The Value of The Uterine Artery Doppler at 22-24 Weeks Gestation In The Prediction of Adverse Perinatal Outcome In an Unselected Population

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OBJECTIVE: To evaluate the value of uterine artery Doppler at 22-24 weeks gestation in the prediction of complications resulting from uteroplacental insufficiency in an unselected population.

STUDY DESIGN: A total of 383 women underwent color flow imaging combined with pulsed wave Doppler of both uterine arteries at 22-24 weeks gestation. The mean resistance index of both uterine arteries greater than 0.58, unilateral or bilateral early diastolic notches was considered abnormal.

RESULTS: The mean resistance index was greater than 0.58 in 17.5% of cases; the prevalence of unilateral and bilateral early diastolic notches was 11.5% and 3.7%, respectively. The prevalence of gestational hypertension, preeclampsia, and small for gestational age were 2.3%, 0.3%, and 10.2% respectively. The negative predictive values of abnormal resistance index, unilateral and bilateral notches for gestational hypertension were 99.1%, 98.2%, and 97.8% respectively. The negative predictive values of each parameter for babies small for gestational age were 91.8%, 92%, and 90.2% respectively. The positive predictive values of each parameter for gestational hypertension and for babies small for gestational age were less powerful. The combination of these Doppler parameters caused a slight increase in the positive predictive values compared to a single parameter.

CONCLUSIONS: The screening efficacy of uterine artery Doppler at 22-24 weeks gestation for adverse perinatal outcome seems poor in population at low risk; however, normal uterine artery Doppler studies in this population could be used to estimate an uncomplicated pregnancy.

The impedance to flow in the uterine arteries decreases with gestation in normal pregnancies, correlating with the trophoblastic invasion of the spiral arteries and their conversion into low resistance vessels. In pregnancies complicated with preeclampsia or fetal growth restriction, the impedance to flow in the uterine arteries increases.[1-3] The partial or complete failure of trophoblastic invasion[4] appears to be the primary defect that predisposes pregnancies to uteroplacental complications despite the reason for this failure is not clear.

Doppler ultrasound provides an indirect evidence of blood flow through the uteroplacental circulation.[1] There is a positive correlation between increased uterine vascular resistance, which is an elevated resistance index (RI) or persistence of an early diastolic notch in the Doppler waveform, and gestational hypertension, especially pre-eclampsia and fetal growth restriction.[1,5,6] Our aim in this study was to assess whether obstetric complications resulting from uteroplacental insufficiency in an unselected population can be predicted by means of uterine artery Doppler at 22-24 weeks of gestation.

Material and Methods

Our prospective study was conducted at the Department of Obstetrics and Gynecology, between December 2003 and January 2006. The protocol for the research project has been approved by a suitably constituted Ethics Committee of the institution within which the work was undertaken and that it conforms to the provisions of the Declaration of Helsinki (as revised in Edinburgh 2000). The subject gave informed consent and patient anonymity was preserved. A total of 691 women delivered in our hospital during the study period. Four hundred and fourteen women at 22-24 weeks gestation were seen in the antenatal clinic, of these 383 were eligible for the study. The causes for exclusion of patients were as follows: Previous history of preeclampsia or previous history of delivery a low birth baby (8 patients), chronic hypertension (10 patients), previous history of renal transplantation due to chronic renal disease (2 patients), and smoking (14 patients).

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The arterial blood pressure was measured in all patients to rule out chronic hypertension. Gestational age was based on the last menstrual period confirmed by a first trimester or an early second trimester ultrasonography. Two hundred and thirty-six (61.6%) patients were primipara and 147 (38.4%) multipara.

Uterine artery Doppler flow measurements were taken at 22-24 weeks of gestation by means of color flow imaging (Philips HDI 5000 Sono CT ultrasound machine with a C5-2 convex probe) combined with pulsed-wave Doppler. The patients were in the semirecumbent position; the transducer was placed longitudinally in the right and the left lower lateral quadrants of the abdomen angled medially. Color flow imaging identified the external iliac and uterine arteries[7] and the pulsed Doppler gate was placed over the uterine artery approximately 1 cm distal to the crossover point between the uterine and external iliac arteries; at least five consecutive similar waveforms were obtained and one waveform was taken for the measurement of RI in all cases. RI was measured and presence of an early diastolic uterine artery notch,[8] which is a clearly defined upturn of the flow velocity waveform at the beginning of diastole, in either one or both sides was noted. The mean RI from the sum of left and right uterine arteries was calculated. Values greater than 0.58 (above the second standard deviation of normal curves)[9] were considered abnormal. The mean resistance index of both uterine arteries greater than 0.58, unilateral or bilateral early diastolic notches was considered abnormal.

