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Comprehensive analysis of uterine artery flow velocity waveforms for the prediction of pre-eclampsia

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ABSTRACT

Objectives *To evaluate the performance of velocimetric indices of uterine artery flow velocity waveforms (FVW's) at 20 weeks' gestation, alone or in combination with qualitative analysis, and establish the optimal screening method for the prediction of pre-eclampsia.*

Methods *A total of 614 primiparous women had color flow/pulsed Doppler (CFPD) imaging of both uterine arteries at 20 weeks gestation. Receiver operator characteristic (ROC) curves were created for the systolic/end-diastolic (A/B) ratio, resistance index (RI) and systolic/early diastolic (A/C) ratio for placental and non-placental uterine arteries, individually or in combination with the presence of unilateral or bilateral notches. Based on data from ROC curves, the sensitivity of each method was compared with the false-positive rate set at 17 and 11%.*

Results *The highest sensitivity (88%) and specificity of (83%) was obtained using bilateral notches/mean RI $\geq$ 0.55 (50th centile) and unilateral notches/mean RI $\geq$ 0.65 (80th centile). When the false-positive rate was set at 17%, the inclusion of bilateral notches significantly improved the sensitivity of RI ($P < 0.001$), placental RI ($P < 0.01$), placental A/C ratio ($P < 0.05$), mean A/C ratio ($P < 0.01$) and mean A/B ratio ($P < 0.05$). Bilateral notches/mean RI or A/B cut-offs were also superior to the persistence of a notch in either artery combined with RI ($P < 0.01$) or A/B ratio ($P < 0.05$). When the false-positive rate was set at 11%, the inclusion of bilateral notches did not improve the sensitivity of the A/C ($P = 1.00$) or A/B ratio ($P > 0.10$). Placental velocimetric indices performed better than mean indices but the differences in sensitivity at the set false-positive rates were not statistically significant.*

Conclusion *At 20 weeks' gestation, bilateral notches with mean RI cut-offs is the best screening method if further screening later in pregnancy is proposed. The A/C ratio is complementary to bilateral notches when the false- positive rate is set at 17% and an effective quantitative substitute when the false-positive rate is set at 11%.*

INTRODUCTION

Since uterine artery Doppler was proposed as an early screening test for pre-eclampsia and related complications[1] in the mid-1980s, conflicting results on its value as a screening tool for the subsequent development of pre-eclampsia have been reported[2–4]. The introduction of color Doppler imaging, the adoption of a standard sampling site (cross-over of external iliac vessels)[5] and restricted time of screening (18–26 weeks) have, however, produced more consistent results[6–9], but variability in its screening efficacy[10] is still being reported. This could be due to a number of factors: the lack of a universally accepted 'gold standard' to analyze flow velocity waveforms (FVWs); the lack of uniformly accepted cut-offs (e.g. fixed false-positive rates); the diverse classification of pre-eclampsia[11]; and the effect of differences in the prevalence of the disease in study populations on the positive predictive value.

The resistance index (RI) and the ratio of peak systolic to end-diastolic velocities (A/B ratio) were the initial simple velocimetric (quantitative) indices used to assess uterine artery FVWs. The presence of an early diastolic notch was noted to perform significantly and consistently better than A/B ratio[12] and RI[5–7]. The persistence of notches in both uterine arteries (bilateral notches) with the use of quantitative RI cut-offs (RI > 50th centile) was subsequently reported to improve screening efficacy compared to any notch and RI cut-offs at 20[13] and 24 weeks[8]. Other studies proposed the systolic/early diastolic ratio (A/C ratio) as an objective index for the notch[7] and this ratio has been reported as having good correlation with the presence or absence of notches[14].

Placental position can also affect the screening efficacy of uterine artery FVWs: the placental side uterine artery RI

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and A/C ratio are reported as better predictors of pre-eclampsia than the non-placental side RI[15], mean A/C ratio (average of both uterine arteries) or non-placental A/C ratio[9]. In a recent study[10] investigating a cohort of nulliparous women, the mean A/C ratio achieved similar results to both the mean A/B ratio and isolated qualitative assessment (persistence of a notch in one or both arteries).

