Ultrasound Obstet. Gynecol. 7 (1996) 122–128

Uterine and spiral artery flow velocity waveforms in pregnancy-induced hypertension and/or intrauterine growth retardation

T. Murakoshi, N. Sekizuka, K. Takakuwa, H. Yoshizawa and K. Tanaka

Department of Obstetrics and Gynecology, Niigata University School of Medicine, Niigata, Japan

Key words: INTRAUTERINE GROWTH RETARDATION, PREGNANCY-INDUCED HYPERTENSION, DOPPLER ULTRASOUND, SPIRAL ARTERY, UTERINE ARTERY, PERINATAL OUTCOME

ABSTRACT

The objectives of this study were to characterize spiral artery flow velocity waveforms in normal pregnancies and pregnancies complicated by pregnancy-induced hypertension and/or intrauterine growth retardation, and to examine the diagnostic potential for predicting adverse perinatal outcomes in complicated pregnancies compared with uterine and umbilical artery flow velocity waveforms.

In this cross-sectional study, 160 normal and 43 complicated pregnancies were assessed by color and pulsed Doppler during 18–41 weeks of gestation. Flow velocity waveforms were obtained from the spiral, uterine and fetal umbilical arteries.

In normal pregnancies, the resistance index of spiral artery flow velocity waveforms decreased significantly with advancing gestation ($r = -0.256$, $p < 0.001$). In abnormal pregnancies complicated by pregnancy-induced hypertension and/or intrauterine growth retardation, the incidence of adverse perinatal outcome was significantly higher in patients with abnormal spiral artery resistance indices than in patients with normal spiral artery resistance indices ($p < 0.001$). An abnormal spiral artery resistance index had a better diagnostic accuracy for adverse perinatal outcome (sensitivity 85.0%, specificity 91.3%, positive predictive value 89.5%, negative predictive value 87.5%, accuracy 88.4%) when compared with the resistance index of uterine and umbilical artery waveforms and presence of a diastolic notch of the uterine artery waveform.

Color flow imaging facilitates the precise analysis of spiral artery flow velocity waveforms and provides more accurate information about the uteroplacental circulation in the evaluation of placental function.

INTRODUCTION

The introduction of Doppler ultrasonography has enabled the non-invasive assessment of human placental circulation. Many studies have reported increased impedance to flow in the uterine artery in pregnancies complicated by pregnancy-induced hypertension (PIH) and/or intrauterine growth retardation (IUGR)[1–4]. Some groups have shown that abnormal uterine artery flow velocity waveforms precede the clinical onset of these complications[5–8]. However, some investigators have failed to find a significant difference between normal and complicated pregnancies[4,9,10]. Because of the technical limitations of conventional continuous wave and pulsed wave Doppler, these studies were restricted to the main uterine artery and its arcuate branches.

The recent advent of color Doppler technology has provided further information about the uteroplacental circulation. This new technique has enabled us to study more distal branches of the uterine artery, such as the radial and spiral arteries, with high reproducibility[11]. However, color Doppler investigation of the spiral artery in the second and third trimesters is still limited[12]. The aims of this study were (1) to establish a reference range for spiral artery flow velocity waveforms in normal singleton pregnancies at 18–41 weeks of gestation; (2) to characterize spiral artery flow velocity waveforms in abnormal pregnancies complicated by PIH and/or IUGR; and (3) to examine the diagnostic powers for predicting adverse perinatal outcomes in complicated pregnancies compared with uterine and umbilical artery flow velocity waveforms.

Correspondence: Dr T. Murakoshi, Department of Obstetrics and Gynecology, Niigata University School of Medicine, 1-757 Asahimachi-Dori, Niigata 950, Japan

Received 24–10–94
Revised 23–10–95
Accepted 2–11–95

MATERIALS AND METHODS

Population

This cross-sectional study was conducted at Niigata University Hospital, from April 1992 to February 1994, after approval was obtained from the Institutional Ethical Committee. The study population consisted of 160 normal and 43 complicated singleton pregnancies between 18 and 41 weeks of gestation. In all cases, gestational age was confirmed by first-trimester ultrasonographic measurement of crown–rump length and/or biparietal diameter.