We investigated whether obstetric complications related with uteroplacental insufficiency including gestational hypertension, preeclampsia, small for gestational age (SGA), and abruptio placenta can be predicted by means of uterine artery Doppler at 22-24 weeks of gestation in an unselected population. We also evaluated the relationship between the abnormal Doppler of the uterine arteries at 22-24 weeks with different pregnancy outcomes.

All patients underwent blood pressure measurements weekly. All Doppler measurements were performed by the same doctor (D.E).

Preeclampsia was defined as blood pressure $\geq$ 140/90 mm Hg with $\geq$300 mg/24 h urinary protein after 20 weeks' gestation.[10] Gestational hypertension was defined as blood pressure $\geq$ 140/90 mm Hg without proteinuria. SGA was defined as birthweight below the 10th percentile for the gestational age.[11] Abruptio placentae was defined as vaginal bleeding and nonreassuring fetal status causing the emergency delivery at which there was evidence of retroplacental clot.

Data were analyzed by means of SPSS software (Statistical Package for the Social Sciences, version 11, SSPS Inc, Chicago, Ill, USA). Chi-square, and Fisher exact chi-square tests were used to determine whether statistically sig-nificant differences occurred between the groups. A P-value of <.05 was considered statistically significant.

Results

A total of 383 patients enrolled in the study. Two hundred and thirty-six (61.6%) patients were primipara and 147 (38.4%) multipara. The mean RI value was greater than 0.58 in 17.5% of cases; the prevalence of unilateral and bilateral early diastolic notches were 11.5% and 3.7%, respectively. Figures 1 and 2 show typical normal and pathological Doppler waveforms in the uterine artery.
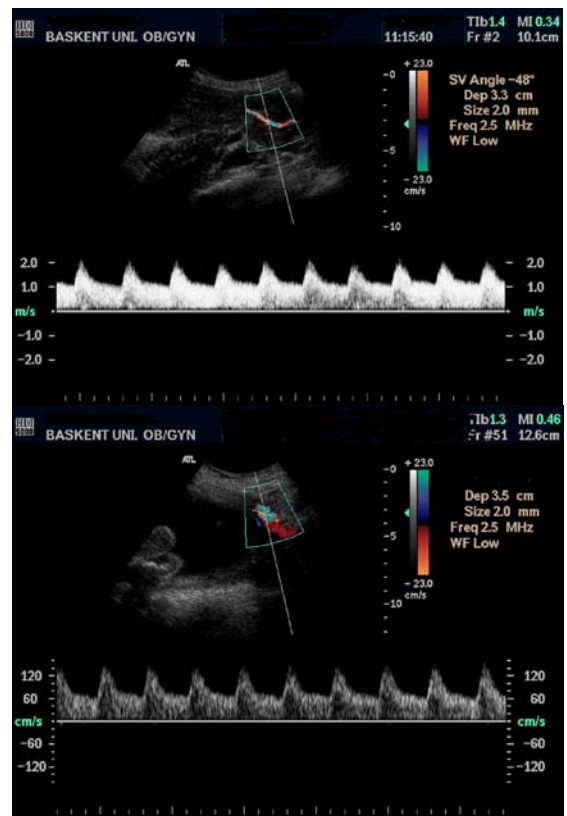

Figure 1. Typical normal flow velocity waveforms from the uterine artery at 24 and 22+4 weeks of gestation
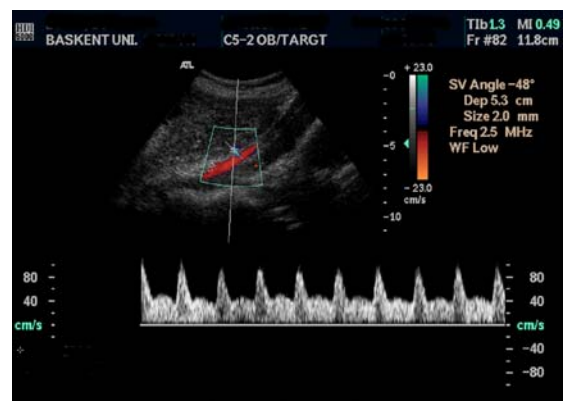

Figure 2. An abnormal flow velocity waveform from the uterine artery at 23 weeks of gestation

The prevalence of gestational hypertension, preeclampsia, SGA, and abruptio placenta were 2.3% (9/383), 0.3% (1/383), 10.2% (39/383), and 2.1% (8/383), respectively. Sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios of the abnormal uterine artery Doppler at 22-24 weeks of gestation for adverse perinatal outcome were shown in Tables 1 and 2. Sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios of the uterine artery resistance index >0.58 combined with unilateral notching of the uterine artery Doppler waveform at 22-24 weeks' gestation for the prediction of complications related with uteroplacental insufficiency were shown in Table 4. Sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios of the uterine artery resistance index >0.58 combined with bilateral notching of the uterine artery Doppler waveform at 22-24 weeks' gestation for adverse perinatal outcome were shown in Table 5.