The lack of uniformity in FVW analysis reflects the uncertainty as to which measurement of resistance, qualitative and/or quantitative, is best for the prediction of pre-eclampsia. As yet no data are available regarding: (1) receiver operator curves (ROC) of bilateral notches with use of variable RI cut-offs; (2) the effect of combining A/B ratio or A/C ratio with qualitative assessment (subjective definition of the notch in one or both arteries); and (3) direct comparison between bilateral notches combined with RI cut-offs and methods using A/B or A/C ratios.

The primary aim of this study was to undertake a comprehensive evaluation of commonly used velocimetric indices, using variable cut-offs, to establish the optimal method for identifying women in the second trimester who will subsequently develop pre-eclampsia. The indices were to be investigated individually and in combination with qualitative assessment of FVWs (unilateral or bilateral notches), also taking into account placental site.

METHODS

Consecutive unselected primiparous women presenting for a routine anomaly scan, between the 19th and 21st week of pregnancy, were offered uterine artery Doppler studies at the same visit. The department caters for an inner-city multi-racial community, which is high risk in terms of prevalence of pre-eclampsia, delivery of small-for-gestational-age babies and poor attendance. Data collected prospectively included race, past medical history, smoking habit, and blood pressure before 20 weeks pregnancy.

Uterine artery flow velocity waveforms were obtained using a Phillips SD-800/Hewlett-Packard Sonos 550 with a 3.5/5 MHz linear array. The high pass filter was set at 100 Hz. The transducer was placed in the lower lateral quadrant of the abdomen angled medially. Color flow/pulsed Doppler (CFPD) was employed to identify the uterine artery, as it appears to cross the external iliac artery. The range gate was placed over the entire diameter of the uterine artery approximately 1 cm distal to the crossover point. In a small proportion of cases where the uterine artery branched before the intersection of the external iliac vessels, FVWs were obtained from the main artery. The quality of the FVWs was maximized by using the smallest possible angle of insonation (range 15–50°) and accepting only those waveforms with a sharp clear outline. The placental position was also noted.

The A/B ratio, RI, and A/C ratio were calculated on four waveforms using in-built software, and the presence or absence of a notch was noted in each of the waveforms from both uterine arteries. Two readings were taken from each uterine artery. The criteria used for the presence of a notch[7] was clarified thus: a notch was considered to be present when there was a *clearly defined* upturn of the flow velocity waveform at the beginning of diastole and which was present in *all* the waveforms on both occasions each uterine artery was sampled. The A/C ratio was measured according to the criteria set by Irion *et al.*[14]. The intra-operator coefficient of variation was calculated in five patients with each patient examined three times. The mean intra-observer coefficient of variation for RI was 4.5 ± 2.0%, A/B ratio 5.2 ± 2.3%, A/C ratio 1.5 ± 1.1%.

One operator (J.A.) performed the majority of measurements. Women with bilateral notches and mean RI ≥ 0.55 plus all unilateral notches/mean RI ≥ 0.65 (method Ie, see below) were offered 4-weekly scans up till 36 weeks in view of the recognized risk of fetal growth restriction[13], unless there were other clinical indications which necessitated closer surveillance. The use of one mean RI cut-off point with bilateral and unilateral notches has already been shown to improve the screening efficacy of qualitative assessment[13]. At the follow-up scans fetal biometry (head and abdominal circumference, femur length) was plotted on growth curves and assessment of amniotic fluid and Doppler studies of the umbilical artery was performed at each scan. If a reduction in the growth velocity was suspected and/or the amniotic fluid was reduced for gestational age (amniotic fluid index < 8 cm) and/or the umbilical artery PI was above the 90th centile, scans were booked every 1–2 weeks. The results of the growth scans were available to clinicians but the results of the uterine artery Dopplers were not routinely reported unless specifically requested.

Analysis

The following quantitative and/or qualitative methods were analyzed. ‘Any notch’ was defined as the presence of a notch in one or both FVWs. ‘Bilateral notches’ were defined as the presence of notches in all the FVWs obtained from both right and left uterine arteries. When the placenta was midline, we agreed that the artery with the lower A/B ratio, RI or A/C ratio represented the dominant artery in terms of blood flow. Therefore the lower value was used instead of calculating the ratio from the mean of both sides as previously described[9].

