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First-trimester uterine artery Doppler and adverse pregnancy outcome: a meta-analysis involving 55 974 women

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KEYWORDS: fetal growth restriction; first trimester; pre-eclampsia; uterine artery Doppler

ABSTRACT

Objectives *To determine the accuracy with which uterine artery Doppler in the first trimester of pregnancy predicts pre-eclampsia and fetal growth restriction, particularly early-onset disease.*

Methods *We searched MEDLINE (1951–2012), EMBASE (1980–2012) and the Cochrane Library (2012) for relevant citations without language restrictions. Two reviewers independently selected studies that evaluated the accuracy of first-trimester uterine artery Doppler to predict adverse pregnancy outcome and performed data extraction to construct 2 × 2 tables. We synthesized sensitivity and specificity for various Doppler indices using a bivariate random-effects model.*

Results *From 1866 citations, we identified 18 studies (55 974 women). The sensitivity and specificity of abnormal uterine artery flow velocity waveform (FVW) in the prediction of early-onset pre-eclampsia were 47.8% (95% CI: 39.0–56.8) and 92.1% (95% CI: 88.6–94.6), and in the prediction of early-onset fetal growth restriction were 39.2% (95% CI: 26.3–53.8) and 93.1% (95% CI: 90.6–95.0), respectively. The sensitivities for predicting any pre-eclampsia and fetal growth restriction were 26.4% (95% CI: 22.5–30.8) and 15.4% (95% CI: 12.4–18.9), respectively, and the specificities were 93.4% (95% CI: 90.4–95.5%) and 93.3% (95% CI: 90.9–95.1), respectively. The number needed to treat (NNT) with aspirin to prevent one case of early-onset pre-eclampsia fell from 1000 to 173 and from 2500 to 421 for background risks varying between 1% and 0.4%, respectively.*

Conclusions *First-trimester uterine artery Doppler is a useful tool for predicting early-onset pre-eclampsia, as well as other adverse pregnancy outcomes. Based on the NNT, abnormal uterine artery Doppler in low-risk women achieves a sufficiently high performance to justify aspirin prophylaxis in those who test positive.* *Copyright © 2013 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Pre-eclampsia and fetal growth restriction are major causes of maternal and fetal morbidity and mortality[1,2]. Early onsets of these conditions are associated with increased risk of complications[3]. Early-onset pre-eclampsia is associated with a 20-fold higher rate of maternal mortality than is late-onset disease and is one of the key contributors to early fetal growth restriction[4]. Women with early-onset pre-eclampsia require admission to a tertiary care facility for treatment and one-third experience complications that may necessitate intensive care[5]. Infants are often delivered preterm, need prolonged intensive care and develop complications, including lifelong disability[6], giving rise to large healthcare costs[5]. Early identification of women at risk is a key aim of antenatal care.

The National Institute of Clinical Excellence (NICE) in the UK has prioritized the need for research to identify those at risk of pre-eclampsia[7]. Currently, clinical risk assessment for pre-eclampsia is carried out in the first trimester[8] for early identification of women who may benefit from preventative treatment, such as aspirin[7]. This includes women with at least one high-risk factor (a previous history of hypertension in pregnancy, chronic kidney

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disease, autoimmune disease, type 1 and 2 diabetes and chronic hypertension) or two moderate-risk factors (first pregnancy, 40 years of age or older, pregnancy interval of more than 10 years, a body mass index (BMI) of ≥ 35, a family history of pre-eclampsia or multiple pregnancy).

Impaired placentation with abnormal blood-flow velocity and resistance in placental vessels is associated with pre-eclampsia and fetal growth restriction. Doppler of the uterine artery, a non-invasive method which can pick up these abnormalities, is currently not part of this assessment. Individual studies, owing to a lack of power, and existing systematic reviews with small numbers of included studies[9,10], have failed to produce robust guidance on first-trimester screening with uterine artery Doppler for adverse pregnancy outcome. We undertook a systematic review of evidence to assess the accuracy of first-trimester uterine artery Doppler in predicting pregnancy complications, such as pre-eclampsia and fetal growth restriction, particularly early-onset disease.