In patients who had a mean RI of greater than 0.58, 9.0% of them developed gestational hypertension, and 19.4% gave birth to SGA babies. There is a significant relation between the abnormal RI of the uterine artery and adverse perinatal outcome (Tables 6 and 7). The 7.1% of cases that had bilateral uterine artery notching developed gestational hypertension, and 21.4% delivered SGA babies. There was no significant relation between bilateral notching in the uterine artery and increased risk for gestational hypertension or delivery of SGA babies (Tables 6 and 7). In patients who had a unilateral notching, gestational hypertension developed in 6.8% of cases, and 27.2% gave birth to SGA babies. Unilateral notching in the uterine artery was significantly related to increased risk for delivery of SGA babies; it did not show a significant relation with increased risk for gestational hypertension (Tables 6 and 7). The relationship between the abnormal RI of uterine arteries at 22-24 weeks gestation with different pregnancy outcomes was shown in Table 3. The relationship between either unilateral or bilateral notching of the uterine artery with different pregnancy outcomes was shown in Table 3.

Discussion

There are many published studies investigating the predictive value of Doppler ultrasound for poor perinatal outcome such as preeclampsia and intrauterine growth restriction.[1,12,13] They show differences in methodology and populations included in the works; additionally different studies were performed at different ranges of gestational age. There are few large studies indicating the relationship between Doppler ultrasound of the uteroplacental circulation and adverse perinatal outcome in unselected populations.[9,14,15,16,17] Bower *et al*.[18] evaluated the value of continuous wave Doppler ultrasound of the uterine arteries at 18-22 weeks as a screening test in an unselected population. They used two different criteria to define an abnormal flow velocity waveform; RI greater than 95th centile for gestation or the presence of an early diastolic notch or a combination of both of these. The negative predictive value of abnormal uterine artery flow velocity waveforms for the prediction of different pregnancy complications including preeclampsia, nonproteinuric hypertension, SGA babies <10th centile, and placental abruption was fairly good; the positive predictive values for these complications were less helpful. The detection of a high proportion of false positive tests was attributed to time of screening and the inclusion of the early diastolic notch in the definition of abnormal flow velocity waveforms. Because the early diastolic notch may persist until 26 weeks' gestation in some pregnancies with normal outcome[6] and trophoblastic invasion may be incomplete between 18-22 weeks of gestation.[19] Zimmermann *et al*.[20] found persistent bilateral notching in the main uterine artery at 21-24 weeks of gestation in 8% of low risk patients. Harrington *et al*.[21] reported incidence of bilateral notching 16.1% at 19-21 weeks and 8.9% at 24 weeks in an unselected population.

In our study, we did a one-stage screening because the time when the investigations were performed was not too early to cause the false positive tests. The predictive values of the mean RI >0.58, unilateral and bilateral early diastolic notches for gestational hypertension, and preeclampsia considered separately; the negative predictive value of each was excellent. The negative predictive value of each parameter for delivery of SGA babies, and abruptio placenta was also powerful. The high negative predictive value of each Doppler parameter meant that gestational hypertension or delivery of SGA babies was not likely to develop in this population. The high negative predictive value of each Doppler parameter also showed that abruptio placenta was not likely to occur in women who had a normal uterine artey Doppler at 22-24 weeks of gestation. The positive predictive value of each parameter for gestational hypertension and for delivery of SGA was less powerful. The combination of these Doppler parameters caused a slight increase in the positive predictive values compared to a single parameter in the prediction of gestational hypertension and delivery of SGA. If the population is at low risk for gestational hypertension or intrauterine growth retardation, the positive predictive values for the prediction of those obstetric complications may become less valid.[20] However, it must be taken into account the low prevalences of pregnancy complications related with uteroplacental insufficiency in our population to be able to make an evaluation about positive and negative predictive values of the abnormal uterine artery Doppler at 22-24 weeks for the prediction of those obstetric complications.

