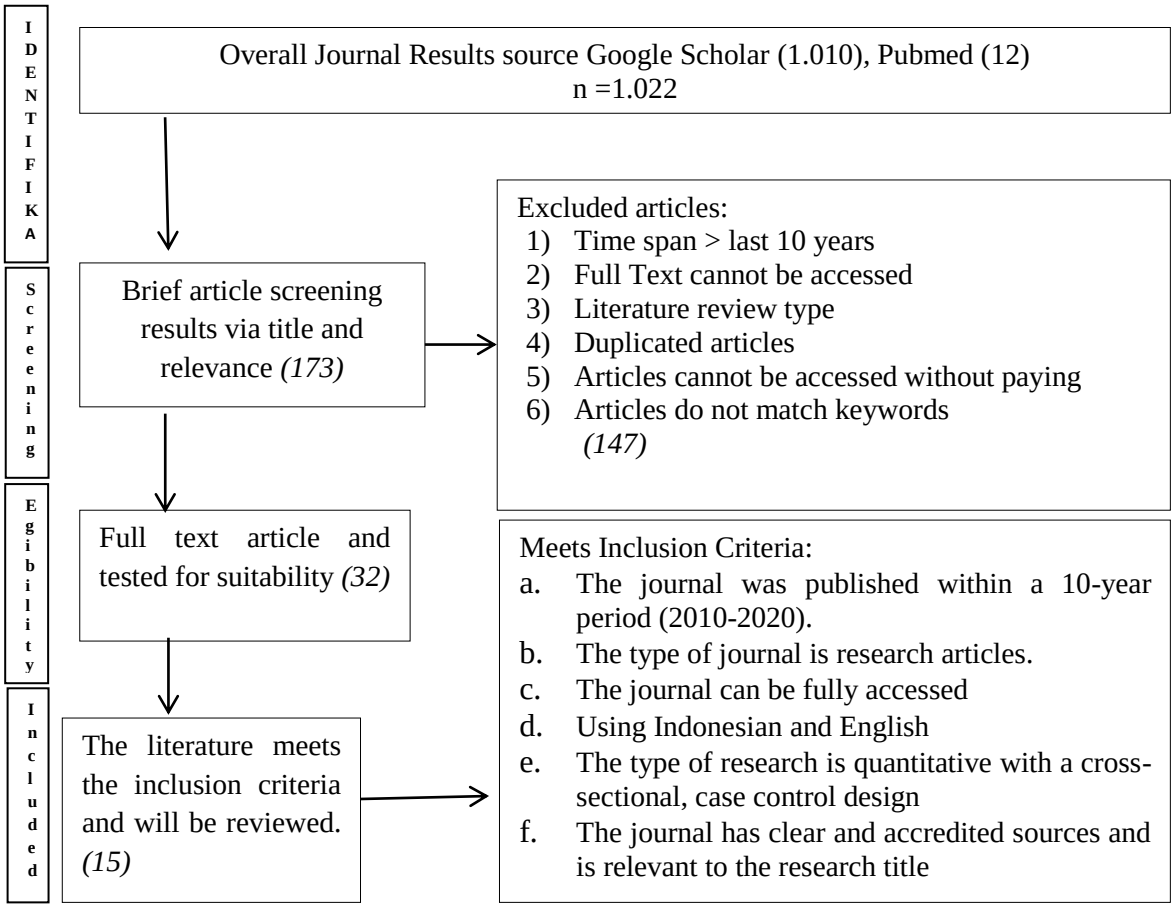


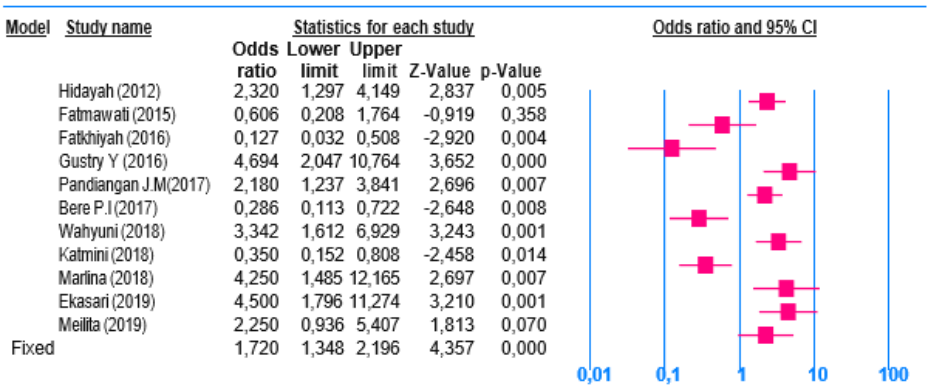

**Figure 1.** Research Protocol with PRISMA Concept

## RESULT AND DISCUSSION

### Maternal age

The number of studies that were combined to analyze the relation between maternal age and preeclampsia are 13 studies of cross sectional and case control studies, with total sample of 1.804. 11 studies stated there is relation between maternal age with preeclampsia

in pregnant woman, with total sample of 1.622 samples. While the other 2 studies stated that there is no relation between maternal age with preeclampsia in pregnant woman, with total sample of 182 samples.




