MOTHER, FETAL AND DISEASE HISTORY FACTORS AS A PREEKLAMPSIA RISK IN ASIA AND AFRICA: A META-ANALYSIS

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Abstract

Background: Preeclampsia accounts for nearly 10 percent of maternal deaths in Asia and Africa. Therefore, it is important to detect signs and symptoms early on by knowing the factors that are at risk for a mother experiencing preeclampsia. Objective: To determine the risk factors for preeclampsia in Asia and Africa through the application of meta-analysis. Method: A systematic review was carried out on 26 case-control and cohort studies related to risk factors for preeclampsia from four databases (PubMed, BioMed Central, ProQuest, and Google Scholar). The pooled odds ratio was calculated with the fixed-effect and random-effect model using Review Manager 5.3. Result: A total of 20 studies consisting of 2,954,769 women were included in the meta-analysis. Risk factors for preeclampsia based on maternal factors were chronic hypertension=9.74(95% CI 1.69-56.04), gestational diabetes=9.28(95% CI 4, 49-19.19), pre-pregnancy body mass index=2.70(95% CI 2.08-3.50), maternal age during pregnancy=2.37(95% CI 2.29-2.46) and nulliparity=2.08(95% CI 1.44-3.01). The fetal factor was multiple pregnancy=4.24(95% CI 3.14-5.73). Four disease history factors were family history of preeclampsia=13.99(95% CI 6.91-28.33), history of chronic hypertension=8.28(95% CI 5.92- 11.59), history of preeclampsia=OR 6.90(95% CI 3.58-13.31) and family history of hypertension=2.81(95% CI 1.75-4.50). Conclusion: The results of a meta-analysis of 10 risk factors for preeclampsia could be used as a screening tool to determine the magnitude of risk and early diagnosis of preeclampsia that allows timely intervention.

Key words: *Maternal Factors, Chronic Hypertension, Preeclampsia, Meta-Analysis.*

A. INTRODUCTION

Preeclampsia and pregnancy-related hypertension disorders as the leading cause of maternal death claimed the lives of nearly 76,000 mothers and 500,000 babies worldwide each year.1 Preeclampsia accounts for nearly 10 percent of maternal deaths in Africa and Asia.2 A 2010 Indonesia Population Census follow-up study showed preeclampsia is one of the leading causes of maternal death in Indonesia.3 Preeclampsia has the greatest impact on maternal and newborn morbidity and mortality. According to the results of a secondary analysis from the WHO Multicountry Survey, near-miss cases in mothers with preeclampsia are eight times more common than mothers without preeclampsia.4 Increased chances of preterm birth in mothers in Southeast Asia with preeclampsia occur as an impact on infants. The impact of preeclampsia can be minimized by finding signs and symptoms early on. This can be started from knowing the risk factors for a mother experiencing

preeclampsia. Knowledge related to risk factors for preeclampsia can help health workers involved in monitoring patients and estimating which pregnant women who are more likely to develop preeclampsia. A large number of studies including meta-analysis studies have been carried out to evaluate risk factors including maternal age during pregnancy6,7, high body mass index8-12, gestational diabetes6,13, nulliparity14,15, multiple pregnancy6 and a history of diseases such as a history of preeclampsia in pregnancy previous pregnancies16, history of chronic hypertension and family history of hypertension13,16 all of which were considered as contributions. These factors are mostly factors that can be modified and carried out early prevention before pregnancy. However, many risk factors for preeclampsia have been identified, mostly carried out exclusively in western countries. The situation in countries in Asia and Africa, especially in low and middle income countries, remains largely unknown. Meta-analysis has a role in scientific research. This is demonstrated through drawing more valid and reliable conclusions by "increasing" the sample size because it reviews several studies with the same subject. The level of statistical significance generated from the meta-analysis study was also greater. This is important to increase the validity of the differences observed so that the information produced is also more reliable This meta-analysis study was conducted to determine the risk factors for preeclampsia in Asia and Africa. Greater statistical power from the results of the meta-analysis can help in extrapolating to a larger population so that the conclusions obtained can be used as a basis in take a public health policy.

