

Screening utility of umbilical artery Doppler indices in patients with preeclampsia

Bibi Shahnaz Aali^{1,2} M.D., Shahin Narooi³ M.D., Babak Mojtabaeian⁴ M.D., Nouzar Nakhaee⁵ M.D.

1 Department of Obstetrics and Gynecology, Kerman University of Medical Sciences, Kerman, Iran.

2 Physiology Research Center, Kerman University of Medical Sciences, Kerman, Iran.

3 Department of Radiology, Kerman University of Medical Sciences, Kerman, Iran.

4 Kerman University of Medical Sciences, Kerman, Iran.

5 Department of Community Medicine, Kerman University of Medical Sciences, Kerman, Iran.

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Abstract

Background: Doppler indices of umbilical artery are used as indicator of fetal well being.

Objective: To compare Doppler parameters of umbilical artery including pulsatility index (PI) and resistance index (RI) in patients with preeclampsia with those of normal pregnancies and to evaluate the diagnostic characteristics of these parameters in preeclampsia.

Materials and Methods: In a case control study, umbilical artery pulsatility and resistance indices were calculated at a free loop of umbilical cord in 25 preeclamptic patients and 75 uneventful pregnancies. Measurements were compared and diagnostic characteristics of the indices were determined.

Results: Mean of pulsatility and resistance index were significantly higher in preeclampsia patients than the control group. Besides, patients with severe preeclampsia showed significantly higher values of PI and RI in comparison to those with mild preeclampsia. For PI, the cut-off of ≥ 0.98 yielded the highest sensitivity and specificity. Also, RI of 0.64 acquired a sensitivity of 100% and specificity of 44%.

Conclusion: Umbilical artery pulsatility index and resistance index increase in preeclampsia and these changes tend to be greater in severe preeclampsia. Umbilical artery PI and RI seem to be more appropriate in excluding preeclampsia rather than confirming it, and we propose the cut-off values of 0.98 for PI and/or 0.64 for RI, to rule-out the disease.

Key words: Preeclampsia, Umbilical artery, Pulsatility index, Resistance index.

Introduction

Assuming that defective placental circulation results in adverse pregnancy outcome, Doppler ultrasonography has been used as a modality to evaluate placental circulation and fetal well being for about three decades(1). Abnormal development of placental vasculature is considered as the pathophysiological basis for development of preeclampsia (2) and this could be reflected in

abnormal umbilical Doppler velocimetry. In normal pregnancies, the fetoplacental circulation acts as a low resistance system unit. Thus, the blood velocity waveforms in umbilical artery (UA) show continuous forward flow throughout the cardiac cycle (1).

Goldkrank *et al* documented a steady increase in the blood flow of the umbilical artery as pregnancy progresses. The diameter of the umbilical artery increases until reaching a plateau at 32-34 weeks' gestation (3), whereas the systolic/diastolic (S/D) ratio, resistance index and pulsatility index (PI) decrease throughout pregnancy (3-4). An abnormally elevated impedance to blood flow in the umbilical

Corresponding Author:

Shahnaz Aali, Department of Obstetrics and Gynecology, Kerman University of Medical Sciences, Kerman, Iran.

Email: shahnaz.aali@gmail.com

artery is an indirect reflection of placental pathology. Studies of placentas obtained from pregnancies with abnormal umbilical artery velocity waveforms end-diastolic flow in the umbilical artery show vascular sclerosis with obliteration of tertiary stem villi (5). The results of Seyam *et al*'s study revealed that fetuses with abnormal UA velocity waveforms are at a significantly increased risk for oligohydramnios, early delivery, decreased birth weight, and neonatal intensive care unit admissions (6). Other studies also showed an association between abnormal UA Doppler indices and lower arterial and venous pH values, an increased likelihood of intrapartum fetal distress, and a higher incidence of respiratory distress syndrome (7). Ertan *et al* also showed that the frequency of preeclampsia, intrauterine growth retardation, oligohydramnios and nicotine abuse were significantly higher in a group of patients with reverse flow of umbilical artery compared to the control group (8).

