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Abstract

Aim: To propose a simple model for predicting preeclampsia (PE) in the 1st trimester of pregnancy on the basis of maternal characteristics (MC) and mean arterial pressure (MAP).

Methods: A prospective cohort was performed to predict PE between 11 and 13+6 weeks of gestation. The MC evaluated were maternal age, skin color, parity, previous PE, smoking, family history of PE, hypertension, diabetes mellitus and body mass index (BMI). Mean arterial blood pressure (MAP) was measured at the time of the 1st trimester ultrasound. The outcome measures were the incidences of total PE, preterm PE (delivery <37 weeks) and term PE (delivery ≥37 weeks). We performed logistic regression analysis to determine which factors made significant contributions for the prediction of the three outcomes.

Results: We analyzed 733 pregnant women; 55 developed PE, 21 of those developed preterm PE and 34 term PE. For total PE, the best model was MC+MAP, which had an area under the receiver operating characteristic curve (AUC ROC) of 0.79 [95% confidence interval (CI)=0.76–0.82]. For preterm PE, the best model was MC+MAP, with an AUC ROC of 0.84 (95% CI=0.81–0.87). For term PE, the best model was MC, with an AUC ROC of 0.75 (0.72–0.79). The MC+MAP model demonstrated a detection rate of 67% cases of preterm PE, with a false-positive rate of 10%, positive predictive value of 17% and negative predictive value of 99%.

Conclusion: The MC+MAP model showed good accuracy in predicting preterm PE in the 1st trimester of gestation.

Keywords: First trimester of pregnancy; maternal characteristics (MC); mean arterial pressure (MAP); prediction; preeclampsia (PE).

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Introduction

Preeclampsia (PE) is the leading cause of maternal and perinatal morbidity and mortality in Latin America and worldwide, affecting 2%–8% of pregnancies [1]; its prevalence can vary from 10% to 18% in developing countries [2]. According to the World Health Organization (WHO), 25.7% maternal deaths in Latin America and the Caribbean are related to hypertensive diseases in pregnancy; in addition, PE incidence may be 7 times higher in developing countries than in developed countries [3]. Furthermore, women who have 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 [4].

Several studies have been conducted to suggest effective ways of preventing PE. A meta-analysis of randomized clinical trials reported that low-dose aspirin (150 mg) started at up to 16 weeks of pregnancy was associated with a 50% reduction in the risk of overall PE and an 80% reduction in early PE (<34 weeks) [5]. More recently, another study stressed that low-dose aspirin (80–160 mg) decreases the risk of PE and fetal growth restriction by half when started <16 weeks of pregnancy [6]. In Australia, it is estimated that >$7,00,000 per year were saved by screening for PE in 5000 women who received care from a gynecology practice [7].

The 1st trimester has been considered ideal for PE screening because of the evidence of effectiveness of low-dose aspirin use by pregnant women risk initiated ≥16 weeks of gestation [8]. Various clinical, biochemical and biophysical tests have been proposed to predict PE, but no predictive test has been shown to be useful for isolated use to adjust pre-existing maternal risk of PE with enough specificity and sensitivity for clinical use. Consequently, the best results are obtained from tests involving the combination of multiple parameters [9].

Among women considered to be at high risk of developing PE because of their maternal characteristics (MC), it is estimated that approximately 25% will develop PE, compared to 5% of the general population [10]. Mean arterial pressure (MAP) is an easy, non-invasive, and cost-effective test than can be conducted in all women from the 1st trimester. In a retrospective study of 1655 women measuring blood pressure (BP) at <20 weeks' gestation, using 92 mm Hg as the cut-off point for MAP, the detection rate was 25%, with a false-positive rate of 10% [11]. Another study explored the possibility of routine screening for preterm PE (<37 weeks) considering only MC and MAP for all pregnancies. The authors observed that when all the pregnant women between 11 and 13 weeks were screened using MC, MAP, pulsatility index of the uterine artery Doppler and placental growth factor, the detection rate for PE was 74% with a false-positive rate of 10%. However, when the screening was performed only with MC and MAP in the first step and the pregnant women were directed to the screening in the second step using pulsatility index of uterine artery Doppler and placental growth factor, the reduction in detection rate was minimal (74%–71%) [12].

Therefore, the objective of this study was to propose a simple and cheap model based on MC and MAP to predict PE in the 1st trimester of gestation in a cohort of pregnant Brazilian women.