Complicated pregnancies consisted of 17 with IUGR, eight with PIH and 18 with both, which were examined between 28 and 41 weeks of gestation. Of these 43, 20 (46.5%) had adverse perinatal outcomes. Perinatal outcomes were defined as adverse when one of the following perinatal complications was present: (1) Cesarean delivery due to fetal distress; (2) 5-min Apgar score of <7; (3) admission to neonatal intensive care unit; or (4) perinatal death. The criteria of PIH and IUGR were as follows: PIH – two recordings of diastolic blood pressure ≥ 90 mmHg, 4 h apart, or one recording of ≥ 110 mmHg at any stage of pregnancy with or without proteinuria (proteinuria was defined as a total protein excretion greater than 300 mg/24 h[13]); IUGR – ultrasonographic estimation of fetal weight and actual birth weight below the 10th centile of Japanese birth weight standard curves[14]. Fetal distress was diagnosed when antepartum or intrapartum fetal heart rate tracing showed one of the following abnormal patterns: loss of beat-to-beat variability; late decelerations; repetitive severe variable decelerations; continuous bradycardia.

The other 160 cases were unselected low-risk pregnancies without any maternal and perinatal complications, and they served as controls. The clinical characteristics of these 160 normal pregnancies and 43 complicated pregnancies are presented in Table 1.

Equipment

In all examinations, a color and pulsed Doppler system incorporating a 3.5-MHz transabdominal convex transducer (SSD 680, Aloka Co., Tokyo, Japan) was used. The spatial peak temporal average intensity was approximately 80 mW/cm^2. The high-pass filter was set at 50 Hz and the pulse repetition frequency ranged from 2 to 25 kHz, depending on blood flow velocities.

Doppler recordings

After informed consent was obtained, ultrasonographic examination including color and pulsed Doppler velocimetry was carried out in a quiet room with the patient in a recumbent position. After routine fetal biometry and amniotic pocket measurement, flow velocity waveforms were obtained from the uterine artery, spiral artery and fetal umbilical artery. The uterine artery flow velocity waveforms were sampled on each side of the ascending uterine artery at the crossing point of the external iliac artery in the lateral wall of the lower quadrant of the uterus. A 3-mm pulsed Doppler gate was used for the uterine artery and the angle between the Doppler beam and the vessel was less than 45°.

Spiral artery flow velocity waveforms were obtained from the color-coded highly vascular area just beneath the placenta. When clear color flow imaging was obtained, a 1-mm pulsed Doppler gate was sited on these vessels. Spiral artery flow velocity waveforms were sampled from three or four different sites beneath the central part of the placenta, at least 3 cm away from the placental margin, avoiding insonation of ultrasonographically detectable pathological lesions such as infarction or clarification. No angle correction was made for the spiral artery, because in these vessels accurate determination of the angle of insonation is very difficult. Umbilical artery flow velocity waveforms were recorded from the free loop of the umbilical cord during fetal apnea and rest.

All Doppler measurements were performed when uterine contractions were absent. All ultrasonographic examinations including Doppler velocimetry were performed by two of the authors (T.M. or N.S.) and they were not aware of the detailed clinical condition of the patients. The intraobserver coefficients of variation were determined by examining three patients (ten measurements for each patient). The intraobserver variations for spiral artery flow velocity waveforms were 6.2 and 7.8% for each observer.

Table 1 Clinical characteristics of 160 normal pregnancies and 43 complicated pregnancies. Data are presented as the number of cases (%) or mean ± SD

	Normal pregnancies	*Complicated pregnancies*	*Statistics*
Maternal age (years)	30.3 ± 4.5	30.3 ± 4.9	NS
Primipara	81 (50.6%)	24 (55.8%)	NS
Gestational age at delivery (weeks)	39.2 ± 1.2	35.2 ± 3.4	$p < 0.001$
Birth weight (g)	3199 ± 363	1770 ± 679	$p < 0.001$
Vaginal delivery	148 (92.5%)	14 (32.6%)	$p < 0.001$
normal	133	12	NS
operative	15	2	NS
Cesarean delivery	12 (7.5%)	29 (67.4%)	$p < 0.001$
due to fetal distress	0	17	$p < 0.001$

NS, not significant

The interobserver variability was also determined by examining three patients (ten measurements for each patient by two observers). There was no significant difference between the observers (Student's *t*-test). For uterine and umbilical artery flow velocity waveforms, the intraobserver variations were within 5%, and no significant differences were found between the observers.

