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Research Article

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Assessment of Uterine Artery Doppler Ultrasound, Mean Arterial Blood Pressure and Maternal Serum PAPP-A during 11-13 Gestational Weeks to Predict Hypertensive Disorders in Pregnancy

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ABSTRACT

Early diagnosis of gestational hypertensive disorders can effectively reduce fetal-maternal mortality and morbidity. This study was designed to assess three screening methods including uterine artery Doppler ultrasound, mean arterial blood pressure (MAP), and maternal serum PAPP-A in the first trimester for predicting gestational hypertensive disorders. This was a prospective and observational study which conducted on the 300 singleton pregnant women at 11-13 weeks. All patients underwent three screening methods including UA-PI, MAP, and PAPP-A. Characteristics information and medical history of all cases were recorded. All participants were followed during pregnancy to detect any occurrence of hypertensive disorders. From 300 singleton pregnant women, 26 (8.7%) cases showed hypertensive disorders which6 (2%) cases had early preeclampsia (before 34th weeks), 9 (3%) cases had late preeclampsia (after 34th weeks), and 11 (3.7%) cases had GHTN. Comparison between preeclampsia and GHTN groups with normal pregnant women showed that MAP and UA- PI increased, while PAPP-A decreased. The cut-off point of 2.35 in uterine PI showed specificity of 93.9% and sensitivity of 83% in predicting early PE. While the cut-off point of 2.1 had specificity of 83.7% and sensitivity of 100%. Finally, according to our results the cut-off point of 2.1 for UA-PI had the highest sensitivity in predicting hypertensive disorders and PAPP-A had lower efficiency. Combination of UA-PI, MAP, and PAPP-A was useful screening methods for predicting hypertensive disorders especially early preeclampsia in the first trimester.

Keywords: Pregnancy-induced hypertension, Uterine artery, Pregnancy-Associated plasma Protein-A, Biochemical screening, Biophysical screening, first trimester

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INTRODUCTION

Hypertension disorders complicate 5-10% of all pregnancies; and along with hemorrhage and infection accounts for third leading cause of maternal mortality (1). Pregnancy induced hypertension is characterized by blood pressure of 140/90 or greater, and will back to normal up to 12 weeks after delivery. Hypertension in pregnancy is termed as preeclampsia if it is associated with proteinuria. Preeclampsia (PE) is divided in two types, early preeclampsia (between 20-34 weeks of gestation) and late preeclampsia (>34th week of gestation). Fetal-maternal mortality and morbidity are more prevalent for early preeclampsia (2).

Although the cause of preeclampsia still remains unknown, its manifestation begins early in pregnancy with covert pathophysiological changes. These changes continue across gestation and eventually become clinically apparent. Ultimately, it can be result in multi-organ involvement and life threatening for both mother and fetus (1).

Various factors have been proposed for predicting gestational hypertension which are biochemical and biophysical markers, or combination of them (3). Biochemical markers reflect fetal-placental endocrine and endothelial dysfunction. These markers include placental protein 13, pregnancy associate plasma protein- A (PAPP-A), Inhibin A and Activin A which belong to β-growth factors family, antigenic and inflammatory factors (4, 5). Normal placenta requires endovascular trophoblastic invasion to maternal decidua, myometerium and blood vessels. Whenever the elastic muscular wall is lost from the spiral arteries; then, low resistance blood can be diffused into intervillous space. This mechanism begins in the early of first trimester and almost ends in the last days of the middle trimester. Abnormal placenta is developed by insufficient placental-fetal blood circulation. Doppler ultrasound is used to determine increased uterine artery velocimetry or to indirect evaluation of trophoblast invasion of the spiral arteries. Histopathological evidences have identified the reduced endovascular trophoblastic invasion and the increased uterine artery resistance indices.

