Multicenter screening for adverse pregnancy outcomes by uterine artery Doppler in the second and third trimester of pregnancy

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Abstract

Aims: Increased uterine artery pulsatility index (PI) is associated with adverse pregnancy outcomes. The aim of the study was to determine the role of uterine artery PI at 18-24 and 30-34 weeks, gestation in predicting adverse pregnancy outcomes.

Material and methods: Color Doppler assessment of the uterine arteries was carried out in 435 consecutive women attending an antenatal clinic at 18-24 weeks and in 134 women at 30-34 weeks. The 95th percentiles of the mean uterine PI and the presence or the absence of bilateral notches was recorded. Using the reference range, performance characteristics in the prediction of pregnancy outcomes were calculated. Association of mean PI at 30-34 weeks with pregnancy outcomes also was studied. The adverse pregnancy outcomes were defined as any or the combination of pre-eclampsia, fetal growth restriction, intrauterine fetal death, preterm delivery and placental abruption. **Results:** The women with adverse pregnancy outcomes had significant higher mean PI (1.27 ± 0.55 vs. 0.99 ± 0.32 ; $p=0.003$) and higher prevalence of bilateral notch (20% vs. 4.6%, $p=0.001$) than those with normal outcomes. The mean ($\pm$ SD) PI in women with severe adverse outcome was 1.66 ± 0.66 vs. 1.0 ± 0.32 in women with normal pregnancy outcome ($p=0.002$). For a screen positive rate of 10.6% (mean PI > 95th percentile for gestational age and/or bilateral notches), the sensitivity for predicting an adverse outcome was 33.3%. The sensitivity increased to 60% for predicting a severe adverse outcome. Increased resistance in the third trimester was also associated with an adverse pregnancy outcome. **Conclusion:** Increased uterine artery PI in second and third trimester of pregnancy is associated with an increased risk of adverse pregnancy outcomes.

Keywords: Uterine artery, Doppler ultrasound, pregnancy trimesters, pregnancy outcomes

Introduction

Impaired placentation is one of the main causes of perinatal mortality and morbidity. Pre-eclampsia, fetal growth restriction (FGR), fetal death and abruptio placentae are the consequence of impaired placentation. Predicting the risk of these complications may improve the outcome by providing appropriate antenatal surveillance

and therapeutic intervention. Impaired placentation is associated with failure or inadequate trophoblastic invasion of the spiral arteries, resulting in increased impedance of flow in the uterine arteries [1]. The uteroplacental circulation is assessed by Doppler velocimetry of the uterine arteries [2]. In normal pregnancy the resistance in the uterine artery flow decreases with advancing gestational age; failure to get a low resistant circulation is associated with a subsequent risk of pregnancy adverse outcome [3]. Extensive research in the past two decades has showed the role of uterine artery Doppler in screening for adverse pregnancy outcomes in the first [4,5] and second [6,7] trimester of pregnancy with different sensitivity and specificity. Newer studies have combined uterine artery Doppler in the first trimester with maternal history and biochemical markers [8-11] and its changes between

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the first and second trimester to improve the detection rate [12]. Some studies investigate the value of uterine artery PI at 30-33 weeks gestation in the prediction of preeclampsia [13] but few studies have continued uterine artery PI measurement in the third trimester of pregnancy [8]. Despite many studies, prediction of women at increased risk of adverse outcome in those areas in which women do not benefit the same level of services is still an important aim and continuing research is needed in this field. Second trimester screening can be still of value for late scheduled and those with unplanned pregnancies who require closer antenatal monitoring.

The aim of this study was to determine the sensitivity, specificity, positive and negative predictive value of the uterine artery Doppler parameters in the prediction of adverse pregnancy outcomes in our population and look at the outcome of those with persistent resistance in the third trimester of pregnancy.

