

Prediction of Preeclampsia using ACC/AHA criteria for diagnosis of Hypertension in 1st trimester of pregnancy

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Abstract- Hypertensive disorders of pregnancy are associated with adverse perinatal outcomes and accounts for 14% of maternal deaths worldwide. The American Heart Association (AHA) and the American College of Cardiology (ACC) Task Force on Clinical Practice Guidelines (2017) have released a new hypertension guideline for adults, with lower blood pressure threshold to identify hypertension. 2017 ACC/AHA criteria for Hypertension are:

- Normal BP: <120/80 mmHg
- Elevated BP: 120-129/<80 mmHg
- Stage 1 HTN: 130-139/ 80-89 mmHg
- Stage 2 HTN: $\geq 140/\geq 90$ mmHg.

AIM: Prediction of preeclampsia using 2017 ACC/AHA hypertension classification in first trimester and to evaluate MAP of Ist trimester for prediction of PE.

Objective: To find out risk of development of PE in women with elevated Blood Pressure and stage 1 Hypertension during Ist trimester.

Methodology: It is a retrospective study conducted at Safdarjung hospital over a period of 6 months, August 2020 and February 2021. Women coming for antenatal registration from a specified region of South Delhi were registered in a randomized control trial– WINGS study (a WHO collaborated study) . Antenatal and labour records of women registered in the trial during 6 months were retrieved from an electronic database and transferred to excel sheet Pregnancy complicated by fetal malformation, women with high risk of developing G.HTN/PE according to ACOG 2018 criteria, women with stage II hypertension and participants with incomplete data were excluded. Women were then divided into 3 groups:

- Group 1: Normal Blood Pressure (<120/80 mmHg)
- Group 2: Elevated Blood Pressure (120-129/<80 mmHg)
- Group 3: Stage 1 hypertension (130-139/ 80-89 mmHg)

Main outcome measures are relative risk of development of G. HTN and PE and a cut off of MAP of first trimester for prediction of PE.

Results: The risk of developing PE increased in elevated and stage I BP category and this association was significant. The risk of PE was three times greater in elevated BP category (RR :3.58 at 95% CI) and five times greater in stage 1 hypertension (RR- 5.21 at 95% CI). The probability of HDU stay and prolong hospital stay increased with higher stages of hypertension in first trimester .There was no co relation between preterm birth and stages of hypertension .The association of different stages of hypertension with SGA and CAPO was weak . The cut off for MAP for prediction of PE from Ist trimester blood pressure is 85.3 mmHg as shown in fig 2. The NPV of Ist trimester blood pressure for G.HTN, PE and eclampsia are 97.4%, 99.8%,100% respectively (fig 2,3 and 4).

Conclusion: Our study shows that even pre hypertensive group (elevated and stage 1 hypertension) have increased risk of developing pre eclampsia. In our study first trimester MAP above 85.3 mmHg shows increased probability of developing PE. So a lower threshold of BP should be established for screening of PE to prevent associated adverse events.

Keywords: 2017 ACC/AHA guideline, blood pressure, hypertension, pregnancy induced hypertension, mean arterial pressure, prediction, pre eclampsia (PE) , first trimester of pregnancy

INTRODUCTION

The American Heart Association (AHA) and the American College of Cardiology (ACC) Task Force on Clinical Practice Guidelines (2017) have released a new hypertension guideline for adults. They have suggested a lower blood pressure threshold to identify hypertension. As per 2017 ACC/AHA hypertension guidelines, Blood pressure (BP) categories have been redefined as normal <120/80 mmHg, elevated 120-129/<80 mmHg, stage 1 HTN 130-139/ 80-89 mmHg, stage 2 HTN $\geq 140/\geq 90$ mmHg [1]. The new criteria for defining hypertension are supported by evidence that targeting lower Blood Pressures may reduce the risk of long-term cardiovascular morbidity in adults [2,3]. However, the ACC guidelines has not commented about its use in pregnancy. Besides this, there is little research in this field. There are few studies which are supporting the use of lower BP threshold because it would help in early prediction of PE [4-6].

