

Second-Trimester Uterine Artery Doppler Ultrasound in Prediction of Pre-Eclampsia

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Citation: Hussien N and El Refaey MH (2019) Second-Trimester Uterine Artery Doppler Ultrasound in Prediction of Pre-Eclampsia. Arch Women Heal Gyn: 114.

Received Date: 05 November, 2019; **Accepted Date:** 11 November, 2019; **Published Date:** 18 November, 2019

Abstract

Objective: The aim of this study is to assess the predictive value of uterine artery Doppler velocimetry measured between 18-22 weeks of gestation in prediction of pre-eclampsia.

Methods: All included women were primigravidae, pregnant at gestations between 18 – 24 weeks. For all included women, bilateral uterine artery Doppler velocimetry was performed, for observation of presence or absence of bilateral persistent diastolic notch, and measurement of the pulsatility index (UA-PI) were noted for included women. A high UA-PI was defined when its value is above the 95% percentile for gestational age. Included women were regularly followed up at the antenatal clinic.

Results: A total of 279 primigravid women were included in the analysis. Of the included 279 women, 32 (11.5%) developed preeclampsia; of them, 15 (5.4%) had severe preeclampsia, and 9 (3.2%) had early-onset preeclampsia (< 32 weeks of gestation). ROC curves showed that UA-PI was significant predictor for development of pre-eclampsia, severe pre-eclampsia and early-onset pre-eclampsia. Presence of high UA-PI and persistent diastolic notch were significantly highly accurate predictors of development of pre-eclampsia [sensitivity: 71.9% and 87.5%, specificity: 91.1% and 95.5%, respectively and respectively], development of severe pre-eclampsia [sensitivity: 80.0% and 93.3%, specificity: 87.5% and 90.9%, respectively and respectively], and development of early-onset pre-eclampsia [sensitivity: 88.9% and 100%, specificity: 86.3% and 89.3%, respectively and respectively].

Conclusion: High UA-PI and presence of persistent diastolic notch are significant predictors of pre-eclampsia, severe pre-eclampsia and early-onset pre-eclampsia.

Keywords: Pre-eclampsia-uterine artery Doppler ultrasound-pulsatility index-persistent diastolic notch.

Introduction

Pre-eclampsia is a pregnancy-unique condition, which can occur in the second half of pregnancy, and is characterized by hypertension plus proteinuria, thrombocytopenia, elevated liver enzymes, impaired kidney function or neurological complications [1]. The hall landmark of the pathophysiology of pre-eclampsia is multi-organ endothelial dysfunction, and the main underlying pathogenic mechanism of pre-eclampsia is around the abnormal trophoblast invasion in early pregnancy [2-4]. Pre-eclampsia hangs on top of the list of high-risk pregnancy conditions and is associated with grave maternal and perinatal morbidity and mortality [5-8]. Prediction of women who are at a higher risk of development of pre-eclampsia is essential in prevention or even containing the risks associated with such disease. Frequent and close antenatal monitoring of such women plus early referral and delivery at tertiary or even well-prepared centers can lessen the morbidity and mortality risks of both mothers and neonates [8]. Abnormal or incomplete trophoblast invasion during the implantation process leads to formation of high-resistance spiral arteries

which causes increased resistance to uterine arteries, then can be measured in the mid-pregnancy interval [9]. Several previous studies have showed the association between high uterine artery resistance measured by Doppler ultrasound in the mid-trimester of pregnancy and subsequent development of pre-eclampsia [11-13]. The aim of the current study is to examine such an association in a group of primigravid Egyptian women.

Methods

This diagnostic test accuracy study was conducted at Tanta University hospital, Obstetrics and Gynecology Department, in the period from April 2017 to April 2018. The study protocol had been approved by the Ethical Committee of Tanta University Department of Obstetrics and Gynecology. All included women signed informed consent before participating in the study. All included women were primigravidae, pregnant at gestations between 18-24 weeks. Women with preterm rupture of the membranes, fetal congenital malformations, or fetal demise; as well as women with chronic hypertension, chronic kidney disease, chronic collagen disease (e.g. systemic lupus erythematosus) or known hereditary or acquired thrombophilia were not included in the study. For all included women, bilateral uterine artery Doppler