Material and methods

Uterine artery color Doppler was carried out in 435 consecutive singleton pregnancies attending for prenatal care at 18-24 weeks in three university hospitals. The participants were asked to attend for a second ultrasound examination at 30-34 weeks' gestation. The study was approved by the local Ethics Committee, and written informed consent was obtained from all participants. Inclusion criteria were singleton pregnancies with normal fetuses, not taking aspirin, heparin, metformin or antihypertensive drugs. Maternal age, parity, and history of medical disease were recorded. Uterine artery Doppler examinations were performed by trained faculties using Accuvix XQ (Medison, Korea), Acuson Sequoia 512, Mountain View, (Siemens Medical Solutions, CA) and voluson expert 730 (GE medical system) ultrasound machines. The abdominal probe was placed on each lower quadrant of the abdomen, angled medially, color Doppler imaging was used to identify the uterine arteries crossing over the external iliac artery, and measurements were taken 1 cm distal to the crossover point. Keeping the angle of insonation less than 30°, pulsed Doppler gate was placed over the target vessel until three consecutive waveforms was obtained. The mean PI was calculated from the left and right arteries. An abnormal Doppler pattern was defined as a mean PI > 95th percentile and/or the presence of a bilateral notch.

The 95th percentiles of the mean uterine PI was calculated separately for each gestational week according to standard methodology [14]. Using the reference range stated by Gomez et al. [15] the sensitivity, specificity,

and positive and negative predictive values for a cut-off of a mean PI > 95th percentile for gestational age and for the presence of bilateral notching in the prediction of pregnancy outcome were calculated. The presence or absence of bilateral notch was recorded. Doppler study was repeated at 30-34 weeks in 134 pregnant women who attended for further ultrasound examinations. The measures of outcome were pre-eclampsia, FGR, preterm delivery, placental abruption and fetal death. Preeclampsia was defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy; blood pressure at least 140/90mmHg on two occasions, 4 hours apart, with 300 mg or more proteinuria during 24 hours after 20 weeks' gestation [16]. Severe adverse outcomes were defined as pre-eclampsia and FGR requiring delivery before 34 weeks, preterm delivery before 34 weeks, placental abruption leading to emergency delivery and fetal death. All pregnant women received routine antenatal care and pregnancy outcomes were extracted from the records of each participating hospital.

Statistical analysis was performed using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA) Normality of distribution was checked by histogram and Kolmogorov-Smirnov test. Since mean uterine artery PI was not normally distributed, logarithmic transformation of the data was performed before statistical analysis. Continuous data were compared by independent t-test and categorical data were compared by Chi-square and Fisher's exact tests. The relationship of pregnancy outcome with Doppler findings was investigated by Binary logistic regression analysis.

Results

A cohort of 435 consecutive singleton pregnancies with uterine artery Doppler examinations between 18-24 weeks' gestation and 134 with second Doppler assessment at 30-34 weeks' with known pregnancy outcome were evidenced on our study population. The demographic characteristics and pregnancy outcomes are shown in Table I. Mean PI and the 95th for mean PI in our population was 1.03 and 1.60 respectively at 18-24 weeks' gestation. There was not significant correlation between mean PI and gestational age ($r = -0.073$, $p = 0.126$). The prevalence of bilateral notching also did not change significantly with gestational age (Table II). The women with combined adverse outcome had significant higher mean PI and higher prevalence of bilateral notching compared with women with normal outcome (Table III). The mean PI ($\pm$ SD) in women with severe adverse outcome was 1.66 ($\pm$ 0.66) versus 1.0 ($\pm$ 0.32)

in compared women ($p=0.002$). For a screen-positive rate of 10.6%, (mean $PI>95^{\text{th}}$ percentile for gestational age and/or bilateral notches), the sensitivity for predicting combined adverse outcomes was 33.3%. It increased to 60% for severe adverse outcome. Table 4 presented the screening characteristics of a mean $PI>95^{\text{th}}$ percentile and/or bilateral notches for any of adverse pregnancy outcomes and the relative odd ratios.

One hundred and thirty four women underwent a second Doppler ultrasound scan between 30–34 weeks: gestation; 111 had normal mean PI and 23 with mean $PI>95^{\text{th}}$ percentile and/or bilateral notches in first Doppler ultrasound scan. Eighty eight of 111 women remained normal in the second exam with a 6.8% rate of adverse outcome compared with a 43.8% rate of adverse pregnancy outcome in those with persistent $PI>95^{\text{th}}$ percentile in the second and third trimester ($p<0.001$).

