

Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis

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ABSTRACT

Background: Alterations in waveforms in the uterine artery are associated with the development of pre-eclampsia and intrauterine growth restriction. We investigated the predictive accuracy of all uterine artery Doppler indices for both conditions in the first and second trimesters.

Methods: We identified relevant studies through searches of MEDLINE, EMBASE, the Cochrane Library and Medion databases (all records to April 2006) and by checking bibliographies of identified studies and consulting with experts. Four of us independently selected studies, extracted data and assessed study validity. We performed a bivariable meta-analysis of sensitivity and specificity and calculated likelihood ratios.

Results: We identified 74 studies of pre-eclampsia (total 79 547 patients) and 61 studies of intrauterine growth restriction (total 41 131 patients). Uterine artery Doppler ultrasonography provided a more accurate prediction when performed in the second trimester than in the first-trimester. Most Doppler indices had poor predictive characteristics, but this varied with patient risk and outcome severity. An increased pulsatility index with notching was the best predictor of pre-eclampsia (positive likelihood ratio 21.0 among high-risk patients and 7.5 among low-risk patients). It was also the best predictor of overall (positive likelihood ratio 9.1) and severe (positive likelihood ratio 14.6) intrauterine growth restriction among low-risk patients.

Interpretation: Abnormal uterine artery waveforms are a better predictor of pre-eclampsia than of intrauterine growth restriction. A pulsatility index, alone or combined with notching, is the most predictive Doppler index. These indices should be used in clinical practice. Future research should also concentrate on combining uterine artery Doppler ultrasonography with other tests.

Une version française de ce résumé est disponible à l'adresse www.cmaj.ca/cgi/content/full/178/6/701/DC1

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Pre-eclampsia and intrauterine growth restriction remain important causes of maternal and perinatal morbidity and mortality.¹⁻³ Maternal complications of pre-eclampsia include coagulopathy, renal and liver failure, and stroke.¹ Adults who were affected by intrauterine growth restriction in utero are at increased risk for cardiovascular disease, hypertension and type 2 diabetes.^{4,5}

Pre-eclampsia and intrauterine growth restriction are characterized by abnormal placenta formation,⁶ which results in inadequate uteroplacental blood flow. This has led to the idea of using Doppler ultrasonography to assess the velocity of uterine artery blood flow as part of routine ultrasound screening.⁷ Low end-diastolic velocities and an early diastolic notch characterize the waveforms of uterine artery blood flow in women who are not pregnant or are in their first trimester. Persistence of a diastolic notch (beyond 24 weeks' gestation) or abnormal flow velocity ratios have been associated with inadequate trophoblast invasion.⁸

Accurate prediction of pre-eclampsia and intrauterine growth restriction is crucial to allow judicious allocation of resources for monitoring and preventive treatment to improve maternal and perinatal outcomes.^{9,10} However, studies investigating the predictive accuracy of uterine artery Doppler indices (Box 1) have revealed considerably varied results. Thus, it is questionable whether uterine artery Doppler ultrasonography should be used as a predictive test. We undertook this review to investigate the accuracy of all uterine artery Doppler indices in predicting pre-eclampsia and intrauterine growth restriction.

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Box 1: Explanation of Doppler indices

A/C ratio	Ratio of peak systolic to early diastolic velocity
Any notching	Presence of early diastolic notching* in waveform; may be unilateral or bilateral
Bilateral notching	Presence of early diastolic notching in waveform of both main uterine arteries
D/S ratio	Ratio of diastolic to systolic velocity
D/S or notching	D/S ratio with or without unilateral or bilateral early diastolic notching
Notch index (or notch depth index)	Notch flow minus early diastolic flow divided by notch flow: $(D - C)/D$
Pulsatility index	Peak systolic flow minus end diastolic flow divided by mean flow: $(A - B)/M$
Pulsatility index and notching	Pulsatility index combined with unilateral or bilateral early diastolic notching
Pulsatility index or notching	Pulsatility index with or without unilateral or bilateral early diastolic notching
Resistance index	Peak systolic flow minus end diastolic flow divided by peak systolic flow: $(A - B)/A$
Resistance index and notching	Resistance index combined with unilateral or bilateral early diastolic notching
Resistance index or notching	Resistance index with or without unilateral or bilateral early diastolic notching
S/D ratio	Ratio of peak systolic to late diastolic velocity (also known as A/B ratio)
S/D or notching	S/D ratio with or without unilateral or bilateral early diastolic notching
Unilateral notching	Presence of early diastolic notching in waveform of one main uterine artery

*Early diastolic notching = characteristic waveform indicating decreased early diastolic flow in the uterine artery compared with later diastolic flow.

Methods**Literature search**

We based our review on our previously published protocols.^{11,12} Experienced clinical librarians performed 2 electronic searches, without language restrictions, in the MEDLINE, EMBASE, Cochrane Library and Medion (www.mediondatabase.nl) databases for all records to April 2006 (details of the search strategies are provided in Appendix 1, available online at www.cmaj.ca/cgi/content/full/178/6/701/DC2). We also checked reference lists of identified articles and consulted with experts (Figure 1). We included studies that reported Doppler assessment of the main uterine arteries in the first and second trimester among pregnant women in any health care setting and at any level of risk for pre-eclampsia or intrauterine growth restriction. We included test-accuracy studies that allowed generation of 2×2 tables.

Quality assessment and data abstraction

For pre-eclampsia, 4 of us (J.C., R.M., G.R. and B.M.) independently screened titles and abstracts of identified studies and, if relevant, the full-text articles for inclusion and data extraction.¹¹ For

intrauterine growth restriction, this work was carried out by 1 of us (R.M.), and 10% of the papers were examined by a second independent reviewer (B.M.).¹² One reviewer (R.M.) assessed the studies for their methodological quality, using the QUADAS (quality assessment of diagnostic accuracy studies) criteria,¹³ and whether any preventive interventions had been used (see Appendix 2, available online at www.cmaj.ca/cgi/content/full/178/6/701/DC2). For multiple publications of the same data set, only the most recent or complete study was included. Disagreements were resolved by consensus or by a third reviewer.