In order to comprehensively analyze the waveforms we analyzed each quantitative index in five different ways:

Group I – methods using mean RI

(a) Mean RI – average of the RI from both uterine arteries.
(b) Mean RI plus any notch – presence of a notch in either uterine artery.
(c) Placental artery RI.
(d) RI placental artery plus any notch.
(e) Bilateral notches/mean RI cut-offs plus all unilateral notches/mean RI ≥ 0.65 (80th centile).

Group II – methods using the A/C ratio

(a) Mean A/C ratio – average of the A/C ratio from both uterine arteries.
(b) Mean A/C ratio plus any notch.
(c) Placental artery A/C ratio.
(d) Placental artery A/C ratio plus any notch.

(e) Bilateral notches/mean A/C cut-offs plus all unilateral notches/mean A/C ≥ 2.5 (80th centile).

Group III – methods using the A/B ratio

(a) Mean A/B ratio – the average of the A/B ratio from both uterine arteries.
(b) Mean A/B ratio plus any notch.
(c) Placental artery A/B ratio.
(d) Placental artery A/B ratio plus any notch.
(e) Bilateral notches/mean A/B cut-offs plus all unilateral notches/mean A/B ≥ 3.0 (80th centile).

The means and the centiles for mean and placental artery A/B ratios, A/C ratios and RI were calculated. The sensitivity and specificity for all the methods were calculated between the 5th and 95th centiles for each velocimetric index, including arbitrary cut-offs between centiles to ensure comparison at arbitrarily fixed false-positive rates. The ROC curves[16] were created for all of the 15 methods. These graphs present sensitivity (true-positive rate) plotted against the false-positive rate (100% minus specificity). The apex of the ROC curve represents the highest sensitivity and specificity but this point is different for each method. This poses a problem when trying to compare the different methods of analyzing the same waveform. To overcome this problem and present a meaningful comparison of the different methods, fixed false-positive rates (using McNemar's method[17]), were arbitrarily set to assess statistical differences in sensitivity between the different methods. The false-positive rates were set at 17 and 11% on the basis that a preliminary review of the data indicated that these false-positive rates were the most suitable cut-offs to compare sensitivities.

The main outcome measure was the development of pre-eclampsia. The development of pre-eclampsia were based on the definitions given by Davey and McGilliviray[18]: pre-eclampsia was diagnosed when gestational hypertension was associated with significant proteinuria which was defined as > 300 mg proteinuria on 24 h urinary collection or the appearance of at least + + on protein stick-testing on two separate occasions 4 h apart, without evidence of urinary tract infection. Gestational hypertension was defined as the occurrence, in a previously normotensive and non-proteinuric women, of: (1) a diastolic blood pressure ≥ 90 mmHg on at least two consecutive occasions at least 4 h apart after the 20th week of gestation; or (2) a diastolic blood pressure ≥ 110 mmHg on a single occasion after the 20th week of gestation. Pre-eclampsia requiring delivery before 37 completed weeks gestation (preterm pre-eclampsia) was evaluated as a subset.

The data was analyzed using a Windows-based SPSS statistical package, version 6.1.3. Statistical significance was assessed using a chi-squared test or Fisher's exact test where cell counts were small. The chi-squared and Mann–Whitney *U*-tests were used to compare categorical and continuous demographic data in women with known outcome and those lost to follow-up. McNemar's test was used to assess the statistical significance of the differences in sensitivities obtained for fixed specificities. Statistical significance was set at $P < 0.05$.

Table 1 Demographic details of study population

	No. of women available for analysis	%	*Women lost to follow up*	%	*P-value*
All women	550	89.6	77	10.4	
Caucasian	304	55.6	36	56.3	0.17
Afro-Caribbean	202	31.3	20	36.3	
Asian	33	12.2	8	6	0.52
Oriental	8	1.5	–	–	
Smoking	131	20.9	13	23.9	