B. DISCUSSION

Efforts to carry out the latest research continue to be made, including meta-analysis research that can be useful to find out other risk factors and correct factors that have been previously known. This type of research is a quantitative review or synthesis with a meta-analysis study design. Meta-analysis is a statistical technique for combining the results of two or more similar studies so that quantitative data is obtained. Through the PRISMA procedure, the research sample is a published article related to risk factors for preeclampsia through the PubMed, BioMed Central, ProQuest, and Google ScholarPubMed, BioMed Central, ProQuest, and Google Scholar databases from 2000-2018. Inclusion criteria were case control and cohort studies. Exclusion criteria were studies that were not available in the form of full text and languages other than English. The ten variables (maternal age during pregnancy, pre-pregnancy body mass index, gestational diabetes, chronic hypertension, nulliparity, multiple pregnancy, history of preeclampsia, history of chronic hypertension, family history of hypertension and family history of preeclampsia) as independent variables (independent); and preeclampsia as the dependent variable.

The search was performed by entering keywords as follows: "(Advanced maternal age OR body mass index pre-pregnancy OR gestational diabetes OR chronic hypertension OR nulliparity OR multiple pregnancy OR family history of hypertension OR history of preeclampsia OR history of chronic hypertension OR family history of preeclampsia) AND preeclampsia AND (Asia OR Africa) ".

Data analysis was performed to obtain the pooled odds ratio value which is the combined odds ratio value of the study using the fixed effect model with the Mantel Haenszel method and the random effect model with the DerSimonian Laird method. Data were analyzed using Review Manager software 5.3. Heterogeneity test was conducted with the aim of determining the incorporation model in the meta-analysis. Test I2 statistics are performed to assess heterogeneity among a number of study effect sizes expressed in terms of percentages. The Cochran Q test was also used to assess heterogeneity with p values. The final meta-analysis is in the form of a forest plot with a combined OR (pooled odds ratio) and an effect size for each study. Funnel plot results are also analyzed for assessment of publication bias on the final meta-analysis. The final value used as an answer to the purpose of the study is the pooled odds ratio which indicates the combined value of several studies. This shows how much risk factors of each the variable under study. data completeness, clarity of definition of risk factors and other conditions as requirements are included in the meta-analysis. Data analysis was performed to obtain the pooled odds ratio value which is the combined odds ratio value of the study using the fixed effect model with the Mantel Haenszel method and the random effect model with the DerSimonian Laird method. Data were analyzed using Review Manager software 5.3. Heterogeneity test was conducted with the aim of determining the incorporation model in the meta-analysis. The I2 statistical test was conducted to assess heterogeneity among a number of study effect sizes expressed in terms of percentages. The Cochran Q test was also used to assess heterogeneity with p values. The final meta-analysis is in the form of a forest plot with a combined OR (pooled odds ratio) and an effect size for each study. Funnel plot results are also analyzed for assessment of publication bias on the final meta-analysis. The final value used as an answer to the purpose of the study is the pooled odds ratio which indicates the combined value of several studies. This shows how big the risk factors of each variable studied. After getting the results of a meta-analysis of 10 variables obtained, the authors entered the results with the best meta-analysis compared to other variables based on the number of studies and OR values of each study combined with the appropriate confidence intervals.

There were 20 studies (14 case controls and 6 cohorts) included in the meta-analysis, 10 studies each from Asia and Africa (table 1) with a total of 10 variables. The risk of preeclampsia in Asia and Africa based on maternal factors is chronic hypertension, gestational diabetes, pre-pregnancy body mass index, maternal age

during pregnancy, and nulliparity. Variations between heterogeneous studies were shown in heterogeneity tests with p = 0.0002 (p <0.05) and I2 = 88%. There is a significant relationship with p value of 0.01 (p <0.05). A pooled odds ratio of 9.74 (95% CI 1.69-56.04) is generated through a random-effect model. This can be interpreted that a mother with chronic hypertension has a 9.74 times greater risk of developing preeclampsia.

Heterogeneity test showed p value greater than 0.05, i.e. p = 0.21 with I2 = 35 percent, meaning that the variation between studies was homogeneous. Gestational diabetes with preeclampsia shows a significant relationship with a p value of 0.00001 (p <0.05). The fixed-effect model produces a pooled odds ratio of 9.28 (95% CI 4.49-19.19). This shows that a mother who has diabetes in her pregnancy has a 9.28 times greater risk of developing preeclampsia. The p value obtained from the heterogeneity test is smaller than 0.05, which is 0.0002 with I2 = 72 percent, which shows variations between studies are heterogeneous. The p value indicates that there is a significant relationship between pre-pregnancy body mass index and preeclampsia with p = 0.00001 (p <0.05). Random-effect models produce a pooled odds ratio of 2.7 (95% CI 2.08-3.5). It can be concluded that a mother who before pregnancy has a body mass index> 24 kg / m2 and> 30 kg / m2 which is categorized as overweight and obesity has a 2.7 times greater risk of experiencing preeclampsia. There are ten studies that examine the pre-pregnancy body mass index with preeclampsia, which is the highest number of studies of other variables included in the meta-analysis. Research by Mrema, et al has the smallest OR value, which is 1.6, but with the largest number of cases and controls, whereas in the Kumar study, et al37 with the smallest number of control cases has an OR of 4.83.