Acceptable reference standards for pre-eclampsia were persistently high systolic (≥ 140 mm Hg) or diastolic (≥ 90 mm Hg) blood pressure and proteinuria (≥ 0.3 g of protein in 24-hour urine collection, or dipstick test result of $\geq 1+$ [equivalent to 30 mg/dL in single urine sample]) of new onset after 20 weeks of gestation. We defined severe pre-eclampsia as a systolic blood pressure of 160 mm Hg or greater or a diastolic blood pressure of 110 mm Hg or greater plus a high level of proteinuria (≥ 2.0 g of protein in 24-hour urine collection or dipstick test result of $\geq 3+$), or the development of pre-eclampsia before 34 weeks' gestation. We defined superimposed pre-eclampsia as the development of proteinuria (≥ 0.3 g of protein in 24-hour urine collection or dipstick test result $\geq 1+$) after 20 weeks of gestation in patients with chronic hypertension.¹⁴

Acceptable reference standards for intrauterine growth restriction included birth weight below the 10th centile adjusted for gestational age and based on local population values. Severe intrauterine growth restriction was defined as birth weight below the fifth or third centile. We also assessed absolute birth-weight thresholds, neonatal ponderal index below the 10th centile, skin-fold thickness and ratio of mid-arm circumference to head circumference.¹⁵⁻¹⁹

Data analysis

We calculated the sensitivity and specificity for each study and pooled the results of studies with similar Doppler indices, outcomes and patient risk. We used a bivariable regression model that takes into account the (negative) correlation between sensitivity and specificity. This method has been extensively described elsewhere and has been recently recommended for meta-analyses of diagnostic tests.^{20,21} To estimate sensitivity and specificity with their 95% confidence intervals (CIs), we used the model with the smallest Akaike's information criterion (a measure of the goodness of fit of an estimated statistical model). This model best accounts for heterogeneity between studies. When several thresholds for a Doppler index were reported, we used the commonest. We derived likelihood ratios from the pooled sensitivities and specificities.²²

We performed subgroup analyses as defined a priori: outcome (severe v. mild or overall), patient risk (low or risk not specified v. high) and gestational age at testing (before v. after 16 weeks). Sensitivity analyses were performed for application of preventive interventions (yes v. no or unclear) and high-quality studies. We considered studies to be of high quality if they met at least 4 of the following criteria: prospective design with consecutive recruitment, appropriate reference standard, adequate description of the index test, follow-up of more than 90% of patients and reporting preventive treatment.

Results

We included 83 studies in total in our review. Fifty-two of them had both pre-eclampsia and intrauterine growth restriction as outcomes. We included these 52 studies in the assessments of each of the 2 outcomes.

Pre-eclampsia

We included 74 studies (69 cohort studies, 3 randomized controlled trials and 2 case-control studies) in which uterine artery Doppler ultrasonography had been used to predict pre-eclampsia; from these studies we were able to construct 180 2 × 2 tables. Of these studies, 50 were prospective, 10 were retrospective, and in 14 this was unclear. Details of the studies are provided in Appendix 3 (available online at www.cmaj.ca/cgi/content/full/178/6/701/DC2). The total number of women was 79 547, of whom 2498 were found to have pre-eclampsia. Samples varied in size from 28 to 16 806 women. In most of the studies, Doppler ultrasonography was performed between 18 and 24 weeks' gestation during a routine prenatal

scan; 7 articles reported Doppler results before 16 weeks' gestation. The median rate of pre-eclampsia was 4.9% (25th–75th centiles 2.2%–9.8%). Rates of pre-eclampsia varied from 0.4% to 18.7% among patients at low or unspecified risk and from 3.2% to 44.3% among high-risk patients.

Intrauterine growth restriction

We included 61 studies (57 cohort studies and 3 randomized controlled trials) in which uterine artery Doppler ultrasonography was used to predict intrauterine growth restriction; from these studies we were able to construct 168 2 × 2 tables. Of these studies, 48 were prospective, 10 were retrospective, and in 2 this was unclear. Details of the studies are provided in Appendix 4 (available online at www.cmaj.ca/cgi/content/full/178/6/701/DC2). The total number of women was 41 131, of whom 3723 had intrauterine growth restriction (as determined by birth weight below the 10th centile or less than 2500 g if several thresholds were reported). The samples varied in size from 28 to 7851 women. Ten articles reported Doppler results before 16 weeks'

