

Relationship between second-trimester uterine artery Doppler and spontaneous early preterm delivery

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KEYWORDS: preterm delivery; transvaginal sonography; uterine artery Doppler

ABSTRACT

Objective To evaluate the relationship between impedance to flow in the uterine arteries at 22–24 weeks and subsequent spontaneous delivery before 33 weeks.

Methods The pulsatility index (PI) in the uterine arteries was measured by transvaginal sonography at 22–24 weeks in 33 629 women with singleton pregnancies attending for routine antenatal care. The distribution of PI in the 237 patients with live births before 33 weeks, after spontaneous onset of labor, was compared to that in 31 633 patients with live births at or after 33 weeks.

Results The median uterine artery mean PI was significantly higher in those women delivering before 33 weeks than in those delivering at or after 33 weeks. The mean PI was 1.57, which is the 95th centile, in 1525 (4.8%) of those delivering at or after 33 weeks and in 19 (8.0%) of the deliveries before 33 weeks. Multiple regression analysis demonstrated that the significant predictors of spontaneous delivery before 33 weeks were ethnic origin, smoking status, previous obstetric history and uterine artery mean PI. However, the prediction of spontaneous early preterm delivery by a combination of maternal characteristics and uterine artery Doppler was not significantly higher than maternal characteristics alone (area under the receiver–operating characteristics curve: 0.704, 95% CI 0.669–0.740 vs. 0.684, 95% CI 0.647–0.722; $P = 0.062$).

Conclusions Uterine artery PI in spontaneous deliveries before 33 weeks is higher than in those women delivering at or after 33 weeks. However, uterine artery Doppler does not provide a significant improvement in the prediction of spontaneous early delivery provided by maternal demographic characteristics and previous obstetric history. Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Preterm delivery is the leading cause of neonatal morbidity and mortality. The outlook for preterm infants is dependent on the gestational age at delivery, survival increasing from less than 10% for those born at 23 weeks to more than 95% by 33 weeks^{1,2}. In about half the cases of early preterm delivery the onset of labor is spontaneous and in the other half it is medically indicated, mainly for severe pre-eclampsia and intrauterine growth restriction (IUGR).

There is extensive evidence that the development of pre-eclampsia and IUGR are a consequence of impaired trophoblastic invasion of the myometrial segment of the maternal spiral arteries, resulting in increased impedance to flow in the uterine arteries³. Doppler ultrasound can be used to identify the uterine arteries and several studies have documented that increased pulsatility index (PI) at 20–24 weeks of gestation can identify, at a false-positive rate of 5%, about 75% of women who subsequently develop pre-eclampsia of sufficient severity to require delivery before 33 weeks^{4–8}.

Histological studies have reported impaired trophoblastic invasion of the maternal spiral arteries in pregnancies complicated by miscarriage and spontaneous preterm delivery with or without preterm prelabor rupture of membranes (PPROM)^{9–13}. However, studies examining uterine artery Doppler in pregnancies resulting in preterm delivery have reported contradictory results. Strigini *et al.*¹⁴ measured the systolic to diastolic ratio (S/D) in the waveforms from the uterine arteries in 417 women at 25–36 weeks of gestation and reported that the S/D was significantly higher in the 31 women with spontaneous preterm delivery. In contrast, Cobian-Sanchez *et al.*¹⁵ reported that the mean resistance index in the uterine arteries at 18–23 weeks in 72 singleton pregnancies that delivered before 34 weeks was not significantly different from that in 5472 patients who delivered at term.

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In this multicenter study of uterine artery Doppler at 22–24 weeks in 33 629 singleton pregnancies we examined the relationship between PI and subsequent spontaneous delivery before 33 weeks (i.e. less than 231 days).

METHODS

The data for the present study were derived from a prospective multicenter screening study carried out between October 1999 and October 2004 in seven maternity hospitals in and around London, UK^{6–8}. The study was approved by the South Thames Multicenter Research Ethics Committee, and written informed consent was obtained from all participating women^{6,7}. The first part of the study was observational; but in the second part, women with mean uterine artery PI above 1.6 were invited to participate in a randomized study of aspirin (150 mg/day) or placebo; the results of the randomized study demonstrated no significant difference in the outcome of the two groups⁷.