METHODS

A systematic review with a prospective protocol according to recommended methods[11,12] was conducted.

The major electronic databases MEDLINE (1951–2012), EMBASE (1980–2012) and the Cochrane Library (2012) were searched for potentially relevant citations (Appendix S1). There were no language restrictions. The reference lists of all known primary and review articles were examined to identify cited articles not captured by electronic searches. The authors of the primary studies for unpublished relevant data were contacted. A combination of Medical Subject Headings (MeSH) and text words was used to generate two subsets of citations, one indexing Doppler (uterine NEAR Doppler) and the other indexing outcomes ('pre-eclampsia', 'fetal growth restriction', 'stillbirth' and 'abruption'). These subsets were combined using 'AND' to generate a subset of citations relevant to the research question. Details of the search strategy are available from the authors.

Studies were selected in a two-stage process. In the first stage, the relevant citations were selected by screening the titles and abstracts of the citations identified by the electronic search. In the next stage, the full papers of identified articles were obtained. Two reviewers (L.V. and S.T.) independently assessed the papers for inclusion or exclusion in the review. Where disagreements occurred, a third reviewer (J.A.) was involved. Studies that met the predefined and explicit criteria regarding population, tests and outcomes were selected. Studies that reported accuracy of first-trimester uterine artery Doppler for the prediction of early-onset pre-eclampsia and early fetal growth restriction, pre-eclampsia and fetal growth restriction at any gestation were included, as were studies on conditions associated with placental insufficiency (such as abruption and stillbirth). Abnormal uterine artery Doppler findings were classified into two categories: flow velocity waveform (FVW) (resistance index or pulsatility index $\geq 90^{th}$ centile); and the presence of notching (unilateral or bilateral). The definitions of pre-eclampsia and fetal growth restriction were as reported by the authors of the primary studies.

Two reviewers (L.V. and S.T.) extracted information from each selected article on study characteristics, quality and test results. Data were used to construct 2×2 tables of Doppler results (test positive if levels were above a threshold as defined in the primary study and test negative if these were below the threshold) and pregnancy outcomes. Data were also extracted on the characteristics of the study population, method of testing, definition of abnormal Doppler and cut-off values of the Doppler results.

The quality of the included studies was assessed using the QUADAS criteria[13]. A study was considered to be of good quality if it had prospective consecutive recruitment, adequate description of the index test, an appropriate reference standard, adequate description of the reference standard and more than 90% follow up. For multiple publications of the same dataset, only the most recent or complete study was included. Studies with a case–control design were excluded.

The sensitivity, specificity, likelihood ratios (LRs) and their 95% CIs were examined for individual studies. The results were pooled amongst studies with similar characteristics, threshold for the index test (FVWs and notching) and outcomes (pre-eclampsia, fetal growth restriction, stillbirth and abruption). The primary analysis included only studies of low-risk patients. A hierarchical bivariate random-effects model[14] was fitted to obtain summary estimates of sensitivity and specificity, and corresponding positive and negative LRs with their 95% CIs. The macro metandi developed for Stata statistical software[15] (StataCorp, College Station, TX, USA) was used. This macro estimates parameters for the model using the xtmelogit Stata command. It fits a two-level mixed logistic regression model, with independent binomial distributions for the true positives and true negatives conditional on the sensitivity and specificity in each study, and a bivariate normal model for the logit transforms of sensitivity and specificity between studies. The model explicitly includes a correlation parameter to allow for the counterbalance between sensitivity and specificity as a result of the presence of a threshold effect.

The clinical applicability of the test accuracy findings was assessed by comparing post-test probability of early-onset pre-eclampsia after a positive test with the probability of the disease conditional on the presence of other (moderate and high) risk factors. Post-test probabilities of the disease after the treatment were estimated using information of the effectiveness of aspirin to prevent early-onset pre-eclampsia[16]. The number needed to treat (NNT) to prevent one case of early-onset pre-eclampsia was calculated after a positive test.

