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 93.3% (95% CI: 90.9–95.1) 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 mortality1,2. Early onsets of these conditions are associated with increased risk of complications3. 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 restriction4. Women with early-onset pre-eclampsia require admission to a tertiary care facility for treatment and one-third experience complications that may necessitate intensive care5. Infants are often delivered preterm, need prolonged intensive care and develop complications, including lifelong disability6, giving rise to large healthcare costs5. 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-eclampsia7. Currently, clinical risk assessment for pre-eclampsia is carried out in the first trimester8 for early identification of women who may benefit from preventative treatment, such as aspirin7. This includes women with at least one high-risk factor (a previous history of hypertension in pregnancy, chronic kidney
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, 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 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, methods of testing, definition of abnormalities 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 was fitted to obtain summary estimates of sensitivity and specificity, and the corresponding positive and negative likelihood ratios with their 95% CIs. The macro metandi developed for Stata statistical software (StataCorp, College Station, TX, USA) was used. This macro estimates parameters for the model using the xtlogit 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. 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 review17–35 (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) studies17,18,21–23,27,35. 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 onset17,18,22–26,28,32,33,35 as the outcome, nine studies (31 431 women) assessed any-onset fetal growth restriction18,20,22–24,27,31,33–35, two studies (9935 women) assessed stillbirth31,32 and two studies (1366 women) assessed abortion as an outcome18,34. Fifteen studies evaluated the test in low-risk pregnancies17,18,20,22–24 and three studies evaluated the test in high-risk women19,21,35. 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%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
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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Doppler test</th>
<th>Studies (n)</th>
<th>Women (n)</th>
<th>Sensitivity (% (95% CI))</th>
<th>Specificity (% (95% CI))</th>
<th>Positive LR (95% CI)</th>
<th>Negative LR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-onset pre-eclampsia</td>
<td>FVW</td>
<td>7</td>
<td>38,611</td>
<td>47.8 (39.0–56.8)</td>
<td>92.1 (88.6–94.6)</td>
<td>6.1 (4.1–8.9)</td>
<td>0.57 (0.48–0.67)</td>
</tr>
<tr>
<td>Early-onset FGR</td>
<td>FVW</td>
<td>4</td>
<td>26,276</td>
<td>39.2 (26.3–53.8)</td>
<td>93.1 (90.6–95.0)</td>
<td>5.7 (4.3–7.6)</td>
<td>0.65 (0.52–0.81)</td>
</tr>
<tr>
<td>Pre-eclampsia at any gestation</td>
<td>FVW</td>
<td>8</td>
<td>37,971</td>
<td>26.4 (22.5–30.8)</td>
<td>93.4 (90.4–95.5)</td>
<td>4.0 (2.7–6.0)</td>
<td>0.79 (0.74–0.84)</td>
</tr>
<tr>
<td>FGR at any gestation</td>
<td>FVW</td>
<td>6</td>
<td>30,454</td>
<td>15.4 (12.4–18.9)</td>
<td>93.3 (90.9–95.1)</td>
<td>2.3 (1.9–2.8)</td>
<td>0.91 (0.88–0.93)</td>
</tr>
<tr>
<td>Pre-eclampsia early onset</td>
<td>Notching</td>
<td>4</td>
<td>4785</td>
<td>58.5 (49.7–66.7)</td>
<td>56.1 (49.6–62.5)</td>
<td>1.3 (1.2–1.5)</td>
<td>0.74 (0.65–0.84)</td>
</tr>
<tr>
<td>Late-onset pre-eclampsia</td>
<td>FVW</td>
<td>3</td>
<td>33,879</td>
<td>21.5 (18.0–25.4)</td>
<td>90.3 (89.8–90.8)</td>
<td>2.2 (1.9–2.6)</td>
<td>0.87 (0.83–0.91)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>FVW</td>
<td>1</td>
<td>9,839</td>
<td>14.3 (6.9–23.8)</td>
<td>91.3 (90.8–91.9)</td>
<td>1.7 (0.9–3.1)</td>
<td>0.94 (0.84–1.00)</td>
</tr>
<tr>
<td>Composite adverse pregnancy</td>
<td>Notching</td>
<td>1</td>
<td>76</td>
<td>100.0 (40.0–100.0)</td>
<td>63.9 (51.7–74.9)</td>
<td>2.5 (1.6–3.8)</td>
<td>0.16 (0.01–2.2)</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>FVW</td>
<td>1</td>
<td>1,123</td>
<td>44.4 (13.7–78.8)</td>
<td>95.2 (93.8–96.4)</td>
<td>9.3 (4.3–20.3)</td>
<td>0.58 (0.33–1.1)</td>
</tr>
<tr>
<td></td>
<td>Notching</td>
<td>1</td>
<td>243</td>
<td>100 (15.8–100.0)</td>
<td>43.2 (36.8–49.7)</td>
<td>1.5 (0.87–2.5)</td>
<td>0.39 (0.03–4.9)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Risk status for pre-eclampsia</th>
<th>Probability of early-onset pre-eclampsia (%)</th>
<th>At baseline</th>
<th>Test positive (or risk factor present)</th>
<th>After treatment*</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td>0.4*</td>
<td>0.36</td>
<td>2500</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.637</td>
<td>0.54</td>
<td>1667</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.036</td>
<td>0.90</td>
<td>1000</td>
</tr>
<tr>
<td>First-trimester uterine artery Doppler</td>
<td>Test all, treat positives</td>
<td>0.4</td>
<td>2.4</td>
<td>2.1</td>
<td>421</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.6</td>
<td>3.5</td>
<td>183</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
<td>5.8</td>
<td>173</td>
</tr>
<tr>
<td>Moderate risk*</td>
<td></td>
<td></td>
<td>0.95</td>
<td>0.86</td>
<td>1053</td>
</tr>
<tr>
<td>BMI &gt; 35</td>
<td></td>
<td></td>
<td>1.7</td>
<td>1.5</td>
<td>588</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td></td>
<td></td>
<td>0.70</td>
<td>0.63</td>
<td>1429</td>
</tr>
<tr>
<td>Interval &gt; 10 years between pregnancies</td>
<td></td>
<td></td>
<td>0.68</td>
<td>0.61</td>
<td>1471</td>
</tr>
<tr>
<td>Age ≥ 40 years</td>
<td></td>
<td></td>
<td>1.2</td>
<td>1.1</td>
<td>833</td>
</tr>
<tr>
<td>Family history of pre-eclampsia</td>
<td></td>
<td></td>
<td>2.7</td>
<td>2.5</td>
<td>368</td>
</tr>
<tr>
<td>High risk*</td>
<td></td>
<td></td>
<td>3.9</td>
<td>3.5</td>
<td>256</td>
</tr>
<tr>
<td>Hypertensive disease in previous pregnancy</td>
<td>treat positives</td>
<td>2.2</td>
<td>2.0</td>
<td>435</td>
<td></td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td></td>
<td></td>
<td>1.5</td>
<td>1.4</td>
<td>667</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td></td>
<td></td>
<td>3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td>2.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Relative risk of pre-eclampsia after treatment with aspirin = 0.9016. 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...
postpartum hemorrhage. Initiation of aspirin treatment is recommended, at the earliest, at 12 weeks of gestation in women with risk factors. 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. 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. 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. These findings reinforce the need for early identification of women at risk for pre-eclampsia.

Figure 3 shows 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.

REFERENCES


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