velocimetry was performed by one of three at-least-3-year-expert sonographers on a single ultrasound machine [SonoAce Medison® X6 Ultrasound Machine, Samsung®, South Korea] at the Fetal Care Unit, Ain Shams University Maternity Hospital. Both observation of presence or absence of bilateral persistent diastolic notch, and measurement and calculation of the pulsatility index (UA-PI) were noted for included women. A high UA-PI was defined when its value is above the 95% percentile for gestational age. Included women were regularly followed up at the antenatal clinic. Women who had a systolic blood pressure ≥ 140 mm Hg and a diastolic blood pressure ≥ 90 mm Hg on two occasions at least 6 hours apart, were defined to have hypertension with pregnancy. Women who had hypertension plus any of the following: significant proteinuria ($\geq 1+$ by dipsticks, ≥ 0.7 mg/mg urinary protein-to-creatinine ratio, or total 24-hour urinary protein ≥ 500 mg), elevated liver enzymes (≥ 2 folds), elevated serum creatinine (double the baseline value or ≥ 1.1 mg/dl) or thrombocytopenia (platelet count $< 100,000$ per cmm) were diagnosed to have pre-eclampsia. Severe pre-eclampsia is defined when hypertension is severe (systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg), end-organ affection, or complication is present (pulmonary edema, cerebral hemorrhage or eclampsia). Early-onset pre-eclampsia was defined when it developed before 32 weeks of gestation.

Statistical Analysis

Statistical analysis was performed using MedCalc® version 19. Association between high UA-PI or persistent diastolic

notch, and development of pre-eclampsia was presented in terms of risk ratio (RR) and its 95% confidence interval (95% CI). The predictable validity of UA-PI for development of pre-eclampsia was estimated using receiver operator characteristics (ROC) curves. The validity of high UA-PI and persistent diastolic notch in prediction of pre-eclampsia was presented in terms of sensitivity, specificity, positive and negative predictive values, along with their 95% CIs. Significance level was set 0.05.

Results

A total of 279 primigravid women were included in the analysis. The mean age of included women was 27.25 ± 5.2 years (range: 18 – 36 years). The mean body mass index (BMI) was 30.97 ± 5.73 kg/m² (range: 19.38 – 45.65 kg/m²). The mean gestational age at recruitment was 20.3 ± 1.42 weeks (range: 18 – 22.86 weeks). Of the included 279 women, 32 (11.5%) developed preeclampsia; of them, 15 (5.4%) had severe preeclampsia, and 9 (3.2%) had early-onset preeclampsia (< 32 weeks of gestation). The mean UA-PI measured at recruitment in included women was 1.39 ± 0.17 (range: 1.1 – 1.95).

ROC curves showed that UA-PI was significant predictor for development of pre-eclampsia [AUC 0.870, 95% CI (0.830 to 0.911)], development of severe pre-eclampsia [AUC 0.870, 95% CI (0.824 to 0.907)] and development of early-onset pre-eclampsia [AUC 0.857, 95% CI (0.810 to 0.896)] (Figures 1-3). Table-1 shows the accuracy indices for the best cutoff values.

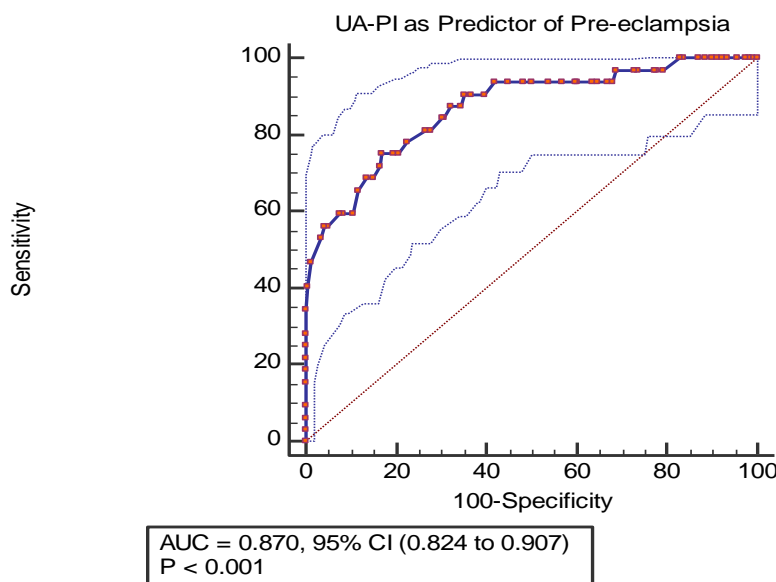


Figure 1: ROC Curve for UA-PI in Prediction of Preeclampsia in Included Women.

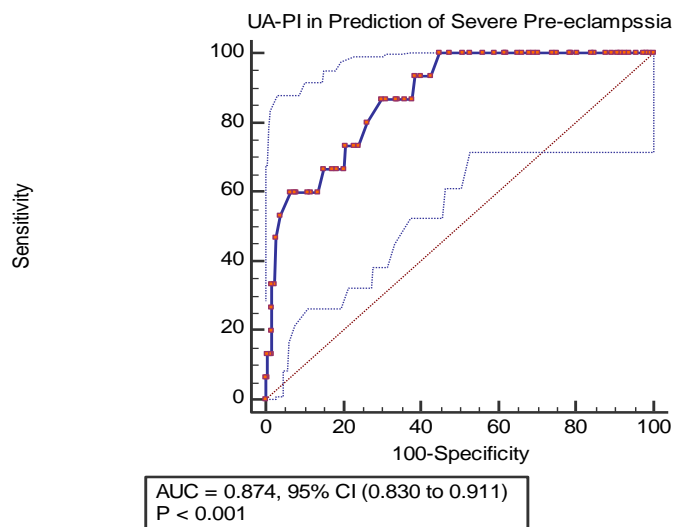


Figure 2: ROC Curve for UA-PI in Prediction of Severe Preeclampsia in Included Women.