Valensise *et al*.[9] also investigated whether Doppler velocimetry of the uterine artery was a screening test for gestational hypertension in a low-risk primigravid women. In this

two-stage screening study, the average RI of both uterine arteries greater than 0.58 was considered abnormal at 22 weeks of gestation. The patients who had a pathological Doppler measurement underwent rescanning at 24 weeks of gestation. Their findings were comparable with our results with regard to the high specificity and the negative predictive value for the prediction of adverse perinatal outcome. Similarly, our results indicated that in a low risk population a normal uterine artery Doppler velocimetry could identify the patients that is not likely to develop complications resulting from uteroplacental insufficiency and other obstetric complications including abruptio placenta, gestational diabetes mellitus, preterm delivery, preterm premature rupture of membranes and oligohydramnios.

However, an abnormal RI in the uterine artery were significantly related to increased risk for gestational hypertension or delivery of SGA babies. Unilateral notching in the uterine artery was significantly related to increased risk for delivery of SGA babies; it did not show a significant relation with increased risk for gestational hypertension. There was no sig-

nificant relation between bilateral notching in the uterine artery and increased risk for gestational hypertension or delivery of SGA babies.

The abnormal Doppler of the uterine artery at 22-24 weeks of gestation seemed less helpful in predicting different pregnancy complications including gestational diabetes mellitus, preterm delivery, preterm premature rupture of membranes and oligohydramnios.

As a conclusion, normal uterine artery Doppler waveforms at 22-24 weeks of gestation in an unselected population are helpful to identify women at low risk of developing obstetric complications resulting from uteroplacental insufficiency. However, the screening efficacy of uterine artery Doppler at 22-24 weeks' gestation for adverse perinatal outcome seems less powerful, and also this test does not seem to be effective for predicting abruptio placenta and other obstetric complications including preterm delivery, preterm premature rupture of membranes, gestational diabetes mellitus and oligohydramnios in this population.

Table 1. The prediction of adverse perinatal outcome by uterine artery resistance index >0.58 at 22-24 weeks

	Preeclampsia	GH	SGA	Abruptio placenta
Sensitivity	100%	67%	33.%	25%
Specificity	83%	84%	84%	83%
PPV	1.5%	9.0%	19.4%	3.0%
NPV	100%	99.1%	91.8%	98.1%
LR + (±95% CI) :	5.79	4.09 (2.03-6.17)	2.12 (1.22-3.39)	1.4(0.27-3.61)
LR - (±95% CI) :	0	0.40 (0.12-0.79)	0.79 (0.60-0.96)	0.9 (0.48-1.16)

GH = *Gestational Hypertension,* **SGA** = *Small for Gestational Age,* **PPV** = *Positive Predictive Value,* **NPV** = *Negative Predictive Value,* **LR+** = *Positive likelihood ratio within 95% confidence interval.* **LR - =** *Negative likelihood ratio within 95% confidence interval*

Table 2. The prediction of adverse perinatal outcome by unilateral and bilateral notching of the uterine artery Doppler waveform at 22-24 weeks

	Preeclampsia	GH	SGA	Abruptio placenta
Unilateral notch (n=44)				
Sensitivity	0	33%	31%	63%
Specificity	88%	89%	91%	90%
PPV	0	6.8%	27.2%	11.4%
NPV	99.7%	98.2%	92%	99.1%
LR + (±95% CI) :	0	3.04 (0.86-6.53)	3.31 (1.78-5.70)	6.0 (2.64-9.93)
LR - (±95% CI) :	1.13	0.75 (0.38-1.02)	0.76 (0.59-0.91)	0.42 (0.12-0.8)
Bilateral notches (n=14)				
Sensitivity	0	11%	8%	0
Specificity	96%	97%	97%	96%
PPV	0	7.1%	21.4%	0
NPV	99.7%	97.8%	90.2%	97.8%
LR + (±95% CI) :	0	3.20 (0.18-14.3)	2.41 (0.58-7.48)	0
LR - (±95% CI) :	1.04	0.92 (0.59-1.04)	0.95 (0.83-1.02)	1.04

GH = *Gestational Hypertension,* **SGA** = *Small for Gestational Age,* **PPV** = *Positive Predictive Value,* **NPV** = *Negative Predictive Value,*
LR+ = *Positive likelihood ratio within 95% confidence interval,* **LR - =** *Negative likelihood ratio within 95% confidence interval*

Table 3. The relationship between uterine artery resistance index >0.58, unilateral and bilateral notching of the uterine artery Doppler at 22-24 weeks with different outcomes