The most common indices in blood flow velocimetry are Palsatility index (PI), Resistance index (RI), and Notching. Transabdominal ultrasound is used to measure the uterine artery PI of the ascending branch of the uterine artery at the level of the apparent crossover with the external iliac arteries. There is an association between increased resistance to the flow in uterine artery and presence of PE and/or intrauterine growth restriction (6). Incidence of PE, intrauterine growth restriction, emergency caesareans, placenta abruption and less harmful consequences for fetal-neonatal are reported to be higher in women with hypertension, increased impedance (the resistance index), and/or early diastolic notch in compare to women with hypertension but normal uterine artery waveforms. Although, PE is much more than simply gestational hypertension with protienuria; so it cannot be predicted or diagnosed by single test. Combining of two or more markers seems to be an effective method to provide a more certain PE prediction. Although the cause and pathophysiology of PE still remain unknown, a variety of strategies used to prevent or modify preeclampsia (7).

This study was designed to evaluate three screening methods including PAPP-A, UA-PI, and MAP for predicting hypertensive disorders in pregnant women.

MATERIALS AND METHODS

This was a prospective study which conducted on the 300 singleton pregnant women in 2013. Pregnant women who were referred to first trimester screening to prenatal clinic in Imam Khomeini hospital (a tertiary, general, referral, and university affiliated hospital), Ahvaz, Iran.

Bilateral uterine Doppler ultrasonography, measurement of arterial blood pressure from bilateral upper-limb, and maternal serum PAPP-A were performed. Maternal blood pressure was measured following a period of maternal rest for at least 10 min; this involved being seated and making two measurements at the level of the heart of systolic and diastolic blood pressure for each arm, and mean arterial pressure was then calculated. Maternal blood pressure was recorded by trained staff using an automated devise. Maternal serum PAPP-A was measured as part of the first trimester screening program. The samples were taken at the time of the first trimester ultrasound visit and analyzed using a Siemens Immulite assay (Immulite XPi; Diagnostic products Corporation, Siemens Medical Solutions Diagnostic, Tarrytown, NY, USA). The raw data were converted to a Multiple of Median (MoM) value.

Characteristics information (BMI, age, smoking, Parity) and medical history of hypertensive disorders were collected. Multiple of the Median (MOM) was used for representing the results of uterine artery PI, maternal serum PPAP-A, and MAP. Sensitivity and specificity of different cut-off points for uterine artery PI, PPAP-A, and MAP were presented. Then, the best cut-off point for predicting early PE, late PE, and GHTN were chosen.

All participants were followed-up during pregnancy to detect any incidence of hypertensive disorders.

All the patients that include the study had singleton pregnancies at 11-14 weeks of gestation (based on Last Menstrual Period). Women who presented with multiple pregnancies were excluded. All participants fully completed the study (we had not any missing data). In addition, All 300 patients were followed-up during pregnancy

to detect any incidence of hypertensive disorders. Ethical approval was gained from the Ethics Committee of the Department of Obstetrics and Gynecology. The experimental procedures of this study were approved by the ethic committee of Ahvaz Jundishapur University of Medical Sciences (ajums.REC.1392.29". Participants' informed consent was gained; voluntary participation and confidentiality were guaranteed.

The analysis was carried out with SPSS version 17. Receiver operating characteristic **(**ROC**)** curve was used to select optimal cut-off and to compare efficiency of different predictors. Statistically significant difference was indicated at significance level (P-Value) of 0.05.

RESULTS

This study was conducted on 300 singleton pregnant women in 11-13 weeks of gestation. The mean ± SD age of participants was 27 ± 4 years old and their mean ± SD BMI was 24 ± 2.5. 26 (8.7%) cases had hypertension disorders consisting of 6(2%) cases with early PE, 9(3%) cases with late PE, and 11(3.7%) cases with GHTN.

Maternal previous hypertension and BMI greater than 25 were significantly correlated with gestational hypertension disorders (p=0.001), while age and parity had not significant correlation with gestational hypertensive disorders individually. Table1 shows MoM results of MAP, UA-PI, and PAPP-A in different pregnancy hypertensive disorders. Increasing of MAP and uterine artery PI had been observed, while PPAP-A decreased in early and late PE as well as GHTN.