In Arauz *et al* study abnormal umbilical artery Doppler velocimetry was present in 52% of preeclamptic patients and they suffered more from adverse neonatal outcomes than those with normal Doppler indices (9).

Regarding malplacentation as the main pathological event in preeclampsia, alteration in umbilical Doppler velocimetry is expectable. However, considering the fact that preeclampsia is a disease of unknown etiology and can present with various degree of different organ dysfunction, the present study was designed to investigate the extent of changes in umbilical artery Doppler indices (pulsatility index and resistance index) in patients with mild and severe preeclampsia in Kerman, Iran, and to evaluate the diagnostic utility of these indices in preeclampsia.

Materials and methods

The study population consisted of 25 preeclamptic patients and 75 women with uneventful pregnancies as normal controls, who attended the maternity center of Afzalipour, main Kerman University hospital, Kerman, Iran, from September 2007 to August 2008. Gestational age was more than 20 weeks in both groups and was established by an accurate menstrual history and/or an ultrasonographic examination before 20th week of pregnancy.

Preeclampsia was diagnosed if a blood pressure of $\geq 140/90$ was detected in the pregnant woman after 20th week of gestation with appropriate cuff

and supine position in at least two occasions 4 hours apart and random proteinuria of $\geq +1$ or 24hours proteinuria more than 300m. Rise of blood pressure to $\geq 160/110$ with a proteinuria of $>+2$ or 24 hours proteinuria of >2 gr, and development of headache, epigastric pain, blurred vision, pulmonary edema, abnormal liver and renal function test was considered as severe preeclampsia.

Patients of all reproductive age groups and gravidity were included in the study as there is no evidence that these variables affect umbilical artery Doppler indices. However, cases with intra uterine growth restriction, fetal anomalies, twin pregnancy, and underlying chronic disease were excluded from the study.

The study protocol was approved by the Ethics committee of Kerman Medical University and all subjects gave informed written consent. All women underwent routine ultrasonographic scan before the Doppler examination by which gestational age was confirmed in every case and pregnancies with intrauterine restriction were excluded.

Also, fetal anatomy scan excluded congenital anomalies. Doppler ultrasound examination of the UA was performed on the women in the left lateral recumbent position using a color Doppler system, Siemens G-40 Germany, with a 3.5 MHz convex probe. The UA was identified and flow velocity waveforms were obtained from a free-floating loop of the cord during fetal quiescence. The sample volume was 2–4 mm and the smallest possible velocity scale and lowest required pulse repetition frequency were used. Recordings were made when at least three nearly identical consecutive waveforms were visible on the screen.

All Sonographic studies were performed by the same expert examiner who was not aware of the study design. Doppler parameters including pulsatility index (PI) and resistance index (RI) were calculated by the dedicated software supplied within the Doppler equipment. The average value of at least two waveforms was considered as the final measurement.

Statistical analysis

Independent t-test was used for continuous variables with normal distribution. Mann-Whitney test was used to calculate the differences between the two groups in case of nonparametric data. Receiver Operating Characteristic (ROC) curve analysis was performed and the area under the curve (AUC) with corresponding confidence intervals (CIs) was calculated. Diagnostic

characteristics of the two indices were determined by means of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and positive likelihood ratio (LR+). SPSS 17 was used to perform data analysis.

Results

The basic characteristics of the patients in the groups are shown in table I. There was no significant difference in the mean maternal age and gestational age between preeclamptic and control groups. However, mean gravidity and living child were less in preeclamptic patients than normal pregnancy group ($p < 0.05$). Of 25 preeclamptic patients, 7 revealed to be severe and 18 were mild cases.

Table II demonstrates the comparison of mean PI and RI in the groups. Both Doppler parameters

of umbilical artery were significantly higher in preeclamptic patients (PI of 1.32 ± 0.23 and RI of 0.77 ± 0.09) when compared to the controls (0.97 ± 0.18 and 0.64 ± 0.08 for PI and RI, respectively) ($p < 0.001$). Similarly, when we compared mild and severe preeclamptic patients using their Doppler indices, significantly higher values were obtained in severe cases than mild ones (Table II).