Methods

A secondary analysis was performed on two prospective cohorts, which proposed multi-parameter models to predict PE in the 1st trimester of pregnancy [13, 14]. The first cohort was developed between August 2009 and February 2011 at the Fortaleza General Hospital [13], whereas the second cohort was developed between February 2012 and January 2014 at the Fortaleza General Hospital and the Gonzaga Mota Hospital in the Messejana district [14]; both of these hospitals are reference centers for low-risk and high-risk pregnancies in Fortaleza, northeastern Brazil. The pregnant women were referred from basic public health units in the Fortaleza metropolitan region for 1st trimester ultrasounds. The inclusion criteria were: consecutive pregnant women invited to participate in the study, singleton pregnancy, appropriate cuff-sizes were used depending on the arm circumference and gestation between 11 weeks and 13 weeks and 6 days. Exclusion criteria were: prior maternal renal disease, major fetal malformations or chromosomal abnormalities, miscarriage and loss of follow-up/incomplete data. Gestational age was determined by the last menstrual period and confirmed by 1st trimester ultrasonography. The prospective cohorts were approved by both hospitals' local research Ethics Committees and all the pregnant women signed a consent form.

The following MCs were assessed when the 1st trimester ultrasound was conducted: maternal age, self-reported skin color (White, Black or mixed race); parity (nulliparous or multiparous); history of prior PE and smoking; family history of PE, hypertension and diabetes mellitus; and body mass index (BMI).

MAP, which was measured at the time of the 1st trimester ultrasound, was measured in the first cohort using a manual sphygmomanometer; the pregnant women were placed in a sitting position and after 10 min of rest, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in one arm. From the values obtained, MAP was calculated using the following formula: $[(SBP + 2 \times DBP) \div 3]$ [13]. MAP was measured in the second cohort using a validated digital sphygmomanometer (3-BTO-A2, Microlife, Taipei, Taiwan); the pregnant women were placed in a sitting position, with their backs supported and their legs uncrossed, with both arms supported on a table at heart level. After 5 min of rest, both SBP and DBP were measured simultaneously in both arms [14]. A second measurement was taken using the same method, 1 min after the first measurement and the average of the two measurements was considered for SBP and DBP. After calculating the right and left MAP, the greater MAP was considered for the data analysis, following a previously validated protocol [15].

All the pregnant women were followed longitudinally to detect PE occurrence. Hypertension in pregnancy was defined as a SBP of ≥140 mm Hg and/or a DBP of ≥90 mm Hg in two different measurements with an interval of 4–6 h between them. Diagnosis of PE was based on the following criteria of the International Society for the Study of Hypertension in Pregnancy: appearance of hypertension and proteinuria (≥300 mg of protein in 24 h urine, or ++ on the Labstix test strip when it was not possible to obtain 24 h proteinurea results) after 20 weeks of gestation in a previously normotensive pregnant woman. PE can be considered preterm (delivery <37 weeks) or term (delivery ≥37 weeks).

The pregnant women were instructed to inform the researchers of the date and hospital where delivery took place and the birth data were obtained either from the medical records at these hospitals or by telephone contact with the women.

The data were transferred to an Excel 2007 spreadsheet (Microsoft Corp., Redmond, WA, USA) and analyzed using SPSS version 23.0 software (SPSS Inc., Chicago, IL, USA), MedCalc version 12.7.0.0 software (MedCalc Software bvba, Ostend, Belgium) and GraphPad Prism version 6.01 software (GraphPad Inc., San Diego, CA, USA). The variables were analyzed descriptively, with the calculation of absolute and relative frequencies as well as mean and standard deviation for each outcome group [no PE (control), total PE, preterm PE and term PE]. Next, univariate analysis was performed, determining the median and the interquartile ranges for the continuous variables using either the unpaired *t*-test (two groups) or one-way ANOVA (3 or more groups) and the chi-square test (χ^2) for nominal variables. Logistic regression analysis with a stepwise selection model was performed to determine the MC that demonstrated a significant contribution in the risk of developing total PE, preterm PE and term PE. We assessed the post-test probability of developing total PE, preterm PE and term PE based on MC and MAP and compared with that achieved by MC alone. An evaluation of the predictive accuracy of the tests was performed using the area under the receiver operating characteristics curve (AUC ROC) and the detection rates for a false-positive rate of 5%, 10% and 20%, considering the test associations [MC, MAP and (MC + MAP)] according to the different outcomes. The accuracy of MC and MAP was also evaluated by calculating sensitivity and specificity as predictors of PE, as well as the positive and negative predictive value. A significance level of (P) values of <0.05 was used in all the analyses.