RESULTS

From 2230 citations, 350 studies were selected after screening the abstracts (Figure 1). After detailed evaluation of the papers, 18 studies (55 974 women) were

included in the review[17–35] (references 22 and 23, references 26 and 34, and references 30 and 31 accounted for one study each and two studies were unpublished). The number of studies and women for each outcome is given in Figure 1.

All studies performed uterine artery Doppler between 11 and 14 weeks of gestation. The accuracy of abnormal FVW was assessed in 13 studies (54 028 women)[19,20,22–26,28,29,31–34] and notching in seven (6003 women) studies[17,18,21–23,27,35]. Uterine artery Doppler was assessed by transvaginal ultrasound in four studies and by transabdominal ultrasound in 12. In two studies, the type of probe was not specified. Eight studies (41 692 women)[17,24,28,30,33,34] (two studies were unpublished) evaluated the accuracy of Doppler in predicting early-onset pre-eclampsia, and four studies (26 276 women)[24,33,34] (one study was unpublished) evaluated early fetal growth restriction. Eleven studies (39 179 women) evaluated any pre-eclampsia of any onset[17,18,22–26,28,32,33,35] as the outcome, nine studies (31 431 women) assessed any-onset fetal growth restriction[18,20,22–24,27,31,33–35], two studies (9935 women) assessed stillbirth[21,32] and two studies (1366 women) assessed abruption as an outcome[18,34]. Fifteen studies evaluated the test in low-risk pregnancies[17,18,20,22–34] and three studies evaluated the test in high-risk women[19,21,35]. Appendix S2 provides a detailed description of the included studies.

The quality of the included studies is summarized in Figure 2. All included studies had adequate quality for the following: appropriate patient spectrum, appropriate reference standard, adequate description of reference standard, index test description, avoidance of differential verification bias and independent reference standard. Two-thirds of the studies had adequate avoidance of partial verification bias (13/18; 72%) and adequate follow up (14/18; 78%). Fewer than half of the studies fulfilled the quality assessment for a clear description of patient selection criteria (six of 18; 33%), availability of clinical data (two of 18; 11%), reporting of uninterpretable results (three of 18; 17%), explanation for withdrawals (five of 18; 28%) and details on the use of preventative intervention, such as aspirin (three of 18; 17%).

For early-onset pre-eclampsia, abnormal FVW had a sensitivity of 47.8% (95% CI: 39.0–56.8) and a specificity of 92.1% (95% CI: 88.6–94.6) (Figure 3). The positive and negative LRs were 6.10 (95% CI: 4.1–8.9) and 0.57 (95% CI: 0.48–0.67), respectively (Table 1). Only two studies assessed the accuracy of notching in the uterine artery Doppler waveform for predicting early-onset pre-eclampsia and it was not possible to obtain pooled estimates. The sensitivities obtained in these two studies were 75.8% (95% CI: 57.7–88.9)[30] and 37.5% (95% CI: 8.5–75.5)[17], and the specificities were 57.0% (95% CI: 55.2–58.7)[30] and 65.9% (95% CI: 62.7–69.0)[17].

For prediction of early fetal growth restriction, abnormal FVW had a sensitivity of 39.2% (95% CI: 26.3–53.8) and a specificity of 93.1% (95% CI: 90.6–95.0) (Figure 3). The positive and negative LRs were 5.7 (95% CI: 4.3–7.6) and 0.65 (95% CI: 0.52–0.81), respectively.

The sensitivity and specificity of first-trimester uterine artery Doppler in predicting pre-eclampsia at any gestation (eight studies) were 26.4% (95% CI: 22.5–30.8) and 93.4% (95% CI: 90.4–95.5), respectively, for abnormal FVW. The positive and negative LRs were 4.0 (95% CI: 2.7–6.0) and 0.79 (95% CI: 0.74–0.84), respectively. Only two studies assessed accuracy of notching for predicting pre-eclampsia and it was not possible to obtain pooled estimates. Accuracy estimates for these studies were 32.5% (95% CI: 18.6–49.1)[17] and 83.3% (95% CI: 51.6–97.9)[18] for sensitivity and 65.4% (95% CI: 62.1–68.6) and 44.2% (95% CI: 37.7–50.8) for specificity.