RESULTS

A total of 614 consecutive, unselected, nulliparous women with singleton pregnancies were entered into the study over a 12-month period. The mean gestation was 20.5 weeks (range, 18–22 weeks). Four pregnancies were excluded: two because of subsequent development of hydrops; one because of Down's syndrome; one because the baby was born with ambiguous genitalia. Sixty pregnancies were lost to follow-up leaving 550 (89.6%) outcomes available for analysis. Flow velocity waveforms were obtained from both sides in all the women studied. There were no significant differences in race, booking weight or blood pressure between the women with a known outcome and those lost to follow-up. Other demographic characteristics are listed in Table 1. Forty women (7.3%) developed pre-eclampsia (40 of 550) of which 15 (2.7%) required delivery before 37 weeks. The placenta was recorded as right sided in 221 of 550 (40.2%), left sided in 165 of 550 (30.0%) and centrally situated in 164 of 550 (29.9%). The means of the velocimetric indices and the values between the 5th and 95th centiles are summarized in Table 2.

ROC curves for methods using RI (Group I)

The ROC curves for methods using RI are illustrated in Figure 1. The apex of the ROC curve closest to the top left-hand corner (highest sensitivity and specificity) was that using bilateral notches and mean RI cut-offs (method e). The cut-off at the apex of the curve was a mean RI ≥ 0.55 (50th centile) and also included all the unilateral notches and mean RI ≥ 0.65 (80th centile). When sensitivities for each method (a–e) were compared at the arbitrarily fixed

Table 2 The means of the quantitative indices and the value between the 5th and 95th centiles

	Mean	*5th*	*50th*	*75th*	*90th*	*95th*
Mean A/B ratio	2.44	1.6	2.2	2.6	3.35	4.05
Placental artery A/B ratio	2.11	1.56	1.99	2.26	2.74	3.11
Mean A/C ratio	2.09	1.4	1.81	2.15	2.75	3.56
Placental artery A/C ratio	1.8	1.3	1.67	1.89	2.28	2.72
Mean RI	0.54	0.4	0.55	0.60	0.68	0.73
Placental artery RI	0.50	0.36	0.50	0.55	0.63	0.68

A/B ratio, systolic/late diastolic ratio; A/C ratio, systolic/early diastolic ratio; RI, resistance index.

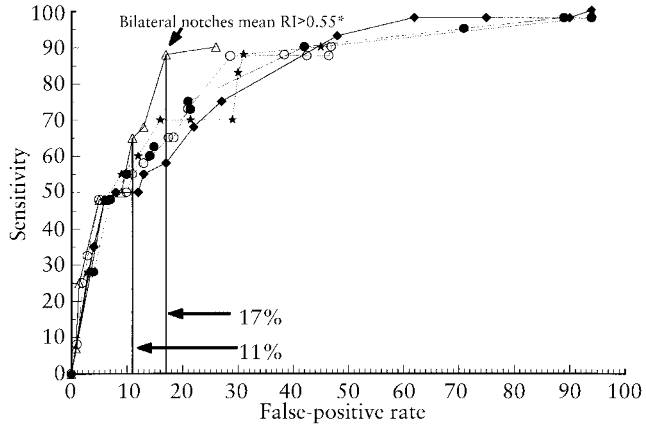

Figure 1 Receiver operator characteristic curves for methods using RI. Mean RI (diamonds), mean RI plus any notch (open circles), placental RI (closed circles), placental RI ratio plus any notch (stars), bilateral notches plus mean RI* (triangles).
* Includes all unilateral notches and mean RI ≥ 80th centile.

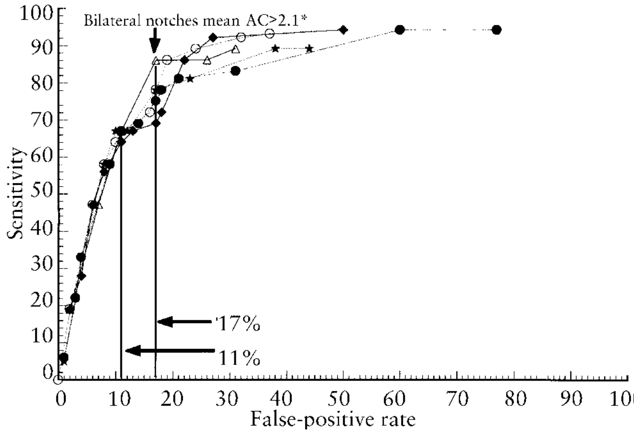

Figure 2 Receiver operator characteristic curves for methods using A/C ratios. Mean A/C ratio (diamonds), mean A/C ratio plus any notch (open circles), placental A/C ratio (closed circles), placental A/C ratio plus any notch (stars), bilateral notches plus mean A/C ratio* (triangles).
* Includes all unilateral notches and mean A/C ratio ≥ 80th centile.