Results

Initially 810 pregnant women were selected; 550 were present in the first cohort [13] and 260 in the second one [14]. Eight were excluded from the first cohort because of miscarriage and 44 because of incomplete data. Seven were excluded from the second cohort because of incomplete data and three because of miscarriage. Therefore, the final statistical analysis considered 733 pregnant women; 55 developed PE, 21 of these developed preterm PE and 34 term PE. Table 1 presents a comparison of the group outcomes according to MC. We note that gestational age at delivery, nulliparity, family history of PE, previous PE, birth weight and BMI were statistically significant for the preterm PE group.

To estimate the risk of developing PE, the following parameters were used: family history of PE, previous PE, BMI and MAP. The formulas used were: $MC = -0.189 + 0.011 \times BMI + 0.127$ (family history of PE) -0.062 (no previous PE), $MC + MAP = -0.426 + 0.004 \times PAM + 0.129$ (family history of PE) -0.059 (no previous PE) $+ 0.006 \times BMI$. The AUC ROC for MC was 0.747 [95% confidence interval (CI) 0.714–0.778], for MAP it was 0.724 (95% CI 0.690–0.756) and for MC + MAP it was 0.787 (95% CI 0.756–0.816). To estimate the risk of developing preterm PE, chronic hypertension, previous PE and BMI were used as parameters. The formulas used were: $MC = -0.051 + 0.109$ (chronic hypertension) $+ 0.083$ (previous PE) $+ 0.003 \times BMI$, $MC + MAP = -0.197 + 0.003 \times MAP + 0.084$ (chronic hypertension) $+ 0.073$ (previous PE). The AUC ROC for MC was 0.773 (95% CI 0.741–0.803), that for MAP it was 0.825 (95% CI 0.795–0.852) and that for MC + MAP it was 0.842

Table 1: Clinical and obstetrical data of participants according to outcome group.

Variable	No PE (n = 678)	Preterm PE (n = 21)	Term PE (n = 34)	P value[a]
Clinical variable				
Age	26.0 (25.5–26.6)	29.9 (27.4–32.4)	25.4 (23.2–27.7)	0.03
Mean arterial pressure	80 (73–87)	93 (83–103)	86 (80–94)	<0.001
Skin color				
White	127 (19%)	2 (10%)	5 (15%)	0.46
Mixed	531 (78%)	19 (90%)	29 (85%)	
Black	20 (3%)	–	–	
Smoking	41 (6%)	–	1 (3%)	0.41
Chronic hypertension	27 (4%)	5 (24%)	1 (3%)	0.002
Diabetes mellitus	17 (3%)	1 (5%)	–	0.66
Obstetrical variables				
GA at delivery	38.8 (38.7–39.0)	32.3 (30.7–34.0)	38.6 (38.3–39.0)	<0.001
Nulliparity	330 (49%)	9 (43%)	21 (62%)	0.004
Family history of PE	80 (12%)	6 (29%)	12 (35%)	<0.001
Prior PE	37 (5%)	6 (29%)	2 (6%)	<0.001
Newborn weight	3298.0 (3259.3–3336.7)	2019.8 (1478.3–2561.4)	3236.2 (3036.7–3435.7)	<0.001
BMI	25.2 (24.8–25.5)	28.7 (26.5–30.9)	28.1 (26.4–29.7)	<0.001

GA = Gestational age, PE = preeclampsia, NB = newborn, BMI = body mass index.
The values were expressed as median (interquartile ranges) or number of cases [proportion (%)].
[a]Significance level obtained by the Kruskal-Wallis test for continuous variables and chi-square (χ^2) test for categorical variables.

(95% CI 0.814–0.868). To calculate the risk of developing term PE, the following parameters were included in the formula: family history of PE, nulliparity and BMI; MAP did not significantly contribute to the calculated risk. The formula used was: MC = −0.161 + 0.093 (family history of PE) + 0.007 × BMI + 0.049 (nulliparous). The AUC ROC for MC was 0.754 (95% CI 0.721–0.785). Figure 1 shows the graphs of the areas under the ROC curve for predicting PE in the three groups. Table 2 presents the performance of the isolated model (MC and MAP) and the combined model (MC + MAP) for each of the outcome groups, considering a false-positive rate of 5%, 10% and 20%. We observed that the best model included MC + MAP, with a detection rate of 67% preterm PE cases (false-positive rate 10%) and AUC ROC of 0.842.