All 5 pregnancies with preeclampsia requiring delivery before 34 weeks were detected by mean $PI>95^{\text{th}}$ percentile and/or bilateral notches (sensitivity 100%) and 4 of 5 pregnancies with FGR requiring delivery before 34 weeks were identified accurately (sensitivity 80%) with a false positive rate less than 10%.

There was not any significant relationship between mean $PI>95^{\text{th}}$ percentile and/or bilateral notches and spontaneous preterm delivery.

Discussion

The present study was performed prospectively in an unselected population of pregnant women who were attending for routine ultrasound at 18–24 weeks of pregnancy in three university hospitals. The 95^{th} percentile mean PI in our population was 1.60 similar to Papageorgiou et al (1.63) [17], and Fonseca et al (1.57) [18] but higher than 1.45 in the study by Lees et al [19]. However, this can be explained by differences in the prevalence of low or high risk pregnant population and gestational age at the time of the Doppler assessment.

A progressive decrease in mean uterine artery PI and the prevalence of bilateral notches with advancing gestational age was not found in this study while our previous study [20] and Napolitano et al study [11] showed a reduction of resistance between 12–20 weeks' gestation. Two studies by Gomez et al. who constructed reference range for uterine artery PI at 11–41 weeks and evaluated sequential changes in the uterine artery PI between the first and second trimester of pregnancy showed decreasing impedance with advancing gestation [15,21]. It seems that the small sample size in the present study could not show a dynamic process of decreasing impedance characteristic of normal placentation.

Table I.: Demographic characteristics and pregnancy outcomes of the study population

	N=435
Characteristic:	
Maternal age (years): mean ($\pm$ SD)	29.3 ($\pm$ 6.1)
Body mass index : mean ($\pm$ SD)	26.3 ($\pm$ 4.6)
Nulliparous: n (%)	214 (49.2)
Previous Intrauterine death: n (%)	26 (6.0)
Previous gestational hypertension: n (%)	17 (3.9)
Previous gestational diabetes: n (%)	8 (1.8)
Smoking in current pregnancy: n (%)	4 (0.9)
Pregnancy outcome:	
Gestational hypertension: n (%)	10 (2.3)
Preeclampsia (mild): n (%)	11 (2.5)
Preeclampsia (severe): n (%)	12 (2.8)
FGR: n (%)	17(3.9)
Placenta abruption: n (%)	8 (1.8)
Intrauterine death: n (%)	5 (1.1)
Combined adverse outcome: n (%)	45 (10.3)
Gestational age at delivery (weeks): median (range)	38 (24 –42)
Spontaneous Preterm delivery: n (%)	24 (5.5)
Birth weight (g): median (range)	3200 (610 – 4500)

Table II. Description of Doppler ultrasound findings at 18–24 weeks, gestation

Gestation- al week	Mean PI			Bilateral notch (%)
	Mean	SD	95^{th} percentile	
18	1.15	0.34	1.71	6.5
19	1.07	0.36	1.66	8.2
20	0.92	0.25	1.34	1.6
21	1.00	0.31	1.51	7.0
22	0.97	0.31	1.49	5.2
23	0.99	0.30	1.48	6.6
24	1.08	0.50	1.91	8.3
over all	1.03	0.35	1.60	6.2

Table III. Comparison of mean uterine artery pulsatility index (PI) and bilateral notch in pregnancies with normal and adverse outcome

Pregnancy outcome	PI	Bilateral notch
	Mean (+SD)	N (%)
Normal: n=390	0.99 (+ 0.32)	18 (4.6)
Combined adverse outcome: n=45	1.27 (+ 0.55)	9 (20)
P value	0.003*	0.001†

*independent sample t-test

†Chi-square test.