false-positive rates of 17 and 13%, the sensitivities were consistently worst for RI (58 and 60%) and best for bilateral notches with RI cut-offs (88 and 65%). The sensitivity using the bilateral notch method was by and large significantly better than all the other methods for both false-positive rates. The results are summarized in Table 3. Placental artery RI performed better than mean RI but inclusion of any notch did not significantly improve the sensitivity of placental RI in direct contrast to mean RI.

ROC curves for methods using A/C ratio (Group II)

The ROC curves for methods using A/C ratio are illustrated in Figure 2. For a false-positive rate of 17%, the sensitivity when using bilateral notches and mean A/C cut-offs (method e) was significantly better than mean A/C ratio ($P < 0.01$) and placental A/C ratio ($P < 0.05$), but just failed to reach statistical significance when compared with the methods where any notch was included with either ratio ($P = 0.08$). For false-positive rates of 11% or lower the inclusion of any or bilateral notches did not improve the sensitivity of either the mean A/C or placental A/C ratio. The results are summarized in Table 4.

ROC curves for methods using A/B ratio (Group III)

Mean A/B ratio plus any notch and bilateral notches with mean A/B cut-offs performed consistently better than all the other methods. The ROC curves for all the methods are illustrated in Figure 3. For a false-positive rate of 17%, the sensitivity for both mean or placental A/B ratio was significantly improved with the addition of any notch or bilateral notches but this trend was not apparent when the false-positive rate was set at 11% (Figure 3 and Table 5). The apex of the ROC curve was obtained using any notch plus mean A/B ratio (sensitivity 78%, specificity 83%). The cut-off for mean A/B ratio at this point was ≥ 2.65 (75th centile).

Comparison of the best method from each group for a false-positive rate of 17%

The highest sensitivity (88%) was obtained using bilateral notches/mean RI ≥ 0.55 and unilateral notches/mean RI ≥ 0.65 (method Ie). When the A/C ratio was utilized, the highest sensitivity (86%) was obtained using bilateral notches/mean AC ≥ 2.1 and unilateral notches/mean A/C ratio ≥ 2.5. For the A/B ratio the highest sensitivity (78%) was obtained using any notch/mean A/B ratio ≥ 2.65 (method IIId). The difference in sensitivity between best (bilateral notches/mean RI) and the worst (A/B ratio plus any notch) (88 versus 78%) reached statistical significance (P-value < 0.05). The results are tabulated in Table 6 and the ROC curves for the best three methods are illustrated in Figure 4.

Table 3 The sensitivity of the various methods using RI (Group I) as the quantitative index when the false-positive rate was set at 17 and 11%

	Sensitivity 17% FPR (%)	*P**	*Sensitivity 11% FPR (%)*	*P**
Mean RI	58	0.001	50	0.02
Mean RI plus any notch	65	0.01	55	0.05
RI placental artery	63	0.01	59	0.08
RI placental artery plus any notch	70	0.01	60	0.08
Bilateral notches/mean RI**	88	–	65	–

FPR, false-positive rate. * Statistical significance between sensitivity of each method compared to that obtained using bilateral notches. ** Includes unilateral notches plus mean RI ≥ 0.65.

