

Prediction of pre-eclampsia by uterine artery Doppler imaging: relationship to gestational age at delivery and small-for-gestational age

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ABSTRACT

Objectives To determine the relationship between pre-eclampsia, small-for-gestational age (SGA) and gestational age at delivery, and the effect of this relationship on the prediction of pre-eclampsia by uterine artery Doppler imaging.

Methods This was a multicenter prospective Doppler study of the uterine artery at 22–24 weeks of gestation in unselected women with singleton pregnancies.

Results In the 30 639 pregnancies examined, the median uterine artery pulsatility index (PI) was 1.0 and the 95th centile was 1.58. In 614 (2%) cases the woman developed pre-eclampsia and in this group there was an inverse significant association between the gestational age at delivery and prevalence of SGA ($r = -0.99$, $P < 0.0001$), and between the gestational at delivery and mean uterine artery PI ($r = -0.51$, $P < 0.0001$) and prevalence of mean uterine artery PI above the 95th centile ($r = -0.99$, $P < 0.0001$). The mean uterine artery PI was above the 95th centile in 77.2% of women who developed pre-eclampsia requiring delivery before 34 weeks, in 35.9% of those delivering at 34–37 weeks and in 21.9% of those delivering after 37 weeks. The respective percentages were 82.3%, 46.9% and 28.8% for those with pre-eclampsia and SGA, and 43.8%, 21.2% and 8.4% for those with SGA but without pre-eclampsia.

Conclusions Pre-eclampsia requiring early delivery is more likely to be associated with SGA than less severe pre-eclampsia in women who deliver at term. Doppler ultrasound assessment of the uterine arteries is more effective in identifying pre-eclampsia requiring preterm than term delivery. Copyright © 2008 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Pre-eclampsia is a heterogeneous disorder with variable maternal and fetal manifestations. Although the diagnosis of the condition relies on the demonstration of hypertension and proteinuria in the mother, the clinical outcome depends primarily on the presence of multisystem dysfunction in the mother and impairment of growth and oxygenation in the fetus. There is evidence that the severity of the fetal compromise is mainly related to the gestational age at the onset of pre-eclampsia. Thus, pathological studies have shown that the prevalence of placental lesions in women with pre-eclampsia is inversely related to the gestational age at delivery^{1,2}. Furthermore, epidemiological studies have reported that preterm pre-eclampsia is associated with low birth weight, whereas the birth weight is often normal or increased in term pre-eclampsia^{3–6}.

Doppler ultrasound studies of the uterine arteries have demonstrated that the clinical manifestations of pre-eclampsia are preceded by evidence of impaired placental perfusion^{7,8}. A multicenter prospective screening study using uterine artery Doppler ultrasound imaging at 22–24 weeks of gestation in about 8000 singleton pregnancies showed that the sensitivity for pre-eclampsia with small-for-gestational age (SGA) is substantially higher than that for pre-eclampsia without SGA (69% versus 24%)⁹. Furthermore, a study of more than 30 000 pregnancies showed that the pulsatility index (PI) was above the 95th centile in 78% of those that subsequently developed pre-eclampsia requiring delivery before 34 weeks, compared with 32% for late pre-eclampsia¹⁰.

In this study we explore further the interrelation between pre-eclampsia, SGA and gestational age at delivery, and the effect of this relationship on the

prediction of pre-eclampsia and/or SGA by uterine artery Doppler imaging.

METHODS

This was a multicenter prospective screening study of pre-eclampsia in unselected low-risk women with singleton pregnancies involving seven hospitals in and around London, UK, from July 1999 to July 2004¹⁰. In each patient transvaginal sonography was carried out at 22–24 weeks of gestation and color flow mapping with pulsed wave Doppler imaging was used to measure PI in the left and right uterine arteries; the mean PI of the two vessels was calculated. The transvaginal, rather than transabdominal, approach was used because the cervical length was measured at the same time to assess the risk of spontaneous preterm delivery. The study was approved by the South Thames Multicentre Research Ethics Committee, as well as the local ethics committees of individual hospitals. Written informed consent was obtained from the women agreeing to participate in the study. The results of the study on the value of combining uterine artery mean PI with maternal factors in the prediction of pre-eclampsia have been reported previously¹⁰.

The primary outcome measure was pre-eclampsia, defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy. This requires two recordings of diastolic blood pressure of 90 mmHg at least 4 h apart in previously normotensive women, and proteinuria of 300 mg or more in 24 h, or two readings of at least ++ on dipstick analysis of mid-stream or catheter urine specimens if no 24-h collection is available¹¹.