For PI, the cut-off of ≥ 0.58 yielded a sensitivity of 100% and specificity of 1.3%. At the cut-off of ≥ 0.98 sensitivity was the same but specificity increased to 53.3%.

With a cut-off of 0.64 for RI, a sensitivity of 100% and specificity of 44.0% was calculated (Table III). PPV, NPV and LR+ for the two indices at different cut-offs are shown in Table III. The AUCs for PI and RI were 0.88 (CI 95%: 0.82-0.95) and 0.86 (CI 95%: 0.78-0.94), respectively.

Table I. Basic characteristics of the control and preeclampsia group.

Group characteristic	Normal pregnancy	Preeclampsia	p-value
Age (year)	25.6 (4.3)	26.4 (4.4)	0.42
Gestational age (week)	33.2 (4.2)	33.6 (2.5)	0.53
Gravidity* (number)	2.1 (1.1)	1.5 (0.9)	0.007
Living child* (number)	0.8 (0.9)	0.4 (0.6)	0.01

*Number are shown as mean (SD).

Table II. Umbilical artery indices in preeclampsia and control groups.

Index	Normal pregnancy	Total	Mild preeclampsia	Severe preeclampsia
Pulsatility index	0.97 (0.18) *	1.32 (0.23)	1.24 (0.17) **	1.52 (0.25)
Resistance index	0.64 (0.08) *	0.77 (0.09)	0.74 (0.08) **	0.83 (0.07)

* $p < 0.001$ comparing normal and preeclamptic individuals, ** $p < 0.05$ comparing mild and severe preeclamptic patients. Number are shown as mean (SD).

Table III. Diagnostic characteristics of PI and RI for predicting preeclampsia at different cut-offs.

Value	Cut-off	Se (%)	Sp (%)	PPV (%)	NPV (%)	LR+
PI	0.58	100	1.3	25.3	100	1.01
	0.78	100	17.3	28.7	100	1.21
	0.98	100	53.3	41.7	100	2.14
	1.18	64.0	85.3	59.3	87.7	4.36
	1.38	40.0	100	100	83.3	NA
RI	0.44	100	1.3	25.3	100	1.01
	0.54	100	9.3	26.9	100	1.10
	0.64	100	44.0	37.3	100	1.79
	0.81	28	100	100	80.6	NA

PI, pulsatility index; RI, resistance index; Se, sensitivity; Sp, specificity; PPV, positive predictive value ; NPV, negative predictive value; LR+, positive likelihood ratio; NA, not applicable.

Discussion

Our results showed higher pulsatility and resistance indices in patients with preeclampsia than normal pregnancies. This confirms a state of high resistance in placental circulation in preeclampsia. Our findings are in line with the study performed by Chen *et al* which showed not only a higher pulsatility index in preeclamptic patients but also a significantly greater PI in severe cases of preeclampsia (10).

On the other hand, Ozeren *et al* could not find any difference in umbilical PI between normal pregnancies and preeclamptic patients without IUGR whereas, preeclampsia group with IUGR showed a significantly higher mean umbilical artery PI.

The discrepancy in the findings can be explained based on the greater sample size and higher gestational age of patients in their study. They had included 62 preeclamptic women with and without IUGR at 31-40 weeks of pregnancy, while we selected preeclamptic patients without IUGR after 20th week of gestation. Mean UA PI in their control group with IUGR was 0.89 ± 0.08 , and preeclamptic patients without IUGR revealed a mean UA PI of 0.88 ± 0.15 (11). Lower values of UA PI in their study in comparison to ours is also related to the greater mean gestational age (i.e., 35.5 weeks) in their patients, because this parameter decreases as pregnancy progresses (4). We found a mean PI of $1(\pm 0.2)$ in the mean gestational age of 33.2 weeks in normal pregnancies.