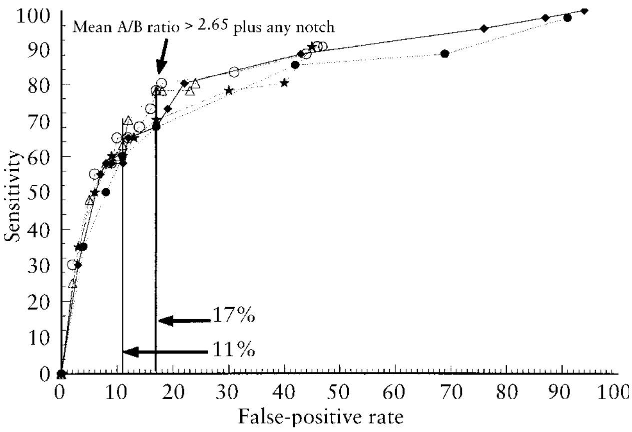

Figure 3 Receiver operator characteristic curves for methods using A/B ratios. Mean A/B ratio (diamonds), mean A/B ratio plus any notch (open circles), placental A/B ratio (closed circles), placental A/B ratio plus any notch (stars), bilateral notches plus mean A/B ratio* (triangles).
* Includes all unilateral notches and mean A/B ratio ≥ 80th centile.

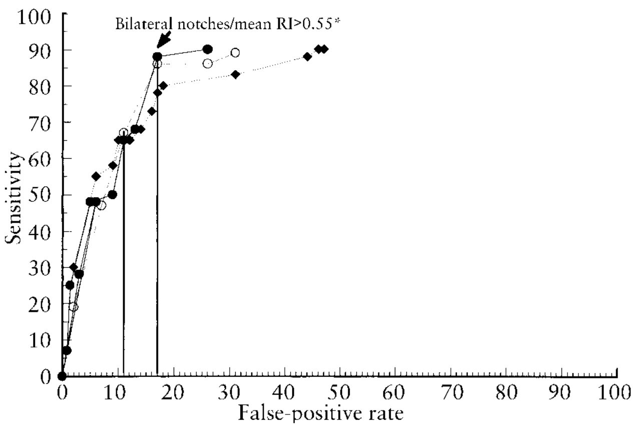

Figure 4 Receiver operator characteristic curves comparing the best method for each velocimetric index; bilateral notches and mean A/C ratio* (open circles), mean A/B ratio and any notch (triangles) and bilateral notches and mean RI* (closed circles).
* Includes all unilateral notches and mean index ≥ 80th centile.

Comparison of the best method from each group for a false-positive rate of 11%

The best sensitivity from each group was very similar: bilateral notches/mean RI ≥ 0.62 and unilateral notches/mean RI ≥ 0.65 [65%, positive predictive value (PPV) 33%], placental artery A/C ratio ≥ 2.1 (69%, PPV 33%), any notch plus mean A/B ratio ≥ 2.9 (65%, PPV 33%). The ROC curves for these methods are represented in Figure 4.

Preterm pre-eclampsia

The highest sensitivity (88%) and specificity (80%), was obtained using bilateral notches/mean RI ≥ 0.55 and unilateral notches/mean RI ≥ 0.65 (method Ie) [odds ratio (OR), 24.8; 95% confidence interval (CI), 5.5–111.6]. The best sensitivity (86%) and specificity (80%) for the A/C ratio was obtained using bilateral notches/mean A/C ratio ≥ 2.1 and unilateral notches/mean A/C ratio ≥ 2.5 (OR, 24.1; 95% CI, 5.3–109.0). The best sensitivity (73%) for A/B ratio was obtained using bilateral notches/mean A/B ratio ≥ 2.3 (OR, 10.6; 95% CI, 3.3–34.0). The difference in sensitivities between bilateral notches/mean RI and bilateral notches/mean A/B ratio just failed to achieve statistical significance (88 versus 73%, *P*-value = 0.08).

DISCUSSION

This study presents a comprehensive comparison of all previously published methods of uterine artery FVW analysis, in the same cohort of women. The use of ROC curves provides us with the most objective appraisal of the best way to analyze FVWs for the prediction of pre-eclampsia by making a direct comparison between the different methods at arbitrarily fixed cut-offs (false-positive rates). The analysis was restricted to primiparous women to exclude possible errors in the diagnosis of pre-eclampsia in multiparous women[19], and because primiparous women do not typically have any identifiable risk factors.

