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The role of uterine artery Doppler in prediction of preeclampsia

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Abstract
Objective: Is to assess the sensitivity of uterine artery Doppler in prediction of PE in pregnant women with high risk for developing PE in first (11 to 14 weeks) and second (19 to 22 weeks) trimesters.
Methods: A prospective study included 100 patients aged from 17 to 41 years for high risk in developing PE seeking antenatal care, divided into two groups, Group A(unaffected group) includes 82 patients, and Group B (affected group) includes 18 patients for developing or non-developing PE.
Results: The result of this study revealed that 18 in number developing PE out of 100 patients, the sensitivity and specificity of PI in prediction of pre-eclampsia for first and second trimester were 27.78%, 92.68% and 66.67%, 86.58% respectively, while the sensitivity and specificity of bilateral notching in prediction of pre-eclampsia for first and second trimester were 83.33%, 60.98% and 72.22%, 85.37% respectively.
Conclusion: In this study it was concluded that Doppler analysis helps not only earlier detection of utero-placental and feto-placental changes associated with the disease but also help to take decision for early intervention. Doppler technology has provided the best opportunity for repetitive non-invasive haemodynamic monitoring in pregnancy for fetal well-being evaluation and predicting perinatal outcome.

Keywords: preeclampsia, uterine artery doppler, prediction

Introduction

Preeclampsia affects roughly 2% to 5% of all pregnancies yet remains an elusive disease regarding prediction and treatment. As it affects so many pregnancies, preeclampsia is an attractive target to identify an effective screening test. Identifying patients at risk would allow us to increase their perinatal surveillance and possibly decrease the inherent maternal and fetal morbidity and mortality associated with severe preeclampsia and eclampsia [1].

Preeclampsia is defined in the literature as hypertension (>140/90) and proteinuria (>300 mg in a 24 h specimen) after 20 weeks gestation. The disease is further subdivided into mild and severe forms with HELLP syndrome (hemolysis, elevated liver function tests, and low platelets) along the spectrum of disease [2].

PE is a multisystemic disease of multifactorial origin: it involves defective placentation, oxidative stress, autoimmunity, platelet and thrombin activation, intravascular inflammation, endothelial dysfunction, an imbalance in angiogenesis and maternal cardiac maladaptation [3].

Defective placental invasion is associated strongly with most cases of early and severe PE [4]. In contrast, defective placentation seems to be less important for the development of PE that manifests later in pregnancy, for example after 34 weeks. Compared with pregnancies affected by early-onset disease, in those complicated with PE at or near term, placentae have a significantly lower frequency of histological abnormalities [5], and maternal factors (e.g. metabolic syndrome or chronic hypertension) have a relatively greater significance [4]. Differences between early and late-onset PE are also seen in risk factors [6], maternal Vascular responsiveness [7], screening performance [8] and prevention effectiveness [9].

Doppler ultrasonography is a non-invasive technique which can be utilized for assessing uterus-placental blood flow. The impedance of uterine artery flow progressively reduces during the first and second trimester of normal pregnancy due to the trophoblastic invasion of the musculo-elastic membrane of uterine spiral arteries [10].

The use of uterine artery Doppler study in predicting preeclampsia has been previously extensively investigated in the second and first trimesters of pregnancy. Abnormal placental behavior that characterizes preeclampsia is associated with increased vascular resistance in the placenta. Ultrasonographic evidence of that problem includes an increase in the pulsatility index (PI) of the uterine artery or persistent diastolic 'notch' in its Doppler waveform [11].

Aim of this study was to assess the sensitivity of uterine artery Doppler in prediction of preeclampsia in pregnant women with high risk for developing preeclampsia in first (11 to 14 weeks) and second (19 to 22 weeks) trimesters.

Patients and Methods

Present prospective study was conducted within a period of period from December 2018 to October 2019, in the department of the department of radiodiagnosis - Al-Azhar University Hospital - Assiut, using high-resolution ultrasonography machine (Semen's Acuson X300) with 3.0 to 5.0 MHz curvilinear transducer.

The study included 100 pregnant women booked for antenatal care referred to Department of radio-diagnosis, who were considered to be at risk of developing preeclampsia.

Inclusion criteria

History of PE or eclampsia in previous pregnancy, history of IUGR or stillbirth, extremes of age (<20 years and >35 years), obese women (BMI ≥ 30.5 kg/m²), history of abruptio placentae, null parity and Pre-existing medical disorders as: HTN, DM, autoimmune disease as SLE and renal disease.

Exclusion criteria

Patient with congenital anomaly of fetus, multiple gestations and patients with unreliable LMP details and not confirmed by early ultrasound.

Informed consent were taken from the patients, and then the cases were subjected to the study.

History, general & Obstetric examination and routine laboratory investigation were subjected to all patients.

Doppler examination

Pulsed wave Doppler equipment was used to obtain the arterial velocity waveform of uterine arteries.

