Prognostic risk factors for early diagnosing of Preeclampsia in Nulliparas

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ABSTRACT

Background: Preeclampsia is of major complications of pregnancy that is associated with maternal morbidity and mortality. Therefore, prediction and early diagnosis of preeclampsia would be helpful for better controlling of related complications. Our study aimed to investigate risk factors helping to predict and early diagnose of preeclampsia. **Materials and Methods:** A total of 739 nulliparous women at their 24-28th weeks of the first pregnancy were enrolled in this multi-center cohort study. Incidence or absence of preeclampsia in this population was evaluated up to the end of pregnancy period. For each case, a record sheet was assigned that contained information about haematocrit level in weeks 24-28th of pregnancy, blood pressure, result of roll-over test in weeks 24-28th of pregnancy and the presence of disease up to end of the study. Diagnosis of preeclampsia was made based on gold standard. **Results**: Overall, 3.9 % of all cases developed preeclampsia. The mean maternal age, body mass index (BMI), years of education and positive roll-over test were significantly higher in preeclampsia group ($P < 0.001$). However, the mean gestational age and changes in the levels of haematocrit were significantly higher in normotensive cases ($P < 0.001$). Our combined model could predict preeclampsia with a sensitivity of 93% and a specificity of 80%. **Conclusion:** Simple combined model of demographic characteristics including maternal age, BMI, years of education and positive roll-over tests can predict preeclampsia without any cost for the patients.

Key words: Preeclampsia, pregnancy, risk factors, roll-over test

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INTRODUCTION

Preeclampsia is a major risk for premature delivery, intrauterine growth restriction, perinatal death and low birth weight; it affects 5-8% of pregnant women in the United States.[1]

Preeclampsia is associated with substantial mortality and morbidity in fetus and maternity. This multisystem disorder can occur after mid-gestation.[2-5] For more than 50 years, investigators have tried to find a test predicting preeclampsia, but there is no widely accepted screening test.[3,6] Nowadays, some tests are being used by determining placental perfusion and vascular resistance.[7]

In a prospective study in the United Kingdom,[8] 7797 women with singleton pregnancies were evaluated during gestational weeks 11th to 13th, of which 157 women developed preeclampsia. An algorithm to predict early preeclampsia that combined the logs of uterine artery pulsatility index, mean arterial pressure, serum pregnancy-associated plasma protein-A, serum-free placental growth factor, the body mass index (BMI) and the presence of nulliparity or previous preeclampsia was developed.[8]

Large longitudinal studies are required to assess the effectiveness of early prediction and to determine the cost benefit. These studies should be structured as randomized to usual care and to early prediction, followed by a more stringent protocol for follow-up in patients who were screened positive for early preeclampsia.[7] Also, preeclampsia can be a prominent factor leading to the increase of cardiovascular events by 2- to 3-fold; the risk is greatest for women with severe preeclampsia.[9] A study demonstrated that eclampsia was associated with increased risk of maternal death, assessed ventilation, respiratory distress syndrome, acute renal failure, obstetric

embolism, neonatal death and other complications, whereas anemia, nulliparity and existing heart disease were reported as risk factors of developing eclampsia.[10] Another study showed that, in women with hypertension disorders during pregnancy, the risk of cardiovascular disease was increased.[11] Ultrasound evaluation of fetal growth and amniotic fluid volume were recommended for prediction of the outcome of the pregnancy and early intervention to reduce mortality and morbidity of complicated pregnancies.[3]

The development of an accurate biomarker for prediction of preeclampsia improves fetal-maternal care by allowing closer prenatal monitoring, earlier diagnosis of preeclampsia, expeditious administration of steroids for fetal lung maturity and appropriate antihypertensive therapy.[12] However, recent studies have confirmed that a single method cannot be clinically useful for prediction of preeclampsia. Combinations of biophysical parameters could be helpful, but more data are needed to confirm their applicability in clinical practice.

The aim of this study was to determine the effective factors that can help physician in early diagnosing of preeclampsia in nulliparous females by giving an efficient model.

MATERIALS AND METHODS

This cohort study was performed in multi-centres on 739 nulliparous females referring to Tabriz-Iran educational hospitals between March 2009 and March 2011.