Data analysis

Uterine, spiral and umbilical artery flow velocity waveforms were assessed by calculating the resistance index (RI = [peak systolic velocity – end-diastolic velocity]/peak systolic velocity) with the use of a built-in analyzer. At each examination, the RI was calculated over three consecutive cardiac cycles and averaged. The averaged values of 3–4 different sites were used for spiral artery flow velocity waveforms. As for the uterine artery flow velocity waveforms, the averaged RI values of both the right and the left were used for further analysis and the presence or absence of a diastolic notch of the uterine artery flow velocity waveforms was also noted.

Reference ranges of the spiral and uterine artery RI with gestation were constructed from 160 normal pregnancies with linear regression analysis. The previously reported reference range was used for the umbilical artery RI[15]. A Doppler value was defined as abnormal when the RI was outside the appropriate reference range. When a diastolic notch was present in either uterine artery, the test was regarded as abnormal. The results of only the umbilical artery Doppler studies were given to the managing obstetricians. However, these Doppler data were not used for clinical decision making. The 43 complicated pregnancies were divided into two groups according to the last spiral artery RI. The differences between groups were analyzed with the use of the χ^2 test (categorical data) or the Mann–Whitney *U* test (continuous data). A *p*-value of < 0.05 was considered to be statistically significant.

To assess the clinical potential of Doppler flow velocimetry for predicting adverse perinatal outcome, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated for each Doppler variable (spiral, uterine and umbilical artery RI and a diastolic notch of the uterine artery flow velocity waveforms). As for the three continuous Doppler variables (spiral, uterine and umbilical artery RI), receiver operating characteristic curves were also constructed to examine the diagnostic potential for predicting adverse perinatal outcome in complicated pregnancies.

RESULTS

In all cases, spiral, uterine and umbilical artery flow velocity waveforms were successfully obtained by color flow imaging. Figure 1 gives an example of spiral artery flow velocity waveforms at 33 weeks of gestation, presenting characteristic waveforms with a high diastolic component and spiky outline profile. Figure 2 shows an abnormal spiral artery flow velocity waveform in a complicated pregnancy at 33 weeks of gestation. The diastolic components of the flow velocity waveforms were decreased and the RI of the spiral artery flow velocity waveform was increased.

Figure 3 demonstrates the relationship between the spiral and uterine artery RI in the total study population. The spiral artery RI showed a significant positive correlation with the uterine artery RI ($r = 0.598$, $p < 0.001$).

In the 160 normal pregnancies, the spiral artery RI decreased significantly with advancing gestation ($r = -0.256$, $p < 0.001$). Figure 4 shows the regression line with lower and upper 95% prediction intervals of the spiral artery RI with gestation. Figure 5 demonstrates the spiral artery RI of 43 complicated pregnancies plotted on the reference range. Of the 43 pregnancies complicated by

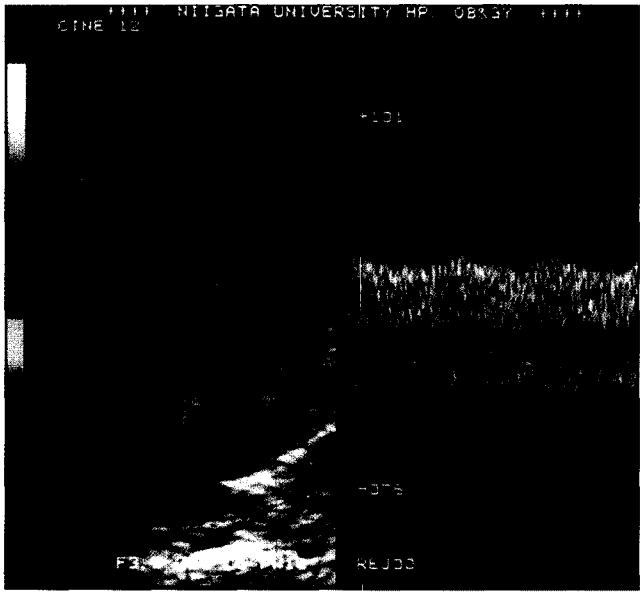

Figure 1 Spiral artery flow velocity waveforms in normal pregnancy at 33 weeks of gestation with a high diastolic component and spiky outline obtained from just beneath the placenta

