Early predictors for hypertensive disorders of pregnancy in developing countries

**By: Ary Indriana Savitri, 3734722**

**Supervisor: Cuno S.P.M Uiterwaal, MD, PhD**

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# Abstract

Hypertensive disorders of pregnancy are still one of the greatest maternal health problems worldwide. These disorders constitute of pre-existing hypertension and gestational hypertension, which then can progress into preeclampsia, eclampsia, and HELLP-syndrome. They contribute greatly to a large proportion of maternal and perinatal death, particularly in the developing countries. Early prediction, followed by proper management and timely treatment is proven to be effective in preventing complications and death related with these conditions. Various predictors such as maternal characteristics, Doppler ultrasound examinations, and biomarker analysis have been developed to accurately predict the women who are at risk. The need for reliable predictors is greatest in the developing countries, where health resources are limited. This thesis aims at giving an overview about the development of predictors for hypertensive disorders of pregnancy, which are suitable for application in developing countries. Various challenges in its implementation are also discussed.

# Introduction

Hypertensive disorders of pregnancy have remained as one of the world’s most important health problem. These disorders comprise of spectrum of diseases that include pre-existing hypertension, gestational hypertension, preeclampsia, eclampsia, and HELLP-syndrome. They contribute greatly to maternal and perinatal morbidity and mortality globally, particularly in developing countries. 1-5 In total, about 10 to 15% of direct maternal deaths are associated with preeclampsia and eclampsia in low and middle income countries. 4,6 The worldwide prevalence of preeclampsia ranges from 3 to 8% of pregnancies, 7 while in the developing countries it ranges from 1.8% to 16.7%.8 It is estimated that the incidence of PE is 7 times higher in developing countries (2.8% of live births) than in developed countries (0.4%).9

The impact of these disorders is also more severe in the developing countries, as reflected by the higher number of maternal deaths and complications related with preeclampsia. These discrepancies are mainly caused by lower access to prenatal care, limited access to timely care, and inappropriate diagnosis and management of the patients. 2 In the developing countries, preeclampsia is still often diagnosed when the women present with eclamptic seizures. 10

Gestational hypertension is defined as systolic blood pressure of 140 mmHg or more and/or a diastolic blood pressure of 90 mmHg or more on two occasions which at least 4 hours apart, and present for the first time after 20 weeks of pregnancy. 11 Diagnosis of preeclampsia is established when proteinuria ≥ 300 mg/day also occur. According to its onset, preeclampsia is classified into early and late preeclampsia using a cut-off of 34 weeks of gestational age.

Despite the fact that these disorders have been studied for centuries, relatively little is known about its pathogenesis. One of the most recognized hypothesis is that preeclampsia develops as a result of immune maladaptation between the mother and the fetus, which occur during the first weeks of pregnancy. 12 Preeclampsia progresses in two stages. At the first stage, alteration of the placental formation occurs. This alteration contributes to a reduction of utero-placental blood flow, which then may induce fetal intrauterine growth restriction (IUGR). Many studies suggest that oxidative stress, insufficient blood perfusion, inflammation, apoptosis, and structural damage of placental vascular also contribute to the pathogenesis. The second stage of these disorders presents as clinical manifestations, which include hypertension and proteinuria after 20 weeks of gestation, and could even progresses to angiospasm of the brain and brain edema that cause severe epileptic seizures. 10

Although their pathogenesis is very complex and has not yet fully understood, evidence shows that early diagnosis and treatment could prevent death and complications related with hypertensive disorders of pregnancy. 7 A pivotal aspect for strategy to reduce hypertensive disorders of pregnancy is by improving our ability to predict pregnant women who will develop these conditions. The women who are detected to be in high risk can then be referred to a larger health center, ensuring proper care. The need for reliable predictors of hypertensive disorders are particularly greatest in the developing countries where health resource are scarce, requiring efficient allocation of care. The present study discussed about recent development of early predictors for hypertensive disorders of pregnancy that suitable for implementation in low and middle-income country.