Females of child-bearing age with their first pregnancy at 24-28th weeks of gestation and who were taking regular iron tablets were enrolled randomly in this study. Women with chronic hypertension, underlying disease history, drug consumption, familial history of hypertension, heart disease, chronic renal disease, chronic pulmonary disease, rheumatologic disease, thyroid disease, anaemia and polycythemia were excluded. Incidence of preeclampsia in these women was evaluated until the end of pregnancy. According to the type of study (follow-up), in order to collect enough samples, women between 24-28th weeks of pregnancy were enrolled.

After expressing the objectives and the nature of the study and after obtaining informed consent from women attending the selected clinics, a check-list was completed through interviews and by using prenatal records. This questionnaire contained information about age, education, occupation, income, weight, height, gestational age (GA) at the time of entering the study, the number of births and abortions, the hematocrit in the beginning of pregnancy and the disease history.

For each case, a record sheet was assigned, which included information on haematocrit during 24-28th weeks of pregnancy, blood pressure (BP) and the result of roll-over test in 28-32nd weeks of pregnancy and the presence or absence of the disease until the end of the study.

Development or non-development of preeclampsia in these women was determined with the gold standard, BP ≥ 140/90 mmHg, proteinuria was defined as excretion of ≥300 mg protein in a 24-h urine collection or urine dipstick +1 or greater.[13] The women were in the left lateral recumbent position; their right arm was supported at the level of the heart. After resting for 5 min, their BP was measured. When the position of subject changed from the left lateral recumbent to the supine position, after resting for 5 min, their BP was measured again. An increase of >20 mmHg in diastolic BP was considered as a positive test result. In this study, some demographic information, medical records and an inexpensive roll over screening test were used to predict preeclampsia and its risk factors.

All participants signed a written consent, and the study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (TUMS), which was in compliance with Helsinki Declaration.

Obtained data were evaluated using descriptive statistics (frequency, percentage and mean ± SD), Chi-square test or Fisher's exact test and independent samples T-test. For examine factors affecting the incidence of preeclampsia, multiple logistic regression model was used. To determine the sensitivity, specificity considering a cut of point and ROC-curve was used. $P \leq 0.05$ was considered statistically significant. The statistical software SPSS™ 17 was used for all data analyses.

RESULTS

In this study, a total of 739 pregnant women were selected to be evaluated, only 29 (3.9%) of them developed preeclampsia before labour, including 21 (72.5%) severe and 8 (27.5%) mild cases [Figure 1]. The mean maternal age, BMI, years of education and positive roll-over test were significantly higher in the preeclampsia group ($P < 0.05$) [Table 1]. However, the mean GA and changes in the levels of haematocrit were significantly higher in normotensive patients ($P < 0.05$) [Table 2]. To evaluate the factors that had an impact on this study, all significant variables were entered in a logistic regression model. Between all variables, years of education ($P < 0.001$), positive roll-over test ($P < 0.001$), GA ($P = 0.035$) and BMI ($P = 0.042$) had significant impact on developing preeclampsia [Tables 1 and 2]. Therefore, positive roll-over test, years of education and BMI had the greatest impact on developing preeclampsia, respectively. The screening model in predicting preeclampsia is given in Table 3; the receiver operating curve (ROC) and a cut-off level of 0.052 was chosen for predicting preeclampsia [Figure 2]. This model can predict preeclampsia with a sensitivity of 93% and a specificity

of 80%. Regarding area under the receiver operating characteristic curves, it was 0.90 coordinate probability between the response, and the predicted values was 90%.

DISCUSSION

Preeclampsia is a major cause of perinatal and maternal morbidity and mortality. Unfortunately, attempts to predict and prevent preeclampsia by prophylactic interventions have been unsuccessful. Therefore, it is essential to predict preeclampsia using innovative methods. In this study, the prevalence of preeclampsia was 3.9%, which is consistent with results of other studies.[14-16] In this cohort study, nulliparous women between 24-28th weeks of gestational age were enrolled. By choosing a cut-off point 0.0052 for our