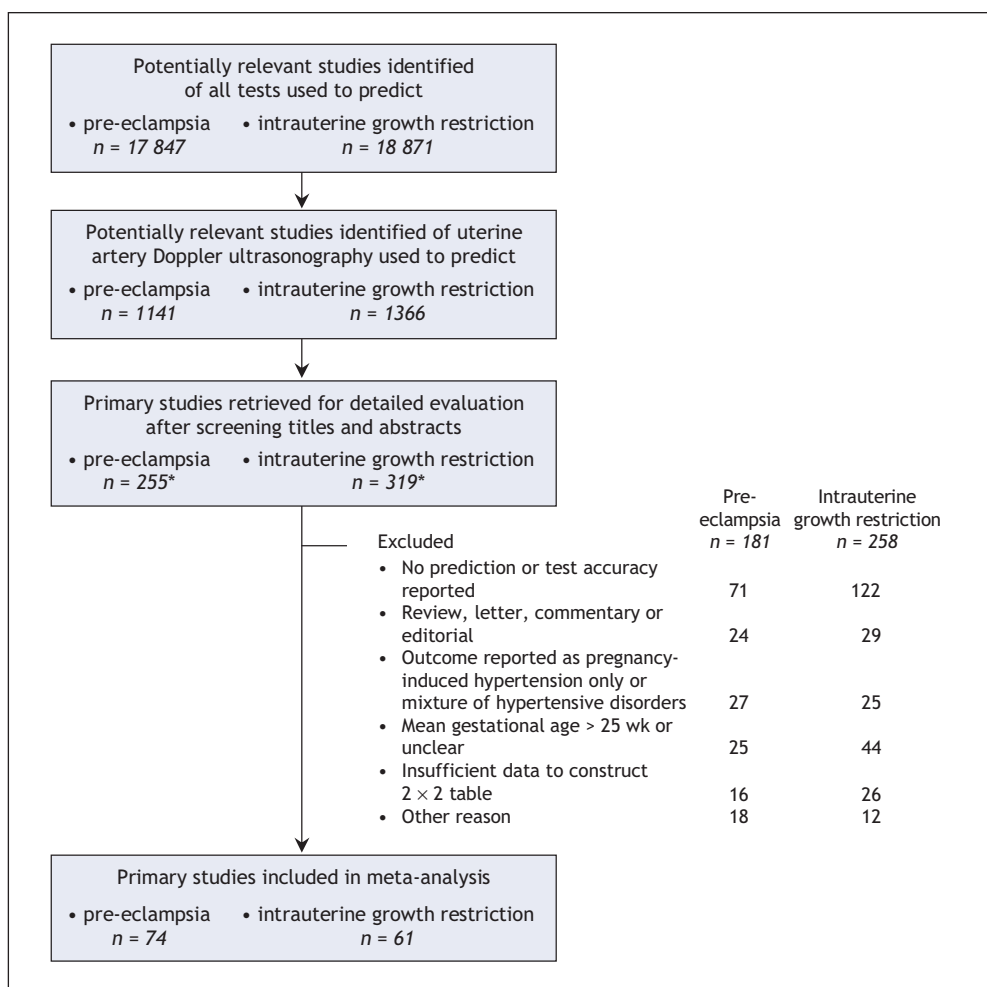


Figure 1: Identification of studies of uterine artery Doppler ultrasonography used to predict pre-eclampsia and intrauterine growth restriction, for inclusion in the meta-analysis. *Includes 6 studies on pre-eclampsia and 8 on intrauterine growth restriction that were added after manual search of bibliographies of selected articles.

gestation. Most of the studies used birth weight below the 10th centile as the reference standard for intrauterine growth restriction. One study reported absolute birth-weight thresholds, and in 2 studies the threshold was unclear. Calculated rates of intrauterine growth restriction correlated poorly with thresholds (birth weight in centiles) based on local population values. The mean rates of intrauterine growth restriction were 9.6% among patients whose risk was not specified, 8.2% among low-risk patients and 20.7% among high-risk patients.

Quality assessment

For both pre-eclampsia and intrauterine growth restriction, over 70% of the studies met the following QUADAS quality-assessment criteria:¹³ avoidance of partial and differential verification, independent reference test, and blind assessment of index test (for the results of the quality assessment, see Appendix 5, available online at www.cmaj.ca/cgi/content/full/178/6/701/DC2). Studies scored poorly in terms of adequate descriptions of selection criteria and reference test, blind assessment of the reference test and availability of clinical data.

Table 1: Pooled and single estimates for uterine artery Doppler ultrasonography in predicting pre-eclampsia in patients at low risk or unspecified risk, by Doppler index, trimester and severity of pre-eclampsia

Doppler index*	No. of studies	No. of women	Sensitivity (95% CI), %	Specificity (95% CI), %	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Second trimester						
<i>Overall pre-eclampsia</i>						
Resistance index (> 0.58 or 90th centile)	11	3 778	74 (62-86)	79 (71-87)	3.5 (2.2-4.8)	0.33 (0.18-0.48)
Resistance index (> 0.70 or 95th centile)	1	346	41 (18-67)	88 (84-91)	3.4 (1.7-5.7)	0.67 (0.42-0.90)
Pulsatility index	7	38 230	42 (25-58)	91 (86-96)	4.5 (1.7-7.3)	0.64 (0.47-0.82)
Bilateral notching	17	36 969	43 (26-60)	93 (90-97)	6.5 (4.3-8.7)	0.61 (0.44-0.79)
Unilateral notching	6	8 016	39 (23-55)	92 (88-95)	4.6 (1.3-7.9)	0.67 (0.48-0.86)
Any notching	8	4 205	74 (60-87)	84 (76-92)	4.6 (2.0-7.3)	0.31 (0.15-0.48)
Resistance index or notching	7	8 151	79 (62-95)	83 (73-92)	4.5 (2.6-6.5)	0.26 (0.08-0.44)
Resistance index and notching	5	1 654	72 (48-96)	87 (79-96)	5.6 (3.1-8.1)	0.32 (0.07-0.58)
Pulsatility index or notching	2	18 563	47 (44-51)	92 (88-96)	5.7 (2.9-8.4)	0.57 (0.53-0.62)
Pulsatility index and notching	1	1 757	23 (14-35)	99 (98-99)	7.5 (5.4-10.2)	0.59 (0.47-0.71)
S/D ratio	2	672	76 (68-84)	71 (62-80)	2.6 (1.8-3.5)	0.34 (0.22-0.46)
A/C ratio	3	1 284	74 (62-86)	82 (71-92)	4.0 (2.4-5.7)	0.32 (0.20-0.43)
Notch index	2	819	12 (9-15)	86 (81-90)	0.8 (0.5-1.2)	1.00 (0.96-1.10)
S/D or notching	2	1 083	28 (18-37)	88 (84-92)	2.4 (1.2-3.5)	0.82 (0.70-0.94)
<i>Severe pre-eclampsia</i>						
Pulsatility index	1	15 392	78 (66-87)	95 (94-95)	15.6 (13.3-17.3)	0.23 (0.15-0.35)
Bilateral notching	1	4 149	65 (38-86)	95 (94-96)	13.4 (8.5-17.4)	0.37 (0.18-0.62)
Any notching	1	4 149	76 (50-93)	85 (84-86)	5.0 (3.4-5.9)	0.28 (0.11-0.56)
Resistance index or notching	1	2 058	79 (60-92)	85 (83-86)	5.3 (4.0-6.0)	0.24 (0.12-0.45)
S/D ratio	1	122	100 (55-100)	74 (65-82)	3.5 (1.9-3.9)	0.11 (0.01-0.65)
First trimester						
<i>Overall pre-eclampsia</i>						
Pulsatility index	3	4 966	25 (20-31)	95 (95-96)	5.4 (4.1-6.7)	0.78 (0.72-0.84)
Bilateral notching	1	626	90 (73-98)	70 (66-74)	3.0 (2.4-3.3)	0.14 (0.05-0.36)
Any notching	2	869	93 (87-98)	46 (43-48)	1.7 (1.6-1.8)	0.16 (0.04-0.28)
<i>Severe pre-eclampsia</i>						
Pulsatility index	1	433	40 (12-74)	90 (87-93)	4.0 (1.6-7.3)	0.67 (0.35-0.93)

Note: CI = confidence interval, S/D ratio = ratio of peak systolic to late diastolic velocity (also known as A/B ratio), A/C ratio = ratio of peak systolic to early diastolic velocity, S/D or notching = S/D ratio with or without unilateral or bilateral early diastolic notching.

