Evaluation of 7 serum biomarkers and uterine artery Doppler ultrasound for first-trimester prediction of preeclampsia: a systematic review
Kuc S, Wortelboer EJ, van Rijn BB, Franx A, Visser GH, Schielen FC

CRD summary
The authors concluded that although the evidence showed that combined tests may help to identify high-risk patients, there was no validated screening test that may accurately predict pre-eclampsia early in pregnancy. The studies were underpowered and most were retrospective, and methods used to evaluate the evidence were unclear. The authors’ cautious conclusions seem appropriate.

Authors’ objectives
To evaluate the accuracy of seven serum biomarkers and uterine artery Doppler ultrasound in predicting risk of first-trimester pre-eclampsia.

Searching
PubMed, EMBASE, CINAHL and The Cochrane Library were searched up to October 2010 for articles published in English, Dutch, German, French and Polish. The search strategy was reported.

Study selection
Eligible studies assessed the accuracy of serum markers in maternal blood and/or uterine artery Doppler ultrasound in predicting pre-eclampsia (as defined in the review) in the first trimester of pregnancy. Serum markers had to be reported in at least three articles and included A disintegrin and metalloproteinase 12 (ADAM12), free β subunit of human chorionic gonadotropin (β-hCG), inhibin A, activin A, placental protein 13 (PP13), placental growth factor (PIGF) and pregnancy-associated plasma protein-A (PAPP-A). Eligible trials had to report detection rates of the tests at a fixed 10% false-positive rate or receiver operating characteristic curves (ROC). Data on maternal characteristics were reported. Case reports were excluded from the review.

Included studies were mostly of women with low prior risk. Serum markers and uterine artery Doppler ultrasound were performed between eight and 14 weeks of gestation in all studies.

Two reviewers independently screened studies for inclusion.

Assessment of study quality
Two reviewers independently assessed study quality using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool.

Data extraction
Detection rates at a 10% false-positive rate, with 95% confidence intervals, were extracted or calculated for serum markers either individually or combined, uterine artery Doppler measures alone or in combination with serum marker and maternal characteristics alone or in combination with serum markers or uterine artery Doppler measures. Multiples of the median were reported.

Primary authors were contacted for further details where necessary. The authors did not state how many reviewers extracted data.

Methods of synthesis
Data were presented narratively by predictive measure and in forest plots by pre-eclampsia group (early onset pre-eclampsia requiring delivery before 34 weeks gestation, late onset pre-eclampsia requiring delivery at or after 34 weeks gestation and unspecified pre-eclampsia). Data in forest plots were presented separately by predictive marker and were not combined to calculate an overall pooled estimate.

Results of the review
Thirty-five case control or cohort studies (138,571 women; 3,654 (2.6%) developed pre-eclampsia) were included in the review; there were only two prospective studies. Quality assessment indicated that none of the studies reported on reference tests and most studies did not blind assessors to index test results.

**Serum markers**: For ADAM12, only one study (of five) reported a detection rate of 38% (95% CI 27% to 50%) for unspecified pre-eclampsia. Fβ-hCG (10 studies) was not shown to be a predictive marker of pre-eclampsia.

For inhibin A and activin A, one of five studies reported detection rates of 35% for inhibin A and 20% for activin A.

Five studies reported PP13 levels in early onset pre-eclampsia; detection rates ranged between 37% and 80%. Detection rates for PIGF in the first trimester were 41% and 59% for early-onset pre-eclampsia; for late onset pre-eclampsia the rate was 33%.

Eight studies assessed PAPP-A. Four studies reported detection rates that ranged from 22% to 43% in early-onset pre-eclampsia.

**Uterine artery Doppler ultrasound**: Abnormal uterine artery waveforms seemed to be a good predictor of pre-eclampsia but detection rates for early onset varied between 29% and 83% and for late onset varied between 5% and 62%.

**Maternal characteristics**: Detection rates for maternal characteristic alone ranged from 23% to 56% in early, late and unspecified pre-eclampsia (15 studies).

**Combined screening**: For combinations of two markers, the best detection rate was reported for the combination of PP13 and uterine artery Doppler ultrasound (90%; one study). For the combination of more than two markers, detection rates ranged from 38% to 100% with the best rates reported for the combination of five markers (Inhibin A, PIGF, PAPP-A, ultrasound and maternal characteristics).

**Authors’ conclusions**
Although the evidence showed that a combination of serum markers, uterine artery Doppler measurements and maternal characteristics may help to identify high-risk patients, currently there is no validated screening test that may accurately predict pre-eclampsia early in pregnancy.

**CRD commentary**
The review question was broadly defined but supported by clearly defined inclusion criteria. Four electronic databases were searched for relevant data but language restrictions were applied and it was unclear whether attempts were made to locate unpublished data. Study quality assessment indicated potential issues with reference tests and blinding, and most studies were retrospective (which have inherent limitations). It was unclear whether data extraction was performed in duplicate so reviewer error and bias could not be ruled out.

Study results were presented but not combined in meta-analyses. Restricting the search to studies that reported a cut off value for detection rates fixed at 10% false-positive rates may have excluded potentially relevant data. Details on participants, reference tests and study methods (such as methods for assessing markers) were lacking so variability across studies could not be assessed. There appeared to be considerable variation in results across studies. Detection rates were reported in only a small number of studies for some tests and confidence intervals were generally wide (which indicates greater uncertainty).

The authors acknowledged that all the studies were underpowered due to very low numbers of pre-eclampsia cases and that most studies were retrospective. Given the limitations of the evidence, the authors’ conclusions seem appropriate but the reliability of their implications for practice regarding early and late onset pre-eclampsia is unclear.

**Implications of the review for practice and research**
**Practice**: The authors stated that single marker screening for pre-eclampsia was unsuitable for clinical practice. Combinations of best performing serum markers with maternal characteristics and/or uterine artery Doppler ultrasound yielded higher detection rates and were more promising. Detection rates for late onset pre-eclampsia were lower compared to early onset pre-eclampsia, which was clinically relevant.
Research: The authors stated that large prospective studies using standardised measurement methods were needed to evaluate the roles of tests in screening for pre-eclampsia in different populations/cohorts.

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