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Prediction of Preeclampsia by Maternal Factors and Biophysical Markers During the First-trimester

Urjindelger Tserensambuu[1], Ariunbold Chuluun-Erdene[2], Munkhtsetseg Janlav[2], Erkhembaatar Tudevdorj[3]

[1]National Center for Maternal and Child Health of Mongolia; [2]Department of Biochemistry and Laboratory medicine, School of Biomedicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; [3]Department of Obstetrics and Gynecology, School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia

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Corresponding Author
Erkhembaatar Tudevdorj, MD, PhD, ScD.
Professor, Mongolian National University of Medical Sciences
Department of Obstetrics and Gynecology, School of Medicine,
Zorig street, Ulaanbaatar 14210, Mongolia
Tel: +976-9911-7590
E-mail: erkhembaatar@mnums.edu.mn

Objectives: In this study, we examined the predictive effect of maternal factors, first-trimester mean arterial pressure (MAP) and uterine artery mean pulsatility index (mUt.A-PI) on the subsequent development of preeclampsia (PE). **Methods:** Maternal characteristics and medical history were recorded and biophysical markers included uterine artery flow velocity wave forms mUt.A-PI and MAP were measured in 393 single pregnancies who getting antenatal care at 11+0-13+6 weeks. **Results:** Sixty six (16.8%) cases had preeclampsia and 327 (83.2%) cases were unaffected by preeclampsia. One hundred nineteen (30.3%) of the 393 pregnancies were nulliparous, 274 (69.7%) pregnancies were multiparous. Seventy one (25.9%) women had a history of preeclampsia in previous pregnancy and 203 (74.1%) women had no history of preeclampsia. For MAP as a predictor of PE, the cutoff point for MAP was 89.5 mmHg (sensitivity 71.2%, specificity 75.5%, J0.467, AUC 0.792, P<.001). The cutoff point of mUt.A-PI was 2.34 (sensitivity 33.3%, specificity 77.7%, J0.12, AUC-0.577, P<.001). Logistic regression analysis showed that woman who had PE previously had highest odds ratio (OR=5.81, p<0.001) for developing PE. **Conclusion:** The strongest predictor of PE was a previous history of PE. The MAP was a more accurate predictor of PE than the mUt.A-PI measurement.

Keywords: Preeclampsia, Pregnancy First Trimester, Mean Arterial Pressure, Ultrasonography Doppler Pulsed

Introduction

Preeclampsia (PE) is major cause of maternal and perinatal morbidity and mortality, particularly in developing countries [1-3]. It affects about 2-8% of pregnancies.

In Mongolia, preeclampsia and eclampsia occurred as 26.3% of pregnancy complications in 2014, 24.4% in 2015 and 24.9% in 2016 [4]. Preeclampsia and eclampsia caused 17.7% of maternal deaths between 2012 and 2015 in Mongolia [5]. Preeclampsia is a syndrome that may arise by different

pathophysiological pathways in which impaired placentation, maternal constitution, abnormal circulatory and immunological adaptation to pregnancy likely play a role [3].

Over the last decade, extensive research has been devoted to screening for preeclampsia with the aims of reducing the prevalence of the disease through pharmacological intervention in those at high risk and minimizing adverse perinatal events for those who develop PE by determining the appropriate time and place for delivery [6, 7].

Screening for markers of placentation may identify early onset PE, whereas maternal characteristics may be related to both early onset and late onset preeclampsia [8].

Several maternal characteristics are also known to be related to the risk of developing PE. Such factors are nulliparous, higher maternal age, high body mass index (BMI), PE in previous pregnancy, family history of hypertensive pregnancy disorders and chronic hypertension [9, 10].

Two biophysical tests related to pregnancy are uterine artery pulsatility index (Ut.A-PI) and mean arterial pressure (MAP). The mean Ut.A-PI shows a progressive decrease until the late stages of pregnancy [11]. Increased Ut.A-PI reflects the underlying mechanism for the development of preeclampsia which is thought to be impaired trophoblastic invasion of the maternal spiral arteries and their conversion from narrow muscular vessels to wide non-muscular channels independent of maternal vasomotor control [12].