The pre-pregnancy body mass variable combines the cut-off point with the categories of overweight and obesity into one analysis. This is based because previous studies have found that the risk of preeclampsia has arisen when maternal BMI is in the overweight category. In addition, several Asian countries, including China, use their own cut-off points. It aims to avoid ignoring the risk impact of preeclampsia that has begun even before the mother falls into the obesity category according to WHO standards. Differences in sample characteristics also cause heterogeneity of research. This variable tends to be dominated by research in Asia, especially China, which is a country with a middle to upper economy, while research in Africa from Ethiopia, Tanzania and Nigeria is included in the country lower middle income. However, ten studies have OR values that are not much different, which shows that the results are quite consistent when studies are carried out in different regions and populations. Variations between studies are homogeneous, this can be seen from the p value in the heterogeneity test is 0.26, greater than 0.05. There is a significant relationship between mothers during pregnancy with preeclampsia, this is evidenced by the value of p <0.05

ie p = 0.00001. The fixed-effect model produces a pooled odds ratio of 2.37 (95% CI 2.29-2.46), so it can be concluded that a mother who is over 35 years old during pregnancy has a 2.37 times greater risk for to experience preeclampsia in the case group compared to the control group. Heterogeneity test with p = 0.0002 and I2 = 82% shows that the variation between studies is heterogeneous. A p value of 0.0001 indicates that there is a significant relationship between nulliparity and preeclampsia (p <0.05). 2.08 (95% CI 1.44-3.01) as a pooled odds ratio value is generated through a random-effect model. This means that a mother who has never given birth before or is her first pregnancy has a 2.08 times greater risk of developing preeclampsia. There is one fetal factor, namely multiple pregnancy as a risk factor for preeclampsia in Asia and Africa. Variations between studies are homogeneous, this can be seen from the p value in the heterogeneity test is 0.29, greater than 0.05, and I2 = 18 percent. There is a significant relationship between multiple pregnancy and preeclampsia, this is evidenced by the value of p <0.05 which is p = 0.00001. The fixed-effect model produces a pooled odds ratio of 3.97 (95% CI 2.99-5.29), so it can be concluded that a pregnant mother with two or more conceived fetuses has a 3.97 times greater risk to experience preeclampsia in the case group compared to the control group. Next is a disease history factor, namely a family history of preeclampsia, a history of chronic hypertension, a history of preeclampsia and a family history of hypertension. The results of the meta-analysis showed heterogeneity test with p = 0.23 and I2 = 30 percent showed that variations between studies were homogeneous. A p value of 0.00001 indicates that there is a significant relationship between family history of preeclampsia and preeclampsia (p <0.05). 13.99 (95% CI 6.91-28.33) as a pooled odds ratio value generated through the fixed-effect model. This means that a mother with a family member who has a history of preeclampsia is 13.99 times more likely to develop preeclampsia.

Heterogeneity test showed p value greater than 0.05, i.e. p = 0.22 which means that the variation between studies was homogeneous. A history of chronic hypertension with preeclampsia showed a significant relationship with a p value of 0.00001 (p <0.05). The fixed-effect model produces a pooled odds ratio of 8.28 (95% CI 5.92-11.59). This shows that a mother with a history of chronic hypertension has a 8.28 times greater risk of developing preeclampsia. The p value obtained from the heterogeneity test is smaller than 0.05, i.e. 0.0002 with I2 = 72 percent, which shows the variation between studies is heterogeneous. The p value indicates that there is a significant relationship between pre-pregnancy body mass index and preeclampsia with p = 0.00001 (p <0.05). Random-effect models produce a pooled odds ratio of 2.7 (95% CI 2.08-3.5). It can be concluded that a mother who before pregnancy has a body mass index> 24 kg / m2 and> 30 kg / m2 which is categorized as overweight and obesity has a 2.7 times greater risk of experiencing preeclampsia. There are ten studies