model (including roll-over test, years of education and BMI) with a sensitivity of 93% and a specificity of 80%, this technique can be useful for predicting preeclampsia. Among different variables of model, positive roll-over test, years of education, employment status and BMI have the greatest impact on developing preeclampsia. These results in context of BMI are in accordance with results reported by Rudra *et al*.[17] Mittendorf *et al*., demonstrated that high level of BMI and low level of education increase the risk of developing preeclampsia by rates of 2.7 and 2, respectively.[18] However, in our study, increased level of BMI and level of education had the same effect in developing preeclampsia. Klonoff-Cohen *et al.*, reported that the prevalence of preeclampsia was higher in employed females (OR = 2.3);[19] however, in our study, the prevalence of preeclampsia in housewives were higher than in employed females (OR = 1.38). Su *et al*.,[20] investigated the role of maternal placental growth hormone at the second
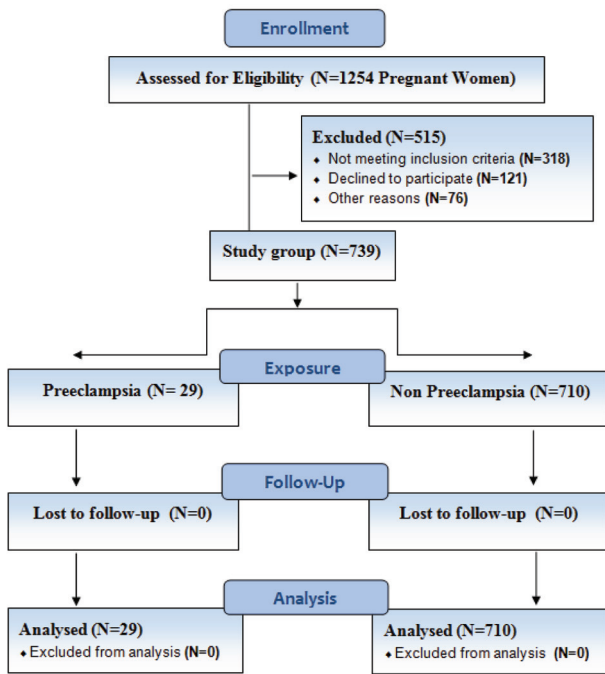
Figure 1: Flowchart of prognostic risk factors for early diagnosing of Preeclampsia in Nulliparas
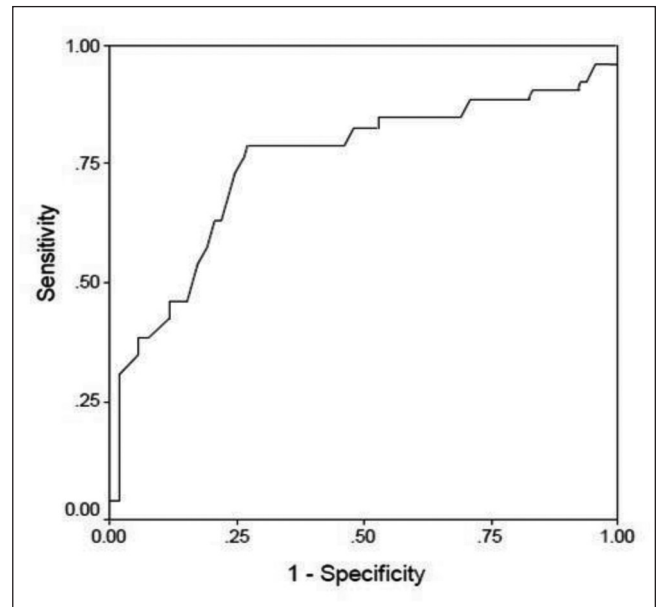
Figure 2: Receiver operator characteristic curve of the roll-over test performance in the prognosis of pregnancy-induced hypertension

Table 1: Comparison of some demographic features in two group of study

Variables	Level	Preeclampsia (*N* = 29)	Non-Preeclampsia (*N* = 710)	*P*
Age (year)		26.9±4.5	25.5±4.1	0.02[a]
Educational Level	Under diploma	11 (37.9)	392 (55.2)	0.03[a]
	Diploma or greater	18 (62.1)	318 (44.8)	
Satisfaction of Income	Satisfied	8 (27.6)	178 (25.1)	0.76[b]
	Dissatisfied	21 (71.4)	532 (74.9)	
Employment Status	Housekeeper	23 (79.3)	497 (70)	0.28[b]
	Out doors	6 (20.7)	213 (30)	
BMI (kg/m²)		32.2±3.1	27.7±3.5	0.02[a]

[a]*P* values were significant (*P* ≤ 0.05), [b]*P* values were not significant (*P* > 0.05), Data are presented as means ± SD, frequency (percentage)
BMI: Body Mass Index

Table 2: Comparison of some laboratory and gestational parameters in two group of study