The uterine artery pulsatility index was measured in both arteries at first-trimester (11 to 14 weeks) and second-trimester (19 to 22 weeks) trans-abdominally.

Follow up of all pregnancies every 4 weeks till 28 weeks then every 2 weeks till delivery for occurrence or non-occurrence of preeclampsia in their pregnancies.

- Pre-eclampsia was defined as high systolic blood pressure ≥140 mmHg or diastolic blood pressure≥90 mmHg and proteinuria ≥300 mg/day in 24-hour urine or spot urine protein/creatinine ratio ≥0.30mg/mg or urine dipstick testing ≥1+ occurring at, or after, 20 weeks of gestation.
- Patients with preeclampsia were sub-classified as either early-onset (≤34 weeks) or late-onset (>34 weeks) disease according to the gestational age at which preeclampsia was diagnosed.
- Small-for-gestational-age was defined as a birth weight (BW) <10th percentile for the gestational age at birth according to the national birth weight distribution of a Hispanic population.

Statistical analysis

Data were analyzed and expressed in tables using Statistical Package for Social Science (SPSS). Statistical methods included descriptive methods (mean, standard deviation, frequency distribution) and significance tests (t-test for quantitative data, correlation coefficient test and analysis of variance (ANOVA) tests). The significance will be adjusted when P equal 0.05 or less.

Results

Our study included 100 high-risk pregnant patients seeking antenatal care. Their ages ranged from 17 to 41 years with mean age 26.62±5.88.

The studied patients were classified into three age groups. Group I less than 20 Y, group II from 20-35 y and group III more than 35 Y

Table 1: Classification of patients according to the age.

Age	No. (n= 100)	%
Less than 20 Y	7	7
20 – 35 Y	82	82
More than 35 y	11	11
Range	17 – 41	
Mean ± SD	26.62±5.88	

Table 2: Distribution of the patients according to the risk factors and developing PE.

Risk factors		Unaffected N = 82	Developed PE N = 18	P. value
Maternal age	<20 Y	6	1	0.806
	>35 Y	9	2	0.689
H/O preeclampsia		14	6	0.216
Chronic hypertension		10	2	0.786
Diabetes mellitus		12	3	0.885
Null parity		26	4	0.609
SLE		2	[[0	-
BMI>30		3	0	-

Table 3: Distribution of cases according to perinatal outcome.

	Unaffected N = 82	Developed PE N = 18
Normal outcome	76 (92.68%)	9 (50%)
Preterm	2 (2.4%)	4 (22.2%)
SGA	4 (4.8%)	4 (22.2%)
IUGR	0	1 (5.5%)

Table 4: Sensitivity, specificity, Positive predictive value, Negative predictive value and P. value of first trimester for early and late pre-eclampsia.

First trimester	Sensitivity	Specificity	PPV	NPV	P. value
Early PE	40.00	90.53	18.2	96.6	0.2161
Late PE	23.08	90.80	27.3	88.8	0.2689

Table 5: Sensitivity, specificity, Positive predictive value, Negative predictive value and P. value of second trimester for early and late pre-eclampsia.

Second trimester	Sensitivity	Specificity	PPV	NPV	P. value
Early PE	80.00	80.00	17.4	98.7	0.0033
Late PE	69.23	83.91	39.1	94.8	0.0001

Table 6: Prevalence of PE according to first trimester PI

	>95th percentile	<95th percentile	P. value
First trimester	11	89	**0.0567**
Developed PE	5	13	

Table 7: Prevalence of PE according to second trimester PI

	>95th percentile	<95th percentile	P. value
Second trimester	23	77	<0.0001
Developed PE	13	5	

Table 8: Sensitivity, specificity, Positive predictive value, Negative predictive value and accuracy analysis.

PI	Sensitivity	Specificity	PPV	NPV	Accuracy
First trimester	27.78	92.68	45.45	85.39	30.85
Second trimester	72.22	87.80	56.52	93.5	50.03

Table 9: Prevalence of PE according to first trimester notching

	Bilateral notch	No bilateral notch	P. value
First trimester	47	53	0.0005
Developed PE	15	3	

Table 10: Prevalence of PE according to second trimester notching

	Bilateral notch	No bilateral notch	P. value
Second trimester	19	81	<0.0001
Developed PE	11	7	

Table 11: Sensitivity, specificity, Positive predictive value, Negative predictive value and accuracy analysis.

Bilateral notching	Sensitivity	Specificity	PPV	NPV	Accuracy
First trimester	83.33	60.97	31.91	94.33	26.25
Second trimester	61.11	90.24	57.89	91.35	49.25

Discussion

Preeclampsia is an abnormality in blood pressure that occurs in the course of pregnancy and is characterized by reduced organ perfusions following severe vascular vasospasm [12]. The World Health Organization estimated that over one million women in the world die due to preeclampsia and its complications each year and maternal deaths in developing countries is due to this situation Moreover, preeclampsia usually occurs in young and nulliparous women and its incidence is greatly influenced by race, ethnicity, and genetic predisposition [13].