In December 2018, the ACOG released new guidelines for managing high blood pressure in pregnancy [7,8]. This new guideline did not comment about the use of 2017 ACC/AHA guideline for the management of chronic (preexisting) hypertension in pregnancy due to lack of research in this field. The adoption of the 2017 ACC/AHA hypertension guideline in pregnant women can result in a substantial increase in the prevalence of gestational hypertension/PE when compared with the previous guidelines. It will also help in early detection of hypertensive disorders of pregnancy (HDP) and in reducing adverse maternal and perinatal outcomes. Therefore, it is essential to investigate the impact of 2017 ACC/ AHA guideline in pregnancy for early diagnosis of HDP.

Hypertensive disorders of pregnancy, including chronic (preexisting) hypertension, gestational hypertension and pre eclampsia, account for 14% of maternal deaths worldwide and are associated with adverse maternal and perinatal outcomes [9-11]. In addition, a history of hypertensive disorders of pregnancy is considered an important risk factor for long-term chronic diseases for mothers [12-15].

Among all HDP, Preeclampsia (PE) is the leading cause of maternal and perinatal morbidity and mortality. In Latin America and worldwide, it affects 2%–8% of pregnancies [16]. In developing countries its prevalence varies from 10% to 18% [17]. According to the World Health Organization (WHO), 25.7% of maternal deaths in Latin America and the Caribbean are related to hypertensive disorders of pregnancy. In developing countries the incidence of PE is upto 7 times higher than in developed countries [18]. Furthermore, women who had PE, have 3–4 times greater risk of developing chronic hypertension and 2 times the risk of ischemic heart disease, venous thromboembolism and stroke [19].

According to the American College of Obstetricians and Gynecologists [ACOG 2018], women are at high-risk of developing PE if they fulfill any of the following factors: Nulliparity, Multifetal gestations, Pre eclampsia in a previous pregnancy, Chronic hypertension, Pre gestational diabetes, Gestational diabetes, Thrombophilia, Systemic lupus erythematosus, Pre pregnancy body mass index greater than 30, Antiphospholipid antibody syndrome, Maternal age 35 years or older, Kidney disease, Assisted reproductive technology, Obstructive sleep apnea.

The aim of this study is to examine the relationship between 1st trimester BP and HDP. To explore this, we will first categorize the first trimester BP as per 2017 ACC/AHA criteria and then evaluate its association with pregnancy outcomes. Mean arterial pressure (MAP) is an easy, non-invasive, and cost-effective test which can be used in all women from the 1st trimester for prediction of PE. Therefore, in this study we will evaluate the cut off of 1st trimester MAP for developing PE. We will also evaluate the diagnostic accuracy of MAP for hypertensive disorder of pregnancy (HDP) and pregnancy outcome.

METHODOLOGY

This is a retrospective study done at Safdarjung hospital, New Delhi, a tertiary care centre of North India. Women coming for delivery who fulfilled the inclusion criteria from urban and peri urban, low-to mid-socioeconomic neighborhoods of South Delhi, India were enrolled in this study between August 2020 to February 2021. These women were registered in a randomized control trial for effect of nutrition, health, water, sanitation and psychosocial factors on intra uterine growth and linear growth of infants. The trial was approved by the ethical committee.