Table1. MoM results of MAP, UA-PI, and PAPP-A in different pregnancy hypertensive disorder

	MAP		UA-PI		PAPP-A	
	MOM	mmHg	MOM	unit	MOM	Mu/l
Normal	0.92-1.15	70-88	0.44-1.23	0.75-2.10	1.00-1.50	1.90-285
Early preeclampsia	1.18-1.26	89-96	1.52-2.17	2.6-3.7*	0.38-0.84	0.73-1.6
Late preeclampsia	1.08-1.18	83-91	1.23-1.45	2.1-2.48*	0.63-1.18	1.2-2.25
GHTN	1.01-1.23	78-93	1-1.23	1.7-2.1*	0.76-1.13	1.45-2.15

MAP: Mean Arterial blood Pressure,
UA-PI: Uterine Artery Pulsatility Index,
PAPP-A: Pregnancy-Associated Plasma Protein-A,
MoM: Multiples of Median,
*Significant correlations are indicated by **

Specificity and sensitivity of each screening method alone and in combination with other method were calculated and presented in tables 2. Figures 1 represent receiver operating characteristic **(**ROC**)** curve to compare efficiency of different predictors.

Table 2. Specificity and sensitivity of univariate and multivariate predictors early PE

	Early Preeclampsia						
	UA-PI	MAP	PAPP-A	A	B	C	D
Cut-off point	>2.35	>78.5	>1.6	>1.73	>-0.193	>1.45	>1.7
P value	0.000*	0.279	0.208	0.004*	0.150	0.000*	0.000*
Sensitivity	83.3	66.7	66.7	83.3	66.7	83.3	83.3
Specificity	93.9	66.3	30	95.6	45.6	95.6	95.6
Overall accuracy	93.7	97.3	26.2	95.7	17.3	91.7	95.4

A: UA-PI + MAP + PAPP-A,
B: MAP + PAPP-A,
C: PAPP_A + UA-PI,
D: MAP + UA-PI;
*Statistically significant values are indicated by *.*

Figure 1. ROC Curve for predicting early PE

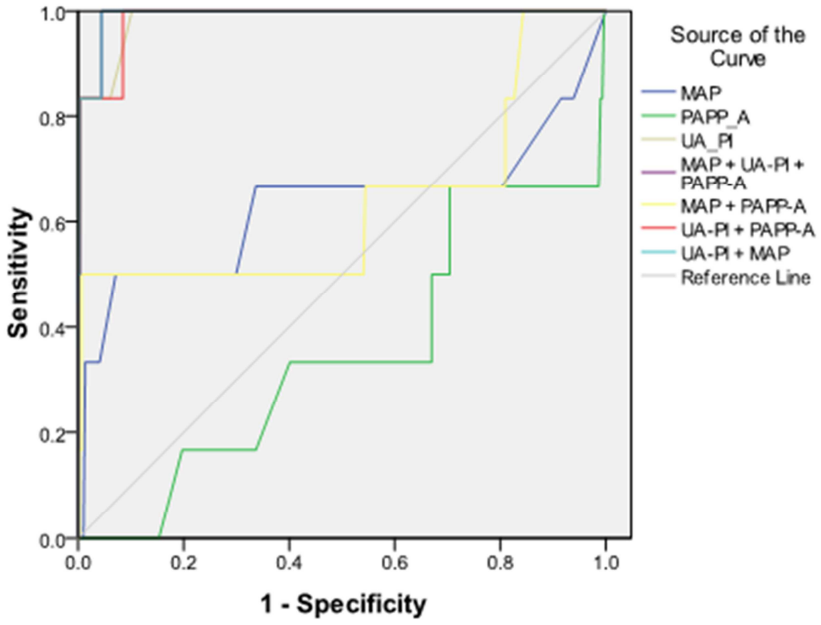
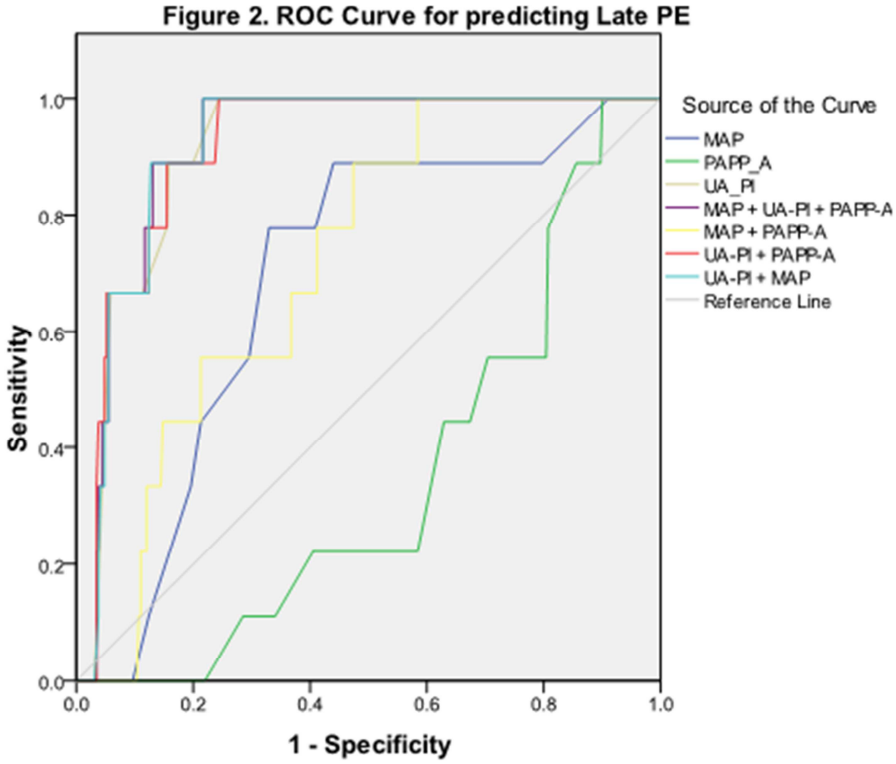