Figure 2 Spiral artery flow velocity waveforms in complicated pregnancy at 33 weeks of gestation. The diastolic component of flow velocity waveforms was decreased and resistance index of the spiral artery was increased

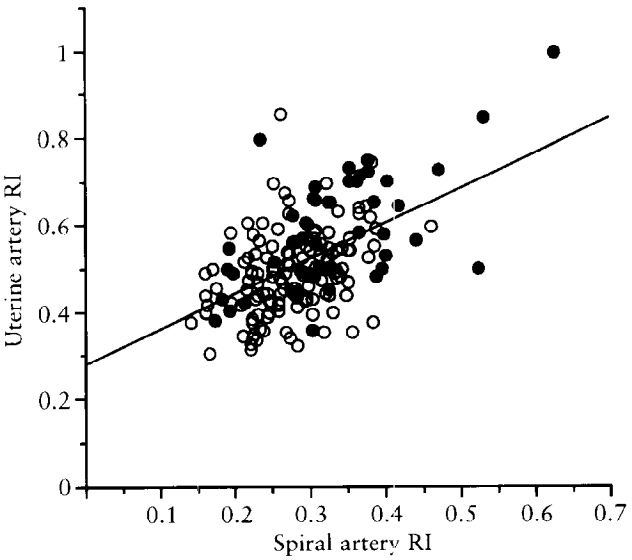

Figure 3 Relationship between the spiral artery resistance index (RI) and uterine artery RI in the total population at 18–41 weeks of gestation ($n = 203$, $r = 0.598$, $p < 0.001$). Open circles, normal pregnancies; filled circles, pregnancy-induced hypertension and/or intrauterine growth retardation

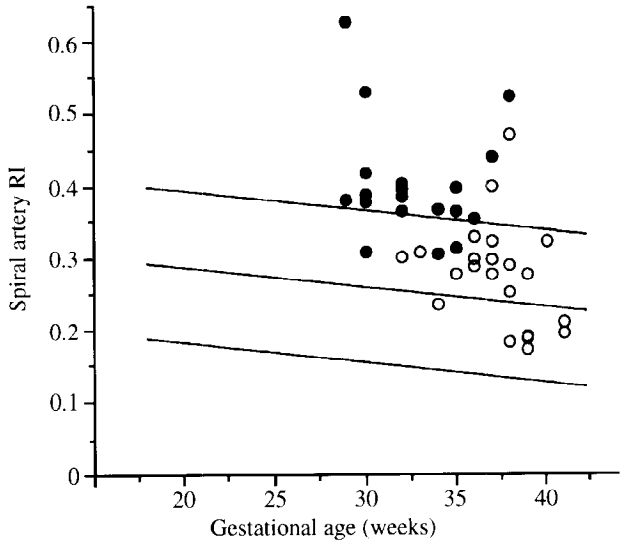

Figure 5 Spiral artery resistance index (RI) values of pregnancy-induced hypertension and/or intrauterine growth retardation plotted on the reference range. Filled circles, adverse perinatal outcome; open circles, good outcome

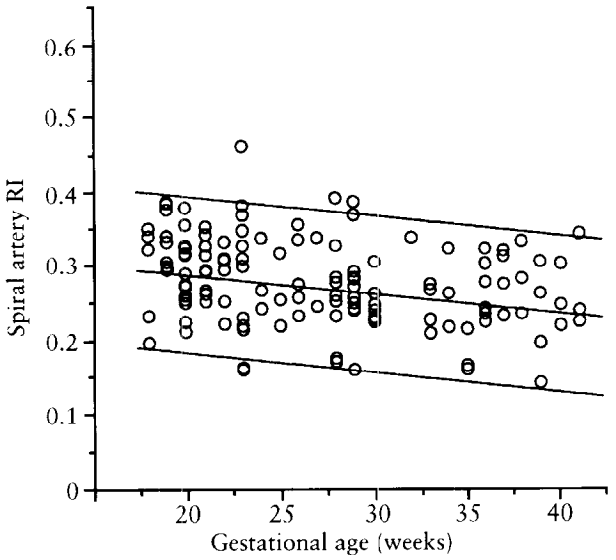

Figure 4 The regression line with lower and upper 95% prediction intervals of the spiral artery resistance index (RI) in normal pregnancies at 18–41 weeks of gestation ($n = 160$, $r = -0.256$, $p < 0.001$)

PIH and/or IUGR, 19 had abnormal (group A) and 24 had normal spiral artery RI (group B).