that examine the pre-pregnancy body mass index with preeclampsia, which is the highest number of studies of other variables included in the meta-analysis. Research by Mrema, et al has the smallest OR value, which is 1.6, but with the largest number of cases and controls, whereas in the Kumar study, et al37 with the smallest number of control cases has an OR of 4.83. Previous history of preeclampsia has been a risk factor for re-occurrence of preeclampsia in mothers in Asia and Africa. In the heterogeneity test, it can be seen that the p value is less than 0.05, ie 0.00001 with I2 = 86 percent, which shows the variation between studies is heterogeneous. The p value indicates that there is a significant relationship between the history of preeclampsia and preeclampsia with a value of p = 0.00001 (p <0.05). Random-effect models produce a pooled odds ratio of 6.9 (95% CI 3.58-13.31). It can be concluded that a mother with preeclampsia in a previous pregnancy had a 6.9 times greater risk of developing preeclampsia. Variations between heterogeneous studies were shown in heterogeneity tests with p = 0.0002 (p <0.05) and I2 = 79 percent. There is a significant relationship with p value of 0.0001 (p <0.05). A pooled odds ratio of 2.81 (95% CI 1.75-4.50) is generated through a random-effect model. This can be interpreted that a mother with a family history of hypertension has a 2.81 times greater risk of developing preeclampsia. Ten studies were included in the meta-analysis on this variable, three of which came from Africa. Research variations show moderate heterogeneity with I2 = 72 percent (Figure 3). This is because the IMT cut off point in each country has quite a variety of variations. Research in Asia tends to use a lower cut-off point in determining obesity categories, whereas studies in Africa use WHO standards which categorize obesity with a BMI ◎30 kg / m2.

The pre-pregnancy body mass variable combines the cut-off point with the categories of overweight and obesity into one analysis. This is based because previous studies have found that the risk of preeclampsia has arisen when maternal BMI is in the overweight category. In addition, several Asian countries, including China, use their own cut-off points. It aims to avoid ignoring the risk impact of preeclampsia that has begun even before the mother falls into the obesity category according to WHO standards. Differences in sample characteristics also cause heterogeneity of research. This variable tends to be dominated by research in Asia, especially China, which is a country with a middle to upper economy, while research in Africa originating from Ethiopia, Tanzania and Nigeria is included in the middle to lower income countries. However, ten studies have OR values that are not much different, which shows that the results are quite consistent when studies are carried out in different regions and populations. Variations between studies are homogeneous, this can be seen from the p value in the heterogeneity test is 0.26, greater than 0.05. There is a significant relationship between maternal age during pregnancy with preeclampsia, this is evidenced by the value of p <0.05 ie p = 0.00001. The fixed-effect model produces a

pooled odds ratio of 2.37 (95% CI 2.29-2.46), so it can be concluded that a mother who is over 35 years old during pregnancy has a 2.37 times greater risk for had preeclampsia in the case group compared to the control group. Heterogeneity test with p = 0.0002 and I2 = 82% shows that the variation between studies is heterogeneous. A p value of 0.0001 indicates that there is a significant relationship between nulliparity and preeclampsia (p <0.05). 2.08 (95% CI 1.44-3.01) as a pooled odds ratio value is generated through a random-effect model. This means that a mother who has never given birth before or is her first pregnancy has a 2.08 times greater risk of developing preeclampsia. There is one fetal factor, namely multiple pregnancy as a risk factor for preeclampsia in Asia and Africa. Variations between studies are homogeneous, this can be seen from the p value in the heterogeneity test is 0.29, greater than 0.05, and I2 = 18 percent. There is a significant relationship between multiple pregnancy and preeclampsia, this is evidenced by the value of p <0.05 which is p = 0.00001. The fixed-effect model produces a pooled odds ratio of 3.97 (95% CI 2.99-5.29), so it can be concluded that a pregnant mother with two or more conceived fetuses has a 3.97 times greater risk to experience preeclampsia in the case group compared to the control group. Next is a disease history factor, namely a family history of preeclampsia, a history of chronic hypertension, a history of preeclampsia and a family history of hypertension. The results of the meta-analysis showed heterogeneity test with p = 0.23 and I2 = 30 percent showed that variations between studies were homogeneous. A p value of 0.00001 indicates that there is a significant relationship between family history of preeclampsia and preeclampsia (p <0.05). 13.99 (95% CI 6.91-28.33) as a pooled odds ratio value generated through the fixed-effect model. This means that a mother with a family member who has a history of preeclampsia is 13.99 times more likely to develop preeclampsia.