	GDM§	PPROM	Preterm delivery	Oligohydramnios	*p-Value**
Resistance index>0.58 (n=67)	7(10.4%)	0	0	1(1.5%)	NS
Resistance index≤0.58 (n=316)	13(4.1%)	4(1.3%)	6(1.9%)	4(1.3%)	
Unilateral notch+ (n=44)	1(7.1%)	0	0	0	NS
Unilateral notch- (n=339)	19(5.1%)	4(1.1%)	6(1.6%)	5(1.4%)	
Bilateral notches+ (n=14)	1(7.1%)	0	0	0	NS
Bilateral notches- (n=369)	19(5.1%)	4(1.1%)	6(1.6%)	5(1.4%)	
Any		Resistance index >0.58		Unilateral notch	Bilateral notches
Sensitivity		22.9%		20%	2.9%
Specificity		83.0%		89.4%	96.3%
PPV		11.9%		15.9%	7.1%
NPV		91.5%		91.7%	90.8%

§ Values are expressed as number (percent).
* Chi-square test was applied.

NS = statistically not significant,
GDM = gestational diabetes mellitus,
PPROM = preterm premature rupture of membranes
PPV = Positive predictive value,
NPV = Negative predictive value.
Any includes at least one of the following complications (GDM, PPROM, preterm delivery and oligohydramnios).

Table 4. The prediction of adverse perinatal outcome by uterine artery resistance index >0.58 combined with unilateral notching of the uterine artery Doppler waveform 22-24 weeks

	Preeclampsia	GH	SGA	Abruptio placenta
Sensitivity	0	33%	10%	25%
Specificity	95%	96%	96%	96%
PPV	0	16.7%	22.2%	11.1%
NPV	99.7%	98.3%	90.4%	98.4%
LR + (±95% CI) :	0	8.31 (2.24-20.4)	2.52 (0.76-6.73)	5.8 (1.06-16.73)
LR - (±95% CI) :	1.05	0.69 (0.35-0.94)	0.94 (0.80-1.01)	0.78 (0.42-1.0)

GH = Gestational Hypertension
SGA= Small for Gestational Age
PPV = Positive Predictive Value
NPV = Negative Predictive Value
LR+ = Positive likelihood ratio within 95% confidence interval
LR - = Negative likelihood ratio within 95% confidence interval

Table 5. The prediction of adverse perinatal outcome by uterine artery resistance index >0.58 combined with bilateral notching of the uterine artery Doppler waveform 22-24 weeks

	Preeclampsia	GH	SGA	Abruptio placenta
Sensitivity	0%	11%	3%	0%
Specificity	99%	99%	99%	99%
PPV	0%	25%	25%	0%
NPV	99.7%	97.9%	90%	97.9%
LR + (±95% CI) :	0	13.8 (0.6-100.6)	2.94 (0.14-23.8)	0
LR - (±95% CI) :	1.01	0.90 (0.58-1	0.98 (0.89-1.02)	1.01

GH = *Gestational Hypertension*
SGA = *Small for Gestational Age*
PPV = *Positive Predictive Value*
NPV = *Negative Predictive Value*
LR+ = *Positive likelihood ratio within 95% confidence interval*
LR - = *Negative likelihood ratio within 95% confidence interval*

Table 6. The incidence of adverse pregnancy outcome with regard to abnormal Doppler findings in the uterine artery

	Normal	GH§	p –Value*
RI > 0.58 (n =67)	61 (91.0%)	6 (9.0%)	0.001
RI <= 0.58 (n =316)	313 (99.1%)	3 (0.9%)	
Bilateral notch + (n =14)	13 (92.9%)	1 (7.1%)	NS
Bilateral notch - (n = 369)	361 (97.8%)	8 (2.2%)	
Unilateral notch + (n =44)	41 (93.2%)	3 (6.8%)	NS
Unilateral notch - (n =339)	333 (98.2%)	6 (1.8%)	

§ Values are expressed as number and percent.
* Chi-square and Fisher exact chi-square tests were used.

RI= Resistance Index
GH= Gestational Hypertension

Table 7. The incidence of adverse pregnancy outcome with regard to abnormal Doppler findings in the uterine artery

	Normal	SGA§	p –Value *
RI > 0.58 (n =67)	54 (80.6%)	13 (19.4%)	0.006
RI <= 0.58 (n =316)	290 (91.8%)	26 (8.2%)	
Bilateral notches + (n =14)	11 (78.6.2%)	3 (21.4%)	NS
Bilateral notches - (n = 369)	333 (90.2%)	36 (9.8%)	
Unilateral notch + (n =44)	32 (72.7%)	12 (27.2%)	0.0001
Unilateral notch - (n =339)	312 (92.0%)	27 (8.0%)	

§ Values are expressed as number and percent
* Chi-square and Fisher exact chi-square tests were used

RI= *Resistance Index*
SGA= *Small for Gestational Age*

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