SGA was defined as birth weight less than the 10th centile after adjustments for gestational at delivery, infant sex, maternal ethnicity, parity, height and weight¹².

Maternal history and Doppler findings were recorded in a computer database at the time of the Doppler studies in each participating center. Data on pregnancy outcomes

were obtained from examination of individual patient notes and labor ward records.

Statistical analysis

Chi-square or Fisher's exact test was used to analyze categorical variables, and unpaired *t*-test, Mann–Whitney *U*-test and regression analysis were used for continuous variables. Two-sided significance tests are reported. Statistical analysis was performed using Microsoft Excel 2000 and Statsdirect version 2.4.1.

RESULTS

In total 32 157 women were recruited to the study. Complete outcome data were available for 30 639 (95.3%) of these, who formed the study population. The mean gestational age at screening was 23 (range, 22–24) weeks. The median PI and 95th centile were 1.02 and 1.58, respectively. There was no significant association between mean uterine artery PI and gestational age at screening.

The patients were subdivided into three groups: those who subsequently developed pre-eclampsia with or without SGA (*n* = 614, 2.0%), those who developed SGA without pre-eclampsia (*n* = 4364, 14.2%), and those unaffected by either pre-eclampsia or SGA (*n* = 25 661, 83.8%). The pregnancy characteristics of the three groups are compared in Table 1.

In the pre-eclampsia group, there was an inverse significant association between the gestational age at delivery and prevalence of SGA ($r = -0.99$, $P < 0.0001$; Figure 1), and between the gestational age at delivery and mean uterine artery PI ($r = -0.51$, $P < 0.0001$; Figure 2a) and prevalence of mean uterine artery PI above the 95th centile ($r = -0.99$, $P < 0.0001$; Table 2). Similarly, in the SGA without pre-eclampsia group there was a significant inverse association between the gestational age at delivery and mean uterine artery PI ($r = -0.27$, $P < 0.0001$;

Table 1 Characteristics of pregnancies resulting in pre-eclampsia (with or without small-for-gestational age (SGA) neonate), SGA without pre-eclampsia and unaffected by pre-eclampsia or SGA

Characteristic	Unaffected (<i>n</i> = 25 661)	Pre-eclampsia (<i>n</i> = 614)	P*	SGA (<i>n</i> = 4364)	P*
Age (years, median (range))	30 (26–34)	31 (26–34)	0.02	30 (25–34)	0.1
Ethnic group (<i>n</i> (%))					
White	18 583 (72.4)	366 (59.6)	0.5	3166 (72.5)	0.9
Black	4642 (18.1)	195 (31.8)		788 (18.1)	
Other	2436 (9.5)	53 (8.6)		410 (9.4)	
Nulliparous (<i>n</i> (%))	12 971 (50.5)	409 (66.6)	< 0.0001	2291 (52.5)	0.01
BMI (kg/m ² , median (IQR))	25 (23–30)	26 (22–28)	< 0.0001	25 (22–28)	0.6
Cigarette smoker (<i>n</i> (%))	3339 (13.0)	50 (8.1)	< 0.0001	1163 (26.6)	< 0.0001
Past history of pre-eclampsia (<i>n</i> (%))	1131 (4.4)	98 (16.0)	< 0.0001	216 (4.9)	0.3
Gestational age at screening (weeks, median (IQR))	23 (22.8–23.3)	23 (22.9–23.4)	0.2	23 (22.9–23.4)	< 0.0001
Uterine artery mean PI (median (IQR))	1.01 (0.9–1.2)	1.42 (0.5–1.8)	< 0.0001	1.12 (0.9–1.4)	< 0.0001
Gestational age at delivery (weeks, median (IQR))	40 (38.9–40.9)	37.1 (33.9–39.0)	< 0.0001	40 (38.7–41.0)	0.9
Birth weight centile (median (IQR))	50.2 (28.7–75.6)	13.3 (1.8–41.4)	< 0.0001	4.3 (1.7–7.1)	< 0.0001

*Compared with 'Unaffected' group. BMI, body mass index; IQR, interquartile range; PI, pulsatility index.