**Total (95% CI) : 1.429 (0,759-2,690)**
**Heterogeneity : Chi$^2$ = 63,469, df = 10 (p = 0,000), I$^2$ = 84,244**
**Tau$^2$ = 0,968**

**Figure 2.** Forest Plot of Combined Research Studies of The Relation Between Maternal Age and Preeclampsia in Pregnant Woman

Based on Figure 2 shows the results of data analysis from 9 articles examining the relationship between maternal age and preeclampsia analyzed using the Random Effect Model. The results of the heterogeneity test show that the variation of the studies is heterogeneous, with a p value = 0.000 and a variation value between studies ($I^2$) of 86.52%. This indicates that the effect size of each study varies with a $T^2$ value = 1.032 which shows that each study has an effect or role on the effect size after being merged. The level of heterogeneity of data variation is stated as high, meaning that the articles have different variations. The plots of each article are in the range of 1-10 and the effect size value can be interpreted.

The results of analyzed data displayed on the forest plot shows that there is a relation between maternal age and preeclampsia with p value <0.05 of p 0.000 and Odds Ratio of 1,429 and 95% CI of 0.759 – 2.690. Thus, it can be concluded that pregnant woman with high-risk maternal age are 1.429 times more likely to experience preeclampsia. The funnel plot shows that effect size value is in the high-influence value range because of the ES value >1,45.[8]

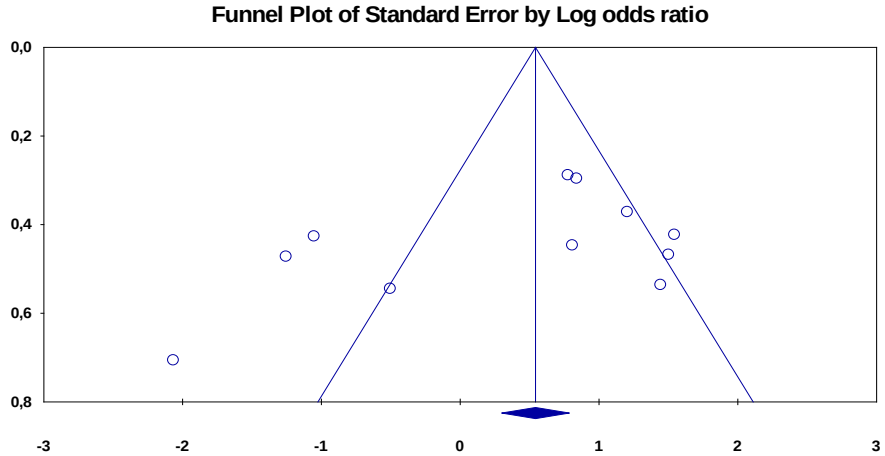



**Figure 3.** Funnel Plot of Combined Research Studies of The Relation Between Maternal Age and Preeclampsia in Pregnant Woman

Based on Figure 3, the results of the funnel plot show that there is a publication bias which is indicated by the asymmetry of the plots on the right and left of the vertical line where the number of plots on the left is 4 and the right and 7 plots are on the right side of the curve. In the 4 plots on the left side of the curve, 3 plots are outside the curve while there is 1 plot touching the

vertical line. While in the 7 plots on the right side of the curve, there are 5 plots below the curve and 2 plots outside the plot. A total of 5 plots are below the curve indicating that the study has a low effect size and 1 plot is close to the upper curve indicating that 1 plot has a high effect size value, while 5 plots outside the curve indicate that the study has a high effect size value outside the 95% CI interval limit. This can be seen from the effect size value which is in the high influence value range because the effect size value is > 1.45

Among 9 studies which stated that there is a relation between maternal age and preeclampsia in pregnant woman, the largest PR value is found in the study conducted by Gustri et al (2016) with a value of 4,694 (CI 2,047 – 10,764), which means that respondents aged <20 or >35 years old have 4,694 times more likely to experience preeclampsia during pregnancy compared to respondents aged 20-35 years old.[9] While the smallest PR value that states there is a relation between maternal age with preeclampsia is found in a study conducted by Fatkhiyah (2016) with value of 0,127 (CI 0,032-0,508), which means respondents aged <20 or >35 years old have 0,127 times more likely to experience preeclampsia compared to respondents aged 20-35 years old. After merging in the meta-analysis test, research studies that stated there was a relation between maternal age and preeclampsia were obtained with p value <0.05 of p 0.000 and Odds Ratio of 1,475 with 95% CI 0.707-3,076. Thus, it can be concluded that mothers aged <20 or >35 years old tend to have 1.475 times increased risk of preeclampsia in pregnant woman.[10]