Variables	Preeclampsia (*N* = 29)	Non-Preeclampsia (*N* = 710)	*P*
Gestational age (week) (at the inclusion time)	25.8±1.50	26.4±1.03	0.014[a]
Hemoglobin	13.13±1.1	13.20±1.3	0.23[b]
Hematocrit (%)	37.5±3.1	38.6±4.3	0.03[a]
Urine calcium to creatinine ratio*	0.13±0.01	0.13±0.04	0.73[b]
CRP	4.21±3.51	2.28±0.88	0.03[a]
Fibrinogen	344.21±62.5	364.2±64.2	0.29[b]
Protein	5.52±1	6.03±0.92	0.04[a]
Uric Acid (mg/dl)	5.5±1.4	4.6±1.7	0.02[a]
Roll over test result*	17 (58.6)	104 (14.6)	< 0.001[a]
Systolic Blood Pressure*	149.8±13.45	107.1±8.96	< 0.001[a]
Diastolic Blood Pressure*	94.6±8.45	68.91±11.23	< 0.001[a]

[a]*P* values were significant (*P* ≤ 0.05); [b]*P* values were not significant (*P* > 0.05); Data are presented as means ± SD; frequency and percentage; *in second trimester

Table 3: Multiple logistic regression model test result in simultaneous effects of significant variables in the study

	β coefficient	OR	%95 CI	*P* value
Age (year)	0.04	1.56	(0.98-1.94)	0.18[b]
Educational level	2.24	5.23	(1.88-11.50)	<0.001[a]
BMI (kg/m²)	0.02	1.27	(1.04-1.32)	0.042[a]
Gestational Age (week)	−0.31	0.043	(0.028-0.79)	0.035[a]
Hematocrit (%)	−0.35	0.7	(0.23-1.16)	0.47[b]
Roll over test result	2.34	9.24	(5.35-18.02)	< 0.001[a]

[a]*P* values were significant (*P* ≤ 0.05), [b]*P* values were not significant (*P* > 0.05)

trimester and prevalence of preeclampsia. They reported that maternal age and BP were significantly higher in the preeclampsia group; however, there was no significant association between BMI, GA and the time of sampling. Also, in this study, according to multiple logistic regression analysis results showed that increase in the maternal age have an impact on developing preeclampsia (OR = 1.56), and area under ROC in predicting preeclampsia was 80% with a sensitivity of 74% and a specificity of 78%. Our study demonstrated maternal age and hypertension as predictor factors in preeclampsia, and this was in accordance with Su's study.[20] In our study, increasing maternal age had lower impact on predicting preeclampsia (OR = 1.38) as compared to that in Su's study.[20] Sibai *et al*., evaluated the impact of Inhibin A and serum level of VEGF in predicting preeclampsia in women with a history of preeclampsia and chronic hypertension, and noted there was no significant correlation between these markers and preeclampsia after 37th gestational week (specificity 75% and sensitivity 38-52%), but, there was significant correlation before the 27th gestational week between preeclampsia and these markers.[21] Our combined screening model predicts preeclampsia with 93% age sensitivity and 80% specificity that show efficiency of our study. Kraemer *et al*., evaluated the mean arterial BP in the 2nd trimester and the roll-over test for gestosis screening in normal, overweight and underweight prim gravid patients and reported that early diagnosis of preeclampsia with roll-over test and mean arterial BP are not possible, but our combined model can predict preeclampsia.[22] Also, Andersen (1980) reported that roll-over test does not have enough sensitivity and specificity for predicting preeclampsia.[23] In 2011, Sohlberg *et al*., approved that short maternal stature and a high BMI increase the risks of preeclampsia of all severities.[15] The associations seem especially strong between short stature and severe types of preeclampsia and high BMI and mild types of preeclampsia. High BMI was reported as a predictive factor for preeclampsia, which correlated with the report in the Sohlberg study.[15] Syngelaki *et al*., reported BMI at 11-13th weeks of gestation as a risk factor in developing preeclampsia.[16] Also, Mehr-Un-Nisa *et al*.,[14] reported that being overweight and obesity has a major impact on developing problems in pregnancy such as preeclampsia; in our study, BMI had an effective roll in predicting preeclampsia (OR = 1.27, 95%CI: 1.04-1.32, *P* = 0.042). Despite being available and easy to perform, items in our combined model can predict preeclampsia with high sensitivity and specificity.

CONCLUSION

Combined model of maternal age, BMI, years of education and positive roll-over tests can predict preeclampsial; however, determination of these factors would be affordable for most patients and it thus a great cost-benefit option in screening programs.

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