*See Box 1 for explanations of Doppler indices. The list of Doppler indices for each category varies depending on whether predictive studies were available.

Whether the study did or did not include the use of preventive treatment was reported in 17 of the studies of pre-eclampsia and 18 of the studies of intrauterine growth restriction. The randomized controlled trials that applied preventive treatment in a series of women after Doppler ultrasonography were analyzed together with the cohort studies. We excluded 2 case-control studies from the analyses to further enhance validity.

Diagnostic test characteristics

For both pre-eclampsia and intrauterine growth restriction, Doppler testing was less accurate in the first trimester than in the second trimester. In this section, we noted the test characteristics that best predicted the *development* of pre-eclampsia and intrauterine growth restriction (largest positive likelihood ratio). Test characteristics that best predicted the *absence* of pre-eclampsia and intrauterine growth restriction were those with the smallest negative likelihood ratio (Table 1, Table 2, Table 3, Table 4).

Pre-eclampsia in low-risk patients was best predicted by an

increased pulsatility index with diastolic notching in the second trimester (> 16 weeks) (positive likelihood ratio 7.5, 95% CI 5.4–10.2; negative likelihood ratio 0.59, 95% CI 0.47–0.71) (Table 1, Figure 2). Severe pre-eclampsia in low-risk patients was best predicted in the second trimester by an increased pulsatility index (positive likelihood ratio 15.6, 95% CI 13.3–17.3; negative likelihood ratio 0.23, 95% CI 0.15–0.35) and bilateral notching (positive likelihood ratio 13.4, 95% CI 8.5–17.4); negative likelihood ratio 0.4 (95% CI 0.2–0.6) (Figure 3). Among high-risk patients, pre-eclampsia was best predicted in the second trimester by unilateral notching (positive likelihood ratio 20.2, 95% CI 7.5–29.5; negative likelihood ratio 0.17, 95% CI 0.03–0.56) and an increased pulsatility index with notching (positive likelihood ratio 21.0, 95% CI 5.5–80.5; negative likelihood ratio 0.82, 95% CI 0.72–0.93) (Table 2, Figure 2). Doppler assessment to predict severe pre-eclampsia in high-risk patients showed low diagnostic characteristics (positive likelihood ratio 3.7) (Table 2, Figure 3). Many estimates were based on single studies or small numbers of women.

Table 2: Pooled and single estimates for uterine artery Doppler ultrasonography in predicting pre-eclampsia in high-risk patients, by Doppler index, trimester and severity of pre-eclampsia

Doppler index*	No. of studies	No. of women	Sensitivity (95% CI), %	Specificity (95% CI), %	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Second trimester						
<i>Overall pre-eclampsia</i>						
Resistance index (> 0.58 or 90th centile)	15	2137	83 (68-98)	72 (61-83)	3.0 (1.8-1.1)	0.24 (0.04-0.44)
Resistance index (> 0.70 or 95th centile)	6	939	51 (22-80)	87 (80-95)	4.0 (1.5-6.4)	0.57 (0.25-0.88)
Pulsatility index	4	547	39 (20-59)	78 (56-100)	1.8 (0.2-3.4)	0.78 (0.52-1.04)
Bilateral notching	8	1081	37 (14-60)	89 (83-95)	3.4 (1.1-5.7)	0.71 (0.46-0.95)
Unilateral notching	1	103	83 (36-100)	96 (90-99)	20.2 (7.5-29.5)	0.17 (0.03-0.56)
Any notching	8	916	63 (41-86)	76 (67-84)	2.6 (1.8-3.4)	0.48 (0.22-0.75)
Resistance index or notching	1	16	86 (42-100)	78 (40-97)	3.9 (1.3-7.3)	0.18 (0.03-0.74)
Resistance index and notching	7	1228	57 (21-93)	86 (79-93)	4.1 (1.5-6.7)	0.50 (0.10-0.90)
Pulsatility index or notching	1	88	54 (37-70)	76 (61-87)	2.2 (1.3-3.8)	0.61 (0.44-0.87)
Pulsatility index and notching	1	351	19 (5-42)	99 (97-100)	21.0 (5.5-80.5)	0.82 (0.72-0.93)
A/C ratio	1	51	50 (7-93)	79 (64-89)	2.4 (0.6-4.6)	0.64 (0.19-1.1)
Notch index	1	94	14 (0-58)	80 (71-88)	0.7 (0.1-2.9)	1.07 (0.61-1.21)
D/S or notching	1	48	100 (55-100)	51 (35-67)	1.9 (1.0-2.1)	0.16 (0.02-0.99)
<i>Severe pre-eclampsia</i>						
Resistance index (> 0.58 or 90th centile)	1	28	80 (28-99)	78 (56-93)	3.7 (1.4-5.3)	0.26 (0.05-0.84)
First trimester						
<i>Overall pre-eclampsia</i>						
Bilateral notching	1	72	91 (59-100)	46 (33-59)	1.7 (1.1-1.9)	0.20 (0.04-0.85)

Note: CI = confidence interval, A/C ratio = ratio of peak systolic to early diastolic velocity, D/S or notching = D/S ratio (ratio of diastolic to systolic velocity) with or without unilateral or bilateral early diastolic notching.

*See Box 1 for explanations of Doppler indices. The list of Doppler indices for each category varies depending on whether predictive studies were available.

