Original Article

A Prospective Cohort Study on the Clinical Utility of Second Trimester Mean Arterial Blood Pressure in the Prediction of Late-onset Preeclampsia Among Nigerian Women

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ABSTRACT

Background: Early detection of preeclampsia will help reduce the morbidities and mortalities associated with the disorder. Late-onset preeclampsia was the predominant presentation in this cohort. The search for biomarkers for predicting preeclampsia is still ongoing. Mean arterial blood pressure (MABP), which has the advantage of presenting a single cutoff value compared with the use of systolic and diastolic blood pressure measurements, merits evaluation. **Aim:** The study aims to evaluate the clinical utility of second trimester MABP in the prediction of preeclampsia. **Methods:** This was a prospective cohort study of 155 normotensive, nonproteinuric pregnant women without prior history of gestational hypertension. The women were booked patients attending the antenatal clinic at the Lagos University Teaching Hospital and were all in their second trimesters of pregnancy. The outcome measures were systolic blood pressure, diastolic blood pressure, and MABP. The end point of the study was the development of preeclampsia. The diagnosis of preeclampsia was made by the attending obstetrician. The data were analyzed using the IBM SPSS statistical software. Statistical significance was set at $P < 0.05$. **Results:** One hundred and fifty-five pregnant women participated in the study. Eleven (7.1%) of the women developed preeclampsia after 34 weeks gestation and 144 (92.9%) had normal pregnancy. The mean gestational age at the time of assessment was 18.88 ± 3.15 weeks with a range of 14 weeks to 27 completed weeks. There was a statistically significant increase in the systolic blood pressure, diastolic blood pressure, and MABP values in the group of women who later developed preeclampsia, $P = 0.005$, 0.001, and <0.001, respectively. At a false-positive rate of 10%, MABP value of 88.33 mmHg predicted preeclampsia with a specificity of 90% and a sensitivity of 45.5%, P <0.05. The area under the receiver-operative characteristics curve (AUC) was 0.732 (95% confidence interval, 0.544-0.919, $P = 0.011$). The negative predictive value (NPV) was 88.88% and the positive predictive value (PPV) was 45.45%, $P < 0.05$. At an MABP cutoff of 88.33 mmHg, preeclampsia was predicted with a relative risk of 4.44 and a positive likelihood ratio of 6.46, $P < 0.05$. **Conclusions:** With an AUC of 0.732, MABP performed moderately (considering that excellent performance has an AUC of 1.0) in the prediction of late-onset preeclampsia in Nigerian women. Its high NPV suggests a strong ability to rule out preeclampsia and help to appropriate management.

KEYWORDS: *Mean arterial blood pressure preeclampsia, systolic blood pressure, diastolic blood pressure, Nigerian women.*

INTRODUCTION

Preeclampsia is a hypertensive disorder of pregnancy complicating 5-10% of all pregnancies with significant maternal and perinatal mortality and morbidity.[1,2] In developing countries, preeclampsia is a very common cause of maternal death second only to

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post-partum hemorrhage.[3] The perinatal complications include prematurity, intrauterine growth restriction, and impaired neurocognitive development.[4] Surviving mothers also have an increased risk of developing cardiovascular disease later in life.[5]

The pathophysiology of preeclampsia is heterogeneous, complex, and poorly understood involving both maternal and placental factors.[6] Abnormalities in the development of placental vasculature is considered to be a primary cause of the placental hypoxia and ischemia, which then leads to release of numerous bioactive factors into the maternal circulation causing widespread endothelial dysfunction[7] and culminating in hypertension, proteinuria and other manifestations of the disease affecting the liver, renal, hematological, and central nervous systems.[8]

Early detection of preeclampsia would allow for appropriate monitoring and management to forestall the development of complications.