# Discussion

## Ideal predictors

Current studies in the prediction for hypertensive disorders of pregnancy rely in three important aspects; maternal clinical characteristics, uterine Doppler ultrasound, and levels of biomarkers in the blood of pregnant women. For wide implementation in developing country, ideal predictors for hypertensive disorders of pregnancy should fulfilled these criteria:

1. They play a central role in the pathogenesis of the disease, thus can give high sensitivity and specificity.
2. They appear early before clinical manifestations emerge, so that necessary action can be taken to prevent complications and death.
3. They should be affordable within context of limited health budgets.
4. They are easy to be performed by midwives and other health workers in the developing country, without the need for rigorous technical training.

## Maternal characteristics

Maternal characteristics such as ethnicity, parity, body mass index (BMI), and family history of preeclampsia are used as traditional method of screening for preeclampsia. Studies in developed countries suggest that this method could predict approximately 30% of early preeclampsia cases.13

A risk prediction model for hypertensive disorders of pregnancy, which applicable in low resource settings has been developed in Ghana, Africa. 14 This model is based on the maternal clinical characteristics available from the first and second routine antenatal care. Various candidate predictors such as age, history of past pregnancies, diabetes, family history of diabetes and hypertension and family history of multiple pregnancies were investigated. Clinical characteristics such as blood pressure, height, weight, and urinary protein were also evaluated.

The predictors in the model were then converted into points on a score chart to accommodate easy application in clinical practice. Using cut off points on scores less than seven, seven to thirteen, and fourteen or more, this model classify women into low, moderate, and high risk of developing pregnancy disorders in pregnancy. The predictors from the first antenatal care visit include height, parental history of hypertension, history of hypertensive disorders of pregnancy, weight, systolic blood pressure, diastolic blood pressure, gestational age, and body mass index. The area under ROC curve for this model was 0.73 (95% CI: 0.69-0.77). This resulted in a positive predictive value (PPV) of 51% and negative predictive value (NPV) 91.1%. Although it has quite high specificity (97.3%), the sensitivity is relatively low (22.7%).

Predictors from the second antenatal care visit consist of height, parental history of hypertension, history of hypertensive disorders of pregnancy, ownership of a valid health insurance card, systolic blood pressure, and diastolic blood pressure. The area under the ROC curve was 0.80 (95% CI: 0.77-0.84). This model resulted in the PPV of 95% and NPV of 90.9%. The specificity was quite high (99.9%), but the sensitivity was relatively low (15.1%).

The Ghanaian prediction model performs well in identifying women with very high risk and women with very low risk. It is also feasible to be implemented in low resource clinical setting in low and middle-income countries because it uses the readily available maternal characteristics, without the need to use any sophisticated tools. However, this prediction model still lacks ability in predicting the risk among moderate risk women since it classifies a relatively large proportion of the women (60%) at moderate risk. Therefore, this prediction model may be particularly useful as initial screening, and further testing with other methods are needed to refine the prediction among women with moderate risk.

A study in the nulliparous women in The Netherlands also found that various maternal characteristics assessed at the first antenatal care visit can accurately identify women at very low and very high risk of developing hypertension before 36 weeks of pregnancy. 15 A prediction model that contains score chart for systolic blood pressure, diastolic blood pressure, and weight was developed. The women were then classified into very low risk, low risk, moderate risk, and high risk. This model performed very well in its study population, as characterized by under curve (AUC) of 0.78 (95% CI 075-0.82). But, it performs poorly when applied in the setting of developing country like Ghana, as shown with the area under the ROC of 0.68. 14

Several other studies have also used maternal characteristics to predict the occurrence of preeclampsia in low resource setting. Using history of preeclampsia, hypertension, and infertility as predictors, a model developed in Iran could predict 90.7% of cases with area under ROC estimated to be 0.67 (95% CI 0.59-0.76). 16 A study in Pakistan found that gestational diabetes, pre-gestational diabetes, family history of hypertension, and mental stress during pregnancy can be used as a screening tool for preeclampsia. 17

The role of maternal pre-pregnancy characteristics to predict hypertensive disorders of pregnancy has also been investigated. A prospective cohort study in population of Aboriginal and Torres Strait Islander women in North Queensland, Australia revealed that pre-pregnancy adiposity and features of the metabolic syndrome are strongly associated with the increased risk of hypertension in pregnancy, thus has a potential to be a predictors. 18