Intrauterine growth restriction in low-risk patients was best predicted in the second trimester by an increased pulsatility index with notching (positive likelihood ratio 9.1, 95% CI 5.0–16.7; negative likelihood ratio 0.89, 95% CI 0.85–0.93) (Table

3, Figure 2). Severe intrauterine growth restriction in low-risk patients was best predicted in the second trimester by an increased pulsatility index (positive likelihood ratio 13.7, 95% CI 10.3–16.9; negative likelihood ratio 0.34, 95% CI 0.23–0.48) or

Table 3: Pooled and single estimates for uterine artery Doppler ultrasonography in predicting intrauterine growth restriction in patients at low risk or unspecified risk, by Doppler index, trimester and severity of growth restriction

Doppler index*	No. of studies	No. of women	Sensitivity (95% CI), %	Specificity (95% CI), %	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Second trimester						
<i>Overall intrauterine growth restriction</i>						
Resistance index (> 0.58 or 90th centile)	9	3 304	53 (42-64)	87 (79-94)	4.0 (1.6-6.3)	0.54 (0.41-0.68)
Resistance index (> 0.70 or 95th centile)	2	665	16 (10-23)	91 (86-97)	1.9 (0.5-3.3)	0.92 (0.83-1.00)
Pulsatility index	3	12 097	18 (16-19)	95 (92-97)	3.4 (1.7-5.1)	0.87 (0.84-0.90)
Bilateral notching	11	10 229	24 (14-34)	91 (86-97)	2.8 (1.7-3.9)	0.83 (0.75-0.91)
Unilateral notching	2	3 819	17 (16-19)	93 (91-95)	2.4 (2.0-2.9)	0.89 (0.89-0.89)
Any notching	4	2 162	44 (32-57)	82 (72-92)	2.5 (1.4-3.5)	0.68 (0.56-0.80)
Resistance index or notching	5	5 043	37 (33-39)	88 (84-93)	3.1 (1.9-4.3)	0.72 (0.67-0.77)
Resistance index and notching	1	946	45 (37-53)	82 (79-84)	2.4 (1.9-3.0)	0.68 (0.58-0.77)
Pulsatility index or notching	2	2 116	23 (19-27)	94 (93-95)	3.9 (3.0-4.7)	0.82 (0.77-0.87)
Pulsatility index and notching	1	1 757	12 (7-18)	99 (98-99)	9.1 (5.0-16.7)	0.89 (0.85-0.93)
S/D ratio	3	1 661	34 (10-57)	88 (79-96)	2.7 (1.6-3.9)	0.76 (0.54-0.97)
Notch index	1	288	33 (13-59)	92 (88-95)	4.3 (1.9-8.4)	0.72 (0.49-0.91)
S/D or notching	3	2 173	29 (25-33)	83 (79-93)	2.1 (1.0-3.2)	0.82 (0.74-0.90)
<i>Severe intrauterine growth restriction</i>						
Resistance index (> 0.58 or 90th centile)	3	1 551	65 (56-73)	88 (80-96)	5.5 (1.8-9.2)	0.40 (0.30-0.50)
Pulsatility index	1	1 757	67 (53-80)	95 (94-96)	13.7 (10.3-16.9)	0.34 (0.23-0.48)
Bilateral notching	2	2 657	18 (11-24)	95 (93-97)	3.5 (1.7-5.2)	0.87 (0.80-0.94)
Any notching	1	890	53 (27-79)	83 (80-85)	3.1 (1.7-4.4)	0.57 (0.30-0.85)
Resistance index or notching	3	3 650	45 (40-49)	88 (82-93)	3.6 (1.9-5.3)	0.63 (0.56-0.70)
Resistance index and notching	2	1 404	44 (36-51)	87 (78-96)	3.4 (0.9-5.8)	0.65 (0.52-0.77)
Pulsatility index or notching	1	1 757	31 (19-45)	93 (92-95)	4.7 (2.9-7.0)	0.74 (0.60-0.86)
Pulsatility index and notching	1	1 757	23 (13-37)	98 (98-99)	14.6 (7.8-26.3)	0.78 (0.68-0.87)
S/D or notching	1	768	26 (12-43)	91 (89-93)	2.9 (1.5-4.9)	0.82 (0.64-0.95)
First trimester						
<i>Overall intrauterine growth restriction</i>						
Resistance index (> 0.70 or 95th centile)	1	1 008	67 (35-90)	75 (72-78)	2.7 (1.6-3.5)	0.44 (0.18-0.81)
Pulsatility index	1	3 045	12 (8-16)	96 (95-96)	2.7 (1.9-3.8)	0.92 (0.88-0.96)
Bilateral notching	3	1 420	74 (55-93)	42 (0-84)	1.3 (0.6-2.0)	0.62 (0.25-0.98)
Any notching	2	866	85 (80-91)	47 (45-50)	1.6 (1.5-1.7)	0.30 (0.19-0.42)
<i>Severe intrauterine growth restriction</i>						
Pulsatility index	1	999	24 (12-41)	95 (94-97)	5.3 (2.8-9.5)	0.79 (0.64-0.91)

Note: CI = confidence interval, S/D ratio = ratio of peak systolic to late diastolic velocity (also known as A/B ratio), S/D or notching = S/D ratio with or without unilateral or bilateral early diastolic notching.

*See Box 1 for explanations of Doppler indices. The list of Doppler indices for each category varies depending on whether predictive studies were available.

an increased pulsatility index with notching (positive likelihood ratio 14.6, 95% CI 7.8–26.3; negative likelihood ratio 0.78, 95% CI 0.68–0.87) (Figure 3). Doppler assessment to predict intrauterine growth restriction in high-risk patients showed low diagnostic characteristics (Table 4, Figure 2). An increased resistance index (> 0.58 or > 90th centile) in the second trimester best predicted severe intrauterine growth restriction in high-risk patients (positive likelihood ratio 10.9, 95% CI 10.4–11.4; negative likelihood ratio 0.20, 95% CI 0.14–0.26).

Subgroup and sensitivity analyses

Our exclusion of studies that applied preventive treatment did not improve the accuracy of Doppler testing in predicting pre-eclampsia and intrauterine growth restriction. When we included only the high-quality studies in the analysis, we found that unilateral notching in the second trimester best predicted pre-eclampsia in patients at low risk or unspecified risk (posi-

tive likelihood ratio 12.5, 95% CI 5.1–20.0; negative likelihood ratio 0.45, 95% CI 0.09–0.80). In high-risk patients, an increased pulsatility index with notching remained the best predictor of pre-eclampsia in the high-quality studies. Results for intrauterine growth restriction showed low to moderate predictive value in both low-risk and high-risk patients. (Data from the subgroup and sensitivity analyses are available from the corresponding author.)