The search for biomarkers for predicting the disorder is ongoing.[9] Several of the factors associated with the pathogenesis of preeclampsia have been assessed as predictive markers of the disorder but with limited success[10] underscoring the fact that the cellular and molecular mechanisms of disease pathogenesis are yet obscure.[11]

The current trend is to use a combination of markers targeting the different pathways of disease pathogenesis to create an algorithm that will predict preeclampsia with good diagnostic sensitivity and specificity.[12] Uterine artery pulsatility index, maternal risk factors, mean arterial blood pressure (MABP), maternal serum pregnancy-associated plasma protein-A (PAPP-A), Placental Protein 13 (PP13), placental growth factor (PlGF), and fetal hemoglobin levels at the time of first trimester aneuploidy screening have been used in combination to identify pregnancies at high risk for preeclampsia.[13,14]

In resource-poor settings of developing countries without routine aneuploidy screening program, most women register for antenatal care in second trimester and can hardly support the cost of preeclampsia screening using many markers and the equipment for screening are not available.[15] A risk assessment by a combination of maternal risk factors and blood pressure seems like a feasible place to start.[16] MABP has been reported to be a better predictor of preeclampsia than systolic or diastolic blood pressure alone.[17] This study examines the clinical utility of second trimester MABP for the prediction of preeclampsia in a cohort of Nigerian women as a first step in the development of a suitable

algorithm for preeclampsia risk prediction for Nigerian women.

SUBJECTS AND METHODS

This was a prospective cohort study of 155 normotensive, nonproteinuric pregnant women without prior history of gestational hypertension. The women were booked patients attending the antenatal clinic at The Lagos University Teaching Hospital and were all in their second trimesters of pregnancy at recruitment. Pregnant women with multiple gestation and sickle cell disorder were excluded from the study. The outcome measures were systolic blood pressure, diastolic blood pressure, and estimation of the MABP. The end point of the study was the development of preeclampsia. Pregnant women were diagnosed with preeclampsia if they developed hypertension with systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg and $\geq 2^+$ of proteinuria.[18] Late-onset preeclampsia was defined as the onset of clinical disease after 34 weeks gestation and early-onset preeclampsia as starting before 34 weeks gestation. The blood pressure was determined using the Accoson's Mercury Sphygmomanometer (cuff size 15 $\times$ 43 cm). The subjects were seated and rested for 5 min before measurement. The systolic blood pressure was taken at the first korotkoff sound and diastolic at the fifth korotkoff sound.[18]

Preeclampsia was defined as the onset, after 20 weeks gestation of proteinuria ($\geq$300 mg/24 h or $\geq$100 mg/L, equivalent to $\geq 2^+$ on dipstix urinaysis) on at least two random urine samples at least 4 to 6 h apart but not more than 7 days apart, and systolic blood pressure $\geq$140 mmHg or a diastolic blood pressure $\geq$ 90 mmHg measured using an appropriate sized cuff repeatable at least 4–6 hours apart but not more than 7 days apart and a remission of these symptoms by 6 weeks postpartum.[18]

Approval for the study was obtained from the hospital's ethics committee and consenting subjects signed an informed consent form. At recruitment, initial blood pressure measurements were recorded and the MABP calculated by dividing the sum of the systolic and twice the diastolic blood pressure by three.[12]

Informations on the index pregnancy such as maternal age, parity, gravidity, and past obstetrics history were obtained using a pretested, interviewer-administered, structured questionnaire. Pregnancy was dated from the last menstrual period and confirmed by ultrasonography scaning. The women were then followed up with blood pressure measurements and urinalysis at antenatal visits till either the development of preeclampsia or delivery.

The data were analyzed using done using the IBM Statistical Software for Social Sciences (SPSS, Inc., Chicago, Illinois, USA) version 20.0. Independent Student's t test and ROC analysis were employed for statistical analysis. The cutoff value of MABP that will predict preeclampsia with a false-positive rate of 10% was determined from the coordinates of the ROC curve. Sensitivity, specificity, positive, and negative predictive values (NPVs) at this level were also estimated. Statistical significance was set at $P < 0.05$.

RESULTS

One hundred and fifty-five pregnant women participated in the study (the minimum sample size was 109, employing the G power calculator[19]). Eleven (7.1%) of the women developed preeclampsia after 34 weeks gestation and 144 (92.9%) had normal pregnancy. The mean gestational age at the time of recruitment into the study was 18.88 ± 3.15 weeks with a range of 14 weeks to 27 completed weeks. [Table 1] shows the baseline demographic and clinical characteristics of the study cohort with preeclampsia and normal pregnancy.

At baseline all the women had similar maternal age, gestational age, BMI, and parity. Despite being normotensive and nonproteinuric at recruitment, baseline blood pressure values were significantly higher in the women who later developed preeclampsia.