The sensitivity and specificity of first-trimester uterine artery Doppler in predicting fetal growth restriction at any gestation were 15.4% (95% CI: 12.4–18.9%) and 93.3% (95% CI: 90.9–95.1%), respectively, for abnormal FVW (Table 1). The positive and negative LRs were 2.3 (95% CI: 1.9–2.8) and 0.91 (95% CI: 0.88–0.93), respectively. Notching in the uterine artery Doppler waveform had a sensitivity and specificity for predicting fetal growth restriction of 58.5% (95% CI: 49.7–66.7) and 56.1% (95% CI: 49.6–62.5), respectively. The positive and negative LRs were 1.3 (95% CI: 1.2–1.5) and 0.74 (95% CI: 0.65–0.84), respectively.

The sensitivity and specificity of first-trimester uterine artery Doppler in predicting stillbirth were 14.5% (95% CI: 6.9–25.8) and 91.3% (95% CI: 90.8–91.9), respectively for abnormal FVW (Table 1). The positive and negative LRs were 1.7 (95% CI: 0.9–3.1) and 0.94 (95% CI: 0.84–1.0), respectively. The sensitivity and specificity of first-trimester uterine artery Doppler in predicting placental abruption were 44.4% (95% CI: 13.7–78.8) and 95.2% (95% CI: 93.8–96.4), respectively, for abnormal FVW. The positive and negative LRs were 9.3 (95% CI: 4.3–20.3) and 0.58 (95% CI: 0.33–1.1), respectively. The sensitivity and specificity of first-trimester uterine artery Doppler in predicting a composite adverse pregnancy outcome were 25.8% (95% CI: 15.5–39.7) and 93.4% (95% CI: 90.8–95.3), respectively, for abnormal FVW. The positive and negative LRs were 3.9 (95% CI: 2.8–5.5) and 0.79 (95% CI: 0.68–0.92), respectively.

None of the studies that evaluated early-onset disease involved high-risk women. Inclusion in the analysis of the studies in high-risk women did not significantly change the estimates for secondary outcomes with notching or for any adverse composite outcome with waveform abnormality (data not shown).

The prevalence of early-onset pre-eclampsia varies from 0.4% to 1%[7,36,37]. In low-risk women with abnormal first-trimester uterine artery Doppler, the risk of early-onset pre-eclampsia varies between 2.4% and 5.8% for varying baseline prevalence of the disease. This is similar to the risk in women with one high-risk factor, which varies from 1.5%[38] to 3.9%[36,39]. For a low baseline prevalence of 0.4%, the NNT to prevent

