Serum screening with Down's syndrome markers to predict pre-eclampsia and small for gestational age: systematic review and meta-analysis

CRD summary
This review found that analytes used for screening for Down's syndrome have low accuracy for the prediction of pre-eclampsia and small for gestational age. The review suffered from a number of limitations, particularly in terms of analysis, but it is unlikely that these had any great influence on the conclusions, so these findings are likely to be reliable.

Authors' objectives
To determine the accuracy of five serum analytes used in Down's serum screening for prediction of pre-eclampsia and/or small for gestational age.

Searching
MEDLINE, EMBASE, the Cochrane Library and Medion were searched from inception to February 2007. Reference lists of included studies and review articles were screened. No language restrictions were applied. Full details of the search strategy were reported in an additional file and included a diagnostic filter.

Study selection
Test accuracy studies that assessed the accuracy of any serum biochemical test used in Down syndrome serum screening before the 25th week gestation in singleton pregnancies, at any level of risk, in any healthcare setting, for the prediction of pre-eclampsia or small for gestational age, were eligible for inclusion. Studies had to report sufficient data to construct a 2x2 table of test performance to be included. Diagnostic case-control studies were excluded from the analysis.

Pre-eclampsia was defined as persistent systolic blood pressure equal to or more than 140 mmHg or diastolic blood pressure (DBP) equal to or more than 90 mmHg with proteinuria equal to or more than 0.3 g/24 hours or equal to or more than 1+ dipstick, new after 20 weeks gestation. Severe pre-eclampsia was defined as systolic blood pressure equal to or more than 160 mmHg or diastolic blood pressure equal to or more than 110 mmHg with proteinuria equal to or more than 2.0 g/24 hours or equal to or more than 3+ dipstick, or of early onset (less than 34 weeks gestation). Superimposed pre-eclampsia was defined as development of proteinuria equal to or more than 0.3 g/24 hours or equal to or more than 1+ dipstick after 20 weeks gestation in chronically hypertensive patients.

Small for gestational age was less than 10th centile adjusted for gestational age and based on local population values and absolute birth weight of less than 2500g. Severe small for gestational age was defined as birth weight less than 5th or 3rd centile or less than 1750 g or/and pre-term small for gestational age for small for gestational age leading to delivery less than 37 weeks. Neonatal ponderal index of less than 10th centile, skin fold thickness, and mid-arm circumference/head circumference were also assessed.

Incidence of pre-eclampsia ranged from 0.6 to 44%. Incidence of small for gestational age ranged from 1.2 to 63% in the included studies. Some studies were included in high risk population (in vitro fertilization patients, patients with abnormal uterine artery Doppler or chronic hypertension). Most studies were conducted between 15 to 20 weeks gestation but some were conducted in the first trimester and others at up to 24 weeks gestation.

Two reviewers independently assessed studies for inclusion. Disagreements were resolved through consensus or referral to a third reviewer.

Assessment of study quality
Studies were assessed for methodological quality based on the following criteria: prospective design; consecutive recruitment; full verification of the test result with reference standard (>90%); adequate description of the index test;
use of appropriate reference standard; and application of any preventive treatments. Small for gestational age papers were also assessed according to whether cases of pre-eclampsia were excluded from the results, whether foetuses with chromosomal and structural anomalies were excluded, and whether stillbirths and intrauterine deaths were excluded from results.

Quality was assessed independently by two reviewers.

**Data extraction**

Data were extracted as 2x2 tables of test performance. These were used to calculate sensitivity, specificity and positive and negative likelihood ratios. Where 2x2 tables contained 0 cells, 0.5 was added to each cell to allow calculations.

Two reviewers independently extracted data, disagreements were resolved by consensus or referral to a third reviewer.

**Methods of synthesis**

Estimates of sensitivity and specificity were pooled for studies that used the same threshold on the index test, the same trimester to testing, and for small for gestational age, the same reference standard threshold. Subgroup analyses based on the following characteristics were conducted for subgroups reported in at least three studies: level of risk of population; type of assay used for index test, whether babies with chromosomal anomalies were excluded; use of preventative treatment; and study quality. Heterogeneity was assessed graphically using summary receiver operating characteristic plots and forest plots of likelihood ratios. The log-likelihood and χ² test were used to assessed heterogeneity with p<0.05 considered as evidence of significant heterogeneity. If data were homogeneous fixed-effect pooling was used otherwise random-effects models were used.

**Results of the review**

Forty-four studies on pre-eclampsia (n=169,637 participants) including 35 cohort studies and nine case-control studies. Patient selection criteria, description of index and reference tests and blinding of the reference standard were poorly reported. The case-control studies were excluded from the meta-analysis.

Eighty-six studies assessed small for gestational age (n=382,005) including 61 cohort studies and 25 case-control studies. Only 40 studies included an adequate description of the index test. Performance of the reference standard, blinding of the reference standard and use of treatment between the index test and reference standard were poorly reported. The case-control studies and eight studies in which thresholds for small for gestational age were not defined were excluded from the meta-analysis.

