Ultrasound Obstet Gynecol 2001; **18**: 583–586

Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler at 11–14 weeks of gestation

A. M. MARTIN, R. BINDRA, P. CURCIO, S. CICERO and K. H. NICOLAIDES

Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK

KEYWORDS: Doppler ultrasound, Fetal growth restriction, First trimester, Pre-eclampsia, Screening

ABSTRACT

Objective *To examine the value of uterine artery Doppler at 11–14 weeks of gestation in the identification of women at risk of developing pre-eclampsia and fetal growth restriction.*

Methods *Uterine artery Doppler was carried out at 11–14 weeks in 3324 consecutive singleton pregnancies attending for routine care in three London hospitals. The right and left uterine arteries were identified using color flow mapping and velocity waveforms were obtained using pulsed Doppler. The mean pulsatility index of the two arteries was determined and the predictive value of a mean pulsatility index > the 95th centile in the prediction of pre-eclampsia and/or fetal growth restriction was calculated.*

Results *Satisfactory flow velocity waveforms were obtained from both uterine arteries in 3195 (96.1%) of the 3324 pregnancies examined and complete outcome information was obtained for 3045 (95.3%) of these women. The 95th centile of the uterine artery mean pulsatility index was 2.35 and did not change significantly with gestational age. The pregnancy was complicated by pre-eclampsia in 63 (2.1%) cases and by fetal growth restriction in 290 (9.5%) cases. The sensitivity of a mean pulsatility index > 2.35 for pre-eclampsia (with or without fetal growth restriction) was 27.0% but for fetal growth restriction alone it was 11.7%. The respective sensitivities for these complications requiring delivery before 32 weeks of gestation were 60.0% and 27.8%, respectively.*

Conclusion *Uterine artery Doppler at 11–14 weeks of gestation identifies a high proportion of women who develop severe pre-eclampsia and/or fetal growth restriction.*

INTRODUCTION

Pre-eclampsia (PET) and fetal growth restriction (FGR) are serious complications of pregnancy, which are associated with high morbidity and mortality. Although the precise etiology of these conditions remains poorly understood there is substantial evidence that failure of trophoblastic invasion of the maternal spiral arteries is a common underlying cause[1,2]. Doppler ultrasound has been demonstrated to be a reliable, non-invasive method of examining uteroplacental perfusion[3]. Although several screening studies have been carried out at 16–24 weeks of gestation, these studies varied widely in populations examined, Doppler methodology, cut-off for abnormal values and definitions of the disease, producing wide differences in sensitivity[4]. A recent multicenter study examined 8335 singleton pregnancies at 23 weeks of gestation and the pulsatility index (PI) in each uterine artery was measured by color Doppler[4]. The sensitivity of increased mean PI (> the 95th centile) for subsequent development of PET (with or without FGR) was 40.7% and for FGR in the absence of PET was 13.2%; for pregnancies with these complications requiring delivery before 32 weeks the sensitivity was 90.0% and 56.3%, respectively.

This study examines the value of uterine artery Doppler at 11–14 weeks of gestation in the identification of women at risk of developing PET and FGR.

PATIENTS AND METHODS

At King's College Hospital, Greenwich Hospital and Lewisham Hospital, London, women attending for routine antenatal care are offered a transabdominal ultrasound scan at 11–14 weeks as a method of screening for chromosomal defects, by the measurement of nuchal translucency thickness[5]. During a 6-month period (July 2000 to January 2001) women attending for this scan were invited to participate in this Doppler screening study, which was approved by the ethics committees of the three hospitals. Written informed consent was obtained from the patients.

Doppler studies were carried out by one of five doctors who had obtained The Fetal Medicine Foundation Certificate of Competence in Placental Doppler. Women were placed in the semirecumbent position and transabdominal ultrasound was used to obtain a sagittal section of the uterus and cervical canal. The internal cervical os was first identified.

Correspondence: Prof. K. H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital Medical School, Denmark Hill, London SE5 8RX, UK (e-mail: fmf@fetalmedicine.com)

Presented at The Fetal Medicine Foundation's Meeting on Research and Developments in Fetal Medicine, London, 30 August–1 September 2001.