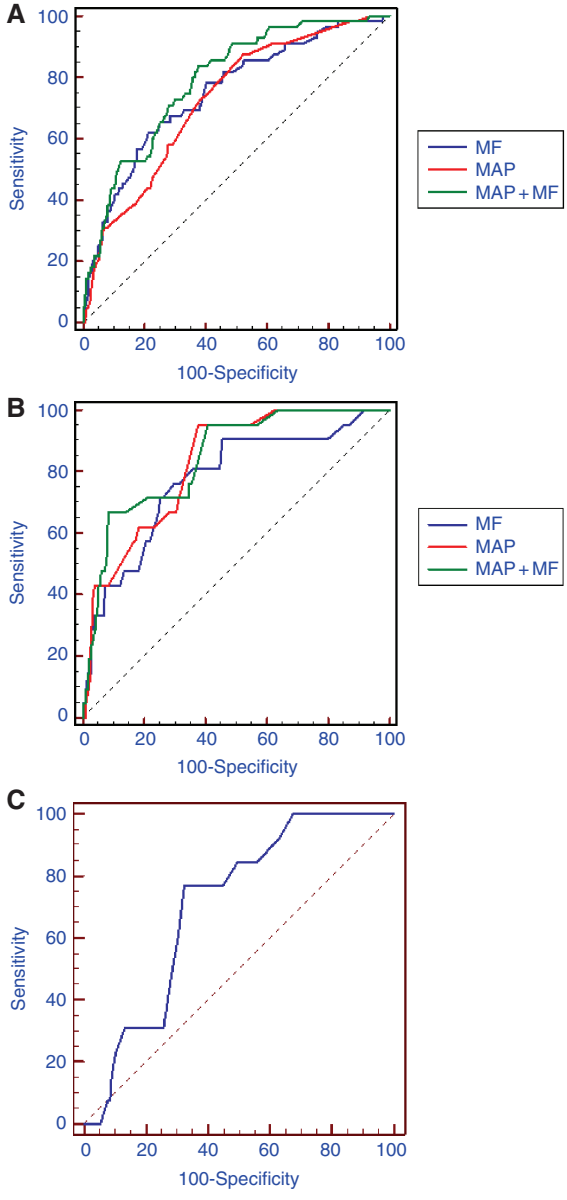

Figure 1: Scatter plots of the areas under the receiver operating characteristics (ROC curve for predicting total PE (A), preterm PE (B) and term PE (C) groups. MF = maternal features, MAP = mean arterial blood pressure.

Table 2: Detection rates for MC, MAP and MC + MAP in each outcome group.

FPR	Detection rates		
	MC	MAP	MC + MAP
Total PE			
5%	26%	20%	22%
10%	38%	31%	44%
20%	56%	40%	53%
Preterm PE			
5%	33%	43%	43%
10%	43%	43%	67%
20%	48%	62%	71%
Term PE			
5%	24%	–	–
10%	44%	–	–
20%	53%	–	–

MC = Maternal characteristics, MAP = mean arterial blood pressure, PE = preeclampsia, FPR = false-positive rate.

Table 3 presents the distribution of participants according to PE risk by the MC + MAP predictive model and the preterm PE occurrence, considering a cutoff of >0.099 for the result obtained on the formula. Thus, considering the true-positive (14), true-negative (642), false-positive (70) and false-negative (7) values for preterm PE in this predictive model, a positive predictive value of 17% [14/(14 + 84)] and a negative predictive value of 99% [642/(642 + 7)] were obtained.

Table 3: Distribution of participants according to PE risk by the MC + MAP predictive model and preterm PE occurrence.

Risk for preterm PE[a]	Preterm PE		
	Yes	No	Total
High	14	70	84
Low	07	642	649
Total	21	712	733

MC = Maternal characteristics, MAP = mean arterial blood pressure, PE = preeclampsia.
[a]High risk of PE was defined when MC + MAP > 0.099; low risk of PE was defined when MC + MAP ≤ 0.099; MC + MAP = −0.197 + 0.003 × MAP + 0.084 (chronic hypertension) + 0.073 (previous PE).

Discussion

The prevalence of PE in this study (7.5%) was higher than that indicated in the recent literature, where values ranged from 1.8% to 4.4% [12, 16–18]. This was also the case with preterm PE (prevalence of 2.9%) compared to rates in other studies, which ranged from 0.6% to 0.9% [16–18]. This fact is likely related to the unique low-income population profile in the northeastern region of Brazil, in which gestational outcomes tend to be worse. A systematic review that included 29 studies found that none of these developed a prediction model for PE in low-income populations [19], but the population profile influences the prevalence of PE and the effectiveness of their prediction models [20].