Study conducted by Gustri, et al (2016) provides the largest p OR values among other studies analyzed, in which respondents aged >35 years old had 4,694 times more likely to experience preeclampsia compared with respondents aged 20-35 years old. In that study, Gustri, et al (2016) stated that at the age >35 years old, a degenerative process occurs and results in structural and functional changes in peripheral blood vessels which are responsible for changes in blood pressure. Process of calcification occurs in the bodies of 8 pregnant women aged >35 years. This situation will affect the food supply to the fetus, an in turn will affect the health of the fetus.[9] The ideal age for pregnancy is the mother's age at pregnancy which is not at risk, including ages 20-35 years. This age is considered safe for pregnancy and childbirth because at this age all reproductive organs and their functions in women are optimal and ready. Meanwhile, the non-ideal age for pregnancy is the mother's age at risk of pregnancy, including <20 years and >35 years. At <20 years of age, the reproductive organs are not ready to accept pregnancy, whereas at >35 years of age, changes occur in the tissues and uterine organs and there is a tendency for other diseases in the mother's body.[11] This is in line with the results of a meta-analysis study by Permatasari which states that there is a relationship between age and the incidence of preeclampsia in pregnant women.[12]

Large p OR value is also found in the study of Marlina & Sakona (2019) which states that pregnant woman aged <20 or >35 years old are more at risk of experiencing preeclampsia. Marlina & Sakona (2019) study also proves the theory of Manuaba (2010) that said, pregnancy under the age of 20 years old is not the best option for pregnancy because of woman' reproductive organs are not yet perfect around that time.[13,14] This relates with degenerative process that causes hardening on the walls of blood vessels which then leads to narrowing of blood vessel. The older a pregnant woman gets, the more obstacle she would face and the greater the risk of hypertension.[15]

Getting older is associated with changes in cardiovascular and, theoretically, preeclampsia is associated with pathology in the endothelium, which is part of the blood vessels.[16] In older women, sclerotic lesions (atherosclerosis process) occur in the myometrial arteries which can lead to a higher risk of perinatal mortality and morbidity outcomes. The process of atherosclerosis causes the narrowing of the arterioles' lumen and lead to peripheral pressure increases and in the end causes preeclampsia.

Likewise, research conducted by Ekasari et al (2019) stated that there are many risk factors causing hypertension in pregnancy.[17] Age is one of the causes of preeclampsia. In pregnant woman, the age at risk of preeclampsia is more than 35 years old. This is closely related to complications that occur during pregnancy, childbirth, postpartum and the health of the baby in the womb and after birth. Maternal age between 20-35 years old can reduce the risk of maternal death caused by preeclampsia compared to pregnant woman who are more than 35 years old.[14] This condition is inversely proportional to the "too young" and "too old" age group, that is the predisposition factor for the occurrence of preeclampsia and is a risk for death due to preeclampsia. Several studies that prove the relation between age and the incidence of preeclampsia, and are all supported the theory of Manuaba (2010) which states that there is a relation between age and the incidence of preeclampsia, are studies conducted by Wahyuni & Rahmawati (2018), Hidayah, et al (2014), Pandiangan & Kusnanto (2017) and katmini & Yunita (2018).[14-21]

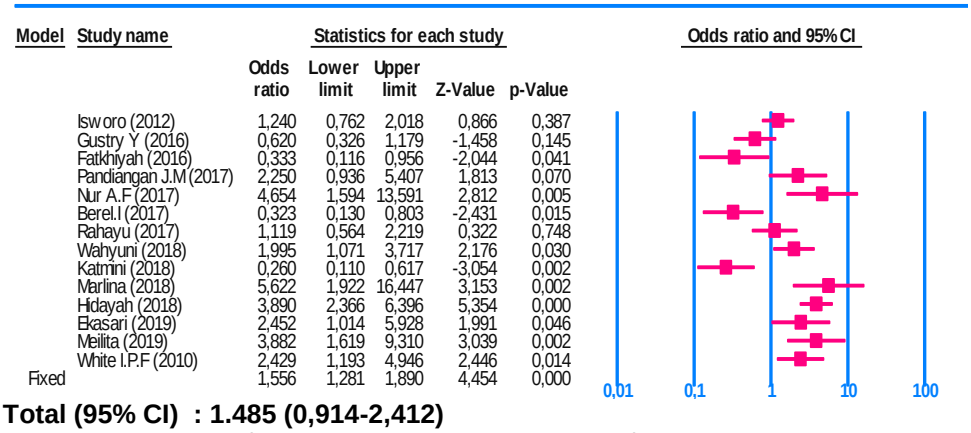
Wahyuni & Rahmawati (2018) explained that the Ministry of Health of the Republic of Indonesia (2012) is also in line with this study which states that many mothers aged <20 years are not mature enough to face life and thus they have not developed enough psychologically and physically. Many pregnant women aged <20 years old experience difficult delivery and preeclampsia. On the other hand, the bodies of pregnant women aged >35 years are no longer ready to face the process of pregnancy and childbirth. Older women often show chronic hypertension along with the increased of age.[18]