The reasons for assessing uterine artery Doppler at 20 weeks were two-fold. Firstly, in our population an anomaly scan is offered routinely to all women at this gestation; it was therefore practical to perform the Doppler studies at the same time. Secondly, it is well recognized that the lower false-positive rate of 24–26 week Doppler studies is achieved while maintaining the sensitivity of earlier screening[7]. However, the selection of women at 24 weeks may limit the effectiveness of prophylactic therapies[20]. It is believed that the earlier the therapy is commenced the more likely it is to be effective, but the effectiveness of aspirin in women selected at 18–22 weeks using uterine artery Doppler is hampered by the recognized

Table 4 The sensitivity of the various methods using A/C ratio (Group II) as the quantitative index when the false-positive rate was set at 17 and 11%

	Sensitivity 17% FPR (%)	*P**	*Sensitivity 11% FPR (%)*	*P**
Mean AC ratio	69	0.01	64	1.00
Mean AC ratio plus any notch	78	0.08	67	1.00
A/C placental artery	75	0.05	67	1.00
A/C placental artery plus any notch	78	0.08	67	1.00
Bilateral notches/mean A/C ratio**	86	–	67	–

FPR, false-positive rate. * Statistical significance between sensitivity of each method compared to that obtained using bilateral notches. ** Includes unilateral notches plus mean A/C ratio ≥ 2.5.

	Sensitivity 17% FPR (%)	P*	Sensitivity 11% FPR (%)	P*
Mean A/B ratio	68	0.05	58	0.08
A/B placental artery	68	0.05	60	0.2
Any notch plus A/B placental artery	70	0.5	60	0.2
Bilateral notches/mean A/B ratio**	78	–	63	0.5
Any notch plus mean A/B ratio	78	–	65	

FPR, false-positive rate. * Statistical significance between sensitivity of each method compared to that obtained using any notch plus mean A/B ratio using McNemar's method. ** Includes unilateral notches plus mean A/B ratio ≥ 3.1.

Table 5 The sensitivity of the various methods using A/B ratio (Group III) as the quantitative index when the false-positive rate was set at 17 and 11%

poor specificity of screening at this gestation[21]. By undertaking a comprehensive analysis, the aim of the study was to try and maximize the screening efficacy of uterine artery Dopplers at 20 weeks of gestation.

The A/C ratio performed better than other quantitative indices (RI, A/B ratio), when these indices were analyzed without inclusion of qualitative assessment. The placental A/C ratio was also marginally better than the mean A/C confirming previous reports[9]. The inclusion of bilateral notches significantly improved the sensitivity of both mean A/C ratio and placental A/C ratio when the false-positive rate was set at 17% but not at 11%. This implies that the A/C ratio is complementary to qualitative analysis (bilateral notches) if the false-positive rate is set at 17%, but would be an effective objective substitute (unlike RI) to bilateral notches if the false-positive rate is set at 11% or lower. Combined assessment using bilateral notches and the A/C ratio did not however, result in any significant improvement in screening efficacy, over bilateral notches and mean RI cut-offs at the set false-positive rates (e.g. 67 versus 65% for a false-positive rate of 11%). The inclusion of any or bilateral notches improved the sensitivity of the A/B ratio in a similar fashion to the A/C ratio, but the screening efficacy of combined quantitative/qualitative analysis using A/B ratio (group IIIa–c) was generally poorer than the methods using RI or A/C ratio.

The reported sensitivities using the placental indices were generally better than the mean of both arteries, confirming the findings from previous studies[9,15]. The inclusion of any notch marginally improved the sensitivity of these indices, but the improvement never achieved statistical significance. Analysis on the basis of using placental location (methods Ic, IIc, IIIc) did not however, result in any significant improvement compared with bilateral notches with mean RI and A/C ratio cut-offs. The results for the prediction of pre-eclampsia requiring delivery before 37 weeks gestation were generally similar to the results for the prediction of all pre-eclamptics. Failure to achieve any statistically significant differences in sensitivity for the set false-positive rates could be attributed to the small numbers ($n = 15$) involved but the trends were essentially similar.

Optimizing the efficacy of any screening test is usually achieved by finding the best trade-off between sensitivity and specificity. Generally the higher the sensitivity the lower the specificity, and vice-versa. When assessing the efficacy of a test, taking the apex of the ROC curve as optimal, assumes that the consequences of both false-positive or false-negative errors are identical. In screening for pre-eclampsia, the choice of trade-off should depend on the type of intervention proposed post-screening.