MABP had a higher AUC than SBP and DBP for the prediction of preeclampsia [Table 2]. It also has an advantage of presenting a single cutoff values for evaluation.

Area under the curve (AUC) = 0.732 (95% CI, 0.544–0.919), P = 0.011, [Figure 1] which implies that compared with an ideal marker, which an AUC of 1, MABP has an AUC of 0.732 at stated confidence level.

Mean arterial blood pressure (MABP) value of 88.33 mmHg predicted preeclampsia with a specificity of 90% and a sensitivity of 45.50% and at a relative risk of 4.44 and a positive likelihood ratio of 6.46 [Table 3]. A pregnant woman with an MABP value above 88.33 mmHg is 4.44 times more likely to develop preeclampsia than another pregnant woman with MABP below the cutoff.
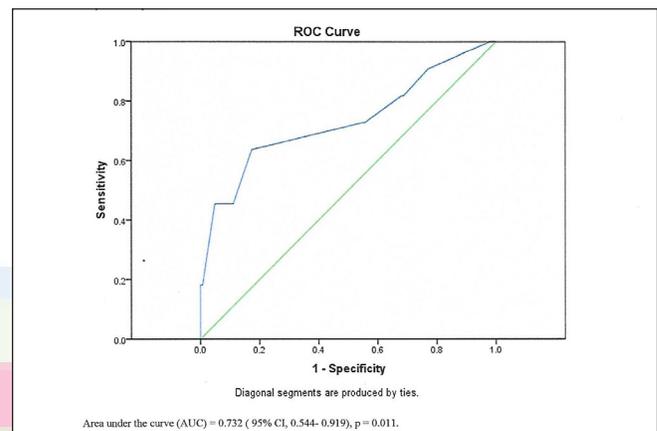
Figure 1: Receiver operative characteristics curve of mean arterial blood pressure for the prediction of preeclampsia.

Table 1: Baseline demographic and clinical characteristics of the study cohort with preeclampsia and normal pregnancy

Characteristics	Preeclampsia (n=11)	Normal pregnancy (n=144)	P value
Age (years)			
20-30	3(27.28)	79(54.86)	0.174
31-40	8(72.72)	63(43.75)	
>40	0(0.00)	2(1.39)	
Mean Age(years)	33.64 ± 4.52	30.47 ± 4.46	0.054
BMI(kg/m2)	29.63 ± 4.07	26.82 ± 4.81	0.61
Gestational age (weeks)	19.36 ± 2.80	18.85 ± 3.17	0.60
Parity			
Nullipara	5(45.45)	61(42.36)	
Primipara	1(9.10)	46(31.94)	0.196
Multipara	5(45.45)	37(25.70)	
SBP(mmHg)	115.27 ± 9.38	108.26±7.67	0.005*
DBP(mmHg)	74.55 ± 10.35	67.50±6.11	0.001*
Mean arterial BP	88.12 ± 9.23	81.08±5.82	0.000*

*Statistically significant.

Table 2: Comparison of the performance of SBP, DBP, and MABP in the prediction of preeclampsia at a false-positive rate of 10% and a specificity of 90%.

Blood pressure parameters	AUC	P value	Sensitivity (%)
SBP	0.708	0.016	30.1
DBP	0.702	0.020	31.7
MABP	0.732	0.011	45.5

AUC = area under curve, DBP = diastolic blood pressure, MABP = mean arterial blood pressure, SBP = systolic blood pressure.

Table 3: Performance characteristics of MABP for predicting preeclampsia at a false-positive rate of 10%.

Characteristics	Values	95% Confidence interval	P value
Specificity(%)	90.00	0.075 – 0.335	0.032*
Sensitivity(%)	45.50	0.276 – 0.886	0.045*
PPV(%)	45.45	0.267 – 0.848	0.014*
NPV(%)	88.88	0.753 – 0.872	0.026*
Relative risk	4.44	1.615 – 19.220	0.033*
Likelihood ratio	6.46	1.878 – 21.130	0.011*

AUC = area under curve, MABP = mean arterial blood pressure, NPV = negative predictive value, PPV = positive predictive value.
*Statistically significant.