Different research results were obtained in the study conducted by Fatmawati et al. (2017). In this study, age is not associated with the incidence of preeclampsia. According to the age group, the incidence of preeclampsia / eclampsia in Gresik District Hopsital was mainly found in pregnant woman aged <20 and >35 years old. This study does not support the theory that stated young or old pregnant woman are 2 times more likely to experience preeclampsia / eclampsia compared to pregnant woman in reproductive age.[22] In line with a study conducted by Sibai (2011) that states preeclampsia often occurs in the early and late reproductive years and is thought to be related to immunological processes.[23] The safest age for women to get pregnant and give birth is during woman's healthy reproductive age, around 20-35 years old. The risk of preeclampsia increases with increasing in maternal age. Maternal age less than 20 and more than 35 years old is a predisposing factor for preeclampsia and the risk of medical complications that can harm the mother and the fetus. Meanwhile, Luealon & Phupong (2010) stated that mothers aged more than 35 years had a significant relationship with the incidence of preeclampsia.[24] Likewise, a study conducted by Daryanti (2019) stated that there is no relation between maternal age and preeclampsia because the number of mothers who experience preeclampsia in both case group and experimental group is almost the same. Thus, it does not show a significant difference because of preeclampsia is experienced by mothers aged <20 or > 35 years old and occurs in mothers aged between 20-35 years old.[25]

Based on several studies, it was found of pregnant woman aged <20 years old are stillprevalent, especially in rural areas due to many early marriages. Pregnant woman aged >35 years old also at risk for preeclampsia. Several studies states that pregnant woman aged < 20 years old is more at risk compared to aged >35 years old, even though they both have a risk for the incidence of preeclampsia. In contrast, study conducted by Gustri, et al (2016) stated that woman aged > 35 years old are more at risk for having preeclampsia, but research, other research combines the risk of age < 20 years and > 35 years in one risk age group, and Bere's research (2018) looks at the age factor by dividing age > 35 years as the risk age and age < 35 years as the non-risk age. In essence, this study classified the maternal age into <20 and >35 years old as age at risk, and 20-35 years old as age not at risk to experience preeclampsia.[9]

## Parity

The number of studies that were combined to analyze the relation between the parity of pregnant woman and preeclampsia are 14 studies of cross-sectional and case-control studies, with a total sample of 2.396. 9 studies stated there is relation between parity with preeclampsia in pregnant woman, with total sample of 2.396 samples. While other 5 studies stated there is no relation between parity with preeclampsia in pregnant woman, with total sample of 1.010 samples.




**Total (95% CI) : 1.485 (0,914-2,412)**
**Heterogeneity : Chi$^2$ = 76,276, df = 13 (p = 0,000), I$^2$ = 82,956**
**Tau$^2$ = 0,829**

**Figure 4.** Forest Plot of Combined Research Studies on The Relation Between Parity and Preeclampsia in Pregnant Woman

Based on Figure 4 shows the results of data analysis from 11 articles examining the relationship between parity and preeclampsia analyzed using the Random Effect Model. The results of the heterogeneity test show that the variation of the studies is heterogeneous, with a p value = 0.000 and a variation value between studies (I2) of 82.9%. This indicates that the effect size of each study varies with a T2 value = 0.829 which shows that each study has an effect or role on the effect size after being merged. The level of heterogeneity of data variation is stated as high, meaning that articles have different variations. The results of analyzed data displayed on the forest plot shows that there is a relation between parity and preeclampsia with p value <0.05 of p 0.000 and Odds Ratio of 1,485 and 95% CI of 0.914 – 2.412. Thus, it can be concluded that pregnant woman with high-risk maternal age are 1.485 times more likely to experience preeclampsia. The funnel plot shows that effect size value is in the high-influence value range because of the ES value >1,45.[8]