The results suggesting chronic hypertension as the biggest risk factor for preeclampsia in Asia and Africa is in line with the results of a systematic review which states that chronic hypertension is associated with many adverse outcomes, including one of which is superimposed pre-eclampsia.19 Systematic research studies on studies The cohort in Asia also supports the results of a meta-analysis that shows that chronic hypertension is one of the risk factors with the highest odds ratio, which is 7.174. Educating women of reproductive age about the importance of controlling blood pressure both before, during and after pregnancy is important. Conduct pre-pregnancy assessments to avoid secondary causes of hypertension, evaluate blood pressure to ensure it is in optimal condition, discuss the increased risk of preeclampsia, and provide education about any drug changes before pregnancy can be carried out. Women with chronic hypertension should also be advised to maintain a low intake of sodium, either by reducing or replacing sodium salt before pregnancy. The results suggest that gestational diabetes is the second largest risk factor for

preeclampsia in Asia. A review studies related to the relationship of preeclampsia and diabetes confirm similar results.22 Gestational diabetes is an independent risk factor for preeclampsia. This is evidenced by a retrospective study of 647,392 pregnancies which found that the chance of preeclampsia was increased among women with gestational diabetes (aOR: 1.29, 95% CI: 1.19-1.41), even after controlling for age, nationality, employment status , smoking, parity, multifetal pregnancy, pre-pregnancy weight status and pregnancy weight gain. Interventions for managing gestational diabetes can also reduce the risk of preeclampsia. A randomized controlled trial (with nutritional counseling treatment, diet therapy, and insulin if needed) vs. no treatment among nearly 1,000 women with mild gestational diabetes found that treatment was associated with a 55 percent reduced risk of preeclampsia (RR: 0.46; 95 % CI: 0.22-0.97). 24 Systematic reviews and meta-analyzes in randomized trials also found that proper gestational diabetes management (nutritional therapy, monitoring of blood glucose alone, administering insulin if target blood glucose concentrations were not only fulfilled with diet) resulted in a reduction in the risk of preeclampsia (relative risk [RR] 0.62; 95% CI 0.43-0.89; 72/1001 [7.2%] compared to 119/1013 [11.7%], with three trial study)

Pre-pregnancy body mass index is a risk factor for preeclampsia in Asia and Africa in this study. Several previous systematic review and meta-analysis studies also show the same thing and are consistent.10,12,14,16 Maternal body mass index is one of the most discussed risk factors for preeclampsia and can be a complex problem among Asian countries and Africa. About 35 percent of adults are now considered overweight or obese and women themselves are more likely to be overweight and obese than men. This has extensive effects on reproductive health and especially pregnancy, with obese women facing an increased risk of reeclampsia. The BMI variable is the variable that is most easily modified, but also has a variety of other factors that influence it. The first step that can be taken to prevent prevention is pre-pregnancy health education. It should be noted that women who are overweight and obese at reproductive age should be encouraged to practice a healthy lifestyle, including weight reduction before pregnancy. A healthy weight before pregnancy can reduce the risk of interference pregnancy - related hypertension, including preeclampsia. The results of this study also show that maternal age ⊚35 years during pregnancy is a risk factor for preeclampsia in Asia and Africa which is consistent with other studies.6,7,14 The relative risk of preeclampsia increases with increasing maternal age. In the age group of 35-39 years it has a risk of 2.99 times ($p < 0.001$) and 40 years of 5.13 times ($p < 0.001$) .27 Provide information to women of childbearing age (WUS) about obstetric risks in pregnancy 35-year-old mother can help make decisions based on information obtained. The last maternal factor is nulliparity. The results suggest nulliparous women have a risk of preeclampsia which is in line with evidence

from a meta-analysis study by Bartsch et al. The secondary survey from the Global World Health Organization (WHO) survey on maternal and perinatal health among countries states that nulliparity (AOR: 2.04; 95% CI 1.92-2.16) was found as a significant risk factor.

Another factor that influences the occurrence of preeclampsia is the fetus. Preeclampsia is more common in women who are likely to have a large placenta, such as women with multiple pregnancies. A case-control study in Tanzania showed that compared to a single pregnancy, women with multiple pregnancies had an increased risk of preeclampsia (OR = 2.6 95% CI 1.7-3.9). 29 A systematic review also showed that mothers with multiple pregnancies has a risk of experiencing preeclampsia of 2.93 times. 14 Health workers need to counsel women with multiple pregnancies during antenatal care regarding potential risks that may occur. Timely follow-up and intervention can also help prevent the bad outcomes associated with multiple pregnancy.