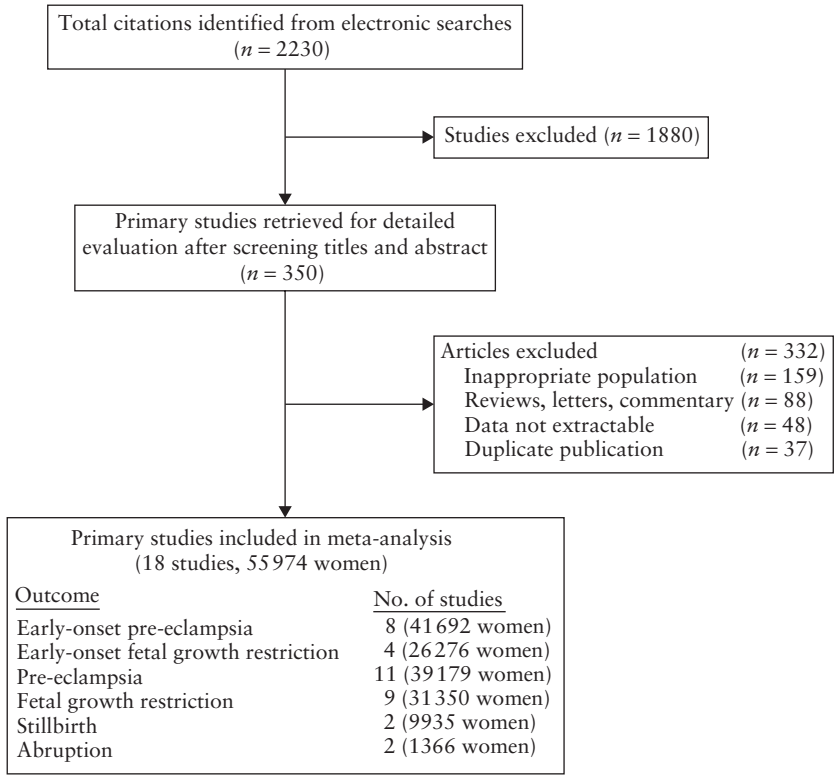

Figure 1 Study selection process for systematic review of first-trimester uterine artery Doppler to predict maternal and fetal complications.

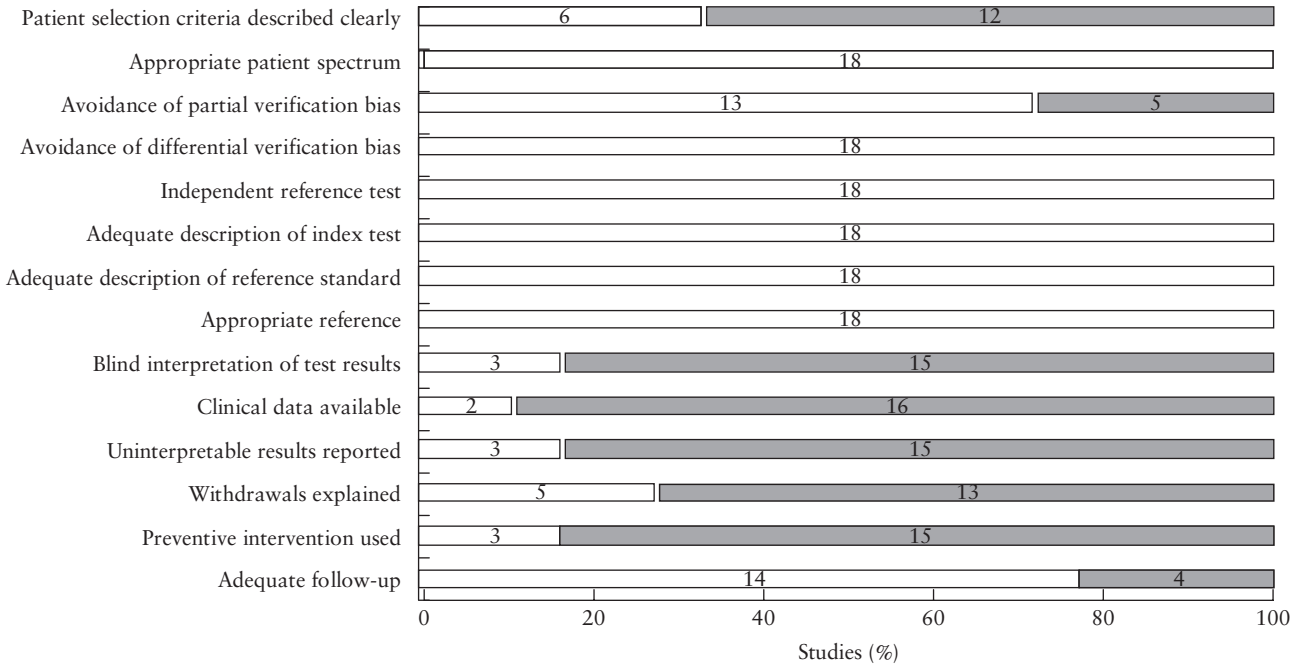

Figure 2 Quality of the studies included in the systematic review of accuracy of first-trimester uterine artery Doppler in predicting maternal and fetal complications. □, Adequate; ■, not adequate/unclear. Numbers inside bars indicate numbers of studies.

one case of early-onset pre-eclampsia with aspirin would be 2500. This fell to 421 among women with abnormal Doppler. For a baseline prevalence of 1%[36], the NNT would be 1000. Among women with abnormal Doppler it fell to 173. According to this measure, abnormal Doppler findings have a similar screening performance to those of the high-risk factors currently being used (Table 2). Sensitivity analysis performed by substituting the lower limits of the confidence interval for LR instead of point estimates yielded NNTs of 617, 414 and 251 for the baseline risks of 0.4%, 0.6% and 1%, respectively.