Table 2 shows the clinical characteristics and perinatal outcomes in the 43 complicated pregnancies classified according to the last spiral artery RI. There were no differences in maternal age, parity and duration from the last Doppler recording to delivery between the groups. Significant differences were found with regard to gestational age at delivery and birth weight. The total incidence of small-for-gestational-age (SGA) infants (< 10th centile) and PIH (with or without proteinuria) did not differ between the groups. However, the incidence of SGA infants below the 5th centile and PIH with proteinuria was significantly higher in group A than in group B. The prevalence of abnormal uterine and umbilical artery RI and a diastolic notch on the uterine artery flow velocity waveform was also much higher in group A. There were five cases of absent or reversed end-diastolic velocity of the umbilical artery flow velocity waveform in the 43 complicated pregnancies (three absent end-diastolic velocity and two reversed end-diastolic velocity). All had an abnormal uterine artery RI with a diastolic notch, and were observed only in group A. The incidence of adverse perinatal outcome in group A was significantly higher than in group B.

Comparative statistics for each Doppler variable are shown in Table 3. Compared with the uterine and umbilical artery RI and presence of a diastolic notch of the uterine artery flow velocity waveform, the spiral artery RI had the best diagnostic accuracy for adverse perinatal outcome (sensitivity 85.0%, specificity 91.3%, positive predictive value 89.5%, negative predictive value 87.5%, accuracy 88.4%). Figure 6 demonstrates the receiver operating characteristic curve for different cut-off levels of three continuous Doppler variables (spiral, uterine and umbilical artery RIs) in prediction of adverse perinatal outcome. It shows that the spiral artery RI was the best predictor for adverse perinatal outcome.

DISCUSSION

Many Doppler studies of the uterine circulation have revealed the potential of this technique to predict and manage high-risk pregnancies[1-7,9]. However, waveforms have been sampled from various branches of the uterine artery by different methods, and the results have shown wide

Table 2 Characteristics and outcomes of the complicated pregnancies divided according to the spiral artery resistance index (RI): abnormal, group A; normal, group B. Data are presented as the number of cases (%) or mean ± SD

	Group A (*n* = 19)	*Group B* (*n* = 24)	*Statistics*
Maternal age (years)	30.8 ± 4.7	30.0 ± 5.1	NS
Primipara	10 (52.6)	14 (56.0)	NS
Gestational age at delivery (weeks)	33.3 ± 3.2	36.8 ± 2.8	$p < 0.001$
Birth weight (g)	1352 ± 562	2101 ± 580	$p < 0.001$
Doppler recording (days before delivery)	0.8 ± 1.1	1.1 ± 1.4	NS
SGA	17 (89.5)	18 (75.0)	NS
below 5th centile	16 (84.2)	13 (54.2)	$p < 0.05$
PIH	13 (68.4)	13 (54.2)	NS
with proteinuria	9 (47.4)	3 (12.5)	$p < 0.05$
Adverse perinatal outcome	17 (89.5)	3 (12.5)	$p < 0.001$
Cesarean delivery due to fetal distress	14 (73.7)	3 (12.5)	$p < 0.001$
perinatal death	0 (0)	0 (0)	
Abnormal uterine artery RI	14 (73.7)	6 (25.0)	$p < 0.005$
Diastolic notch on uterine artery waveform	18 (94.7)	6 (12.5)	$p < 0.001$
Abnormal umbilical artery RI	11 (57.9)	3 (12.5)	$p < 0.005$
AREDV of umbilical artery	5 (26.3)	0 (0)	$p < 0.01$

Uterine artery RI calculated from the average of right and left measurements. NS, not significant; SGA, small for gestational age; PIH, pregnancy-induced hypertension; adverse perinatal outcome, Cesarean delivery due to fetal distress, 5-min Apgar score of < 7, admission to neonatal intensive care unit, perinatal death; AREDV, absent or reversed end-diastolic velocity