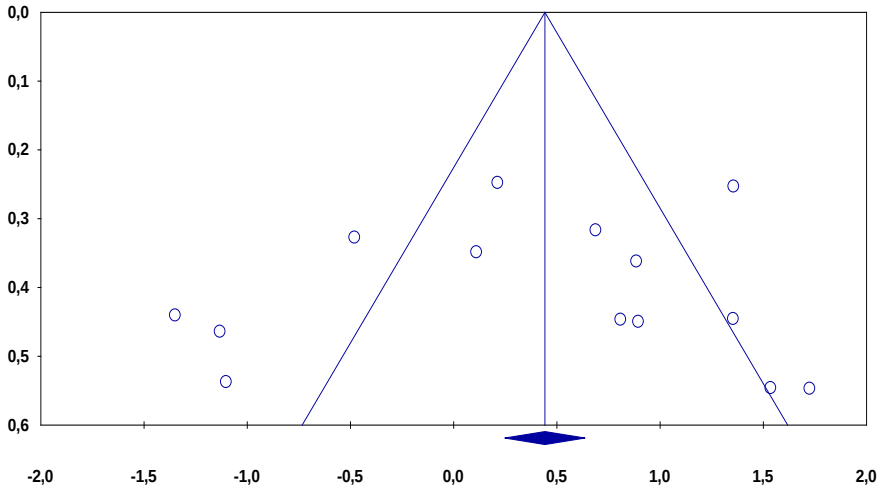



**Figure 5.** Funnel Plot of Combined Research Studies on The Relation Between Parity and Preeclampsia in Pregnant Woman

Based on Figure 5, the results of the funnel plot show that there is publication bias marked by the asymmetry of the plots on the right and left of the vertical line where the number of plots on the left is 6 and the right and 8 plots are on the right side of the curve. In the 6 plots on the left side of the curve, there are 2 plots below the curve while there are 4 plots outside the curve. While in the 8 plots on the right side of the curve, there are 4 plots below the curve and 4 plots outside the plot. A total of 6 plots are below the curve indicating that the study has a low effect size and 8 plots are outside the curve indicating that the study has a high effect size value outside the 95% CI interval limit. This can be seen from the effect size value which is in the high influence value range because the effect size value is > 1.45

Out of 9 studies that states there is a relation between maternal parity and preeclamspia in pregnant woman, the largest PR value is found in the study conducted by Marlina & Sakona (2019) with a value of 5,622 (CI 1,922-16,450) which means that respondents who have parity at risk is parity 1 that has risk of 5,622 times to experience preeclampsia in pregnancy compared to respondents with parity not at risk. While, the smallest PR value which states a relation between maternal age and preeclampsia is a study conducted by Bere (2018) with a value of 0,323 (CI 0.130-0.804) which means that respondents who have parity at risk have a 0,323 times risk of experiencing preeclampsia compared to respondents with preeclampsia who are not at risk.

Nur & Arifuddin (2017) in their research stated that parity was significantly related to the occurrence of preeclampsia in pregnant woman, especially primigravida. Primigravida or mothers who are pregnant for the first time often experience stress in the face of childbirth. Emotional stress that occurs in primigravida causes an increase in the release of corticotropic-releasing hormone (CRH) by the hypothalamus, which then leads to an increase in cortisol. The effect of cortisol is to prepare the body to respond to all stressors by increasing sympathetic responses, including responses aimed at increasing cardiac output and maintaining blood pressure. Hypertension in pregnancy results from a combination of increased cardiac output and total peripheral resistance. In woman with preeclampsia, there is no decrease in sensitivity to these vasopeptide, so a large increase in blood volume directly increases cardiac output and blood pressure. The results showed that primigravida is a risk factor

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for preeclampsia. Based on the results of statistical test, the OR value is 4,656. This shows that primigravida is a risk factor for the incidence of preeclampsia or in other words, primigravida has 4,654 times greater at risk of developing preeclampsia than multigravida. The lower limit value of the statistical test is 1,549 and the upper limit is 13,593.[26]

Marlina & Sakona (2019) in their research explains that their research is in accordance with the theory and research results. Theoretically parity, or the frequency of mothers giving birth, as preeclampsia's risk factor is greatly affecting maternal health. Parity 2-3 times is the safest parity in terms of maternal mortality. Parity 1 time and high parity (>=4 times) have higher maternal mortality rates. Higher parity, higher maternal mortality. High parity with delivery spacing that is too close will cause complications for the mother, for example, preeclampsia.[13] The risk in parity 1 time can be managed with better obstetric care, while the risk in high parity can be reduced or prevented by family planning programs.[27] In the study of Hidayah, et al stated that preeclampsia can be influenced by maternal parity due to during pregnancy the uterus requires more blood circulation in the uterine wall, so substances that cause vasospasm and hypertension are released from the placenta or decidua. So, if all arterioles in the body experience vasospasm, the blood pressure rises to overcome the increase in peripheral pressure so that tissue oxygenation can be fulfilled. Immunologically, the formation of blocking antibodies in the first pregnancy is not perfect, resulting in an unfavorable immune response in the ability to form placental tissue and then leads to arterial vasoconstriction and increased in blood pressure. Then extravasation, blood seeps out of the blood vessels, occurs which results in tissue edema and thickened blood. Whereas in grande multipara, the mother physically experiences a setback to undergo pregnancy, making her prone to complications during pregnancy, including complications of preeclampsia / eclampsia.[19]