Table 1 Accuracy estimates of first-trimester uterine artery Doppler in predicting maternal and fetal complications in low-risk women

Outcome	*Doppler test*	*Studies (n)*	*Women (n)*	*Sensitivity (% (95% CI))*	*Specificity (% (95% CI))*	*Positive LR (95% CI)*	*Negative LR (95% CI)*
Early-onset pre-eclampsia	FVW	7	38 611	47.8 (39.0–56.8)	92.1 (88.6–94.6)	6.1 (4.1–8.9)	0.57 (0.48–0.67)
Early-onset FGR	FVW	4	26 276	39.2 (26.3–53.8)	93.1 (90.6–95.0)	5.7 (4.3–7.6)	0.65 (0.52–0.81)
Pre-eclampsia at any gestation	FVW	8	37 971	26.4 (22.5–30.8)	93.4 (90.4–95.5)	4.0 (2.7–6.0)	0.79 (0.74–0.84)
FGR at any gestation	FVW	6	30 454	15.4 (12.4–18.9)	93.3 (90.9–95.1)	2.3 (1.9–2.8)	0.91 (0.88–0.93)
	Notching	4	4785	58.5 (49.7–66.7)	56.1 (49.6–62.5)	1.3 (1.2–1.5)	0.74 (0.65–0.84)
Late-onset pre-eclampsia	FVW	3	33 879	21.5 (18.0–25.4)	90.3 (89.8–90.8)	2.2 (1.9–2.6)	0.87 (0.83–0.91)
Stillbirth	FVW	1	9859	14.5 (6.9–25.8)	91.3 (90.8–91.9)	1.7 (0.9–3.1)	0.94 (0.84–1.0)
	Notching	1	76	100.0 (40.0–100.0)	63.9 (51.7–74.9)	2.5 (1.6–3.8)	0.16 (0.01–2.2)
Placental abruption	FVW	1	1123	44.4 (13.7–78.8)	95.2 (93.8–96.4)	9.3 (4.3–20.3)	0.58 (0.33–1.1)
	Notching	1	243	100 (15.8–100.0)	43.2 (36.8–49.7)	1.5 (0.87–2.5)	0.39 (0.03–4.9)
Composite adverse pregnancy outcome	FVW	3	4513	25.8 (15.5–39.7)	93.4 (90.8–95.3)	3.9 (2.8–5.5)	0.79 (0.68–0.92)

FGR, fetal growth restriction; FVW, flow velocity waveform; LR, likelihood ratio.

Table 2 Clinical application of first-trimester uterine artery Doppler in the prediction and prevention of early-onset pre-eclampsia

		Probability of early-onset pre-eclampsia (%)			
Risk status for pre-eclampsia	*Strategy*	*At baseline*	*Test positive (or risk factor present)*	*After treatment**	*NNT*
Low risk					
None	No test, treat all	0.4[8]		0.36	2500
		0.6[37]		0.54	1667
		1.0[36]		0.90	1000
First-trimester uterine artery Doppler	Test all, treat positives	0.4	2.4	2.1	421
		0.6	3.5	3.2	183
		1.0	5.8	5.2	173
Moderate risk[8]	Test all,				
BMI > 35	treat positives		0.95	0.86	1053
Multiple pregnancy			1.7	1.5	588
Interval > 10 years between pregnancies			0.70	0.63	1429
Age ≥ 40 years			0.68	0.61	1471
Family history of pre-eclampsia			1.2	1.1	833
High risk[8]	Test all,				
Hypertensive disease in previous pregnancy	treat positives		2.7	2.5	368
Chronic hypertension			1.5	1.4	667
Autoimmune disease			3.9	3.5	256
Diabetes			2.2	2.0	455

*Relative risk of pre-eclampsia after treatment with aspirin = 0.90[16]. BMI, body mass index; NNT, number needed to treat.