Interpretation

We evaluated the accuracy of 15 uterine artery Doppler indices in predicting pre-eclampsia and intrauterine growth restriction. Uterine artery Doppler ultrasonography predicts pre-eclampsia, the maternal consequence of placental disease, more confidently than intrauterine growth restriction. Specifically, an increased pulsatility index with notching in the sec-

Table 4: Pooled and single estimates for uterine artery Doppler ultrasonography in predicting intrauterine growth restriction in high-risk patients, by Doppler index, trimester and severity of growth restriction

Doppler index*	No. of studies	No. of women	Sensitivity (95% CI), %	Specificity (95% CI), %	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Second trimester						
<i>Overall intrauterine growth restriction</i>						
Resistance index (> 0.58 or 90th centile)	6	885	74 (55-94)	68 (56-81)	2.4 (1.7-3.1)	0.37 (0.14-0.61)
Resistance index (> 0.70 or 95th centile)	4	527	38 (18-58)	85 (78-92)	2.6 (2.0-3.1)	0.73 (0.54-0.91)
Pulsatility index	2	445	58 (25-91)	75 (72-78)	2.3 (1.0-3.6)	0.56 (0.12-1.00)
Bilateral notching	4	588	29 (6-52)	92 (91-94)	3.8 (0.7-7.0)	0.77 (0.51-1.00)
Unilateral notching	2	151	45 (23-67)	85 (76-94)	3.0 (1.7-4.3)	0.65 (0.43-0.86)
Any notching	10	989	51 (46-57)	78 (72-84)	2.3 (1.7-3.0)	0.62 (0.54-0.70)
Resistance index or notching	4	629	69 (54-83)	69 (48-90)	2.2 (0.5-3.9)	0.45 (0.18-0.73)
Resistance index and notching	4	444	45 (38-52)	90 (81-99)	4.3 (0.6-8.1)	0.62 (0.52-0.71)
Pulsatility index or notching	2	138	68 (47-89)	81 (75-87)	3.6 (2.0-5.1)	0.40 (0.14-0.65)
D/S ratio	1	48	78 (40-97)	62 (45-77)	2.0 (1.1-2.7)	0.36 (0.10-0.94)
D/S or notching	1	48	89 (52-100)	54 (37-70)	1.9 (1.1-2.2)	0.21 (0.04-0.85)
<i>Severe intrauterine growth restriction</i>						
Resistance index (> 0.58 or 90th centile)	2	362	82 (76-87)	92 (92-93)	10.9 (10.4-11.4)	0.20 (0.14-0.26)
Pulsatility index	1	351	6 (2-14)	95 (92-97)	1.2 (0.5-3.2)	0.99 (0.92-1.00)
Bilateral notching	1	351	6 (2-14)	97 (95-99)	2.3 (0.8-6.7)	0.97 (0.92-1.00)
Resistance index or notching	1	182	64 (41-83)	29 (22-37)	0.9 (0.6-1.2)	1.21 (0.64-2.07)
Resistance index and notching	1	170	42 (23-63)	80 (72-86)	2.1 (1.2-3.4)	0.72 (.50-0.95)
First trimester						
<i>Overall intrauterine growth restriction</i>						
Pulsatility index	3	785	34 (24-44)	76 (75-79)	1.5 (1.0-1.9)	0.86 (0.73-0.99)
Bilateral notching	1	72	75 (19-99)	41 (29-54)	1.3 (0.5-1.7)	0.61 (0.11-1.78)

Note: CI = confidence interval, D/S ratio = ratio of diastolic to systolic velocity, D/S or notching = D/S ratio with or without unilateral or bilateral early diastolic notching.

*See Box 1 for explanations of Doppler indices. The list of Doppler indices for each category varies depending on whether predictive studies were available.

ond trimester best predicted overall pre-eclampsia in low-risk and high-risk patients. An increased pulsatility index or bilateral notching best predicted severe pre-eclampsia. An increased pulsatility index alone or in combination with notching best predicted severe intrauterine growth restriction in low-risk patients, whereas the best predictor in high-risk patients was an increased resistance index. Other Doppler indices showed low to moderate predictive value.

Previous reviews have reported that uterine artery Doppler ultrasonography has limited accuracy in predicting pre-

eclampsia and intrauterine growth restriction.^{23–25} However, these reviews were restricted in terms of the thresholds and Doppler indices they reviewed or they reported independently pooled likelihood ratios, which is now discouraged.²² Two reviews reporting on pre-eclampsia, intrauterine growth restriction and perinatal death were limited to articles retrieved through MEDLINE: one review²³ was based on a search of articles published before January 1997, and the other²⁴ included patients with unspecified risk in articles up to 2001. A third review,²⁵ on pre-eclampsia, has been criticized for its methodol-