Subsequently, the transducer was gently tilted from side to side and color flow mapping was used to identify the uterine arteries (Figure 1) as aliasing vessels coursing along the side of the cervix and uterus. Pulsed wave Doppler was used to obtain flow velocity waveforms from the ascending branch of the uterine artery at the point closest to the internal os. When three similar consecutive waveforms were obtained the PI was measured and the mean PI of the left and right arteries was calculated. The presence or absence of an early diastolic notch in the waveform was recorded.

Patient characteristics and ultrasound findings were entered into a fetal database. Details of pregnancy outcome were obtained from the hospital perinatal computer. For women who did not deliver in the three participating hospitals outcome data were obtained from their hospital, general practitioners or from themselves.

Outcome measures were PET (with or without FGR) and FGR (without PET). Pre-eclampsia was 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 midstream or catheter urine specimens if no 24-h collection is available[6]. Fetal growth restriction was defined as birth weight < the 10th centile for gestation[7].

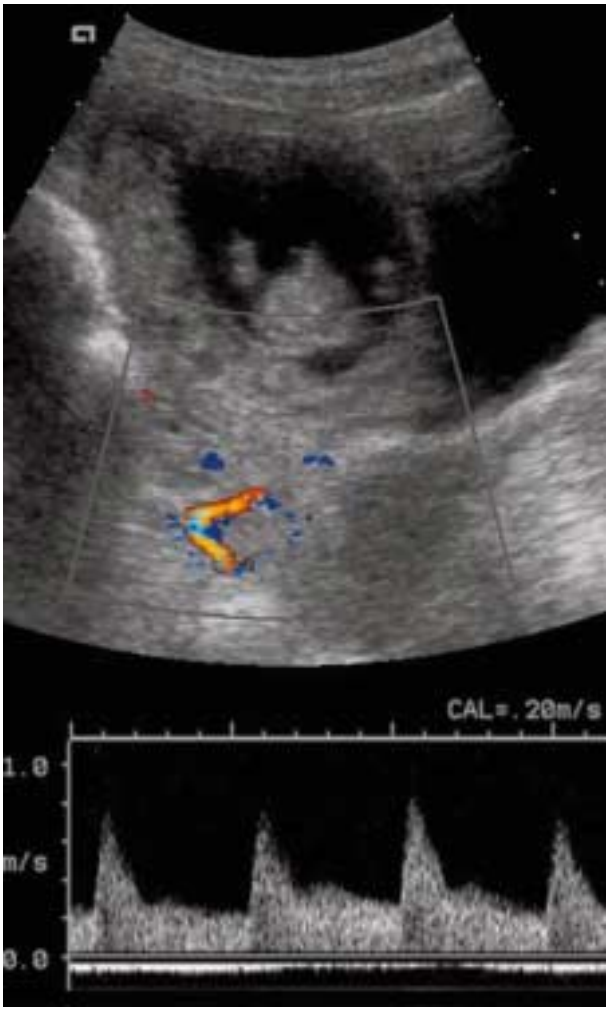

Figure 1 Uterine artery visualized by transabdominal color flow mapping at 11–14 weeks.

Statistical analysis

The 95th centile of uterine artery mean PI for crown–rump length (CRL) was determined by regression analysis of the calculated 95th centile of PI for each 1-mm interval in CRL. The sensitivity, specificity, positive predictive value and negative predictive value for a cut-off mean PI of 2.35 (the 95th centile) in the prediction of PET and FGR were calculated.

RESULTS

Satisfactory waveforms were obtained from both uterine arteries in 3195 (96.1%) of the 3324 women who agreed to participate in the study and complete pregnancy outcomes were obtained in 3045 cases (95.3%). The demographic characteristics of the women and pregnancy outcome are shown in Table 1.

The 95th centile of the uterine artery mean PI was 2.35 and did not change significantly with fetal CRL (Figure 2; $r = -0.124$; $P = 0.603$). The mean PI was > the 95th centile in 155 (5%) cases. An early diastolic notch in the waveform was observed bilaterally in 1691 (55.5%) cases and unilaterally in 567 (18.6%). Screening characteristics for PET and FGR are shown in Table 2. The essential findings were that the uterine artery mean PI > the 95th centile had a sensitivity of 27.0% for PET (with or without FGR) and 11.7% for FGR, but the sensitivity was higher for these complications requiring delivery before 32 weeks (60.0% and 27.8%, respectively). The sensitivities for PET and FGR, according to gestational age at delivery, are compared to those of our 23-week Doppler study[4] in Figure 3.