DISCUSSION

First-trimester uterine artery Doppler is a highly specific test for predicting early-onset pre-eclampsia with moderate sensitivity. The specificity for predicting pre-eclampsia and fetal growth restriction at any gestation is high, but the sensitivity is low. The NNT with aspirin to prevent early-onset pre-eclampsia after uterine artery Doppler screening is comparable to that based on the 'high-risk' clinical factors currently being used.

We collated the largest dataset so far on the evidence relating to uterine artery Doppler in the first trimester. Our search did not have any language restrictions and we included both published and unpublished data, assessing the quality in a uniform manner. Most of the studies included were of good quality, which reduced the risk of bias. We also used the most robust statistical methods for meta-analysis of diagnostic test data.

Some limitations, such as differences in information provided on the reference standard, lack of blinding and use of preventive therapy, were observed, which contributed to the heterogeneity. However, the latter would reduce the test accuracy. We were not able to assess the effect of other clinical variables, such as age and parity, on the accuracy of the performance of uterine artery Doppler owing to a lack of data in the majority of the studies. Reporting a reference standard for definition of pre-eclampsia was homogeneous, but definitions for fetal growth restriction varied considerably. Our findings merit consideration as we were conservative in the estimates of screening performance, particularly for the prediction of early-onset pre-eclampsia.

Although the strategy of treating all mothers with aspirin is shown to be cost effective, this is not recommended because of the adverse effects associated with the use of aspirin, such as maternal antepartum or