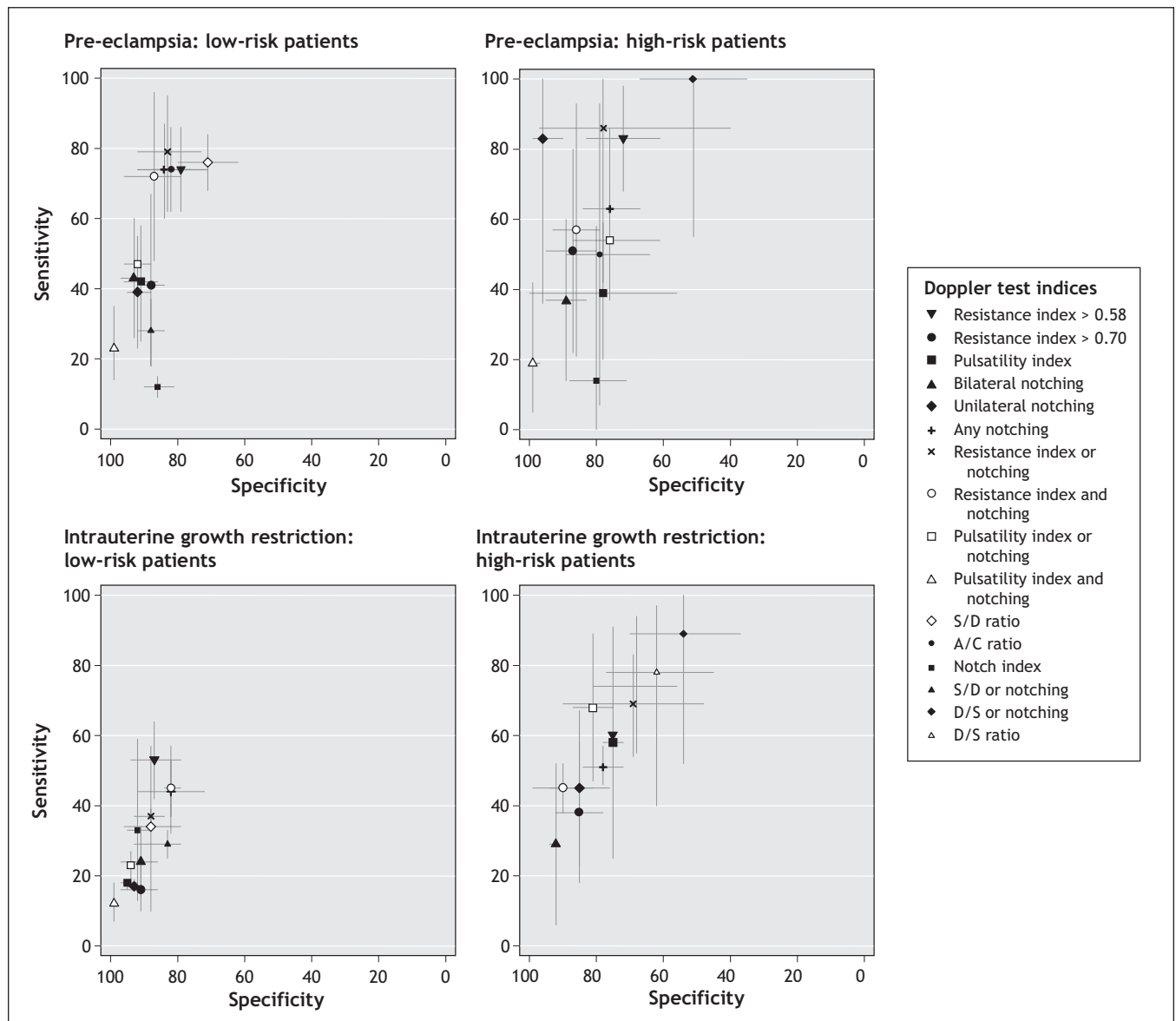


Figure 2: Plots of receiver operating characteristics showing pooled and single accuracy estimates, with 95% confidence intervals, for uterine artery Doppler indices to predict pre-eclampsia and intrauterine growth restriction in the second trimester according to patient risk. Note: the x axis shows reversed specificity. The closer the index values are to the upper left corner of each graph, the greater the accuracy of that index. The test index that best predicted the development of pre-eclampsia (highest positive likelihood ratio) in low- and high-risk patients was an increased pulsatility index with notching. This index was also the best predictor of intrauterine growth restriction in low-risk patients. For intrauterine growth restriction in high-risk patients, the Doppler indices showed low predictive value. (The thresholds for the Doppler indices reported in the studies we reviewed are provided in Appendices 3 and 4 [available online at www.cmaj.ca/cgi/content/full/178/6/701/DC2].)

ogy.²⁶ A fourth review⁹ concluded that Doppler assessment identifies high-risk women in whom acetylsalicylic acid therapy results in a significant reduction in pre-eclampsia. Since these reviews were published, substantial new evidence has emerged allowing for more robust and specific inferences for clinical practice.

The strength of our review was that we carried out extensive literature searches without language restrictions, assessed the quality of studies and their reporting and used recently developed statistical methods. However, our study had

several limitations. First, our quality assessment was hindered by the lack of information in many studies, which is a common problem in diagnostic reviews. Poor study design and conduct can affect estimates of diagnostic accuracy,^{27,28} although it is not entirely clear how individual aspects of quality may affect accuracy and to what magnitude. Of many strategies applied to account for differences in quality, none has led systematically to less optimistic estimates than that of ignoring methodologic quality in meta-analyses of test accuracy studies.^{29,30} The reporting of details of how the index test