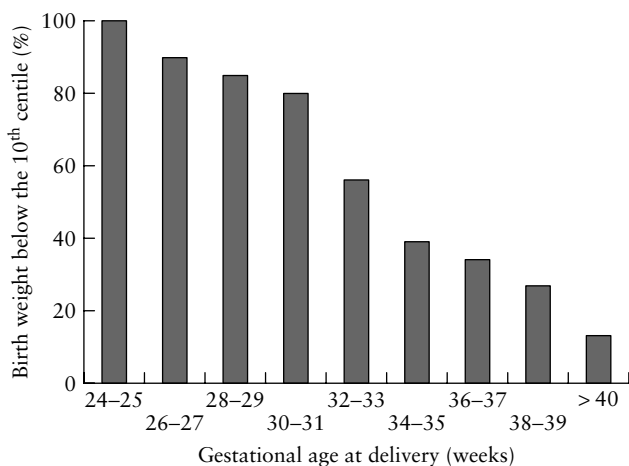


Figure 1 Relationship between gestational age at delivery and prevalence of small-for-gestational age neonates in women with pre-eclampsia.

Figure 2b) and prevalence of mean uterine artery PI above the 95th centile ($r = -0.827$, $P = 0.006$; Table 2).

The mean uterine artery PI was above the 95th centile in 77.2% of women who developed pre-eclampsia requiring delivery before 34 weeks, in 35.9% of those delivering at 34–37 weeks and in 21.9% of those delivering after 37 weeks. The respective percentages were 82.3%, 46.9% and 28.8% for those with pre-eclampsia and SGA, and 43.8%, 21.2% and 8.4% for those with SGA but no pre-eclampsia.

The prevalence of pre-eclampsia was higher in nulliparous (409/15 671, 2.6%) than in parous (205/14 969, 1.4%) women but the performance of uterine artery Doppler imaging in predicting pre-eclampsia was similar in the two groups. The mean uterine artery PI was above the 95th centile in 39.6% (162/409) cases of pre-eclampsia in the nulliparous women and in 43.4% (89/205) cases among parous women ($P = 0.4$).

DISCUSSION

The finding that a high proportion of pregnancies developing pre-eclampsia and/or SGA have increased impedance to flow in the uterine arteries at mid-gestation is compatible with the results of previous Doppler ultrasound studies^{7,8}. Our data demonstrate that pre-eclampsia requiring early delivery is more likely to be associated with SGA than less severe pre-eclampsia with delivery at term. The results also show that Doppler ultrasound assessment of the uterine arteries is more effective in identifying severe early pre-eclampsia associated with SGA than pre-eclampsia without SGA or SGA without pre-eclampsia.

The mechanism underlying pre-eclampsia and SGA is thought to be impaired trophoblastic invasion of the maternal spiral arteries and their conversion from narrow muscular vessels to wide non-muscular channels. Our findings suggest that there is a wide spectrum of such impaired placentation, with severe impairment leading