Likewise, research conducted by Bere I. P (2017) stated that parity affects the incidence of preeclampsia. Previous statement was based on immunological theory that suggested in primigravida / primiparas the formation of blocking antibodies against antigens was not perfect. Thus, it could inhibit the invasion of the maternal spiral arteries by trophoblast to a certain extent and finally could interfere with the function of the placenta. In Bere's study (2018) the prevention of preeclampsia is very limited due to its etiology is still unknown. Examination by screening has not been able to show adequate results to determine risk factors for preeclampsia. Therefore, midwives need to take a wise approach by identifying pregnant woman who are at risk or pregnant woman who show symptoms. These risk factors can usually be identified through an assessment of the history of illness in pregnant woman and the results of careful examination. These various risk factors have their respective roles, and the interaction of these risk factors is not fully understood. However, there is a tendency that a pregnant woman who has more risk factors will generally show a worse condition.[28]

Ekasari et al (2019) also explained that parity is the number of fetuses that have been born either alive or dead with a weight of 500 grams or more. In terms of maternal mortality, parity 2 – 3 times is a very safe parity compared to the first parity because it is related to mother's lack of experience and knowledge about pregnancy.[17] Low parity and high parity (more than three times) are the causes of preeclampsia.[29] Wahyuni & Rahmawati (2018) in their study explains that parity is at risk for complications are pregnancy that that has gap time of 8 years or more since the last pregnancy, experiencing pregnancy with a duration of at least 20 weeks for 5 times or more, and pregnancy occurring within 3 months from last delivery.[18] Parity 2 – 3 times is the safest parity in terms of maternal mortality. While parity 1 time and parity >3 times have a higher maternal mortality rate. The higher the parity, the higher the maternal mortality. This happens due to stretching of the uterus during pregnancy. If pregnancy continues, the uterus will weaken. Thus, it is feared that disturbances will occur during pregnancy, childbirth, and postpartum.[30]

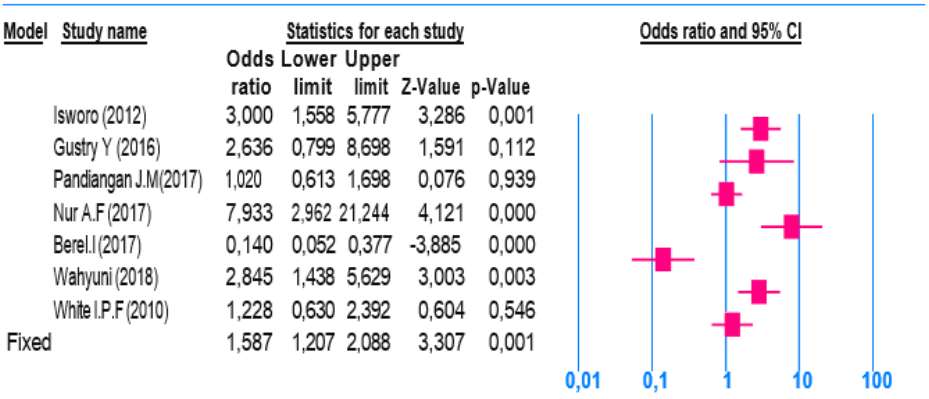
Different research results were obtained in the study of Gustri, et al (2016) which stated that age was not associated with the incidence of preeclampsia, with a significant value of 0.194, OR = 0.620, and CI of 0.326-1.179. It can be concluded from the study that the number of mothers who experienced preeclampsia between experimental and control groups is almost the same. Therefore, parity can't provide a significant difference and does not prove the theory.[9]

Based on by Gustri, et al (2016) divides parity into primigravida and multigravida, but some studies divide parity into high-risk which consist of primigravida and grande multipara and not high-risk group which is multipara. Some studies divide parity into primipara, multipara and grandemulti. Theoretically, parity at risk were primipara and grande multipara.[9]

**ANC Visit**

Total studies combined to analyze the relation odd ANC visit with preeclampsia are 7 studies of cross sectional dan case control studies, with a total sample of 1.804 samples. 4

studies stated there is relation between ANC visit with preeclampsia in pregnant woman, with total sample of 762 samples. 3 studies stated there is no relation between ANC visit with preeclampsia in pregnant woman, with total sample of 663 samples.




**Total (95% CI) : 1.633 (0,756-3,529)**
**Heterogeneity : Chi$^2$ = 43,865, df = 6 (p = 0,001)**
**Tau$^2$ = 0,953, p = 0,000, I$^2$ = 86,322**

**Figure 6.** Forest Plot of Combined Research Studies on The Relation Between ANC Visit with Preeclampsia in Pregnant Woman

Based on Figure 6 shows the results of data analysis from 7 articles examining the relationship between ANC visits and preeclampsia analyzed using the Random Effect Model. The results of the heterogeneity test show that the variation of the studies is heterogeneous, with a p value = 0.000 and a variation value between studies (I2) of 86.32%. This indicates that the effect size of each study varies with a T2 value = 0.953 which shows that each study has an effect or role on the effect size after being merged. The level of heterogeneity of data variation is stated as high, meaning that the articles have different variations. The results of analyzed data displayed on the forest plot shows that there is a relation between ANC visit and preeclampsia with p value <0.05 of p 0.001 and Odds Ratio of 1,633 and 95% CI of 0.756 – 3.529. Thus, it can be concluded that pregnant woman with high-risk parity are 1.633 times more likely to experience preeclampsia. The funnel plot shows that effect size value is in the high influence value range because of the ES value >1,45.[8]