Effective prediction of preeclampsia can be achieved at 11-13 weeks gestation by combination of maternal characteristics, mean arterial pressure, uterine artery pulsatility index, maternal serum placental growth factor (PlGF), and pregnancy-associated plasma protein-A (PAPP-A) [9].

A useful biophysical marker in screening for PE is a MAP [13, 14]. However, MAP is dependent on other characteristics, most importantly maternal weight and chronic hypertension, and for its effective use in risk assessment and screening, these covariates need to be taken into account.

The aim of our study was to examine the performance of maternal characteristics, first trimester MAP and mUt.A-PI as predictors of the subsequent development of PE.

Materials and Methods

1. Study subjects

Study participants were 429 singleton pregnant women at 11^{+0}-13^{+6} weeks, who were visiting antenatal care services for National Center for Maternal and Child Health and Health Centers of Districts of Ulaanbaatar between March 2015 and June 2017.

Data were gathered prospectively. Exclusion criteria were multiple pregnancies high risk for an euploidy, and lower than 45 mm and higher than 84 mm for crown-lump length (CRL).

Written informed consent was obtained from study participants. The study was approved by the Ethics Committee of Mongolian National University of Medical Sciences.

2. Patient characteristics

Patient characteristics included maternal age, method of conception (spontaneous/in-vitro fertilization), cigarette smoking during pregnancy (yes/no), medical history (including chronic hypertension, kidney diseases, diabetes mellitus, systemic lupus erythematosus), family history of PE in the mother of the patient (yes/no) and obstetric history including parity (multiparous/nulliparous if no previous pregnancies at or after 24 weeks), previous pregnancy with PE (yes/no), and interval in years between the birth of the last child. Maternal height and weight were measured and the body mass index was calculated using kg/m^2 formula.

3. Biophysical markers

Blood pressure measurements were obtained using automated blood pressure measurement machines (HEM-7120, Omron, Japan). Measurements were obtained with the women in the sitting position with their arms supported at the level of the heart using a normal (22 to 32 cm) adult blood pressure cuff. After rest for three to five minutes, two recordings of blood pressure were made in both arms simultaneously. The MAP was calculated from the formula MAP, where DP represents diastolic blood pressure and SP- systolic blood pressure. We calculated the final MAP as the average of all four measurements.

Trans-abdominal and trans-vaginal ultrasound (Voluson E8, GE, USA) examination were carried out for measurement of fetal CRL, biparetial diameter (BPD), heart rate (HR), nuchal thickness (NT) and Ut.A-PI. For the Doppler studies, a sagittal section of the uterus was obtained, and cervical canal and internal os were identified. Subsequently, the transducer was gently tilted from side to side and color flow mapping was used to identify each uterine artery along the side of the cervix and uterus at the level of the internal os. Pulsed wave Doppler imaging was used with the sampling gate set at 2 mm to cover the whole vessel and care was taken to ensure that the angle of insonation was less than 30^0. When three to five similar consecutive uterine artery waveforms had been obtained the velocity was measured. The mean Ut.A-PI for the left and right arteries were calculated as follows Ut.A-PI = uterine artery systolic velocity –uterine artery diastolic velocity / mean uterine artery velocity.

All ultrasound and Doppler studies were carried out by the doctor who had received the appropriate Certificate of Competence in the 11^{+0} - 13^{+6} week scan from the Doppler of The Fetal Medicine Foundation (http://www.fetalmedicine.com) [15]. Data on pregnancy outcome were prospectively collected from the hospital maternity records or from the patients.

4. Statistical analysis

Data analyses were performed using SPSS 21.0 (IBM corporation, USA). Continuous data were represented as mean±SD. Statistical significance was evaluated by t-test to compare the preeclampsia and unaffected groups, while Mann-Whitney test was used for variables not normally distributed. Categorical variables were compared using Chi-square test. Spearman correlation test was used to determine the relationship between biophysical markers MAP, mUtA-PI and gestational age. The biophysical markers for preeclampsia were assessed using receiver-operating characteristics (ROC) curves. Multiple logistic regression analysis was performed to assess the effect of the maternal and pregnancy characteristics on the development of preeclampsia. Differences were considered statistically significant when $p<0.05$.