## Doppler Ultrasound

Uterine artery Doppler examinations performed in the first trimester can be an effective method to screen preeclampsia. 19,20 Assessment was done to the blood that flows through the umbilical veins and arteries. Abnormality in placental vasculature present as an increased impedance to flow in the uterine arteries is found in 25% of women who subsequently develop preeclampsia. 20 According to a review by World Health Organization (WHO) in 2004, prediction rate of preeclampsia in both low risk and high-risk populations using Doppler ultrasound was found to be moderate to minimal. 1 Doppler ultrasound was also found did not improve the performance of maternal characteristics model for prediction of preeclampsia. 21 However, some other study showed that Doppler ultrasound examination may significantly improved the prediction of preeclampsia if used in combination with maternal characteristics. 22 Furthermore, combination with maternal serum biomarker may improve its ability to predict hypertensive disorder in pregnancy in the first trimester.

Applicability of Doppler ultrasound in developing countries is still limited. This method is relatively expensive and requires advanced technical skills and training which often not available in limited resource setting in low and middle-income countries.

## Biomarkers

Many of the pathophysiologic changes associated with hypertensive disorders of pregnancy are evident before its clinical manifestations. Reliable biochemical markers for prediction of hypertensive disorders of pregnancy will have a great impact on the improvement of patient’s prognosis. 7 Various biomarkers, either alone or in combination with other biomarker or Doppler ultrasound, have been shown quite promising in predicting this condition. 10

Placenta is considered to play a central role in the etiology and pathogenesis of preeclampsia, therefore many studies have been directed to focus on the level of pro- and anti-angiogenic factors, such as vascular endothelial growth factor (VEGF), placental growth factor (PIGF), VEGF receptor-1 (also known as fms-like tyrosine kinase 1 [Flt1]), and endoglin (Eng). 23,24 Other biomarker that also has been thoroughly investigated are placental protein (placental protein 13/PP13), pregnancy-associated protein A (PAPP-A), free fetal hemoglobin (HbF), alpha-1-microglobulin (A1M), metabolomics, and proteomics.10,25,26

PIGF is excreted in urine, and its reduced concentration in urine has been suggested as a promising marker of this condition. A small study reported that urinary concentrations of PIGF to be significantly lower in pregnant women with preeclampsia compared to in normal controls. 27 However the performance of reduced urinary PIGF levels in predicting preeclampsia still needs to be evaluated in a larger population. A simple predictive method likes this, if performs well, will give great value to be implemented in developing countries where access to healthcare technology are limited.

Uric acid level is associated with preeclampsia and gestational hypertension with hyperuricemia, therefore it is potentially useful as a rule out test. 28 On the other hand, serum concentrations of uric acid rise only one week before the clinical appearance of disease, which make it less convenient for prediction purposes. 29 A portable device for measuring salivary uric acid is now under development, and may be adaptable for the purpose of preeclampsia prediction in the developing countries. 30

Although there are numerous biochemical markers that have been evaluated for predicting preeclampsia, the data in many studies are contradictory and none of them has been independently proved to be clinical value. 12,25,29,31 Many of the recent studies put efforts into investigating new biomarkers, as well as their possible combinations with maternal characteristics and Doppler ultrasound examinations in predicting preeclampsia.

## Combination

Studies shows that prediction model for preeclampsia which combines demographic, clinical, and ultrasound examination in 22-24 weeks can detect nearly 100% of early onset preeclampsia (CI 95% 85-100%), with a false positive results of 10%.32 These models if applied in the first trimester of pregnancy to screen preeclampsia is superior than maternal characteristics only. 33-35 Using a combination of mean arterial pressure, uterine artery pulsatility index (PI), pregnancy-associated plasma protein-A, and placental growth factor early in pregnancy, 18.3% of gestational hypertension can be detected with a false positive rate of 5%. The detection rate for early and late preeclampsia with this model are even greater, 93.1% and 35.7%, respectively.33

Other algorithm that combined maternal characteristics, uterine artery PI and mean arterial pressure (MAP) with serum levels of PAPP-A, PlGF, PP13, inhibin-A, activin-A, sEng, pentraxin-3 and p-selectin has been developed. 36 In a large study involving 33,602 pregnant women at 11+0 to 13+6 weeks of gestational age, this algorithm give prediction rates of 91%,79.4% and 60.9% for early onset preeclampsia, intermediate onset preeclampsia, and late onset preeclampsia. On the other hand, algorithm that consist of serum PIGF, free-β-HCG, and chronic hypertension to predict the occurrence of early preeclampsia, a study achieved a ROC curve (AUC=0.893). 37