Table IV. The screening characteristics of a mean uterine artery PI >95th percentile and/or bilateral notches and relative odd ratios

Outcome	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	OR (95% CI)
Preeclampsia	7/23 (30.4)	373/412 (90.5)	7/46 (15.2)	373/389 (95.9)	4.2 (1.6 - 10.8)
Severe preeclampsia	6/12 (50.0)	383/423 (90.5)	6/46 (13.0)	383/389 (98.5)	9.6 (2.9 - 31.1)
FGR	8/17 (47.1)	380/418 (90.9)	8/46 (17.4)	380/389 (97.7)	8.9 (3.2 - 24.4)
Placenta abruption	3/8 (37.5)	384/427 (89.9)	3/46 (6.5)	384/389 (98.7)	5.3 (1.2 - 23.2)
Intrauterine death	3/5 (60)	387/430 (90.0)	3/46 (6.5)	387/389 (99.5)	13.5 (2.2 - 83.0)
Combined adverse outcome	15/45 (33.3)	359/390 (92.1)	15/46 (32.6)	359/389 (92.3)	5.8 (2.8 - 11.9)
Severe adverse outcome	9/15 (60)	383/420 (91.2)	9/46 (19.6)	383/389 (98.5)	15.5 (5.2 - 46)

The association between adverse pregnancy outcome and the higher uterine artery mean PI or the prevalence of diastolic notch in this study is in agreement with other uterine artery Doppler studies in the second trimester [6,7,22,23].

The sensitivity of abnormal uterine artery Doppler for all adverse outcomes was 33% which is compatible with ranges from 20-60% of older studies [24-26]. The newer studies have reported higher sensitivity [27,28]. The sensitivity was increased from 33% to 60% for severe adverse outcome that is consistent with the study by Albaiges et al [29] who showed increasing sensitivity from 45% to 90% for pre-eclampsia requiring delivery before 34 weeks' gestation. Papageorgiou et al also reported sensitivity of 70% for pre-eclampsia with FGR comparing 24% and 13% for isolated pre-eclampsia and FGR in a multicenter study [17]. Martin et al reported a stepwise increase in sensitivity with the severity of pre-eclampsia required in early delivery in a study with a large sample size [30].

There was no association between uterine artery PI >95th percentile and spontaneous preterm delivery in our study while the result of the study by Fonseca et al showed higher resistance in women with preterm delivery before 33 weeks [18].

The persistence of high resistance flow in third trimester in this study raised the risk of adverse pregnancy outcome. There was significant difference in the rate of adverse pregnancy outcome in those with persistently increased impedance to flow in the third trimester compared with those who converted low resistance (43.8% vs. 6.8%, $p < 0.001$). It seems women with a normal pattern of Doppler ultrasound in the second trimester do not require further Doppler assessment, but women with abnormal Doppler ultrasound in the second trimester would be better to have another Doppler examination in the third trimester, since if they remain abnormal, the risk of an adverse outcome would be increased, whereas if they establish low resistance, this risk probably would be very low.

Ghi et al reported the persistence of abnormal Doppler findings at 26-28 weeks was associated with increased risk of pre-eclampsia, SGA and NICU admission [31]. Maroni et al. evaluated pregnancy outcome in patients with increased uterine artery PI at 34 weeks' gestation and reported higher chance of delivering SGA babies, but the risk of other complications was not increased [32]. They suggested reassessment of uterine artery Doppler at 26 to 28 weeks in those with increased resistance in the second trimester of pregnancy as we also concluded. Kurdi et al. reported late normalization was not a benign process as it was associated with adverse pregnancy outcome [33]. Similarity Lai et al showed that the testing of uterine artery at 30-33 weeks could effectively identify women at risk for subsequent development of preeclampsia [13]. The study has the limitation of loss of follow up all the patients in the third trimester but patients in both groups, normal and abnormal uterine artery PI, were followed in the second trimester.

Conclusion

1. Uterine artery PI was higher in complicated pregnancies than those with normal outcome
2. Sensitivity of uterine artery PI for predicting severe adverse outcome was increased
3. Persistence of resistance in the third trimester was associated with adverse pregnancy outcome.

This information may be useful to improve pregnancy outcome by increased surveillance and timely intervention.

Conflict of interest: none

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