Figure 2. ROC Curve for predicting Late PE



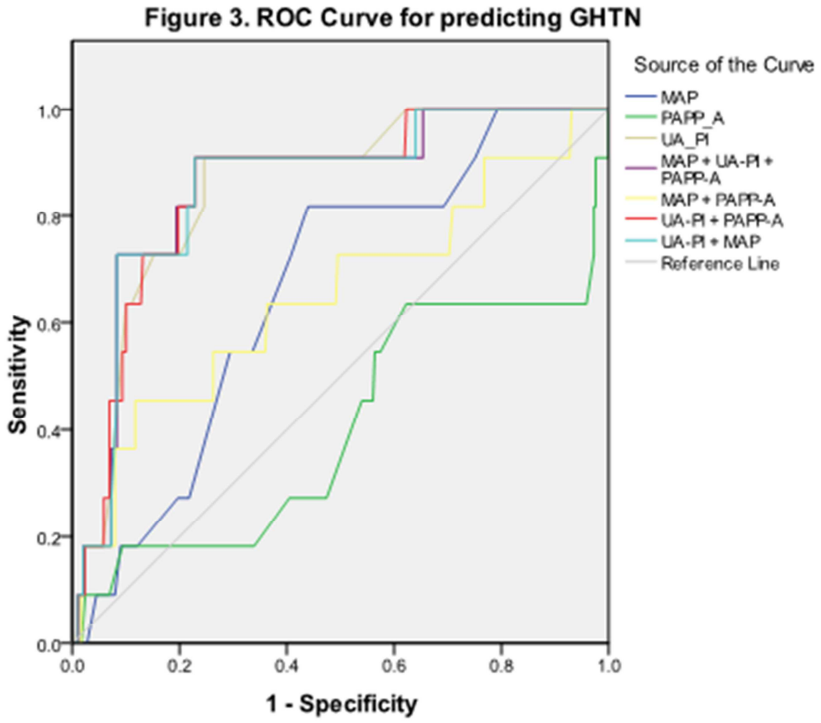


Table 3. Specificity and sensitivity of univariate and multivariate predictors of late PE