Antenatal and labour records of women registered in the trial during 6 months were retrieved from an electronic database and transferred to the excel sheet. Women with high risk of developing G.HTN/PE according to ACOG 2018 criteria, women with stage II hypertension, pregnancy complicated by fetal malformation and participants with incomplete data were excluded. Women were then divided into 3 groups:

- Group 1: Normal Blood Pressure (<120/80 mmHg)
- Group 2: Elevated Blood Pressure (120-129/<80 mmHg)
- Group 3: Stage 1 hypertension (130-139/ 80-89 mmHg)

Systolic and Diastolic BP were recorded of all patients in the trial, coming to Safdarjung Hospital for antenatal booking. Trained nurses recorded the Blood Pressure. Blood pressure was recorded after a rest of 15 min, in a sitting position with their arms supported at the level of their heart. Blood pressure was measured with an adult cuff, on both arms simultaneously using Omron 1300 digital blood pressure device. Higher BP was registered in the database. Mean

Arterial Pressure (MAP) was calculated by adding systolic blood pressure to twice of diastolic blood pressure and then dividing it by 3 i.e. $(SP+ 2DP)/3$.

The participants were categorized as term preeclampsia (≥ 37 weeks) (PE), early-onset pre eclampsia (< 34 weeks) (EO PE) and late onset preeclampsia (> 34 weeks) (LO PE) .

Maternal and perinatal outcome were traced and confirmed through the records of participant in the database. Main outcome measures are relative risk of development of G. HTN and PE and a cut off of MAP of first trimester for prediction of PE.

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software , IBM manufacturer, Chicago, USA, ver 21.0.

For statistical significance , p value of less than 0.05 was considered statistically significant.

OUTCOMES:

All maternal and perinatal complications were confirmed through manual assessment of medical records . The outcomes are G. HTN, PE, EO-PE, LO-PE, Eclampsia, GDM, preterm birth, small for gestational age (SGA), CAPO (stillbirth, neonatal death, admission to neonatal intensive care unit for 48 hours, or birthweight $< 3^{\text{rd}}$ percentile) and CAMO (eclampsia, HELLP syndrome [hemolysis, elevated liver function, low platelets], high-dependency unit (HDU) stay of mother , prolong hospital stay of mother , intensive care unit admission or maternal death) (table 2) . Gestational hypertension was defined as new-onset hypertension (SBP > 140 mm Hg or DBP > 90 mm Hg on 2 occasions) after 20 weeks period of gestation taken four hours apart in the absence of other features of PE [20] . PE was classified according to the American College of Obstetrician and Gynecologists 2018 criteria, which defines PE as de novo hypertension after 20 weeks of gestation with 1 or more features of end-organ dysfunction[21]. . Preterm birth was defined as delivery before 37 weeks of gestation. Small for gestational age (SGA) is defined as a birthweight $< 10^{\text{th}}$ percentile (but $> 3^{\text{rd}}$ centile) for gestational age. As the incidence of CAMO was too low to analyze so only prolong hospital stay/HDU stay of mother was analysed. In the chronic hypertensive population, superimposed PE was defined as “a rise in blood pressure with the development of proteinuria[20]. Perinatal death was defined as “stillbirth or neonatal death of a baby of 28 or more completed weeks of gestation or of 500 grams or more birthweight when gestational age is unknown[22].

RESULT AND OBSERVATIONS:

Total 1046 subjects were enrolled in the study. 49 were excluded due to exclusion criteria and incomplete data. So 997 subjects were included for analysis. Maternal characteristics and pregnancy outcomes are summarized in [Table 1 and 2](#) . The mean age of participants was 23.62 years while mean BMI was 22.15 kg/ m². 70.91% of women were multiparous, 28.43 % were small for gestational age, 11.23 % had preterm birth and 8.93 % had composite adverse perinatal outcome. The median gestation at delivery was 38.36 weeks, mean birthweight was 2822 gm. With regards to maternal outcomes, 1.4 % had PE, 20.36 % had GDM & eclampsia was seen in 0.2% . None of the subjects had HELLP syndrome, 0.40 % had prolonged hospital stay/HDU stay and there were no maternal deaths (0.0%). 49 subjects could not be assessed due to lack of data related to family history, socioeconomic status, BP records and delivery details.