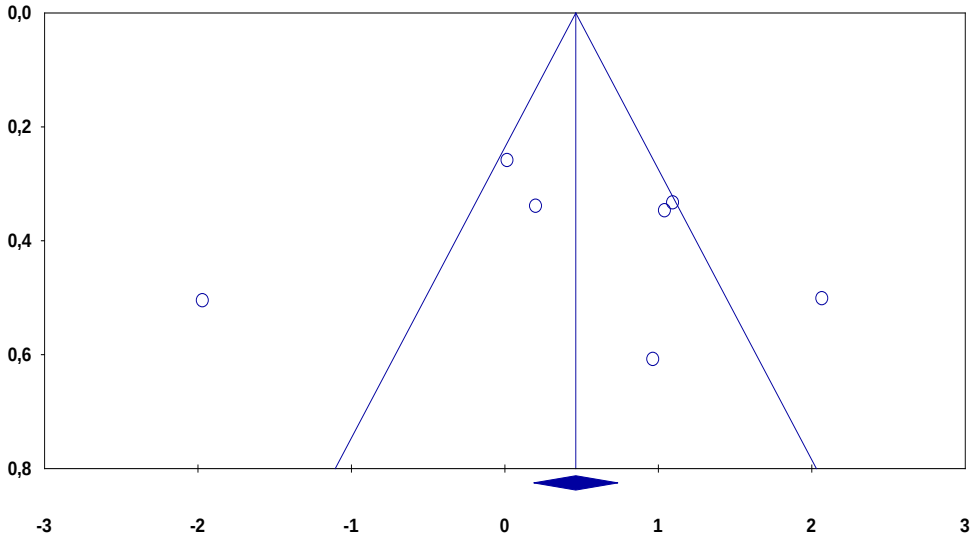



**Figure 7.** Funnel Plot of Combined Research Studies on The Relation Between ANC Visit with Preeclampsia in Pregnant Woman

Based on Figure 7, the funnel plot results show that there is no publication bias indicated by the symmetry of the plots on the right and left of the vertical line where the number of plots on the left is 3 and the right and 4 plots are on the right side of the curve. In the 3 plots on the left

side of the curve, there are 2 plots below the curve while there is 1 plot outside the curve. While in the 4 plots on the right side of the curve, there are 2 plots below the curve, 1 plot intersects the curve line and 1 plot is outside the plot. The plots below the curve indicate that the study has a low effect size and the plots outside the curve indicate that the study has a high effect size value outside the 95% CI interval limit. This can be seen from the effect size value which is in the high influence value range because the effect size value is> 1.45.

Out of 4 studies that stated there is relation between ANC visit with preeclampsia in pregnant woman, the largest PR value is found in a study conducted by Nur & Arifuddin (2017) with a value of 7,933 (CI 2,963-21,249) which means that respondents with incomplete ANC visit, defined as ANC visit <4 times, has a risk of 7.933 times of experiencing preeclampsia during pregnancy compared to respondents with complete ANC visit. While the smallest PR value which states a relation between maternal age and preeclampsia is found in a study conducted by Bere (2018) with a value of 0,140 (CI 0,052-0,378) which means that respondents with ANC visit are at risk of having a 0.323 times risk of experiencing preeclampsia compared to respondents with preeclampsia who are not at risk.[26, 28]

Nur & Arifuddin (2017) Antenatal Care (ANC) is one of the efforts that can be done as an early prevention of preeclampsia. Initial data or information related to blood pressure before pregnancy will be very helpful for health workers to distinguish between chronic hypertension and preeclampsia.[26] From the results obtained showed that the ANC visit is a risk factor for the incidence of preeclampsia. Based on the results of statistical test, the OR is 7,933. This shows that Antenatal Care (ANC) pregnancy visit were a risk factor for the incidence of preeclampsia, in other words, the risk is 7,933 times greater for having preeclampsia compared to those who did not have ANC visit >2 times. The lower limit value of the statistical test is 2,963 and the upper limit is 21,240.