The mean PI in this gestational age has been reported as 0.92 in Parra-Cordero *et al* study (12); however, they calculated the mean PI for every single week of pregnancy, instead of mean gestational age of 33 weeks as we did in our study. Also, Acharya *et al* in serial measurement of umbilical artery Doppler indices in 130 low risk pregnancies obtained a 50th percentile and 95th percentile umbilical artery PI of 0.88 and 1.22, respectively (4) whereas, 50th percentile RI calculated to be 0.60 and 95th percentile RI was 0.74 in 33rd week of gestation. The difference in the methods and the number of umbilical artery waveforms studied can account for the different values reported in various studies. Mean gravidity

was expectedly less in our preeclamptic group than the controls because generally, preeclampsia tends to occur more frequently in primigravidas (2).

Umbilical artery Doppler indices have been used to predict fetal outcome, for instance, Tchirikov *et al* found a sensitivity of 51.5% and specificity of 100% for umbilical artery PI and concluded that combining the normalized umbilical volume flow rate with the pulsatility index in the umbilical artery yields a Doppler parameter that increases the sensitivity (13). We aimed to find a valuable cut-off of UA PI and RI for prediction of the effects of preeclampsia on umbilical cord circulation.

Generally, the tests were considered positive if the umbilical artery Doppler indices were above the cut-off level and negative if they were below the cut-off. As shown in Table III, based on the cut-off levels, both indices could be 100% sensitive or 100% specific. Sensitivity and specificity are in trade-off with each other and as one of them increases, the other one decrease (14). Depending on the clinical situation, it is an arbitrary decision to select both or one of them. When there is a serious penalty in failing to detect an important disease such as preeclampsia, choosing a highly sensitive test has a pivotal role in the prevention of neglecting such cases. On the other hand, a specific test is used when a false positive result can pose a great harm to the patient (15).

Accordingly, two cut-off values may be used for each of the indices. The lower cut-offs (i.e. 0.98 and 0.64 for PI and RI, respectively) which were associated with 100% sensitivity and a higher specificity could be used to rule-out preeclampsia (Table III), and if the purpose of doing the test is to rule-in preeclampsia specificity is logically more important than sensitivity, hence, higher cut-offs would be more appropriate (i.e. 1.38 and 0.81 for PI and RI, respectively). It is noteworthy to mention that for a highly sensitive test, a negative result and for a highly specific test, a positive result is more helpful to the physician than vice versa (15).

Considering the deadly consequences of missing preeclampsia, it seems that a highly sensitive test is preferable to a specific one. It should be reminded that the sensitivity and

specificity are useful when we decide to request a test. Once the tests have been done and the results are ready, PPV and NPV replace specificity and sensitivity (14, 15), putting in mind that they are dependent on the prevalence of the disease.

In clinical practice the latter diagnostic characteristics are more appropriate for answering questions encountered by physicians than the sensitivity and reliability (15). PI lower than 0.98 and/or RI lower than 0.64 had a negative predictive value of 100% for diagnosing preeclampsia. This implies that if a pregnant woman has negative results from the PI and/or RI tests (i.e., values lower than the abovementioned cut-offs), the clinician can be 100% confident that she does not have preeclampsia.

The highest LR+ was associated with the lowest cut-off value for both indices (Table III), and similarly, when sensitivity and specificity were considered simultaneously ROC curve analysis yielded AUC of 0.88 and 0.86 for PI and RI, respectively, which could be categorized as “good” according to Swets (16) which states that the accuracy of PI and RI in diagnosing preeclampsia are comparable. According to Fletcher *et al* although ROC curves help us to find the best cut-off point for a test there may be “clinical reasons for minimizing either false negative or false positives” which influence the selection process of the cut-off point (15). Emphasizing the importance of screening and early detection of preeclampsia, a highly sensitive test seems to be more essential than a specific one (17).

Therefore, in selecting the cut-off point, a 100% sensitivity accompanied with the highest specificity is warranted. As mentioned above such a value corresponds to cut-offs of 0.98 and 0.64 for PI and RI, respectively.

In conclusion, PI and RI as very safe and noninvasive tests seems to be more appropriate in excluding preeclampsia rather than confirming it, and we propose the cut-off values of 0.98 for PI and/or 0.64 for RI, to rule-out the disease.

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