[Table 2](#) and [Table 3](#) summarises pregnancy outcome and relationship between 2017 ACC/AHA BP categories respectively . Data are presented as Risk Ratio (RR) in [Table 3](#). The risk of developing PE increased in elevated and stage I BP category and this association was significant. The risk of PE was three times greater in elevated BP category (RR :3.58 at 95% CI,) and five times greater in stage 1 hypertension (RR- 5.21 at 95% CI). When late-onset PE (> 34 weeks of gestation) was assessed, a similar trend was observed with both elevated and stage 1 hypertension groups, demonstrating an increased risk of late-onset PE (RR of LO PE in stage 1 HTN group being significant). For analysis of early onset PE sample size was very small. The probability of HDU stay and prolong hospital stay increased with higher stages of hypertension in first trimester .There was no co relation between preterm birth and stages of hypertension .The association of different stages of hypertension with SGA and CAPO was weak .

The cut off for MAP for prediction of PE from Ist trimester blood pressure is 85.3 mmHg as shown in fig 2. The NPV of Ist trimester blood pressure for G.HTN, PE and eclampsia are 97.4%, 99.8%,100% respectively (fig 2,3 and 4).

Table 1 : Distribution of baseline characteristics of study subjects

Age :	Mean Age \pm SD : 23.62889 \pm 3.095645 Range: 18 – 30	
BMI:	Mean BMI \pm SD : 22.15188 \pm 3.710323	
BMI Category	Frequency	Percentage
<18.5	149	14.94
18.5 and 24.99 kg/m ²	623	62.49
\geq 25 kg/m ²	225	22.57
Primi	290	29.09
Multigravida	707	70.91
BPL Card		
Non Holder	959	96.19
Holder	38	3.81
Education(12 th)		
No (<12 th)	483	48.45
Yes	514	51.55
ACC/AHA HTN Category		
Normal BP	709	71.11
Elevated BP	157	15.75
Stage 1 BP	131	13.14

Table 2:-Distribution of outcome of study subjects.

Outcome	Frequency	Percentage
G. HTN (997)	47	4.71
PE (997)	14	1.40
EOPE (997)	1	0.10
LOPE (997)	13	1.30
Eclampsia (997)	2	0.20
GDM (997)	203	20.36
Preterm Birth (997)	112	11.23
SGA (904)	257	28.43
HDU/Prolong hospital stay of mother (997)	4	0.40
CAPO (997)	89	8.93
Birth weight (908)	Mean \pm SD: 2.822629 \pm .4608694	
Gestational Age at delivery (994)	Mean \pm SD : 38.36147 \pm 1.470322	

Table 3: Fetomaternal outcome according to new ACC /AHA 2017 hypertension classification

	Normal (n=709)	Elevated (n=157)	Stage 1 (n=131)	Elevated ^a		Stage 1 ^{ab}	
				Unadjusted RR (95% CI)	Adjusted RR ^b (95% CI)	Unadjusted RR (95% CI)	Adjusted RR ^b (95% CI)
Preeclampsia	5 (0.7)	4 (2.6)	5 (3.8)	3.61	3.58	5.41	5.21