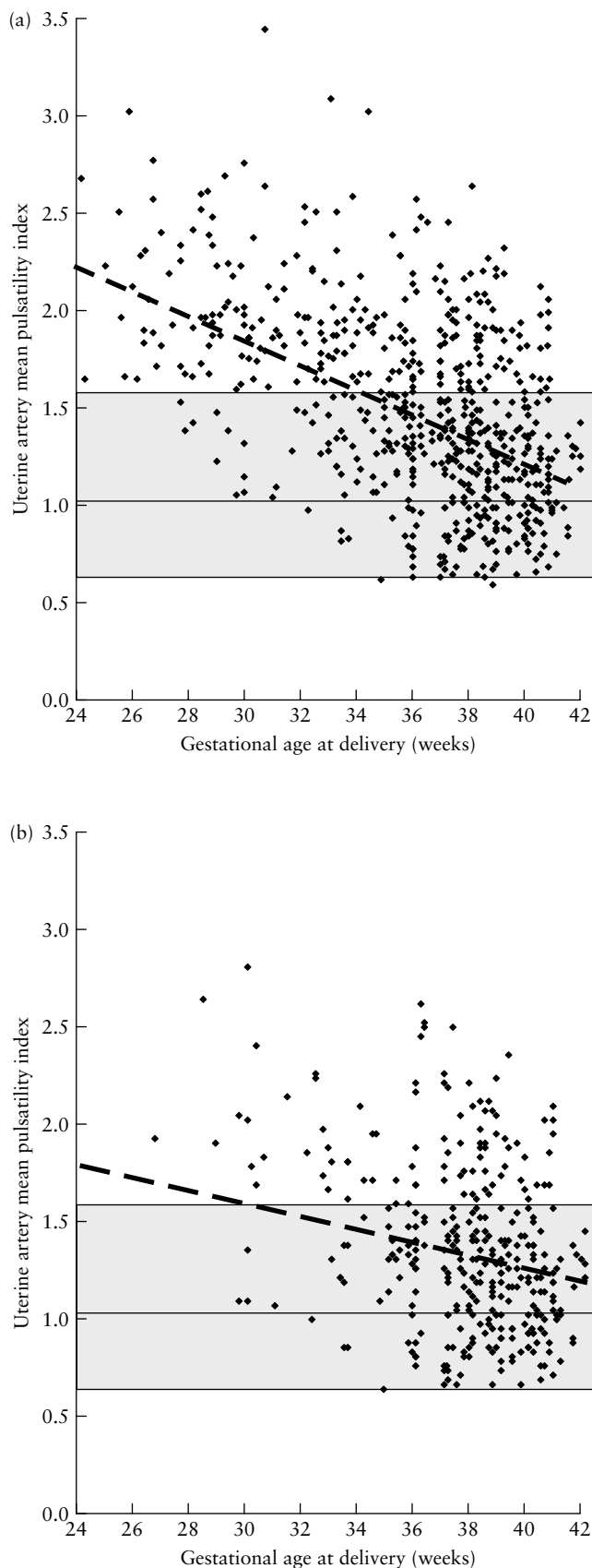


Figure 2 Relationship between gestational age at delivery and mean uterine artery pulsatility index (PI) in women who developed pre-eclampsia (a) and those who delivered small-for-gestational age neonates without developing pre-eclampsia (b). The three horizontal lines represent the 5th, 50th and 95th centiles of mean uterine artery PI in all pregnancies.

Table 2 Mean uterine artery pulsatility index (PI) above the 95th centile in women who subsequently developed pre-eclampsia and small-for-gestational age (SGA) according to gestational age at delivery

GA at delivery (weeks)	Pre-eclampsia and SGA			Pre-eclampsia without SGA			SGA without pre-eclampsia		
	Total	High PI		Total	High PI		Total	High PI	
		n	% (95% CI)		n	% (95% CI)		n	% (95% CI)
24–25	7	7	100.0 (59.0–100.0)	0	0	0	12	6	50.0 (21.1–78.9)
26–27	20	18	90.0 (68.3–98.9)	1	1	100.0 (2.5–100.0)	15	5	33.3 (11.8–61.6)
28–29	30	26	86.7 (69.3–96.2)	4	3	75.0 (19.4–99.4)	20	9	45.0 (23.1–68.5)
30–31	25	21	84.0 (63.9–95.5)	10	7	70.0 (34.8–93.3)	33	19	57.6 (39.2–74.5)
32–33	42	30	71.4 (55.4–84.3)	19	9	47.4 (24.5–71.1)	50	18	36.0 (22.9–50.8)
34–35	43	21	48.9 (33.3–64.5)	29	7	24.1 (10.3–43.5)	113	38	33.6 (25.0–43.1)
36–37	53	24	45.3 (31.6–59.6)	84	23	27.4 (18.2–38.2)	402	71	17.7 (14.1–21.8)
38–39	42	14	33.3 (19.6–49.6)	113	29	25.7 (17.9–34.7)	1456	167	11.5 (9.9–13.2)
40–42	17	3	17.6 (3.8–43.4)	75	8	10.7 (4.7–19.9)	2263	147	6.5 (5.5–7.6)
Total	279	164	58.8 (52.8–64.6)	335	87	26.0 (21.4–31.0)	4364	480	11.0 (10.1–12.0)

GA, gestational age.

to early-onset pre-eclampsia with SGA, and less severe impairment causing late-onset pre-eclampsia without SGA or SGA without pre-eclampsia. The alternative hypothesis is that there are two types of pre-eclampsia: the first type, which presents early in gestation and is associated with SGA, is secondary to impaired placentation; the second type, which tends to present later in pregnancy without SGA, occurs in the presence of normal placentation and must have a different etiology. If the latter hypothesis is correct then we would have expected a bimodal distribution in mean uterine artery PI.

Screening by uterine artery Doppler imaging is particularly effective in identifying severe early-onset pre-eclampsia with SGA rather than late-onset disease with less effect on fetal growth. For a screen-positive rate of 5% the detection rate of pre-eclampsia requiring delivery before 34 weeks was 77%, compared with 22% for those with pre-eclampsia delivering after 37 weeks. This is particularly important because it is early-onset pre-eclampsia rather than the late-onset disease which is associated with an increased risk of perinatal mortality and morbidity, and both short-term and long-term maternal complications^{13,14}. In the long term, women who develop pre-eclampsia requiring preterm delivery have an eightfold increased risk of dying from cardiovascular disease and a fivefold increased risk of dying from a stroke compared with women who had a normotensive pregnancy or one complicated by pre-eclampsia with delivery at term¹⁵.

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