An algorithm to predict preeclampsia in the setting of developing countries has been refined in two studies in Chile. 38,39 In a multicenter study, algorithm consisted of predictors such as maternal age, parity, previous history of preeclampsia, hypertension, diabetes mellitus, weight, systolic blood pressure, diastolic blood pressure, mean arterial pressure, logUtAPI (Uterine Artery Pulsatility Index), and history of preterm labor was evaluated. 38 This prediction model gives an area under receiver operating characteristics (ROC) curve of 89.53% for prediction of early preeclampsia performed at 11-14 weeks of gestational age. In other study, a model, which composed of maternal characteristics, uterine artery Doppler, and PIGF level, could predict approximately half of pregnancies that subsequently complicated with early preeclampsia.39

## Challenges in the developing countries

Efforts in the development of predictors for hypertensive disorders of pregnancy in the developing countries are still hampered with various limitations. Many developing countries are still suffered from limited health resources. Basic clinical equipment (e.g. mercury sphygmomanometer for blood pressure monitoring) is often lacking, therefore health workers are required to make careful clinical assessment based on the available resources. There are only few studies have been performed in the population of pregnant women in developing countries. 14,16,17 All of these studies developed prediction models for hypertension disorders of pregnancy that was solely built upon maternal demographic and clinical characteristics. However, evidence shows that performance of maternal characteristics in predicting this disorders are relatively poor. 13

Doppler ultrasound and biomarker tests have been evaluated in the developed countries and proven to have a high predictive value. However, its performance in the low resource clinical setting is very little studied. Application of maternal characteristics combined with Doppler ultrasound and/or biomarker analysis has been shown to give promising predictive performance in several studies in a setting of low-middle income countries. 38,39 Nevertheless, this model still needs to be validated in a larger population in other parts of the world.

So far, the applicability of Doppler ultrasound and various biomarker tests for a large-scale use in developing countries is considered to be unrealistic.3,40 This is particularly because they are still too expensive and need high level of technology in their application, 38 which is impossible in low resource setting. Although research on biomarker assessment for preeclampsia prediction has been progressing tremendously in developed countries, relatively little studies are conducted in the context of developing countries. Future research needs to put more concern on the development of reliable predictors in low resource clinical setting. Development of screening tools that can translate advance biomarker technology into a simple and affordable screening device will give a great impact.

## Conclusion

Prediction of hypertensive disorders of pregnancy in developing countries remains a great challenge. There is a great need for an affordable and reliable method for prediction of these disorders. Future studies are encouraged to put more attention on the development of an accurate prediction model suitable for use in the developing countries.

# References

1. Conde-Agudelo A, Villar J, Lindheimer M. World Health Organization systematic review of screening tests for preeclampsia. *American College of Obstetricians and Gynecologists*. 2004;104(6):1367-1391.

2. Ghulmiyyah L, Sibai B. Maternal mortality from preeclampsia/eclampsia. *Semin Perinatol*. 2012;36(1):56-59. doi: 10.1053/j.semperi.2011.09.011.

3. Villar J, Say L, Shennan A, et al. Methodological and technical issues related to the diagnosis, screening, prevention, and treatment of pre-eclampsia and eclampsia. *International journal of gynaecology and obstetrics*. 2004;85 Suppl 1:S28-S41. doi: 10.1016/j.ijgo.2004.03.009.

4. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol*. 2009;33(3):130-137. doi: 10.1053/j.semperi.2009.02.010.

5. Firoz T, Sanghvi H, Merialdi M, von Dadelszen P. Pre-eclampsia in low and middle income countries. *Best practice research.Clinical obstetrics gynaecology*. 2011;25(4):537-548. doi: 10.1016/j.bpobgyn.2011.04.002.

6. Khan K, Wojdyla D, Say L, Gülmezoglu AM, Van Look PFA. WHO analysis of causes of maternal death: A systematic review. *Lancet (London, England)*. 2006;367(9516):1066-1074. doi: 10.1016/S0140-6736(06)68397-9.

7. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *The Lancet*. 2010;376(9741):631-644. doi: 10.1016/S0140-6736(10)60279-6.

8. Osungbade K, Olusimbo K. Public health perspectives of preeclampsia in developing countries: Implication for health system strengthening. *Journal of Pregnancy*. 2011;2011.