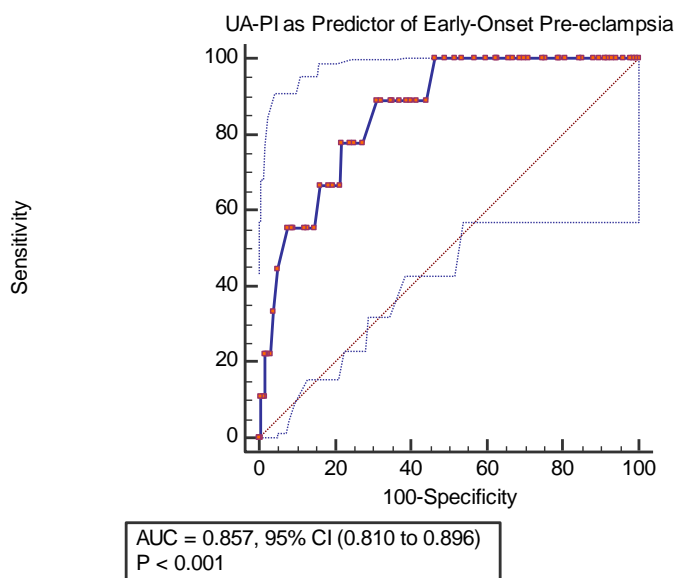


Figure 3: ROC Curve for UA-PI in Prediction of Early-Onset Preeclampsia in Included Women.

	UA-PI Cutoff Value	Sensitivity	Specificity	LR+	LR-
Preeclampsia	> 1.48	86.6% (59.5 to 98.3)	70.1% (74.2 to 75.5)	2.9 (2.2 to 3.8)	0.19 (0.05 to 0.7)
Severe Preeclampsia	> 1.52	75.0% (56.5 to 88.5)	83.0% (77.7 to 87.5)	4.4 (3.1 to 6.2)	0.3 (0.2 to 0.6)
Early-Onset Preeclampsia	> 1.48	88.9% (51.8 to 99.7)	68.9% (63.0 to 74.4)	2.9 (2.1 to 3.8)	0.16 (0.03 to 1.0)

UA-PI uterine artery pulsatility index
 LR+ positive likelihood ratio
 LR- negative likelihood ratio
 Data presented as the parameter in percentage (95% confidence interval)

Table 1: Accuracy of UA-PI Cutoff Values in Prediction of Preeclampsia in Included Women.

Of the included 279 women, 45 (16.1%) had a UA-PI above the 95th percentile for gestational age, and 38 (13.6%) had persistent diastolic notch.

There was a significant association between both presence of high UA-PI (for gestational age) and presence of persistent diastolic notch (on one side) and development of pre-eclampsia [RR 13.3, 95% CI (6.6 to 26.8) and RR 44.4,

95% CI (16.5 to 119.5), respectively], development of severe pre-eclampsia [RR 20.8, 95% (6.1 to 70.8) and RR 88.8, 95% CI (12.1 to 666.9), respectively] and

development of early-onset pre-eclampsia [RR 41.6, 95% CI (5.3 to 324.5)] (on the other side) among included women (Table-2).

	High UA-PI			Persistent Diastolic Notch		
	Yes	No	RR (95% CI)	Yes	No	RR (95% CI)
Preeclampsia						
Yes	23 (51.1%)	9 (3.8%)	13.3	28 (73.7%)	4 (1.7%)	44.4
No	22 (48.9%)	225 (96.2%)	(6.6 to 26.8)	10 (26.3%)	237 (98.3%)	(16.5 to 119.5)
Severe Preeclampsia						
Yes	12 (26.7%)	3 (1.3%)	20.8	14 (36.8%)	1 (0.4%)	88.8
No	33 (73.3%)	231 (98.7%)	(6.1 to 70.8)	24 (63.2%)	240 (99.6%)	(12.1 to 666.9)
Early-Onset Preeclampsia						
Yes	8 (17.8%)	1 (0.4%)	41.6	9 (23.7%)	0 (0%)	
No	37 (82.2%)	233 (99.6%)	(5.3 to 324.5)	29 (76.3%)	241 (100%)	NE
Data presented as frequency (percentage)						
UA-PI uterine artery pulsatility index						
RR (95% CI) risk ratio and its 95% confidence interval						
NE not estimable						

Table 2: Association between Development of Preeclampsia and UA-PI in Included Women.