				(0.98 to 13.30)	(0.96 to 13.42)	(1.59 to 18.43)	(1.51 to 17.95)
Gestational hypertension	23 (3.2)	8 (5.1)	16 (12.2)	1.57 (0.71 to 3.51)	1.22 (0.54 to 2.77)	3.77 (1.99 to 7.13)	3.48 (1.81 to 6.72)
Eclampsia	2 (0.3)	0	0	-	-	-	-
Early onset Preeclampsia	0 (0.0)	1 (0.6)	0 (0.0)	-	-	-	-
Late onset Preeclampsia	5 (0.7)	3 (1.9)	5 (3.8)	2.71 (0.65 to 11.34)	2.58 (0.60 to 11.13)	5.41 (1.57 to 18.69)	5.16 (1.51 to 17.95)
Preterm	84 (11.8)	17 (10.8)	11 (8.4)	0.92 (0.54 to 1.54)	0.88 (0.52 to 1.49)	0.71 (0.38 to 1.33)	0.69 (0.36 to 1.30)
Small for gestational age babies	176 (27.4)	45 (31.0)	36 (30.8)	1.13 (0.82 to 1.57)	1.20 (0.86 to 1.67)	1.12 (0.78 to 1.61)	1.19 (0.82 to 1.71)
Prolonged hospital stay of mothers	2 (0.3)	1 (0.6)	1 (0.8)	2.26 (0.20 to 24.90)	1.77 (0.15 to 20.37)	2.71 (0.25 to 29.84)	2.19 (0.19 to 25.10)
Composite adverse perinatal outcomes	60 (8.5)	14 (8.9)	15 (11.5)	1.05 (0.59 to 1.89)	1.12 (0.62 to 2.01)	1.35 (0.77 to 2.38)	1.47 (0.82 to 2.61)

Our study supports the evidence that lower BPs currently accepted as Normal are associated with increased risk of pre eclampsia , more specifically there is increased risk of PE in stage 1 hypertension. In our study we have demonstrated that the relative risk of developing PE increases above MAP of 85.3 mmHg . In our study , women with pre hypertensive BPs do not have any association with preterm birth, SGA and CAPO .

DISCUSSION

There are many studies which support that stage 1 hypertension is associated with increased incidence of PE. In a study by Sutton et al (2947 women were included) stage 1 hypertension was associated with 2 to 3 times increased risk of PE as compared with the normotensive group [23]. Similarly in our study , Pre eclampsia was found to be statistically significant in elevated hypertension category as well as in stage I hypertension category. PE was also found to be statistically significant even at a lower MAP in first trimester .This also suggests that there is dose response relationship between PE and BP and so the threshold for defining hypertension in pregnancy should be reduced to a MAP of 85.3 mmHg.

In our study there is no association between different stages of hypertension and pre term birth. HDU/Prolonged hospital stay has a weak association with different stages of hypertension. We have also seen that composite adverse perinatal outcome and small for gestational age is not statistically significant in our study as found in the study of Maya Reddy et al and Sutton et al [23].

Few studies have shown that these outcomes have varied results . In a study by Sutton et al, there is 4 times increased risk of preterm birth in stage 1 hypertension category [21] . In contrast, in the study of Hu et al there was no significant difference in preterm birth rates in stage 1 hypertension group when compared with the normotensive population [24]. Besides this, there are no other studies that have examined the relationship between BP as per 2017 ACC/AHA guidelines and pregnancy outcome.

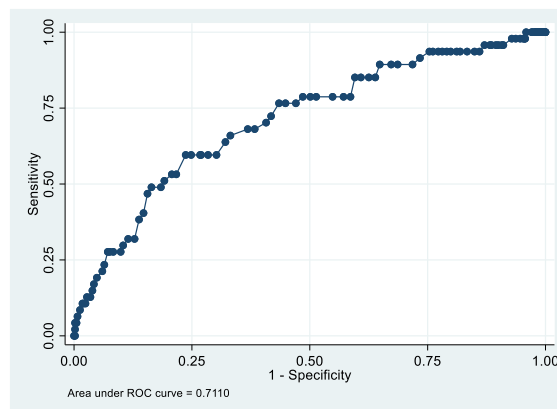
In our opinion , on the basis of our study and a few supporting studies, SBP >140 mmHg or DBP >90 mm Hg may not be the ideal threshold for screening of women for hypertensive disorders of pregnancy. We know that the HAPO study (Hyperglycemia and Adverse Pregnancy Outcomes) demonstrated a continuous relationship between glycemic levels and adverse pregnancy outcomes [25]. This landmark study has steered changes in pregnancy guidelines, which recommends lower glucose thresholds for the diagnosis of gestational diabetes. This helps to identify a wider group of women who are at risk of associated adverse events. However, these guidelines are not accepted widely due to lack of evidence. Similarly, we have demonstrated that 3.8 % of women with stage 1 hypertension will develop PE as compared with the baseline risk of 0.70 % in the normotensive population.