In all patients one ultrasound examination was carried out at 11 + 0 to 13 + 6 weeks, for pregnancy dating and early diagnosis of major fetal defects, and another at 22–24 weeks, for examination of fetal anatomy and growth. At the second-trimester scan women were given the option of transvaginal ultrasonographic measurement of the uterine artery PI to screen for pre-eclampsia and IUGR. Women with major fetal abnormalities, painful regular uterine contractions, or a history of ruptured membranes or cervical cerclage *in situ* were excluded from screening. Color flow mapping was used to identify the left and right uterine arteries at the level of the internal cervical os and pulsed-wave Doppler was then used to obtain three similar consecutive waveforms and the PI was measured. The mean PI of the two arteries was calculated. All sonographers had received the Certificate of Competence in Doppler of The Fetal Medicine Foundation (<http://www.fetalmedicine.com>).

Patient characteristics, including demographic data and obstetric and medical history, were obtained from the patients at the first hospital visit and entered into a computer database. Data on pregnancy outcome were collected from the hospital maternity records or the patients' general medical practitioners. The obstetric records of all patients delivering before 33 weeks were examined to determine if the preterm delivery was medically indicated or spontaneous. The latter category included those women with spontaneous onset of labor and those with PPRM.

Statistical analysis

Two groups of patients were examined: those with spontaneous onset of labor leading to delivery of liveborn infants before 33 weeks and those with delivery of liveborn infants at or after 33 weeks. The significance of differences in uterine artery mean PI between the two

groups was determined using an unpaired *t*-test of unequal variance after log₁₀ transformation of the uterine artery mean PI to achieve a Gaussian distribution of the data.

Univariate regression analysis was used to investigate the effect on spontaneous delivery before 33 weeks of log₁₀ mean uterine artery PI as a continuous variable, and the following as categorical variables: maternal age (less than 20 years, 20–35 years or more than 35 years), body mass index (less than 18.5 kg/m², 18.5–24.9 kg/m² or more than 24.9 kg/m²), ethnic origin (Caucasian, Afro-Caribbean, Asian or Oriental), cigarette smoking (no or yes), obstetric history (previous deliveries at term, primigravidae and those with previous fetal losses at less than 16 weeks, at least one previous delivery at 16–23 weeks, at least one previous delivery at 24–32 weeks, or at least one previous delivery at 33–36 weeks) and previous pre-eclampsia (no or yes). Multiple logistic regression analysis was subsequently performed to determine the significant independent contribution of those variables yielding a value of *P* < 0.05 in the univariate analysis. Receiver–operating characteristics (ROC) curves were constructed and the area under the curve were used to compare the performance of mean uterine artery PI, maternal characteristics and obstetric history in the prediction of spontaneous preterm delivery before 33 weeks' gestation.

All statistical analysis was performed using Medcalc version 8.0.0.1 (<http://www.medcalc.be>) and SPSS version 12 (SPSS, Woking, UK).

RESULTS

Uterine artery PI was measured in 33 629 patients, but for the present study the following groups were excluded from further analysis: 1437 (4.3%) with no follow-up, 162 (0.5%) stillbirths and 160 (0.5%) iatrogenic deliveries of live births before 33 weeks, mainly for pre-eclampsia or IUGR. The study population comprised 31 870 patients with live births, including 237 (0.7%) that delivered before 33 weeks and 31 633 that delivered at or after 33 weeks.

The demographic characteristics of the study population are shown in Table 1. The median of the uterine artery mean PI was significantly higher in the deliveries before 33 weeks than in those delivering at or after 33 weeks (1.10 vs. 1.00; *P* < 0.001) (Table 1, Figure 1). The uterine artery mean PI was above 1.57, which is the 95th centile, in 1525 (4.8%) of those delivering at or after 33 weeks and in 19 (8.0%) of those delivering before 33 weeks.

In 71/237 spontaneous live births before 33 weeks there was PPRM, and in this group the median uterine artery mean PI was 1.13, which was not significantly different from the median value of 1.05 in the 166 that were not preceded by PPRM (*P* = 0.312). The uterine artery mean PI was above the 95th centile in 9.9% (7/71) and 7.2% (12/166) of the cases with spontaneous preterm delivery with and without PPRM, respectively (*P* = 0.660).