Presence of high UA-PI and persistent diastolic notch were significantly highly accurate predictors of development of pre-eclampsia [sensitivity: 71.9% and 87.5%, specificity: 91.1% and 95.5%, respectively and respectively], development of severe pre-eclampsia [sensitivity: 80.0%

and 93.3%, specificity: 87.5% and 90.9%, respectively and respectively], and development of early-onset pre-eclampsia [sensitivity: 88.9% and 100%, specificity: 86.3% and 89.3%, respectively and respectively] (Table-3).

	High UA-PI	Persistent Diastolic Notch
Preeclampsia		
Sensitivity	71.9% (53.2 to 86.2)	87.5% (71.1 to 96.5)
Specificity	91.1% (86.8 to 94.3)	95.9% (92.7 to 98.0)
PPV	51.1% (39.9 to 62.2)	73.7% (60.1 to 83.9)
NPV	96.2% (93.5 to 97.8)	98.3% (95.9 to 99.3)
Severe Preeclampsia		
Sensitivity	80.0% (51.9 to 95.7)	93.3% (78.1 to 99.8)
Specificity	87.5% (82.9 to 91.2)	90.9% (86.8 to 94.1)
PPV	26.7% (19.5 to 35.3)	36.8% (28.0 to 46.6)
NPV	98.7% (96.5 to 99.5)	99.6% (97.3 to 99.9)
Early-Onset Preeclampsia		
Sensitivity	88.9% (51.8 to 99.7)	100% (66.4 to 100.0)
Specificity	86.3% (81.6 to 90.2)	89.3% (84.9 to 92.7)
PPV	17.8% (12.9 to 23.9)	23.7% (18.0 to 30.4)
NPV	99.6% (97.3 to 99.9)	100% (92.3 to 100.0)
Data presented as parameter (95% CI)		
UA-PI uterine artery pulsatility index		
PPV positive predictive value		
NPV negative predictive value		

Table 3: Accuracy of High UA-PI in Prediction of Preeclampsia in Included Women

Discussion

The current study showed that in a group of primigravid women, abnormal uterine artery Doppler ultrasound indices (in terms of a PI above the 95th percentile for gestational age or persistent diastolic notch) measured at 18-22 weeks of gestation seems to be a significant predictor

of development of pre-eclampsia, development of severe pre-eclampsia, and development of early-onset pre-eclampsia. Measurement of vascular resistance of uterine arteries has been dating as early as 1983 when Campbell et al [14]. introduced pulsed Doppler ultrasound in measuring velocimetry in uterine arteries. Physiologically, there

should be a reduction in the vascular resistance of uterine artery in the second trimester of pregnancy, reflecting a second wave of trophoblast invasion of spiral arteries, which usually occurs between 16 and 18 weeks of gestation [15]. In pregnancies that are subsequently complicated by pre-eclampsia and/or fetal growth restriction, uterine artery vascular resistance is not reduced in the second trimester reflecting abnormal trophoblast invasion¹⁵. The findings of the current study and several previous studies go in agreement to such an assumption [11-19,16,17].

In a study conducted by Lees et al [11]. the mean UA-PI above the 95th percentile, measured at 23 weeks' gestation had a significant association with fetal growth restriction, placental abruption, pre-eclampsia and even fetal demise. In the same year, Papageorghiou et al. [18] showed that high mean UA-PI in the second trimester was observed in 41% of women who had pre-eclampsia and in 16% of those complicated by fetal growth restriction. In spite of the obviously low sensitivity in that study, the same cutoff value (above the 95th centile) was able to detect 93% of the preeclampsia cases and 56% of the fetal growth restriction cases that required delivery before 32 weeks of gestation; i.e. early-onset pre-eclampsia. In 2008, Yu et al [16]. assessed around 30,000 pregnancies, and, in a very similar way, found that UA-PI could predict most cases of early-onset pre-eclampsia, but could not be that predictive for the term-onset pre-eclampsia. In a rather recent meta-analysis including 18 studies and around 55,000 pregnancies, An UA-PI above the 90th percentile could identify 47% of the cases of early-onset pre-eclampsia and 39.2% of the cases of early-onset FGR, with a false-positive rate of 7% [19]. In the same meta-analysis, however, persistent diastolic notching had a low sensitivity and specificity. Technically-speaking there is consistent measurement and considerably low intra- and inter-observer variation in measurement of Doppler ultrasound indices of uterine arteries [20].

In conclusion, high UA-PI and presence of persistent diastolic notch are significant predictors of pre-eclampsia, severe pre-eclampsia and early-onset pre-eclampsia.

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