In our study the risk of developing PE appears to increase significantly at even lower thresholds (MAP 85.3 mm Hg). Our study also shows that the prehypertensive group is at an increased risk of HDU/Prolong hospital stay though not statistically significant. This is particularly important as BP is currently used as a screening tool for PE and is only a

part of a heterogenous syndrome which results in adverse outcomes. Therefore, as a screening tool, lower thresholds may be more appropriate in identifying a larger group of women that can benefit from detail investigation, close monitoring and early intervention such as aspirin prophylaxis. However, similar to the controversies in gestational diabetes, before implementation there is a need for more supporting studies with large sample size. We know that blood pressure alone is not used for screening women for PE, other risk factors are also considered. The poor predictive value of BP alone is highlighted by our study, as the majority of women with elevated and stage 1 hypertension do not develop PE or associated adverse outcomes. Perhaps, a multifactorial risk assessment is more appropriate for the prediction of PE and adverse outcomes rather than BP alone. The Fetal Medicine Foundation has developed a predictive algorithm for PE using a combination of maternal characteristics, MAP, uterine artery Doppler, and biochemical markers such as placental growth factor and soluble fms-like tyrosine kinase [26-28]. This algorithm has a detection rate of 75%, 85%, and 98% (10% false-positive rate) for preterm PE in the first, second and third trimesters, respectively, which outperforms risk assessment with BP alone.[26-28].

Randomized control trials with large sample size are required before revising the threshold of blood pressure for screening of PE. There needs to be careful consideration between sensitivity and specificity and resource implications when implementing a lower BP threshold. A lower threshold will likely increase detection rates for PE thereby increasing false-positive rate. Furthermore, there is no literature to support that closer monitoring and earlier intervention in the prehypertensive group improves pregnancy outcomes. So, more intervention studies in the prehypertensive group are required. This may include a randomized control trial in which maternal and perinatal outcomes are assessed in women with stage 1 hypertension who are randomized to routine clinical practice or closer monitoring with tighter BP control.

Fig 1: . ROC curve MAP and gestational hypertension

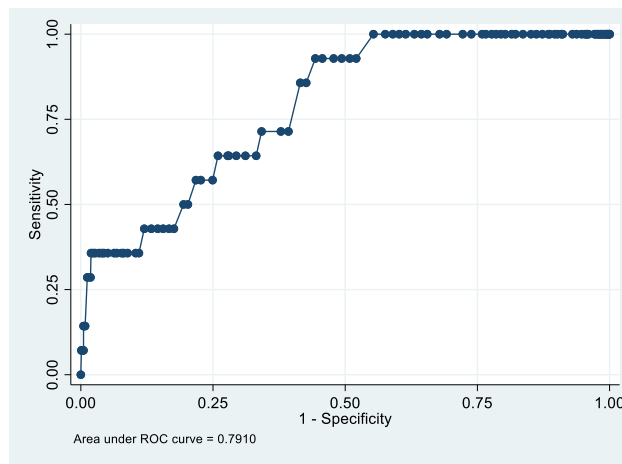


Area under curve (95% CI): 0.71 (0.68 to 0.74)

Optimal cut point for MAP 89.3 mm Hg

Diagnostic accuracy	Estimate (95% CI)
Sensitivity	59.6 (44.3 to 73.6)
Specificity	76.3 (73.5 to 79)
PPV	11.1 (7.5 to 15.6)
NPV	97.4 (96 to 98.5)