Table 1 Demographic characteristics of the study population and pregnancy outcome (n = 3045)

Maternal age (years, median (range))	31.3 (16–47)
Body mass index (median (range))	23.4 (15.3–52.1)
White (n (%))	2116 (69.5)
Black (n (%))	724 (23.8)
Asian (n (%))	165 (5.4)
Oriental (n (%))	40 (1.3)
Primiparous (n (%))	1351 (44.4)
Cigarette smoker (n (%))	501 (16.5)
Live birth (n (%))	2981 (97.8)
Miscarriage (n (%))	31 (1)
Intrauterine death (n (%))	15 (0.5)
Neonatal death (n (%))	2 (0.1)
Termination of pregnancy (n (%))	15 (0.5)
Pre-eclampsia (n (%))	63 (2.1)
Pre-eclampsia requiring delivery before 32 weeks (n (%))	10 (0.33)
Fetal growth restriction (n (%))	290 (9.5)
Fetal growth restriction requiring delivery before 32 weeks (n (%))	18 (0.59)

The intra- and interobserver repeatability of uterine artery PI was assessed by two operators in 40 consecutive patients. In each patient each operator measured the PI in the same uterine artery twice. Operators were blinded to their own and each other's results, and the order in which they performed the measurements was determined by computer-generated randomization. Using the method suggested by Bland and Altman[8] it was found that on 95% of occasions two readings by the same observer did not differ by more than ±0.28 (intraobserver repeatability). Between observers the 95% prediction interval was ±0.41 for single measurements and ±0.29 for the mean of two measurements.

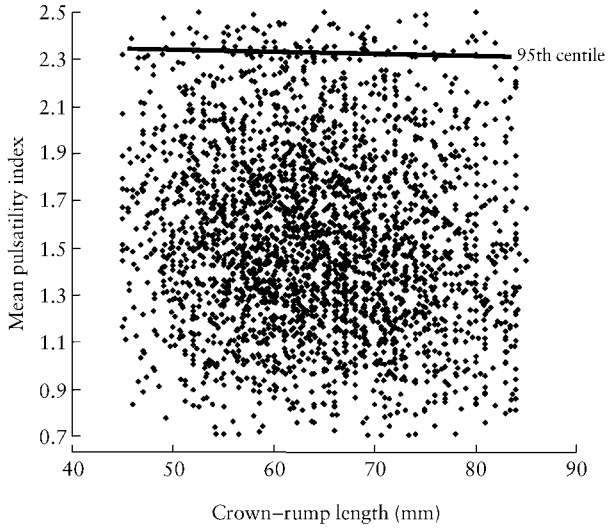

Figure 2 Distribution of uterine artery mean pulsatility index in 3045 singleton pregnancies examined at 11–14 weeks of gestation. The 95th centile was 2.35 and did not change significantly with fetal crown–rump length.

Table 2 Screening characteristics of a mean pulsatility index > 2.35, which was found in 155 of the 3045 (5.0%) pregnancies

Characteristic	n	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
All patients					
Pre-eclampsia	63	27.0	95.4	11.0	98.4
FGR no pre-eclampsia	290	11.7	95.6	21.9	91.1
Delivery before 38 weeks					
Pre-eclampsia	32	34.4	95.2	7.1	99.3
FGR no pre-eclampsia	86	22.1	95.4	12.3	97.7
Delivery before 36 weeks					
Pre-eclampsia	20	40.0	95.1	5.2	99.6
FGR no pre-eclampsia	41	22.0	95.1	5.8	98.9
Delivery before 34 weeks					
Pre-eclampsia	14	50.0	95.1	4.5	99.8
FGR no pre-eclampsia	25	24.0	95.1	3.9	99.3
Delivery before 32 weeks					
Pre-eclampsia	10	60.0	95.1	3.9	99.9
FGR no pre-eclampsia	18	27.8	95.0	3.2	99.6

PPV, positive predictive value; NPV, negative predictive value; FGR, fetal growth restriction.