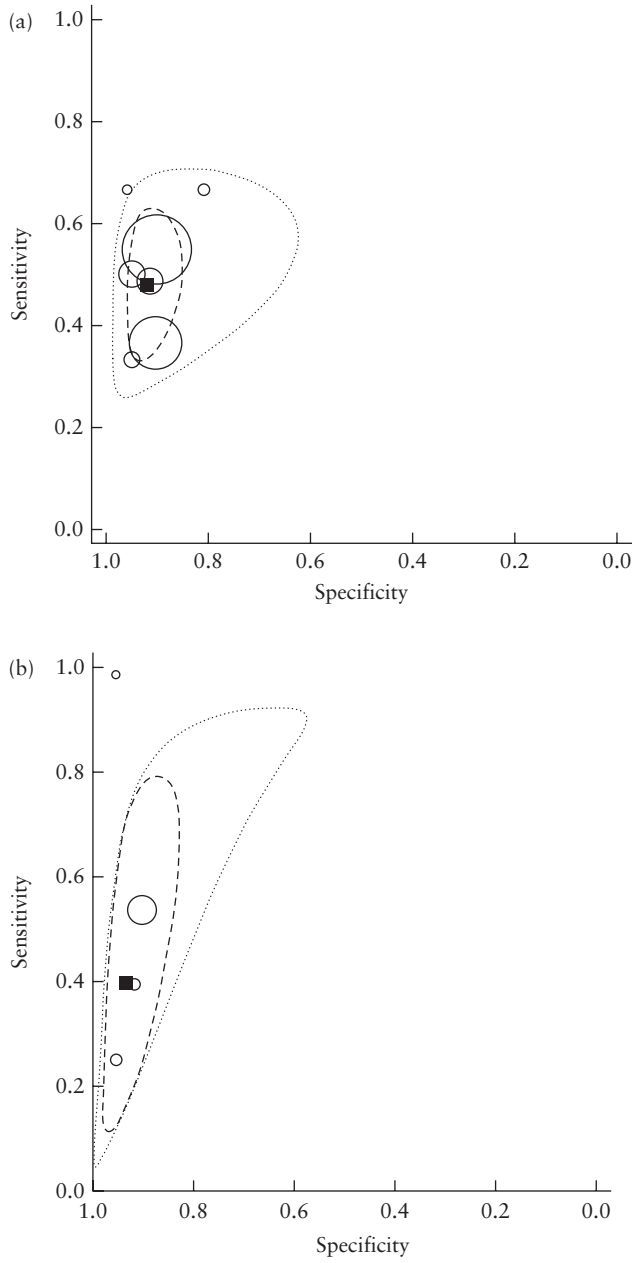

Figure 3 Summary estimates of accuracy of first-trimester uterine artery Doppler in the prediction of early-onset pre-eclampsia (a) and early fetal growth restriction (b) obtained with a bivariate model. Pooled sensitivity and specificity values were 0.48 (95% CI: 0.39–0.57) and 0.92 (95% CI: 0.89–0.95), respectively, for (a) and 0.39 (95% CI: 0.26–0.54) and 0.93 (95% CI: 0.91–0.95), respectively, for (b). ○, Study estimate; ■, summary point; - - - -, 95% confidence region; ·····, 95% prediction region.

postpartum hemorrhage[7]. Initiation of aspirin treatment is recommended, at the earliest, at 12 weeks of gestation in women with risk factors[7]. The meta-analysis by Bujold *et al.* showed that commencement of aspirin before 16 weeks of pregnancy halves the risk of pre-eclampsia, with no significant effect if commenced after that period[10]. The studies that commenced aspirin before 16 weeks in this meta-analysis included women who were at moderate or high risk for pre-eclampsia. However, an individual patient data meta-analysis did not identify any significant subgroup effect for aspirin commenced before or after 20 weeks of pregnancy[16]. It is likely that early administration of aspirin reduces the risks by improving placentation, with a beneficial effect particularly on the risks of early- compared with late-onset pre-eclampsia. A meta-analysis of five randomized trials demonstrated that commencement of low-dose aspirin before 16 weeks of pregnancy significantly reduces the risk of early-onset pre-eclampsia, with no effect on term pre-eclampsia[40]. These findings reinforce the need for early identification of women at risk for pre-eclampsia.

Current recommendations (for commencing prophylactic aspirin for prevention of pre-eclampsia) target women with one clinical high-risk factor or two moderate-risk factors. Uterine artery Doppler in the first trimester will enable clinicians to identify women at risk of developing pre-eclampsia and fetal growth restriction and its complications, and initiate preventive measures such as aspirin and regular fetal monitoring to minimize adverse outcomes. There is no significant difference in the screening performance of uterine artery Doppler with the use of either lower or mean pulsatility indices[41].

All women currently undergo a routine scan in the first trimester in the UK and in most resourced settings. The only added cost of implementing uterine artery Doppler will be around £18–25 and an additional 5 min of time[42,43]. The false-positive rate is low for uterine artery Doppler, thereby minimizing anxiety for the mothers. Given the low sensitivity, clinicians and mothers need to be aware of the possibility of not identifying women who may develop early-onset pre-eclampsia later in pregnancy. Further management will need to be based on subsequent clinical findings in test-negative women.

Our analysis shows that the NNT estimates for abnormal uterine artery Doppler in low-risk women with the 'test all, treat test positives' strategy achieve the same performance as clinical high-risk factors. This makes a strong case for introducing uterine artery Doppler assessment in the first trimester and commencing aspirin in those who test positive.

It is possible that the statistical heterogeneity observed could impact on the results. We have taken into account the imprecision of the estimates by our sensitivity analysis. The NNT estimates computed with the lower limit of the confidence intervals of the LRs are comparable with those obtained for women with traditional high-risk factors of pre-eclampsia.

The findings of our review have highlighted the need for development of prediction models, incorporating the clinical characteristics with uterine artery Doppler to increase the accuracy of risk assessment[44]. An individual patient data meta-analysis will allow development of optimal testing strategies for prediction of maternal and fetal complications[45].

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Search strategy for systematic review of the role of first-trimester uterine artery Doppler in predicting adverse pregnancy outcome

Appendix S2 Characteristics of studies included in systematic review of first-trimester uterine artery Doppler in predicting maternal and fetal complications