9. WHO. Make every mother and child count, in the world health report . *World Health Organization, Geneva, Switzerland*. 2005.

10. Anderson UD, Olsson MG, Kristensen KH, Åkerström B, Hansson SR. Review: Biochemical markers to predict preeclampsia. *Placenta*. 2012;33, Supplement(0):S42-S47. doi: 10.1016/j.placenta.2011.11.021.

11. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: Statement from the international society for the study of hypertension in pregnancy (ISSHP). *Hypertension in pregnancy*. 2001;20(1):IX-XIV. doi: 10.1081/PRG-100104165.

12. Monte S. Biochemical markers for prediction of preclampsia: Review of the literature. *Journal of Prenatal Medicine*. 2011;5(3):69-77.

13. Yu CKH, Smith GCS, Papageorghiou A, Cacho A, Nicolaides K. An integrated model for the prediction of pre-eclampsia using maternal factors and uterine artery Doppler velocimetry in unselected low-risk women. *Obstet Gynecol*. 2006;195(1):330-330. doi: 10.1016/j.ajog.2006.06.010.

14. Antwi E, Groenwold R, Jansen K, et al.  Predictors of pregnancy induced hypertension in an urban low resource setting. in press.

15. Nijdam M, Janssen K, Moons K, et al. Prediction model for hypertension in pregnancy in nulliparous women using information obtained at the first antenatal visit. *J Hypertens*. 2010 Jan;119(26).

16. Direkvand Moghadam A, Khosravi A, Sayehmiri K. Predictive factors for preeclampsia in pregnant women: A unvariate and multivariate logistic regression analysis. *Acta Biochim Pol*. 2012;59(4):673-677.

17. Shamsi U, Hatcher J, Shamsi A, Zuberi N, Qadri Z, Saleem S. A multicentre matched case control study of risk factors for preeclampsia in healthy women in Pakistan. *BMC Womens Health*. 2010;10:14-14. doi: 10.1186/1472-6874-10-14.

18. Campbell S, Lynch J, Esterman A, McDermott R. Pre-pregnancy predictors of hypertension in pregnancy among aboriginal and Torres Strait islander women in North Queensland, Australia: A prospective cohort study. *BMC Public Health*. 2013;13(1):138. [http://www.biomedcentral.com/1471-2458/13/138](http://www.biomedcentral.com/1471-2458/13/138" \t "_blank).

19. Kalache K, Dückelmann AM. Doppler in obstetrics: Beyond the umbilical artery. *Clin Obstet Gynecol*. 2012;55(1):288-295. doi: 10.1097/GRF.0b013e3182488156.

20. Papageorghiou A, Yu CKH, Nicolaides K. The role of uterine artery Doppler in predicting adverse pregnancy outcome.*.Clinical obstetrics gynecology*. 2004;18(3):383-396. doi: 10.1016/j.bpobgyn.2004.02.003.

21. North R, McCowan L, Dekker G, et al. Clinical risk prediction for pre-eclampsia in nulliparous women: Development of model in international prospective cohort. *BMJ*. 2011;342.

22. Kleinrouweler CE, Bossuyt PM, Thilaganathan B, et al. The added value of second trimester uterine artery Doppler to patient characteristics in the identification of nulliparous women at increased risk for pre-eclampsia: An individual patient data meta-analysis. *Ultrasound in Obstetrics & Gynecology*. 2013:n/a-n/a. doi: 10.1002/uog.12435.

23. Hawfield A, Freedman B. Pre-eclampsia: The pivotal role of the placenta in its pathophysiology and markers for early detection. *Therapeutic advances in cardiovascular disease*. 2009;3(1):65-73. doi: 10.1177/1753944708097114.

24. Ghosh S, Raheja S, Tuli A, Raghunandan C, Agarwal S. Serum placental growth factor as a predictor of early onset preeclampsia in overweight/obese pregnant women. *Journal of the American Society of Hypertension*. 2013;7(2):137-148. doi: 10.1016/j.jash.2012.12.006.

25. Masoura S, Kalogiannidis IA, Gitas G, et al. Biomarkers in pre-eclampsia: A novel approach to early detection of the disease. *Journal of obstetrics and gynaecology*. 2012;32(7):609-616. doi: 10.3109/01443615.2012.709290.