Table 1 Characteristics of the study population

Variable	Delivery \geq 33 weeks	Delivery < 33 weeks	P
Age (years) (<i>n</i> (%))			0.04
< 20	1406 (4.4)	18 (7.6)	
20–35	25 777 (81.5)	182 (76.8)	
> 35	4450 (14.1)	37 (15.6)	
Ethnic origin (<i>n</i> (%))			0.003
Caucasian	22 494 (71.1)	145 (61.20)	
Afro-Caribbean	6398 (20.2)	69 (29.1)	
Asian	2366 (7.5)	18 (7.6)	
Oriental	375 (1.2)	5 (2.1)	
Body mass index (<i>n</i> (%))			0.082
< 18.5	813 (2.6)	11 (4.6)	
18.5–24.9	16 307 (51.5)	112 (47.3)	
> 24.9	14 513 (45.9)	114 (48.1)	
Smoking (<i>n</i> (%))			0.001
Yes	4617 (14.6)	53 (22.4)	
Obstetric history (<i>n</i> (%))			< 0.001
Delivery at \geq 37 weeks	13 324 (42.1)	64 (27.0)	
Nulliparous	16 206 (51.2)	103 (43.5)	
Delivery at 16–23 weeks	396 (1.3)	13 (5.5)	
Delivery at 24–32 weeks	587 (1.9)	38 (16.0)	
Delivery at 33–36 weeks	1120 (3.5)	19 (8.0)	
Previous pre-eclampsia (<i>n</i> (%))			0.874
Yes	1402 (4.4)	10 (4.2)	
Uterine artery Doppler			< 0.001
Median mean PI (SD (%))*	1.00 (10.9)	1.10 (11.0)	
Mean PI above 1.57 (<i>n</i> (%))	1525 (4.8)	19 (8.0)	0.032

*Since a logarithmic transformation was used for the mean pulsatility index (PI) the SD for this variable is expressed as a percentage of magnitude.

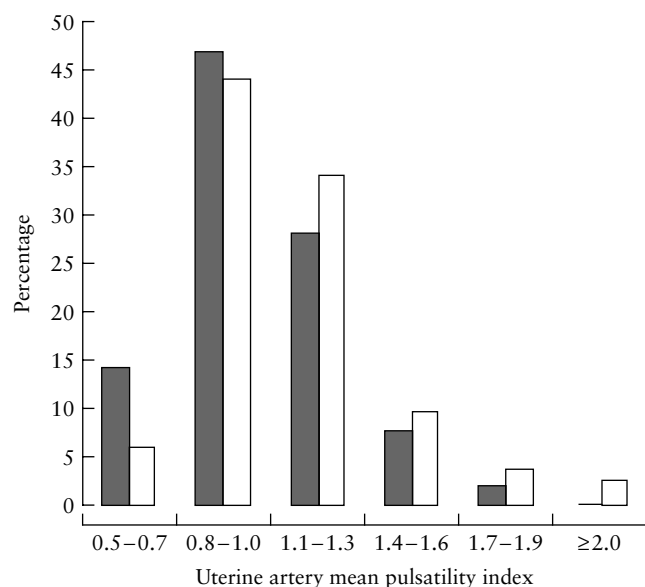


Figure 1 Frequency distribution of uterine artery mean pulsatility index at 22–24 weeks in 31 633 singleton pregnancies with live births at or after 33 weeks (filled bars) and 237 spontaneous live births before 33 weeks (empty bars).

Univariate regression analysis demonstrated that significant predictors of delivery before 33 weeks ($n = 237$) were maternal characteristics (demographic and previous obstetric history) and uterine artery mean PI (Table 2). Multiple regression demonstrated that the significant

predictors of delivery before 33 weeks were ethnic origin, smoking status, previous obstetric history and uterine artery mean PI. The ROC curves comparing the performance of uterine artery PI alone, maternal characteristics alone, and the model combining the two in the prediction of spontaneous live birth before 33 weeks are shown in Figure 2. The performance of the combined model was significantly higher than uterine artery Doppler alone (area under the ROC curve (AUC): 0.704, 95% CI 0.669–0.740 vs. 0.584, 95% CI 0.548–0.619; $P < 0.001$) but not maternal characteristics alone (AUC: 0.684, 95% CI 0.647–0.722; $P = 0.062$). For a false-positive rate of 5%, the detection rates of spontaneous live birth before 33 weeks were 28.7% for the combined model, 8.0% for mean uterine artery PI alone and 27.0% for maternal characteristics alone.

DISCUSSION

The present study has demonstrated a significant association between increased uterine artery mean PI at 22–24 weeks and spontaneous early delivery, irrespective of whether this was preceded by PPROM or not.