The pregnant woman who would develop preeclampsia has a 6.46 chance that her second trimester MABP will be >88.33 mmHg [Table 3].

DISCUSSION

The widespread endothelial dysfunction implicated in the pathogenesis of preeclampsia results in reduced vascular compliance and vasoconstriction resulting in hypertension. Although hypertension is a secondary sign of the disease, it is a very important sign because not only is it a therapeutic target in the management of preeclampsia, it is also an early indication of the disease. This study reports a statistically significant increase in the systolic blood pressure, diastolic blood pressure, and MABP values in the group of women who later developed preeclampsia before the onset of the disease. A similar finding was reported in American and European women.[20,21] This finding that women who subsequently develop preeclampsia have higher blood pressure values before the onset of clinical disease suggests that early blood pressure readings may have clinical utility in predicting preeclampsia.

MABP is derived by dividing the sum of the systolic and twice the diastolic blood pressure by three.[12] Apart from the convenience of a single cutoff value for decision making, a systematic review and meta-analysis[17] showed that MABP was a better predictor of preeclampsia among low-risk women in the first or second trimester than either systolic or diastolic values alone.

The present study reports a moderate performance for MABP in the prediction of preeclampsia. At a false-positive rate of 10% (i.e., a specificity of 90%) and at a MABP cutoff value of 88.33 mmHg, MABP predicted/detected preeclampsia with a sensitivity of 45.50%, an NPV of 88.88% and a positive predictive value of 45.45%. Area under the curve (AUC) = 0.732 (CI, 0.544-0.919, $P = 0.011$).

Some authors had similar findings. Some reported a detection rate of 59% for preeclampsia at a false-positive rate of 10% for detecting late-onset preeclampsia in a cohort of British women.[22] Others reported significant prediction of late-onset preeclampsia with an AUC of 0.676 (CI, 0.606-0.704, $P = 0.0006$) in a cohort of 200 women in India.[23] Findings by a few authors differed slightly probably because of small sample size and differences in the population characteristics of the cohorts. One study[24] reported that MABP was a better predictor of gestational hypertension than preeclampsia and another[25] found MABP to be a poor predictor of preeclampsia in a cohort of women with chronic hypertension. The systematic review[17] that included

60,599 women, 3341 of whom had preeclampsia, reported that for low-risk women, the area under the summary receiver operative characteristics curve for MABP for the prediction of preeclampsia was 0.76 (95% CI, 0.70–0.82) with a relative risk of 3.5 (2.0-5.0), similar to findings from this study. The above review[17] also reported similar patterns of results when the first and second MABP readings were analyzed at values ≥ 90 mmHg.

This study evaluated the performance of second trimester MABP for preeclampsia prediction at a low false-positive rate of 10%, corresponding to a high specificity of 90% and an MABP cutoff of 88.33 mmHg. At this high specificity, the test however recorded a low sensitivity (detection rate) of 45.5%. The high specificity and high NPV however suggest a strong ability to rule out preeclampsia in women with MABP below 88.33 mmHg.

Currently there is emerging evidence that early risk assessment for preeclampsia could play an important role in the prevention of preeclampsia and subsequent adverse pregnancy outcome.[26] Low-dose aspirin is thought to improve the placental vasculature and therefore reduce the risk for preeclampsia with minimal risk to the fetus.[26] MABP with its high negative discriminating ability will have clinical usefulness in this setting, excluding women for whom aspirin therapy will not be required and directing attention to areas of greater need. Not narrowing down to a specific gestational age in second trimester and the low patient turn out in the tertiary centers are possible weaknesses of the study. The strength of the study lies in its ability to discriminate between MABP values at the stated level of significance.

Going forward, prospective studies assessing the performance of combining maternal risk factors with MABP to improve the sensitivity of detection of preeclampsia in Nigerian women will be needed.

CONCLUSIONS

MABP performed moderately (considering that excellent performance has an AUC of 1.0) in the prediction of late-onset preeclampsia in Nigerian women. Its high NPV at 90% specificity suggest a strong ability to rule out preeclampsia in women with MABP below 88.33 mmHg. The above findings suggest that MABP will have clinical utility in resource-poor settings to rule out preeclampsia and direct scarce resources appropriately.

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Conflicts of interest
There are no conflicts of interest.

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