Table 3 Clinical validity of Doppler flow velocimetry for predicting adverse perinatal outcomes in 43 complicated pregnancies. Uterine artery resistance index (RI) was calculated from the average of right and left measurements

	Spiral artery RI	*Uterine artery RI*	*Notch of uterine artery*	*Umbilical artery RI*
Sensitivity (%)	85.0	80.0	90.0	65.0
Specificity (%)	91.3	82.6	73.9	95.7
Positive predictive valuc (%)	89.5	80.0	75.0	92.9
Negative predictive value (%)	87.5	82.6	89.5	75.9
Accuracy (%)	88.4	81.4	81.4	81.4

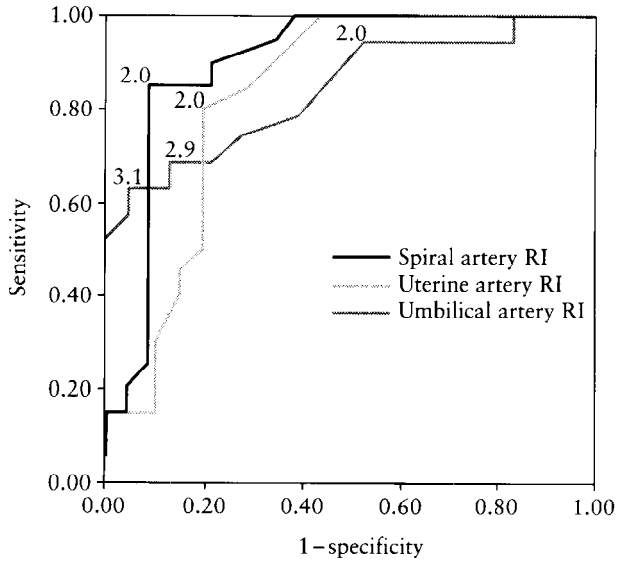

Figure 6 Receiver operating characteristic curves for different cut-off levels of three continuous Doppler variables in prediction of adverse perinatal outcomes in 43 complicated pregnancies. Numbers indicate each cut-off value in SD. RI, resistance index

variations. When our data from normal pregnancies were converted into systolic/diastolic ratio, the results showed a lower mean and narrower confidence interval as compared to the earlier study of Trudinger and Cook[9], in which uteroplacental bed arteries were investigated with continuous wave Doppler. It is speculated that these differences may have been caused by the technical limitations of the continuous wave Doppler method, in which waveforms were recorded from arcuate or radial arteries by a blind technique. In this study, we were able to insonate spiral arteries accurately at the site where these vessels directly attach to the placenta with the aid of color flow imaging.

The current study demonstrated that spiral artery RI decreases significantly with advancing gestation in the second and the third trimesters of normal pregnancy. Our previous study, conducted with transvaginal color Doppler, revealed that spiral artery RI also decreases in the first trimester of gestation[8]. These results support the histological findings that trophoblastic invasion of the subplacental spiral arteries begins early in the first trimester and continues throughout gestation[16,17]. In a normal pregnancy, trophoblasts invade the muscular portions of the spiral arteries in decidual and myometrial layers, and change them into non-muscular, dilated vessels with poor contractility[16,18]. This morphological change in the spiral arteries converts the uterus into a low-resistance vascular organ and causes dynamic changes in uteroplacental flow velocity waveforms with advancing gestation. A significant linear correlation between uterine and spiral artery RI is consistent with these histological observations. It is suggested that impedance to flow in the uterine artery depends on

downstream impedance to flow in the spiral artery. It has been well documented that the diastolic component of uteroplacental flow velocity waveforms is decreased in the pregnancies complicated by PIH or IUGR[1–5,8]. Histopathological investigations have revealed that trophoblastic invasion is incomplete in such high-risk pregnancies[19,20].

In our study group of pregnancies complicated by PIH and/or IUGR, patients with abnormally high spiral artery RIs had worse perinatal outcomes and a higher prevalence of abnormal uterine and umbilical artery flow velocity waveforms compared to those with normal indices. On the other hand, adverse perinatal outcomes were found in only three cases (12.5%) of the 24 complicated pregnancies with normal spiral artery RIs. We also found that an abnormal spiral artery RI accurately reflects the severity of PIH and IUGR. These results suggest that spiral artery flow velocimetry may be useful for discriminating high-risk pregnancies with poor outcomes from those with good outcomes.