In the case of pregnancies developing pre-eclampsia and IUGR that require iatrogenic early delivery, increased uterine artery PI, which is found in about 75% of cases^{4–8}, is thought to be the consequence of impaired trophoblastic invasion of the myometrial segment of the maternal spiral arteries³. In pregnancies resulting in spontaneous early

Table 2 Univariate and multivariate analysis in the prediction of spontaneous live birth before 33 weeks of gestation ($n = 237$) by maternal age, ethnicity, body mass index, smoking, previous obstetric history, previous history of pre-eclampsia and uterine artery Doppler

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Age (years)			0.04			0.11
< 20	1			1		
20–35	0.55	0.34–0.89		0.58	0.35–0.96	
> 35	0.65	0.37–1.14		0.59	0.32–1.07	
Ethnic origin			0.003			0.03
Caucasian	1			1		
Afro-Caribbean	1.67	1.25–2.23		1.48	1.10–1.99	
Asian	1.18	0.72–1.93		1.28	0.78–2.12	
Oriental	2.07	0.84–5.07		2.37	0.96–5.88	
Body mass index			0.09			
< 18.5	1			—	—	
18.5–24.9	0.51	0.27–0.95		—	—	
> 24.9	0.58	0.31–1.08		—	—	
Smoking	1.68	1.24–2.29	0.001	1.58	1.14–2.18	0.006
Obstetric history			< 0.0001			< 0.001
Delivery at ≥ 37 weeks	1			1		
Nulliparous	1.32	0.97–1.81		1.28	0.93–1.77	
Delivery at 16–23 weeks	6.83	3.73–12.51		6.10	3.31–11.23	
Delivery at 24–32 weeks	13.48	8.95–20.30		11.73	7.75–17.75	
Delivery at 33–36 weeks	3.53	2.11–5.91		3.32	1.98–5.57	
Previous pre-eclampsia			0.875			
No	1			—	—	
Yes	0.95	0.50–1.80		—	—	
Uterine artery Doppler						
Log uterine artery mean PI	14.83	4.94–44.55	< 0.0001	7.32	2.42–22.18	< 0.0001

OR, odds ratio; PI, pulsatility index.

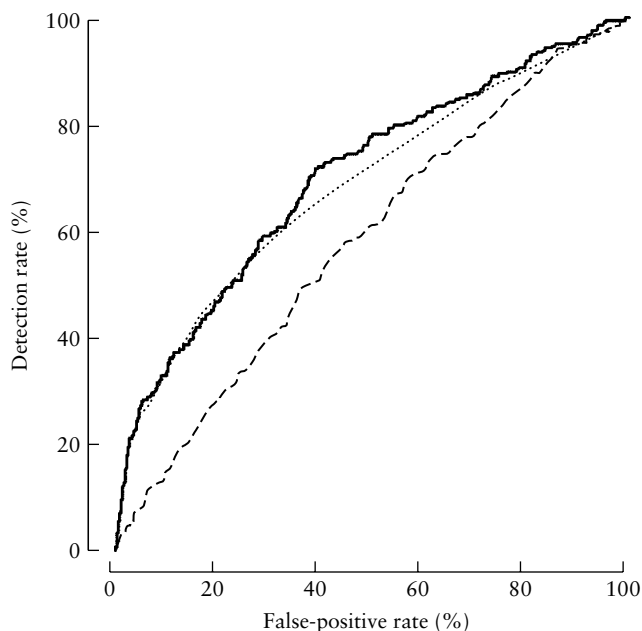


Figure 2 Receiver–operating characteristics curves comparing the performance of uterine artery mean pulsatility index (PI) at 22–24 weeks alone (dashed line), maternal characteristics and previous obstetric history (dotted line) and the model for uterine artery mean PI, maternal characteristics and previous obstetric history (solid line) in the prediction of spontaneous live birth before 33 weeks.

delivery, the observed increase in uterine artery PI is also likely to be the consequence of impaired placentation, because histological studies in such patients demonstrated failure of the physiological transformation of the spiral arteries^{10–13}.

In patients with spontaneous early delivery, compared to those delivering at or after 33 weeks, the median uterine artery PI was significantly higher and the individual values were above the 95th centile in twice as many cases. However, uterine artery Doppler does not provide a significant improvement in the prediction of spontaneous early delivery provided by maternal demographic characteristics and previous obstetric history. This is because only a small proportion of patients with spontaneous early delivery had increased uterine artery PI, which is compatible with the observations of Kim *et al.*¹³. These authors demonstrated that in spontaneous preterm delivery, compared to pre-eclampsia, the percentage of spiral arteries with failure of physiological transformation in the myometrium was much lower (31% vs. 81%) and the percentage of patients in whom no vessels were transformed was lower (19% vs. 56%)¹³.

In conclusion, uterine artery PI in spontaneous deliveries before 33 weeks is higher than in those women delivering at or after 33 weeks. However, uterine artery

Doppler does not provide a significant improvement in the prediction of spontaneous early delivery provided by maternal demographic characteristics and previous obstetric history.

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