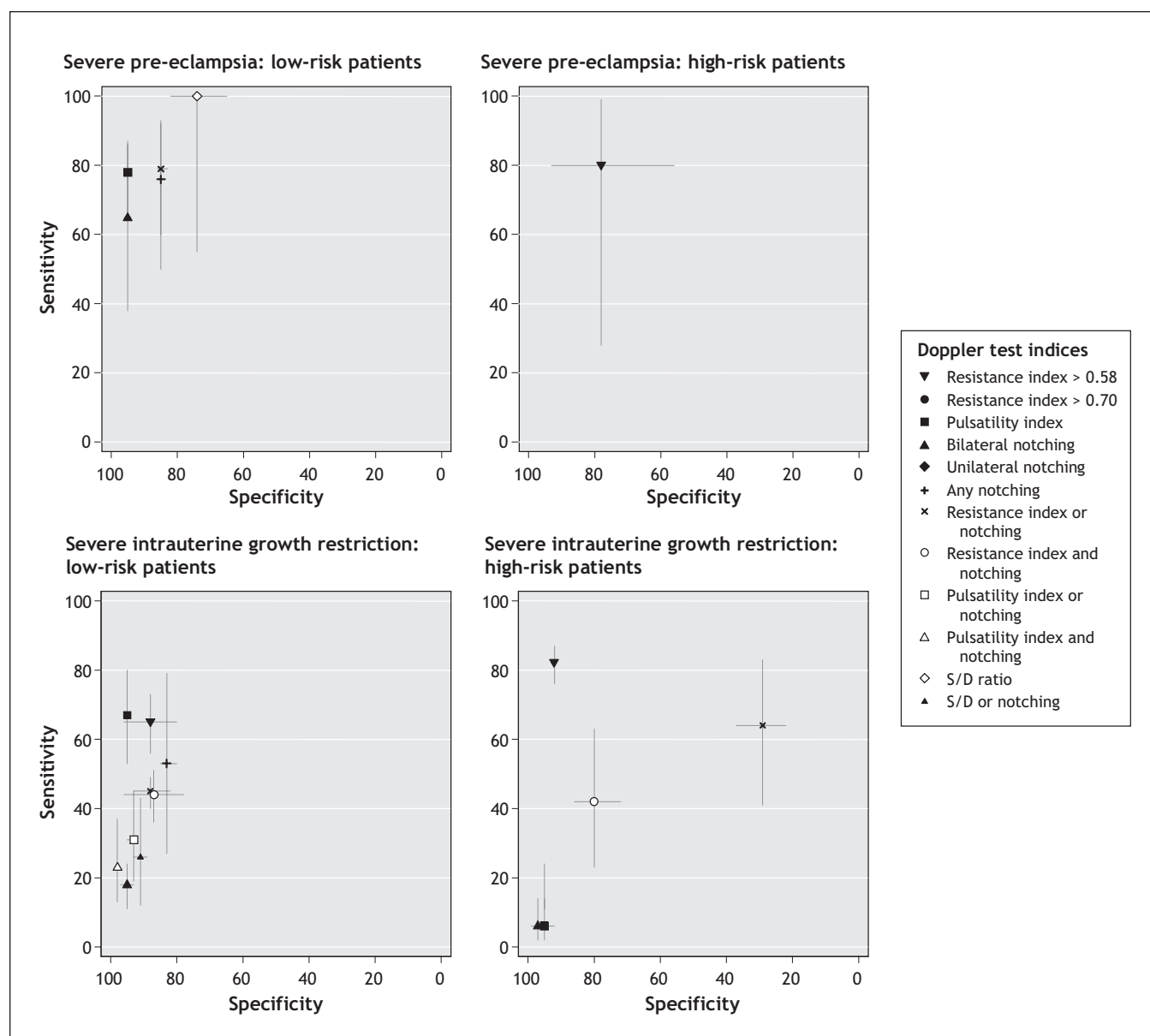


Figure 3: Plots of receiver operating characteristics showing pooled and single accuracy estimates, with 95% confidence intervals, for uterine artery Doppler indices to predict severe pre-eclampsia and severe intrauterine growth restriction in the first and second trimester. Note: the x axis shows reversed specificity. The closer the index values are to the upper left corner of each graph, the greater the accuracy of that index. In low-risk patients, an increased pulsatility index was the test characteristic that best predicted the development of severe pre-eclampsia or severe intrauterine growth restriction (highest positive likelihood ratio). In high-risk patients, the best predictor of each outcome was an increased resistance index > 0.58. (The thresholds for the Doppler indices reported in the studies we reviewed are provided in Appendices 3 and 4 [available online at www.cmaj.ca/cgi/content/full/178/6/701/DC2].)

was carried out and reference standards were applied was uniformly poor in the studies we reviewed. Second, definitions of pre-eclampsia have changed over time. Earlier definitions were also based on increases in blood pressure and edema. The measurement of blood pressure has been poorly reported, and the importance of recording diastolic blood pressure with Korotkoff phase V (which is more reliably recorded and reflects true diastolic blood pressure) has been underestimated.^{31–33} Third, for intrauterine growth restriction, there is still no agreement on the best definition of the condition at birth, nor on the best predictor of future infant and childhood morbidity and mortality for term infants. Although population-based birth-weight standards have been used most commonly, they do not distinguish between the small healthy infant and the compromised infant. Customized growth charts that are adjusted for sex, gestational age, parity, maternal weight and height, and ethnicity have been shown to improve the detection of infants at risk of stillbirth,³⁴ whereas neonatal indices have been shown to identify the malnourished infant at risk of peripartum asphyxia³⁵ and long-term neurologic sequelae.³⁶ Unfortunately, these have rarely been used as outcome measures. Fourth, poor reporting of patient selection criteria may explain in part the great variation in rates of pre-eclampsia among so-called high-risk and low-risk patients. The term “high risk” can have multiple origins and varying rates. Large cohort studies (> 300 000 women) of populations without specified risk levels have shown pre-eclampsia rates ranging from 0.8% to 5.1%.^{37–39} This suggests that small studies of populations at low or unspecified risk may be prone to selection bias.

Both pre-eclampsia and intrauterine growth restriction have a relatively low prevalence. A clinically useful test for either would thus have to have a high positive likelihood ratio (> 10) and low negative likelihood ratio (< 0.10).⁴⁰ Based on the results of our review, pulsatility index and bilateral notching are the most promising Doppler indices to meet these requirements and should be used in daily clinical practice, although the results vary according to patient risk. Doppler assessment is noninvasive and thus acceptable to patients. It is specialized, both in terms of the equipment required and the operator's expertise. In industrialized countries, Doppler assessment could be fairly easily performed at the time of a detailed anomaly scan; in developing countries, it would be difficult to introduce this test into routine antenatal practice. For mothers, being identified as at risk in an antenatal test can cause considerable anxiety. Currently, no pharmacologic treatment or management strategy has been shown to be effective in preventing pre-eclampsia or intrauterine growth restriction or ameliorating their complications. Research into treatment with acetylsalicylic acid, which is inexpensive and readily available, has shown a small preventive effect (relative risk 0.9 for both pre-eclampsia and intrauterine growth restriction)¹⁰ in the absence of any serious side effects. In this case, a false-negative test result is potentially more harmful than a false-positive test result. When looking at predictive test accuracy and test-treatment combinations in pre-eclampsia and intrauterine growth restriction, we should consider whether it is more harmful to classify a patient's results as false positive or as false negative.

It is imperative to differentiate between mild and severe disease, because early or severe pre-eclampsia is associated with increased maternal morbidity and mortality and pronounced risks for the fetus, such as severe intrauterine growth restriction.^{41,42} Future research should also concentrate on the use of combinations of tests — a diagnostic process that is used in clinical care and may improve the predictive accuracy of the tests to clinically important values.

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