Preeclampsia is a main cause of maternal and fetal mortality and morbidity. Many screening tests have been investigated to predict preeclampsia, including the biochemical screening markers used for Down's syndrome as they have been proposed for their relation to abnormal uteroplacental circulation, and only a few of them reached satisfactory sensitivities and specificities. Due to its heterogeneous nature, preeclampsia prediction could not be achieved by a single test [14].

During normal pregnancy, uterine blood flow increases to perfuse the inter-villous space of the placenta and support fetal growth. This demand is met by a process known as physiologic transformation of the spiral arteries of the uterus, in which trophoblasts invade the arterial wall and destroy the media. This process transforms the spiral arteries from narrow to large diameter vessels, in order to perfuse the placenta [15].

In PE or eclampsia, the placental bed shows failure of physiologic transformation of the myometrial segment of the spiral artery, a process that takes place in the second trimester of pregnancy [15]. Failure of physiologic transformation of the spinal arteries is thought to be the explanation for the uteroplacental ischemia observed in PE [16].

In our study, we measures and observe the changes occurs during pregnancy at our selected population in the uterine artery by their pulsatility indices and presence or absent of the pre diastolic notch in both first and second trimester.

In our study, the age of patient range from 17 to 41 years with mean 26.6 which close to [10] which range from 17 to 43 years with mean 28.

In our study 18 out of 100 developed pre-eclampsia, while in the work of [17] 27 out of 135 developed pre-eclampsia.

In first trimester, our study used PI cut-off value was taken as >2.35 and found that sensitivity and specificity of first-trimester uterine artery PI in predicting pre-eclampsia at any gestation were 27.78% and 92.68% respectively, where in [18] found that the sensitivity and specificity of first-trimester uterine artery PI in predicting pre-eclampsia at any gestation were 27% and 95.4% respectively.

Also [19] found that sensitivity and specificity of first-trimester uterine artery PI in predicting pre-eclampsia at any gestation were 26.4% and 93.4% respectively.

(Yıldırım Köpük *et al*. 2019) found that sensitivity and specificity of first-trimester uterine artery PI in predicting pre-eclampsia 42.31% and 82.10%, respectively, which differ that in our study, we can explain that their used lower PI cut-off value as >2.23.

In our study the sensitivity of bilateral notching at first-trimester was 83.33% which lower than [20] which found that the presence of bilateral notches achieved a sensitivity of 93% for the prediction of preeclampsia.

In spite of the sensitivity of bilateral notches at 11–14 weeks is relatively high, the specificity is low which in our study about 60.98, that agree with [21] who found that the specificity 55%.

In second trimester, regarding to PI sensitivity and specificity for prediction of pre-eclampsia were 66.67% and 86.58% respectively which compatible with [22] who found that sensitivity and specificity of PI 61.9% and 86.8% respectively.

Our result is higher than [23] which found that the sensitivity and specificity were 66.67% and 86.58% respectively, we can explain this as they use PI $>90^{th}$ percentile rather than 95^{th}. And also differ from (24) which found that the sensitivity and specificity were 87.5% and 82.8% respectively.

While PPV and NPV of our study 56.52% and 93.5% which likely close to [23] which found that the PPV and NPV 50% and 87.22% respectively.

There are some sort of variation at this area in which [22] found that the PPV and NPV 36.8% and 94.0% respectively, and [24] found that the PPV and NPV 61.7% and 95.4% respectively.

In our study the sensitivity of bilateral notching at second-trimester was 72.22% which compatible with (25) where the sensitivity 72.2%, but our specificity was 85.37%, which higher from what [25] found 73.1%.

The PPV and NPV of bilateral notching were 57.89% and 91.35% respectively; while in [25] the PPV and NPV of bilateral notching at second-trimester were 48.1% and 88.3%.

Although the mean uterine artery PI evaluated by Doppler is significantly elevated in patients who will develop early and severe forms of PE or FGR, the accuracy of this test as a standalone screening tool is poor, with low sensitivity and positive predictive value. Its use as part of predictive algorithms that combine maternal characteristics, maternal history and other biophysical and biochemical markers seems more promising [26] with higher detection rates and acceptable false-positive rates [27].

Conclusion

In conclusion, Doppler ultrasonography is a non-invasive technique, which can be utilized for assessing uterus-placental blood flow. The impedance of uterine artery flow progressively reduces during the first and second trimester of normal pregnancy due to the trophoblastic invasion of the musculo-elastic membrane of uterine spiral arteries.

Second trimester uterine artery Doppler is best for prediction of preeclampsia for both PI and bilateral notching regarding to the results, where the sensitivity 66.67%, 72.22% and specificity 86.58%, 85.37% respectively.

Uterine arteries Doppler ultrasonography has relatively high NPV for prediction of preeclampsia, abruption, and LBW and so in the high-risk women who have normal Doppler

study in second trimester we can assure the patient to have a normal pregnancy outcome with low complication rate.

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