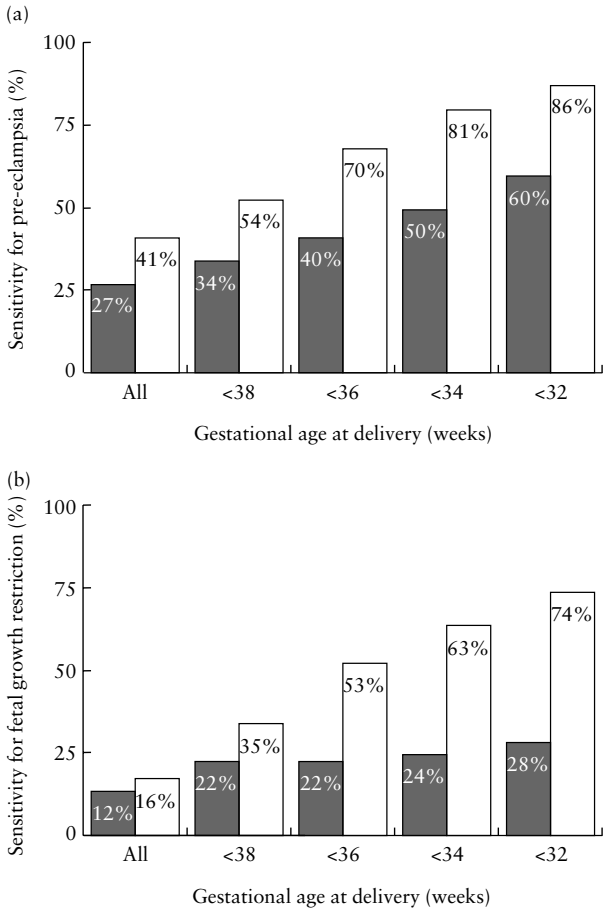

Figure 3 Sensitivity for pre-eclampsia (a) and fetal growth restriction without pre-eclampsia (b) of uterine artery mean pulsatility index > the 95th centile for gestation at 11–14 weeks (■), compared to values from a previous study at 22–24 weeks (□)[4].

DISCUSSION

The findings of this study demonstrate the feasibility of assessing the uteroplacental circulation by transabdominal ultrasound at 11–14 weeks of gestation. Using color flow mapping it was possible to visualize both uterine arteries and obtain satisfactory waveforms in about 96% of the patients examined. An early diastolic notch in the waveform from one or both uterine arteries was observed in about 75% of pregnancies and it is therefore unlikely to be useful in screening for pregnancy complications.

The 5% of the population with a uterine artery mean PI > 2.35 at 11–14 weeks contained 27% of women who subsequently developed PET and 12% of those who delivered a growth-restricted baby in the absence of PET. The respective sensitivities for these complications requiring delivery before 32 weeks were 60% and 28%. The finding that the sensitivity for both PET and FGR was inversely related to the gestational age at delivery demonstrates that Doppler assessment of the uterine arteries is much better at identifying the more severe and therefore clinically most relevant cases of PET. This is similar to findings in second-trimester Doppler studies[4,9].

In pregnancy the spiral arteries are transformed into distended low-resistance channels, capable of increasing the

blood supply to the fetoplacental unit in the third trimester to 10 times that of the non-pregnant uterus. This uteroplacental vascular adaptation is dependent on invasion of the spiral arteries by trophoblasts, which become incorporated into the vessel wall[10–13]. This invasion occurs in a stepwise fashion starting with plugging of the distal ends of the arteries followed by migration into the decidual segments and, after several weeks' delay, into the myometrial segments. The first phase of this process starts from at least 8 weeks of gestation and continues to the 10th week, and the second phase is at 14–24 weeks[10–13].