5. Outcome measures

Preeclampsia was defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg on at least two occasions, 4 hours apart, after 20 weeks gestation in a previously normotensive woman with proteinuria of 300mg or more in 24 hours or two readings of at least ++ on dipstick analysis of midstream urine specimens.

Results

Data were collected for 429 singleton pregnancies. We excluded 36 cases because they had missing data (n=27), or the pregnancy resulted in miscarriage or was terminated (n=9). The maternal and pregnancy characteristics of the study population are summarized in Table 1.

In the study population, 66 (16.8%) cases experienced preeclampsia and 327 (83.2%) cases were unaffected. One hundred nineteen (30.3%) of the 393 pregnancies were nulliparous. Of the 274 (69.7%) pregnancies for which PE data were available, 71 (25.9%) women had a history of preeclampsia during a previous pregnancy and 203 (74.1%) women had no history of preeclampsia. Correlation analysis showed that mUt.A-PI was significantly negative related with gestational age (r=-0.172, p=0.001), while MAP had no significant correlation with gestational age (Table 2).

Using the criteria for preeclampsia defined by International Society for the Study of Hypertension in Pregnancy (ISSHP), we divided the study population into two groups: preeclampsia and unaffected groups.

The women who developed preeclampsia were significantly older, nulliparous, heavier, more frequently smoked and had higher MAP and mUt.A-PI measurements. Their babies were delivered at a lower gestational age and had lower birth weights.

The utility of MAP and mUt.A-PIfor determining who would develop PE was assessed by ROC curves (Figure 1, 2). The best Youden's index and area under curve (AUC) for MAP in Figure 2 and mUt.A-PI as a predictor of PE were shown in Figure 3. The chosen cutoff point for MAP was 89.5 mmHg (sensitivity-71.2%; specificity-75.5% J-0.467; AUC-0.792; P<0.001). The cutoff

Table 1. Maternal and pregnancy characteristics in the screening population

Characteristics	Mean ± SD, N (%)
Maternal age (years)	33.4±6.0
Gestational age (weeks)	12.3±0.6
Maternal weight (kg)	63.2±10.8
BMI (kg/m^2)	24.3±3.9
<18.5	14 (3.6)
18.5-24.99	232 (59.0)
25.00-29.9	107 (67.2)
>30	40 (10.2)
Medical history	
Chronic hypertension	20 (5.1)
Renal disease	40 (10.2)
Diabetes I type	3 (0.8)
Lupus erythematosis	2 (0.5)
Normal	294 (74.8)
Other	34 (8.7)
Previous preeclampsia	
Yes	71 (25.9)
No	203 (74.1)
Family history of PE	
Yes	33 (8.4)
No	299 (76.1)
Unknown	61 (15.5)
Parity (n, %)	
Nulliparous	119 (30.3)
Parous	274 (74.1)
Preeclampsia	
Yes	66 (16.8)
No	327 (83.2)
Birth weight (gr)	3441.1±503.5
GA at delivery (weeks)	39.0±1.5

Values are indicated as mean±standart deviation; BMI, body mass index;PE, preeclampsia; GA, gestational age.

Table 2. Correlations among biophysical markers and gestational ages.

	MAP	mUtA-PI	Gestational age
MAP	1		
mUtA-PI	-0.004	1	
Gestational age	0.032	-0.172*	1

mUtA-PI, mean uterine artery pulsatility index; MAP, mean arterial pressure; *p<0.05

Table 3. Maternal and pregnancy characteristics according to study group

	Preeclampsia (n=66)	Unaffected (n=327)	p-value
Maternal age (year)	36.1±5.6	32.8±5.9	<0.001
BMI (kg/m^2)	26.7±4.1	23.8±3.7	<0.001
Smoking (yes/no)	11/54	39/288	<0.001
Parity (nulliparous/parous)	15/88	45/214	<0.001
MAP (mmHg)	94.05 ±9.05	84.55±8.15	<0.001
mUt.A-PI	2.16±0.55	2.0±0.50	0.019
GA at delivery (weeks)	38.0±1.8	39.0±1.4	<0.001
Birth weight (gr)	3283.63±633.19	3472.92±467.86	0.005

BMI, body mass index; MAP, mean arterial pressure; mUtA-PI, mean uterine artery pulsatility index; GA, gestational age;