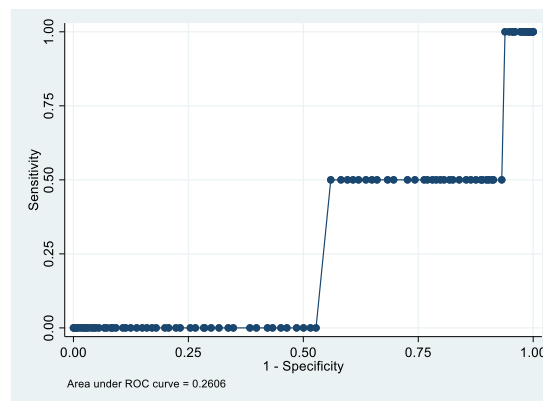
Fig 2: ROC curve MAP and pre-eclampsia



Area under curve (95% CI): 0.79 (0.76 to 0.82)
 Optimal cut point for MAP 85.3 mm Hg

Diagnostic accuracy	Estimate (95% CI)
Sensitivity	92.9 (66.1 to 99.8)
Specificity	55.6 (52.5 to 58.8)
PPV	2.9 (1.6 to 4.9)
NPV	99.8 (99 to 100)

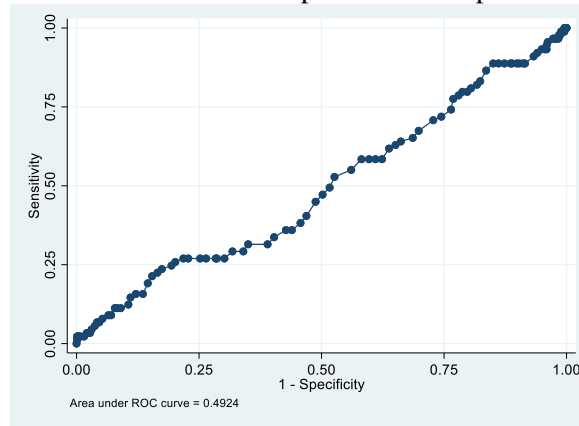
Fig 3: ROC curve MAP and eclampsia



Area under curve (95% CI): 0.26 (0.23 to 0.29)
 Optimal cut point for MAP 73 mm Hg

Diagnostic accuracy	Estimate (95% CI)
Sensitivity	100 (15.8 to 100)
Specificity	6.1 (4.7 to 7.8)
PPV	0.2 (.03 to 0.8)
NPV	100 (94.1 to 100)

Fig 4: ROC curve MAP and Composite adverse perinatal outcomes



Area under curve (95% CI): 0.49 (0.46 to 0.52)

Optimal cut point for MAP 91 mm Hg

Diagnostic accuracy	Estimate (95% CI)
Sensitivity	23.6 (15.2 to 33.8)
Specificity	82.6 (80 to 85)
PPV	11.7 (7.4 to 17.4)
NPV	91.7 (89.6 to 93.5)

Strengths of this study: is its large sample size which allows for greater generalizability of the findings. Furthermore, as we have used clinically collected data, the results are reflective of routine clinical practice and have greater applicability. This study is also unique in that we have not limited our analysis to the predefined ACC criteria. By examining mean arterial pressure, we have also established a relationship between MAP of first trimester in predicting PE along with a lower threshold of MAP which is yet to be accepted by more supporting studies.

Limitation of this study : it is a retrospective study design, which can be associated with inaccurate record keeping, interobserver variability in BP measurement and an inability to control for all confounding factors. However, to minimize the impact of this design, all adverse pregnancy outcomes were confirmed by thorough examination of individual patient records. Another limitation exists in the volume of missing data. Although analysis revealed that the data is likely missing and multiple imputation did not show any difference in results. To overcome such limitations, a prospective study with consistent measurement of BP is required.

CONCLUSION

Our study shows that even pre hypertensive group (elevated and stage 1 hypertension) have increased risk of developing pre eclampsia. We have also demonstrated that MAP of first trimester can be used to predict development of pre eclampsia . In our study first trimester MAP above 85.3 mmHg shows increased probability of developing PE. So a lower threshold of BP should be established for screening of PE to prevent associated adverse events.

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