Establishment of the uteroplacental circulation in the second trimester is not a random phenomenon, but rather a consequence of events in the first trimester. This is supported by the findings of a Doppler study in 55 pregnancies, which reported a significant association between measurements of the uterine artery PI at 10–14 weeks and those at 19–22 weeks[14]. There are also two previous uterine artery Doppler studies which reported an association between abnormal results in early pregnancy and the subsequent development of PET and FGR. Examining 352 women at 12–13 weeks of gestation, van den Elzen *et al.*[15] found that in the group with PI in the highest quartile, compared to those with PI in the lowest quartile, the risk for subsequent development of hypertensive disorders and FGR was higher by a factor of four and two, respectively. Harrington *et al.*[16] examined 652 pregnancies at 12–16 weeks and reported that a seven parameter model, including vessel diameter, PI, resistance index, time averaged mean velocity, peak systolic velocity, volume flow and the presence or absence of a diastolic notch, identified 93% of those developing PET with a specificity of 85%. In this study there was no breakdown of the number of women scanned at each gestational age and it is therefore not possible to evaluate the efficiency of the test in the first trimester.

The sensitivity of the uterine artery mean PI > the 95th centile in the prediction of PET and FGR is lower when the test is carried out at 11–14 weeks rather than at 22–24 weeks[4,9]. However, the potential advantage of earlier screening is that prophylactic intervention, such as maternal ingestion of low-dose aspirin, may be more effective in the prevention of the subsequent development of PET and FGR. The extent to which this proves to be the case awaits the results of ongoing randomized trials.

ACKNOWLEDGMENT

The study was funded by The Fetal Medicine Foundation (Registered Charity 1037116).

REFERENCES

1 Brosens IA. Morphological changes in the utero-placental bed in pregnancy hypertension. *Clin Obstet Gynaecol* 1977; 4: 573–93
2 Khong TY, De Wolf F, Robertson WB, Brosens I. Inadequate maternal vascular response to placentation in pregnancies complicated by PET and by small-for-gestational age infants. *Br J Obstet Gynaecol* 1986; 93: 1049–59
3 Campbell S, Pearce JM, Hackett G, Cohen-Overbeek T, Hernandez C. Qualitative assessment of uteroplacental blood flow: early screening test for high-risk pregnancies. *Obstet Gynecol* 1986; 68: 649–53
4 Papageorghiou AT, Yu CKH, Bindra R, Pandis G, Nicolaides KH for The Fetal Medicine Foundation Second Trimester Screening Group. Multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. *Ultrasound Obstet Gynecol* 2001; 18: 441–9
5 Snijders RJM, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal translucency thickness at 10–14 weeks of gestation. *Lancet* 1998; 351: 43–6
6 Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 1988; 158: 892–8
7 Yudkin PL, Aboualfa M, Eyre JA, Redman CW, Wilkinson AR. New birthweight and head circumference centiles for gestational ages 24–42 weeks. *Early Hum Dev* 1987; 15: 45–52
8 Bland J, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1: 307–10
9 Albaiges G, Missfelder-Lobos H, Lees C, Parra M, Nicolaides KH. One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation. *Obstet Gynecol* 2000; 96: 559–64
10 Pijnenborg R, Dixon G, Robertson WB, Brosens I. Trophoblastic invasion of human decidua from 8 to 18 weeks of pregnancy. *Placenta* 1980; 1: 3–19
11 Pijnenborg R, Bland JM, Robertson WB, Dixon G, Brosens I. The pattern of interstitial trophoblastic invasion of the myometrium in early human pregnancy. *Placenta* 1981; 2: 303–16
12 Pijnenborg R, Bland JM, Robertson WB, Brosens I. Uteroplacental arterial changes related to interstitial trophoblast migration in early human pregnancy. *Placenta* 1983; 4: 397–413
13 Kingdom JC, Kaufmann P. Oxygen and placental vascular development. *Adv Exp Med Biol* 1999; 474: 259–75
14 Kaminopetros P, Higueras MT, Nicolaides KH. Doppler study of the uterine artery blood flow: comparison of findings in the first and second trimester of pregnancy. *Fetal Diagn Ther* 1991; 6: 58–64
15 van den Elzen HJ, Cohen-Overbeek TE, Grobbee DE, Quartero RW, Wladimiroff JW. Early uterine artery Doppler velocimetry and the outcome of pregnancy in women aged 35 years and older. *Ultrasound Obstet Gynecol* 1995; 5: 328–33
16 Harrington K, Goldfrad C, Carpenter RG, Campbell S. Transvaginal uterine and umbilical artery Doppler examination at 12–16 weeks and the subsequent development of PET and intrauterine growth retardation. *Ultrasound Obstet Gynecol* 1997; 9: 94–100