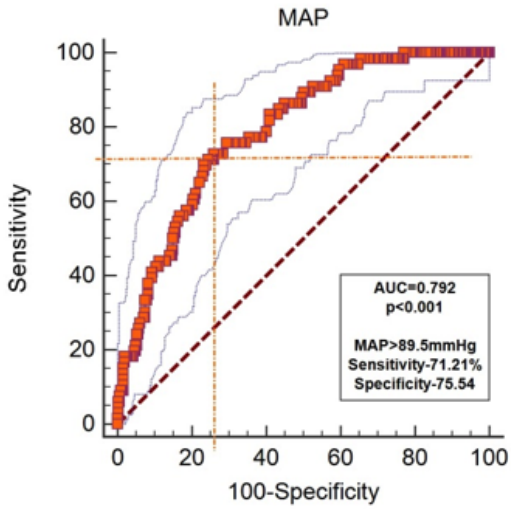

Figure 1. ROC curves for MAP as a predictor of PE. The cutoff points were illustrated by intersection of dotted lines.

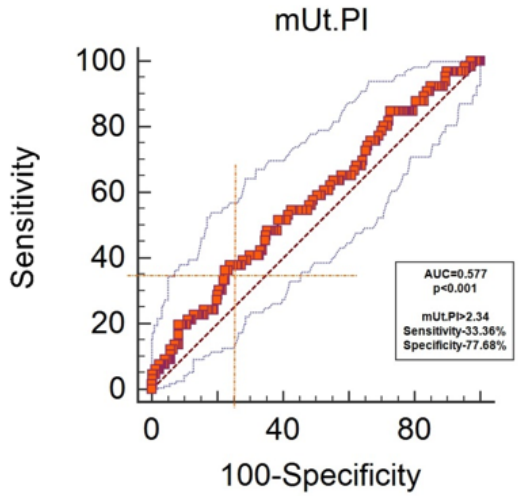

Figure 2. ROC curves form Ut.A-PI as a predictor of PE. The cutoff points were illustrated by intersection of dotted lines.

Table 4. Independent risk factors for development of preeclampsia at first trimester.

Risk factors	OR (95% CI)	p-value
Previous PE	5.81 (3.27-11.16)	<0.001
Chronic hypertension	7.06(2.79-17.84)	<0.001
Obesity	3.87 (1.89-7.92)	<0.001
Birth interval>10years	2.08 (1.03-4.19)	0.033
Renal disease	1.76 (0.81-3.82)	0.143
Smoking	1.05 (0.72-3.12)	0.270

OR, Odds ratio; 95% CI, confidential index; PE, preeclampsia.

point for mUt.A-PI was 2.34 (sensitivity-33.3%; specificity-77.7% J-0.12; AUC-0.577; P<0.001).

Independent risk factors influencing to the development PE were evaluated by logistic regression analysis (Table 4). Pregnant women with a history of PE (p<.001), chronic hypertension (p<.001), birth interval greater than 10 years (p<.033) and obesity (p<.001) had a higher risk for development of PE compared to the unaffected group.

Discussion

In the last 20 years throughout most developed and developing countries it has become evident that by 11-13 weeks of gestation maternal characteristics data, biophysical findings and biochemical tests can be combined to define the patient-specific risk for a wide spectrum of pregnancy complications, including fetal abnormalities, miscarriage, still birth, preeclampsia, preterm delivery, gestational diabetes, fetal growth restriction and macrosomia [16]. In Mongolia, screening for Down syndrome using maternal and pregnancy characteristics, free-beta hCG, PAPP-A and nuchal thickness (NT) has been carried out since 2012. However, preeclampsia was only screened for by using maternal history, maternal systolic and diastolic blood pressures and clinical symptoms. This study sought to determine the utility of screening for preeclampsia using MAP and the uterine artery Doppler ultrasound pulsatility index.

The findings of this study are consistent with the few studies that report the development of preeclampsia linked to a first-trimester increase in uterine artery PI and MAP and a decrease in serum PLGF and PAPP-A, by using mini-combined test [17].

According to Pilalis A, Souka AP, Antsaklis P et al. abnormal uterine artery Doppler ultrasound was the sole predictor of placental abruption, achieving an impressive detection rate of about 43% for a 5% positive screening rate [18]. In our study, there were no cases of placental abruption.