If uterine artery Doppler at 20 weeks of gestation is used as a first-line screening method with further screening at 24 weeks[7,10], then our results suggest that the method with the highest sensitivity and specificity (bilateral notches with RI or A/C cut-offs) should the method of choice. This would ensure that the highest possible number of true-positive women are selected for the second phase of screening, when the specificity is improved due to the normalization of the uterine circulation in low risk women[22], accepting that the implications of a high false-positive result (17%) will only result at worst, in a further scan. The choice of bilateral notches with quantitative cut-offs confirms the findings from a previous study[23] at the same gestation, but in that study the authors used RI cut-offs greater than the 90th centile. This resulted in a very low false-positive rate (3.15%) and not surprisingly a very low sensitivity (21.74%).

If the intervention proposed post-screening is the institution of therapeutic trials a screening test with a lower false-positive rate (11%), but an acceptable sensitivity (65–69%) should be selected. With a lower false-positive rate, selection of women for therapeutic trials would ensure that any potential benefit of the

	Sens (%)	Spec (%)	PPV (%)	OR (CI)
Any notch plus mean A/B ratio ≥ 2.64	78	83	26	14.6 (6.9–30.9)
Bilateral notches/mean A/C ratio ≥ 2.1*	86	83	28	31.0 (11.6–82.3)
Bilateral notches plus mean RI ≥ 0.55*	88	83	28	33.1 (12.6–86.9)

Sens, sensitivity; Spec, specificity; OR, Odds ratios; PPV, positive predictive value; CI, 95% confidence intervals. * includes unilateral notches plus mean RI ≥ 0.65 or A/C ratio ≥ 2.5.

Table 6 The best sensitivity, specificity and PPV using the best method from each group (I–III) represented by the apex of the ROC curves therapy is not diluted in a large number of false-positive patients. This implies that besides bilateral notches/mean RI cut-offs, any method using the A/C ratio (methods IIa–e) or any notch and mean A/B ratio (method IIIb) could be used in this scenario. Evidence from previous studies suggests that giving of low-dose aspirin in the second trimester, to women with a prevalence (or PPV if selected by a screening test) of pre-eclampsia of 20%[24], would not result in a significant reduction in the incidence of pre-eclampsia. The implication of these findings is that, for the purposes of selection for therapeutic trials, a higher PPV is probably essential. For a false-positive rate of 11%, we achieved a PPV of 33%; whether selection of women for prophylaxis on the basis this screening method would result in a significant reduction in the incidence of pre-eclampsia is an issue which needs to be evaluated in future studies.

The higher prevalence of pre-eclampsia in our study (7.2%) compared with a study[9] (3.3%) using the same methodology (nulliparous women screened at 18–20 weeks, using placental or mean A/C ratio) can partly explain the improved PPV obtained in our study (33 versus 14%). The improved sensitivity (69 versus 53%) for similar false-positive rates (11 versus 12%) could also partly account for the improved PPV. Our results contrast with those from a more recent and larger study of nulliparous women[10], who underwent two-stage screening at 18–26 weeks. In that study, however, FVWs were not obtained in 3% of the population. It is not clear where these women were included for the purposes of analysis. Failure to obtain a waveform, especially using CFPD, typically occurs because the blood flow is particularly poor. In fact in other studies[9,25] all women in whom FVWs were not obtained subsequently had an adverse outcome.

Our findings are generally in agreement with most of the previous studies reporting on the predictive value of uterine artery Doppler screening for pre-eclampsia. Analysis using fixed false-positive rates has enabled accurate comparison between different methods of FVW analysis. This comprehensive evaluation of uterine artery FVWs reiterates the fact that bilateral notches with quantitative RI cut-offs appear to be the most effective method for two-stage screening. We were unable to significantly improve the screening efficacy at 20 weeks using other methods of FVW analysis. In trained hands, uterine artery Doppler remains one of the best screening tests currently available in terms of screening efficacy and practicality for everyday use in an antenatal setting. There is limited evidence from small-scale studies that combining uterine artery Doppler data with other tests of trophoblastic dysfunction will improve the specificity and PPV of the test[26]. Future research should therefore concentrate on combining uterine artery Doppler with other early markers of pre-eclampsia[27], or tests that evaluate maternal maladaptation to pregnancy[28].

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