With regard to MC, a subtle increase in age was seen in the preterm PE group, approaching 30 years, the age that is already considered a risk factor for PE in some studies [21, 22]. The vast majority of participants were of mixed race (79.0%), an ethnic profile, which is very specific to underdeveloped or developing countries. Afro-Caribbean and African-American ethnicities have been reported as risk factors for early PE in other studies [22, 23], but no studies have evaluated mixed race. As for maternal diseases, the prevalence of chronic high BP and diabetes mellitus was higher in the preterm PE group, with statistical significance for hypertension, in agreement with what has been reported in previous research [12, 17]. Of the pregnant women, 44.1% were nulliparous, which is considered the main risk factor for PE in relation to individual clinical risk factors determined at the 16th week of gestation [22, 23]. Among the participants, 6.2% had a history of PE in a previous pregnancy, similar to results found in other studies (2.8% and 6.9%) [17, 24].

The average MAP was 81.1 mm Hg overall, but with some differences between the groups. Higher rates were reported among the women who developed preterm PE compared to those who did not have PE and this difference was also observed in other studies [24, 25]. The use of automatic equipment to measure BP in PE screening has been recommended in protocols and validated in many studies [15, 26], but the manual sphygmomanometer remains the gold standard for non-invasive monitoring of BP because its lower cost makes it widely available throughout healthcare settings, although its performance and safety have been questioned [27].

MAP favored an increased predictive value of the preterm PE model group, because when it was added to MC, the detection rate increased from 43% to 67%. The detection rate obtained reveals that the model we created is effective for predicting PE in the studied population because lower values have been reported in other studies with a model that addresses MC and MAP for preterm PE, e.g. 53.7% [28], 58.0% [17], 59.3% [22] and 62.5% [15]. These results are promising because they indicate it is possible to perform early screening and identify 67/100 women who could develop preterm PE. Moreover, it is a simple and cheap model that can be applied in primary healthcare units in underdeveloped or developing countries. This systematic review indicated that models that include MC + MAP for prediction of PE had AUC ROC ranging from 0.670 to 0.900. Additional costs of the biophysical and biochemical examinations and clinic use must be determined, along with the cost effectiveness of these factors to guide the use of aspirin [19].

In this study, the prediction of PE showed a positive predictive value of 17% because 14 of the 84 women at high risk for preterm PE actually developed the disease. However, the studies that included biophysical and biochemical parameters in addition to MC and MAP obtained lower results, with a positive predictive value of 7% [24, 28]. On the other hand, the negative predictive value was 99%, similar to previous studies [16, 24].

Several clinical risk prediction models were developed to predit PE which included risk models based on readily available maternal characteristics “simple models” and more complex models that include specialized tests “specialized models”, such as the one developed by the Fetal Medicine Foundation. Our point is that most of these tests, such as uterine artery Doppler and biochemistry (i.e. placental growth factor), are not routinely performed or readily available in general antenatal, especially on developing countries. This is not the case just of South and Latin America, but also Africa and South Asia. We developed a simple algorithm using maternal factors and MAP that could be used in a routine antenatal care setting even on these less privileged areas of the world. The main limitation of our algorithm is the non-inclusion of known predictors of PE such as uterine artery Doppler and serum biomarkers as well as external validation in different ethnic populations. On the other hand, the main goal of a prediction algorithm is to predict a high-risk group for preterm PE (delivery <37 weeks) and our combined algorithm performed well in this regard (MC + MAP reached a DR of 67% with 10% false-positive rate).

Family history of PE was reported in 12% in our cohort which could be considered a “moderate” risk population instead of low risk. These patients were seen in two major tertiary and secondary hospitals and were keen to be part of a “screening for Down syndrome” program, practice that is not very spread on public Brazilian hospitals. Furthermore, despite only 10% of the cases with chronic hypertension and previous PE, the prevalence of preterm

PE was 21/733 (3%) and most cases with any of these risk factors (9/21 = 43% vs. 57/712 = 8% without preterm PE), which led to a good area under the curve only with these two factors. The BMI contributes only marginally. These potential biases were recognized as a limitation of our study.

In summary, we have determined a simple model to predict PE in the 1st trimester of pregnancy based on MC and MAP with a good rate of preterm PE prediction. We believe that because of its low cost and effectiveness, this model could be applied in primary health units in Brazil and other underdeveloped or developing countries, in order to track the groups at greater risk, so that early aspirin treatment can be initiated and these pregnant women can be referred to specialized services, thereby contributing to decrease perinatal morbidity and mortality.

Author's statement

Conflict of interest: Authors state no conflict of interest.

Material and methods: Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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