The studies conducted by Martin et al., Parra et al., and Gomez et al. on a total of 4993 patients at 11-14 weeks reported an overall 25% sensitivity for predicting preeclampsia, improving to about 60% for early onset severe disease, at a 5% cut-off [19-21]. In our study the sensitivity of mUt.A-PI was 33.3%, specificity was 77.7%. In the study by Pilaliset al., using the combination of uterine artery PI and maternal history of preeclampsia better predicted the development of PE than using uterine artery Doppler alone [18]. While, in our study, in the group which developed preeclampsia group had a significantly higher mUt.A-PI (p<0.05), compared with the unaffected group.

The meta-analysis of Cnossen et al. from 2008, which included more than 60000 women with 3300 cases of PE, showed that MAP was more predictive of PE among low-risk women in the first or second trimester than either systolic or diastolic readings alone [22]. Other research has show that maternal characteristics integrated with biophysical markers i.e. first trimester MAP and Ut.A-PI are a strong tool to predict PE in the first trimester [23]. Moreover, incorporation of maternal characteristics and first trimester MAP resulted in a higher detection rate, which is in line with other publications [22]. Also, MAP is linked to the maternal vascular adaptation and maternal characteristics that determine the susceptibility of the mother [23]. According to the study by Leona et al. predicting the development of preeclampsia was based 43.3% based on history alone, 37.5% for MAP alone and 62.5% for combined testing. In our study, the detection rate of preeclampsia was 71.2% (AUC=0,792, p<0.001). Furthermore, in our study, in the preeclampsia group the MAP was considerably higher (94.0±59.05; 84.55±8.15; p<.001) compared to the unaffected group.

Effective early identification of the high-risk group for subsequent development of preeclampsia could potentially improve outcomes by directing high-risk patients to specialty clinics for close surveillance and could be the basis for future studies investigating the potential role pharmacological interventions, such as aspirin beginning in the first trimester, to improve placentation and reduce the prevalence of the disease. Recent evidence suggests that the prophylactic use of low-dose aspirin started in early pregnancy can potentially reduce the incidence of preeclampsia by 50% [6].

There is significant correlation between MAP and uterine artery PI in PE and unaffected pregnancies. Therefore, when combining these two biophysical markers in calculating the patient specific risk for PE, the analysis needs to partition the effect of each factor as well as their interaction to accurately assess the risk of developing PE. Estimated Detection Rate (DR) of PE requiring delivery before 34, 37 and 42 weeks gestation by screening for maternal factors and biophysical markers are 80, 55 and 35%, respectively, at False Positive Rate (FPR) of 5% and 90.72 and 57% respectively at FPR of 10% [24].

Risk for developing PE increased with obesity (BMI>30) by a factor of 3.87 (1.89 – 7.92) (OR 95%CI) and the finding that a family member was diagnosed with PE history were increased by 5.81 fold (OR 95% CI). According to Duckitt et al., the risk of developing PE increased by 7-fold and 3-fold in women with respective personal and family history of the disease [25].

Early identification of high-risk groups should also stimulate further research that will define the best protocol for their follow-up and development of strategies for the prevention of disorders of pregnancy or their adverse consequences [16].

Furthermore, an early assessment of the risk for preeclampsia could be undertaken at around 12 weeks gestation at the same time the risk of trisomy 21 in assessed in Mongolia. This would simply require uterine artery Doppler ultrasound in addition to PAPP-A serum test that is now widely performed in Mongolia.

In conclusion, our study shows that the sensitivity of MAP for preeclampsia was 71.2% (AUC=0,792 p<.001), while that form Ut.A-PI was 33.3%. Hence, detecting the risk of preeclampsia by MAP was more accurate than the systolic and diastolic reading alone. MAP measurement can be easily obtained using readily available equipment and is cost effective, but we need to extend the knowledge that MAP is a strong predictor of preeclampsia to primary health professionals.

Limitations of this study include the relatively low number of participants (393) compared to other studies in European countries. Our study will be continued by evaluating biochemical markers like PAPP-A and PlGF in case controls study between PE affected and unaffected groups.

Conflict of Interest

The authors declare that they have no competing interests.

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