	Late Preeclampsia						
	UA-PI	MAP	PAPP-A	A	B	C	D
Cut-off point	>2.35	>79.5	>1.7	>1.59	>2.44	>1.59	>1.65
P value	.000*	.052	.120	.000*	.028*	0.000*	0.000*
Sensitivity	66.7	55.6	44.4	66.7	55.6	55.6	55.6
Specificity	90.2	70	33	94.5	63.2	94.8	94.5
Overall accuracy	90.3	95	26	93.3	18.3	90.7	93

A: UA-PI + MAP + PAPP-A,
B: MAP + PAPP-A,
C: PAPP_A + UA-PI,
D: MAP + UA-PI;
*Statistically significant values are indicated by *.*

Table 4. Specificity and sensitivity of univariate and multivariate predictors of GHTN

	GHTN						
	UA-PI	MAP	PAPP-A	A	B	C	D
Cut-off point	>2.35	78.5>	>1.9	>1.39	>1.42	>1.50	>1.46
P value	.000*	.067	.277	.000*	.113	0.000*	0.000*
Sensitivity	27.3	54.5	27.3	45.5	27.3	36.4	27.3
Specificity	93.1	66.4	52	92.7	92	93.1	92.7
Overall accuracy	90.7	57	26.7	91.3	18.3	89.3	91

A: UA-PI + MAP + PAPP-A,
B: MAP + PAPP-A,
C: PAPP_A + UA-PI,
D: MAP + UA-PI;
*Statistically significant values are indicated by *.*

DISCUSSION

The purpose of this study was to evaluate efficiency of PAPP-A, mean uterine artery pulsatility index (UA-PI), mean arterial blood pressure (MAP), and combination of them for early predicting of gestational induced

hypertensive disorders. Most importantly, our results are consistent with evidences reported in the previous studies (8-12). According to our findings, low level of PAPP-A at 11-13 weeks' gestation was associated with higher risk of pregnancy induced hypertensive disorders, especially early preeclampsia, but the mean value was not statistically significant in compare to late preeclampsia and GHTN. Pertaining to uterine artery PI and MAP parameters, we observed their higher values had significant relation with early PE in compare to late PE and GTTN. The findings of Akolekar and et al. (2011) have shown sensitivity of 91%, 79.4%, and 60.9% for predicting early PE, intermediate, and late PE respectively, when used maternal serum, biophysical, and biochemical markers (11).

In the present study, the cut-off point of 2.35 of uterine artery PI showed specificity of 93.9% and sensitivity of 83% for predicting early PE. While the cut-off point of 2.1 had specificity of 83.7% and sensitivity of 100%. Therefore, the cut-off point of 2.1 had a better sensitivity (100% vs 83.7%) compared to cut-off point of 2.3 of uterine artery PI. The cut-off point of 2.1 of uterine artery PI for predicting late PE and GHTN had sensitivity of 88.9% , 72% respectively, which was less sensitive compared with predicting early PE.

With cut-off point of 2.3 of PAPP-A and MAP to predict early PE disorder had sensitivity of 66.7%, 66.7% respectively. In cut-off point of 2.1, uterine artery PI was with high sensitivity to predict pregnancy induced hypertensive disorders. Findings of Poon et al.'s study support our results regarding combination of three tests. They observed that these three tests had 5% false positive with sensitivity of 88.5% in predicting early PI, 46.7% in predicting late PI, and 35.5% in predicting GHTN (13). While in our study we found sensitivity of 83.3%, 66.7%, and 45.5% in predicting early PE, late PE, and GHTN respectively.

CONCLUSION

This study provides evidence that uterine artery PI, PAPP-A, and MAP were useful in predicting pregnancy induced hypertensive disorders, especially early PE. Among three tests uterine artery PI had highest efficiency and PAPP-A had poor effect in predicting these disorders. With consideration that preeclampsia is the common disorder related with fetal-maternal morbidity and mortality, early predicting of preeclampsia can reduce its complications. Therefore, we suggest that pregnant women with preeclampsia would be managed by experienced perinatalogist and gynecologist. Trend of research can be guided to improve pathophysiological and cure knowledge of pregnancy induced hypertensive disorders.

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