C. CONCLUSION

This meta-analysis confirms factors (chronic hypertension, gestational diabetes, pre-pregnancy body mass index, maternal age of pregnancy and nulliparity), fetal factors (multiple pregnancy), and disease factors (family history of preeclampsia, history of chronic hypertension, history of preeclampsia, and family history hypertension) as a risk factor for preeclampsia in Asia and Africa. risk of preeclampsia in mothers with a family history of hypertension. Women with a family history of hypertension have a seven times greater chance of experiencing it. For health workers, the variable can be preeclampsia compared to those used as a screening tool for those who do not know the magnitude of the risk of preeclampsia in maternal and early diagnosis by developing practical lists (such as check lists) based on risk factors associated with preeclampsia in Asia and Africa. There are modifiable risk factors, such as chronic hypertension and pre-pregnancy IMT. Health workers and mothers can focus on making changes in health behaviors, such as before planning a pregnancy can be done ideal weight loss by setting a balanced nutritional pattern. For researchers, meta-analysis is important to do as a form of data utilization, in this case published articles, both on this variable and on other variables and topics.

D. REFERENCES

1. Eleni Tsigas. World Preeclampsia Day: Reducing Preventable Deaths From Preeclampsia – Maternal Health Task Force [Internet]. MHTF Blog. 2017. Available from:https://www.mhtf.org/2017/05/22/world-preeclampsia-day-reducing-preventable-deaths-from-preeclampsia/
2. World Health Organization. Prevention and treatment of pre-eclampsia and eclampsia. 2011.
3. Afifah T, Tejayanti T, Saptarini I, Rizkianti A, Usman Y, Senewe FP, et al. Maternal Death in Indonesia: Follow-up Study of the 2010 Indonesia Population Census. 2016;1–13.
4. Abalos E, Cuesta C, Carroli G, Qureshi Z, Widmer M, Vogel J, et al. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. RCOG. 2014;14–24. DOI: 10.1111/1471-0528.12629.
5. Cripe SM, O'Brien W, Gelaye B, Williams MA. Perinatal outcomes of Southeast Asians with pregnancies complicated by gestational diabetes mellitus or preeclampsia. J Immigr Minor Heal. 2012;14(5):747–53. DOI: 10.1007/s10903-011-9537-7.
6. Dawson LM, Parfrey PS, Hefferton D, Dicks EL, Cooper MJ, Young D, et al. Familial risk of preeclampsia in Newfoundland: A population-based study. J Am Soc Nephrol. 2002;13(7):1901–6. DOI: 10.1097/01.ASN.0000017224.24670.82.
7. Valadan M, Tanha FD, Sepahi A. Pregnancy Outcomes in Women of Advanced Age. J Fam Reprod Heal. 2011;5(2):57–62.
8. Bodnar LM, Catov JM, Klebanoff MA, Ness RB, Roberts JM. Prepregnancy body mass index and the occurrence of severe hypertensive disorders of pregnancy. Epidemiology. 2007;18(2):234–9. DOI: 10.1097/01.ede.0000254119.99660.e7.
9. Bodnar LM, Ness RB, Markovic N, Roberts JM. The risk of preeclampsia rises with increasing prepregnancy body mass index. Ann Epidemiol. 2005;15(7):475–82. DOI: 10.1016/j.annepidem.2004.12.008
10. O'Brien TE, Ray JG CW. Maternal Body Mass Index and the Risk of Preeclampsia: A Systematic Overview. Vol. 14, Epidemiology. 2003.
11. Sohlberg S, Stephansson O, Cnattingius S, Wikström AK. Maternal body mass index, height, and risks of preeclampsia. Am J Hypertens [Internet]. 2012;25(1):120–5. Available from: http://dx.doi.org/10.1038/ajh.2011.175/nature06264

12. Wang Z, Wang P, Liu H, He X, Zhang J. Maternal adiposity as an independent risk factor for pre-eclampsia: A meta-analysis of prospective cohort studies. Obes Rev. 2013;14(6):508–21. DOI: 10.1111/obr.12025.
13. Jeyabalan A. Epidemiology of preeclampsia: impact of obesity. Nutr Rev [Internet]. 2013;71 Suppl 1(0 1):S18-25. DOI: 10.1111/nure.12055.
14. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: Systematic review of controlled studies. Br Med J. 2005;330(7491):565–7. DOI: 10.1136/bmj.38380.674340.E0.