Fleischer and co-workers[2] have reported that a diastolic notch of the uterine artery flow velocity waveform usually disappears by 26 weeks of gestation in normal pregnancies, and its persistence beyond this point is an important predictor of adverse perinatal outcome. In our study of normal pregnancies, the incidence of a diastolic notch was 40.7% before and 6.9% after 26 weeks of gestation. Of the 43 complicated pregnancies, 24 (55.8%) had a diastolic notch of either uterine artery flow velocity waveform (16 with abnormal and eight with normal uterine artery RI). Adverse perinatal outcomes were found in 18 (75.0%) of these 24 pregnancies with a diastolic notch. The findings that five (62.5%) of eight cases with normal uterine artery RI and a diastolic notch had an abnormal spiral artery RI, and that four (80.0%) of these five had adverse perinatal outcomes, are remarkable. These findings are consistent with the reports of Aristidou and associates[21] and Bower and colleagues[22] that the presence of a diastolic notch of uterine artery flow velocity waveform is a better predictor of poor perinatal outcome or pre-eclampsia than the uterine artery RI. These observations strongly suggest that a diastolic notch of the uterine artery flow velocity waveform in the third trimester reflects high vascular resistance in the uteroplacental bed caused by incomplete trophoblastic invasion of the spiral arteries.

Some investigators have shown that second-trimester Doppler assessment of uterine artery flow velocity waveforms is a useful method of predicting high-risk pregnancies complicated by PIH and/or IUGR[5,7]. It is logical to speculate that color Doppler assessment of spiral artery flow velocity waveforms has the potential to predict such high-risk pregnancies at an earlier stage of gestation compared to uterine artery flow velocity waveforms. In fact, our preliminary transvaginal color Doppler study demonstrated that IUGR with adverse perinatal outcome was combined with abnormal spiral artery RI in the first trimester[8]. Early identification of high-risk obstetric cases with uteroplacental vascular compromise would facilitate earlier preventive interventions, such as low-dose aspirin therapy.

In summary, abnormal spiral artery flow velocity waveforms reflect poor placental perfusion, and indicate that placental function is impaired, leading to adverse perinatal outcome. Color flow imaging enables precise analysis to be made of spiral artery flow velocity waveforms and provides more accurate information about uteroplacental circulation in the evaluation of placental function. A large prospective study in the mid-trimester before the onset of complications would be necessary to confirm whether measurement of spiral artery flow velocity waveforms could be a useful predictor for the development of pregnancy-induced hypertension and/or intrauterine growth retardation.

ACKNOWLEDGEMENT

We would like especially to thank Dr Kazuo Maeda (Department of Obstetrics and Gynecology, Seirei Hamamatsu General Hospital) for his help and advice in the revising of this manuscript.

REFERENCES

1. Campbell, S., Diaz-Recasens, J., Griffin, D. R., Cohen-Overbeek, T. E., Pearce, J. M., Willson, K. and Teague, M. J. (1983). New Doppler technique for assessing uteroplacental blood flow. *Lancet*, **1**, 675–7
2. Fleischer, A., Schulman, H., Farmakides, G., Bracero, L., Grunfeld, L., Rochelson, B. and Koenigsberg, M. (1986). Uterine artery Doppler velocimetry in pregnant women with hypertension. *Am. J. Obstet. Gynecol.*, **154**, 806–13
3. Trudinger, B. J., Giles, W. B. and Cook, C. M. (1985). Uteroplacental blood flow velocity–time waveforms in normal and complicated pregnancy. *Br. J. Obstet. Gynaecol.*, **92**, 39–45
4. McCowan, L. M., Ritchie, K., Mo, L. Y., Bascom, P. A. and Sherret, H. (1988). Uterine artery flow velocity waveforms in normal and growth-retarded pregnancies. *Am. J. Obstet. Gynecol.*, **158**, 499–504
5. Campbell, S., Pearce, J. M. F., Hackett, G., Cohen-Overbeek, T. and Hernandez, C. (1986). Qualitative assessment of uteroplacental blood flow: early screening test for high-risk pregnancies. *Obstet. Gynecol.*, **68**, 649–53
6. Schulman, H., Winter, D., Farmakides, G., Ducey, J., Guzman, E., Coury, A. and Penny, B. (1989). Pregnancy surveillance with Doppler velocimetry of uterine and umbilical arteries. *Am. J. Obstet. Gynecol.*, **160**, 192–6
7. Valensise, H., Bezzecheri, V., Rizzo, G., Tranquilli, A.-L., Garzetti, G. G. and Romanini, C. (1993). Doppler velocimetry of the uterine artery as a screening test for gestational hypertension. *Ultrasound Obstet. Gynecol.*, **3**, 18–22
8. Sekizuka, N., Murakoshi, T. and Yoshizawa, H. (1994). The uterine and spiral artery flow velocity waveforms in early pregnancy: a transvaginal color and pulsed Doppler study. *J. Matern. Fetal Invest.*, **4**, 229–32
9. Trudinger, B. J. and Cook, C. M. (1990). Doppler umbilical and uterine flow waveforms in severe pregnancy hypertension. *Br. J. Obstet. Gynaecol.*, **97**, 142–8
10. Kurmanavichius, J., Baumann, H., Huch, R. and Huch, A. (1990). Uteroplacental blood flow velocity waveforms as a predictor of adverse fetal outcome and pregnancy-induced hypertension. *J. Perinat. Med.*, **18**, 255–60
11. Jurkovic, D., Jauniaux, E., Kurjak, A., Hustin, J., Campbell, S. and Nicolaides, K. H. (1991). Transvaginal color Doppler