Complete ANC care, or ANC care that fulfilled its standards, can detect symptoms and signs that may develop during pregnancy. If the mother is examined by the second half of pregnancy, the diagnosis of chronic hypertension will be difficult because blood pressure usually decreased during the second and third trimesters in women with hypertension. ANC care has a significant effect on the incidence of preeclampsia, because of lack of ANC care provided to pregnant woman. Bere (2018) in his research found that out of the proportion of pregnant woman with a frequency of antenatal care (ANC) who experienced preeclampsia, the highest percentage found in the ANC group > 4 times by 27 (75%) and the lowest percentage found in the ANC group < 4 times by 13 (29.5%). Similarly, out of pregnant women who did not experience preeclampsia, the highest percentage found in the ANC group <4 times by 31 (70.5%) and the lowest percentage found in the ANC group > 4 times by 9 (25%). So there is a difference in the proportion of pregnancy examination variables (ANC) where the most pre-eclampsia occurs in the case group, namely ANC > 4 times, while the most pre-eclampsia does not occur in the control group, which occurs in the ANC < 4 times group.[28]

Different results are shown by Gustry Y (2016) that stated there is no relation between ANC visit and preeclampsia. This can be seen in the results of Gustri Y's study (2016) where the number of mothers who experience preeclampsia both in the group who regularly visit ANC and the number of those who do not routinely make ANC visit is almost the same. Thus, it does not show any significant difference. The results of Gustry Y's study (2016) show that age and history of hypertension are the factors that have the greatest influence on the incidence of preeclampsia.[9]

Bere's study (2018) explains that ANC is an examination process that is carried out from the start of pregnancy until the delivery process to monitor and assess the health of the mother and baby. The results showed that there was a significant relationship between risk factors for antenatal care (ANC) and the incidence of preeclampsia with OR = 0,140 (0.052-0.378) and p = 0.000 (26). This study is in line with Langelo, et al. (2013), that said there is a significant relation between antenatal care and the incidence of preeclampsia with p value = 0.000 and Odd Ratio = 2,72 with 95% CI value of 1,39-5,33. The results of this study also found that 70.5% of pregnant woman only did pregnancy checks <4 times. This is caused by many factors including people do not know about the benefits of prenatal care, demographic factors, the distance to health care facilities is very far, health workers are often not at the service, many deliveries are still assisted by traditional births attendants. Likewise, pregnant woman who live in urban areas also found to have not had regular prenatal check-ups.[3]

Other than age, parity, and ANC visit variables, several studies analyzed also used variables such as gestational distance, gestational age, BMI or obesity, education, occupation, gemelli, history of preeclampsia which also influenced the occurrence of preeclampsia.

**Table 1. Comparison of The Relation Between Research Variables with Preeclampsia in Pregnant Woman Study's Result**

| Study Variable | Heterogeneity Test | Overall Effect Result | Average of Effect Size |
|---|---|---|---|
| **Maternal Age** | p =0.000<br>$I^2$ = 84,24%<br>(Heterogen) | p = 0.000<br>p-OR= 1.429<br>(95%CI = 0.759-2.690) | 2,264 |
| **Parity** | p =0.000<br>$I^2$ = 82,956%<br>(Heterogen) | p = 0.000<br>p-OR= 1.485<br>(95%CI = 0.914 – 2.412) | 2,219 |
| **ANC Visit** | p =0.000<br>$I^2$ = 86,32%<br>(Heterogen) | p = 0.001<br>p-OR= 1.633<br>(95%CI = 0.756 – 3.529) | 2,686 |

Table 1 shows a comparison in the average of Effect Size, combined from related article and unrelated article, between maternal age, parity, and ANC visit variables. The largest average of Effect Size is 2,686 and found in the variable of ANC visit from the analysis of the articles which states there is relation between ANC visit and preeclampsia in pregnant woman. The smallest Effect Size found is 2,219 on the parity variable from the analysis of the articles which states there is relation between ANC visit with preeclampsia in pregnant woman.

Based on the results obtained in the meta-analysis, the risk factor / tendency associated with the largest incidence of preeclampsia from the three variables studied is ANC visit, with the p OR value of 7,933, CI 95% = 2,962-21,244 greater than the p OR value of the parity variable, with the value of p OR 1,485 (CI 0,914-2,412). While the smallest is maternal age variable, with p OR of 1,429 (CI 0,759-2,690).

The analysis based on the average effect size value from research variable study shows that the ANC visit variable has higher average effect size value compared to age and parity. Thus, ANC visit is a variable that has the strongest relation tendency with the independent variable, incidence of preeclampsia.

The results of the study for the ANC visit variable have a fairly large range. ANC visit variable shows OR value that has the largest effect size, with 7,933 (CI 2,963-21,242). In the age variable the largest effect size is 4,964(CI 2,047-10,764). While in the parity variable, the largest effect size is 5,622 (CI 1,922-16,447).

## CONCLUSION

Based on the results of a meta-analysis of 14 articles studied, it was found that there was a significant relationship between age, parity, ANC visits with the incidence of preeclampsia in pregnant women. The greatest relationship with the incidence of preeclampsia in pregnant women was in ANC visits, with a p OR value of 7.933 and a 95% CI of 2.962-21.244. ANC visits also tended to have the strongest relationship because they had the largest OR effect size range of 7.933 (CI 2.963-21.242).

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