26. Myers JE, Tuytten R, Thomas G, et al. Integrated proteomics pipeline yields novel biomarkers for predicting preeclampsia. *Hypertension*. 2013;61(6):1281-1288. doi: 10.1161/HYPERTENSIONAHA.113.01168.

27. Aggarwal P, Jain V, Sakhuja V, Karumanchi S, Jha V. Low urinary placental growth factor is a marker of pre-eclampsia. *Kidney International*. 2006;69:621-624.

28. Laughon SK, Catov J, Powers R, Roberts J, Gandley R. First trimester uric acid and adverse pregnancy outcomes. *American journal of hypertension*. 2011;24(4):489-495. doi: 10.1038/ajh.2010.262.

29. Kharb S. Serum markers in pre-eclampsia. *Biomarkers*. 2009;14(6):395-400. doi: 10.1080/13547500903033415.

30. von Dadelszen P, Ansermino JM, Dumont G, et al. Improving maternal and perinatal outcomes in the hypertensive disorders of pregnancy: A vision of a community-focused approach. *International Journal of Gynecology & Obstetrics*. 2012;119, Supplement 1(0):S30-S34. doi: 10.1016/j.ijgo.2012.03.012.

31. Myatt L, Clifton RG, Roberts JM, Spong CY, Hauth JC, Varner MW, Thorp JM Jr, Mercer BM, Peaceman AM, Ramin SM, Carpenter MW, Iams JD, Sciscione A, Harper M, Tolosa JE, Saade G, Sorokin Y, Anderson GD. First-trimester prediction of preeclampsia in nulliparous women at low risk. *Obstet Gynecol*. 2012 Jun;119(6):1234-1242.

32. Onwudiwe N, Yu CKH, Poon LCY, Spiliopoulos I, Nicolaides KH. Prediction of pre-eclampsia by a combination of maternal history, uterine artery Doppler and mean arterial pressure. *Ultrasound in obstetrics gynecology*. 2008;32(7):877-883. doi: 10.1002/uog.6124.

33. Poon LCY, Kametas NA, Maiz N, Akolekar R, Nicolaides KH. First-trimester prediction of hypertensive disorders in pregnancy. *Hypertension*. 2009;53(5):812-818. doi: 10.1161/HYPERTENSIONAHA.108.127977.

34. Poon LCY, Stratieva V, Piras S, Piri S, Nicolaides KH. Hypertensive disorders in pregnancy: Combined screening by uterine artery Doppler, blood pressure and serum PAPP-A at 11-13 weeks. *Prenat Diagn*. 2010;30(3):216-223. doi: 10.1002/pd.2440.

35. Scazzocchio E, Figueras F, Crispi F, et al. Performance of a first-trimester screening of preeclampsia in a routine care low-risk setting. *Obstet Gynecol*. 2013;208(3):203.e1-203.e10. doi: 10.1016/j.ajog.2012.12.016.

36. Akolekar R, Syngelaki A, Sarquis R, Zvanca M, Nicolaides K. Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11-13 weeks. *Prenat Diagn*. 2011;31(1):66-74. doi: 10.1002/pd.2660.

37. Di Lorenzo G, Ceccarello M, Cecotti V, et al. First trimester maternal serum PIGF, free β-hCG, PAPP-A, PP-13, uterine artery Doppler and maternal history for the prediction of preeclampsia. *Placenta*. 2012;33(6):495-501. doi: 10.1016/j.placenta.2012.03.003.

38. Caradeux J, Serra R, Nien J, et al. First trimester prediction of early onset preeclampsia using demographic, clinical, and sonographic data: A cohort study. *Prenat Diagn*. 2013:1-5. doi: 10.1002/pd.4113.

39. Parra Cordero M, Rodrigo R, Barja P, et al. Prediction of early and late pre-eclampsia from maternal characteristics, uterine artery Doppler and markers of vasculogenesis during first trimester of pregnancy. *Ultrasound in obstetrics gynecology*. 2013;41(5):538-544. doi: 10.1002/uog.12264.

40. Danso K, Opare Addo H. Challenges associated with hypertensive disease during pregnancy in low-income countries. *International journal of gynaecology and obstetrics*. 2010;110(1):78-81. doi: 10.1016/j.ijgo.2010.01.026.