assessment of the uteroplacental circulation in early pregnancy. *Obstet. Gynecol.*, 77, 365–9
12. Locci, M., Nazzaro, G., De Placido, G., Nazzaro, A., Colacurci, N., Montagnani, S. and Montemagno, U. (1993). Correlation of Doppler and placental immunohistochemical features in normal and intrauterine growth-retarded fetuses. *Ultrasound Obstet. Gynecol.*, 3, 240–5
13. Davey, D. A. and MacGillivray, I. (1988). The classification and definition of the hypertensive disorders of pregnancy. *Am. J. Obstet. Gynecol.*, **158**, 892–8
14. Nishida, H., Sakanoue, M., Kurachi, K., Asada, A., Kubo, S. and Funakawa, H. (1984). Fetal growth curve of Japanese. *Acta Neonat. Jpn.*, **20**, 90–7
15. Sekizuka, N. (1993). Combined examination of middle cerebral artery and umbilical artery flow velocity waveforms in growth-retarded fetuses. *Asia-Oceania J. Obstet. Gynaecol.*, **19**, 13–19
16. Pijnenborg, R., Bland, J. M., Robertson, W. B. and Brosens, I. (1983). Uteroplacental arterial changes related to interstitial trophoblast migration in early human pregnancy. *Placenta*, **4**, 397–414
17. Pijnenborg, R., Anthony, J., Davey, D. A., Rees, A., Tiltman, A., Vercruysse, L. and Assche, A. (1991). Placental bed spiral arteries in the hypertensive disorders of pregnancy. *Br. J. Obstet. Gynaecol.*, **98**, 648–55
18. Sheppard, B. L. and Bonnar, J. (1974). The ultrastructure of the arterial supply of the human placenta in early and late pregnancy, *J. Obstet. Gynaecol. Br. Commonw.*, **81**, 497–511
19. Sheppard, B. L. and Bonnar, J. (1981). An ultrastructural study of utero-placental spiral arteries in hypertensive and normotensive pregnancy and fetal growth retardation. *Br. J. Obstet. Gynaecol.*, **88**, 695–705
20. Voigt, H. J. and Becker, V. (1992). Uteroplacental insufficiency – comparison of uteroplacental blood flow velocimetry and histomorphology of placental bed. *J. Matern. Fetal. Invest.*, **2**, 251–5
21. Aristidou, A., Van den Hof, M. C., Campbell, S. and Nicolaides, K. (1990). Uterine artery Doppler in the investigation of pregnancies with raised maternal serum alpha-fetoprotein. *Br. J. Obstet. Gynaecol.*, **97**, 431–5
22. Bower, S., Bewley, S. and Campbell, S. (1993). Improved prediction of preeclampsia by two-stage screening of uterine arteries using the early diastolic notch and color Doppler imaging. *Obstet. Gynecol.*, **82**, 78–83