**Prediction of pre-eclampsia**: All but one of the tests evaluated showed poor diagnostic performance for the prediction of pre-eclampsia, especially for ruling out pre-eclampsia. Results were reported for the most accurate threshold:

- Maternal serum alpha fetoprotein greater than 2.0 multiples of median (MoM): positive likelihood ratio 2.36 (95% confidence interval (CI): 1.46 to 3.83); negative likelihood ratio 0.96 (95% CI: 0.95 to 0.98); 16 studies, 10 contributed to pooled estimate.

- Maternal serum human chorionic gonadotrophin greater than 2.0MoM; positive likelihood ratio 2.45 (95% CI: 1.57 to 3.84); negative likelihood ratio 0.89 (95% CI: 0.83 to 0.96); 21 studies, 11 contributed to pooled estimate.

- Maternal serum unconjugated estriol greater 0.5 MoM: positive likelihood ratio 1.50 (95% CI: 1.02 to 2.19); negative likelihood ratio 0.99 (95% CI: 0.97 to 1.00); four studies, two contributed to pooled estimate.

- Maternal serum pregnancy associated plasma protein A less than 5th centile: positive likelihood ratio 2.10 (95% CI: 1.57 to 2.81); negative likelihood ratio 0.95 (95% CI: 0.93 to 0.98); (16 studies, five contributed to pooled estimate).

- Maternal serum inhibin A greater than 2.79 MoM: positive likelihood ratio 19.52 (95% CI: 8.33 to 45.79); negative likelihood ratio 0.30 (95% CI: 0.13 to 0.68); (six studies, one study contributed to summary estimate).

Performance was considerably worse for all other thresholds evaluated with summary positive likelihood ratio <8.
Prediction of small for gestational age: Tests also showed poor performance for the prediction of small for gestational age. Results were reported for the most accurate threshold for predicting birth weight <10th centile:

Maternal serum alpha fetoprotein less than 10th centile: positive likelihood ratio 8.80 (95% CI: 5.57 to 13.91); negative likelihood ratio 0.02 (95% CI: 0.00 to 0.34); 30 studies, one study contributed to summary estimate.

Maternal serum human chorionic gonadotrophin greater than 2.0MoM: positive likelihood ratio 1.74 (95% CI: 1.48 to 2.04); negative likelihood ratio 0.95 (95% CI: 0.93 to 0.96); 22 studies, seven studies contributed to pooled estimate.

Maternal serum unconjugated estriol less than 0.75 MoM: positive likelihood ratio 2.54 (95% CI: 1.54 to 4.19); negative likelihood ratio 0.75 (95% CI: 0.63 to 0.89); seven studies, two studies contributed to pooled estimate.

Maternal serum pregnancy associated plasma protein A less than 1st centile: positive likelihood ratio 4.36 (95% CI: 3.27 to 5.80); negative likelihood ratio 0.97 (95% CI: 0.96 to 0.98); 10 studies, one study contributed to pooled estimate.

Maternal serum inhibin A greater than 2.0 MoM: positive likelihood ratio 4.45 (95% CI: 3.92 to 5.06); negative likelihood ratio 0.92 (95% CI: 0.91 to 0.93); one study.

Triple test (serum alpha fetoprotein, human chorionic gonadotrophin and unconjugated estriol: positive likelihood ratio 1.07 and 2.71; negative likelihood ratio 0.98 and 1.19; two studies.

Subgroup analysis was only possible for incidence of disease and no significant differences were found between any of the subgroups investigated.

Authors' conclusions
The accuracy of Down's serum screening analytes for the prediction of both pre-eclampsia and small for gestational age was low. They may be a useful means of risk assessment or of use in prediction when combined with other tests.

CRD commentary
The review addressed a focused question, supported by clearly defined inclusion criteria. The literature search was limited to two main databases for primary studies and included a diagnostic filter, which means that it is likely that relevant studies may have been missed. Appropriate steps were taken to minimise bias and errors at all stages of the review process. Study quality was assessed and the results were clearly reported but were not adequately incorporated into the analysis.

The analysis suffered from a number of limitations; results were pooled separately, according to threshold of disease, and less robust methods for pooling diagnostic data were used. Conclusions were based on the most accurate threshold for each serum marker, which was often based on a very small proportion of the total number of studies, and in some cases, on single studies assessing each marker. A more sophisticated analysis would have pooled all data irrespective of threshold and used more sophisticated models such as the hierarchical summary receiver operating curve (HSROC) or bivariate models. This would have allowed more data to contribute to the pooled estimates and more meaningful sensitivity analysis, and investigation of heterogeneity could have been undertaken. The data presented supported the authors' conclusions that the accuracy of the analytes assessed was low, but did not support their conclusion that they may be a useful means of risk assessment; their use when combined with other tests was not evaluated.

The review suffers from a number of limitations, particularly in terms of analysis, but it is unlikely that these had any great influence on the conclusions, so the results are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that future studies should address the limitations in the primary studies including poor reporting; exclusion of intrauterine deaths and chromosomal abnormalities and structural anomalies from the results;
separation of pre-eclampsia and small for gestational age; and prediction of severe disease. This may not necessarily require new primary studies but could involve meta-analysis of individual patient data. Future research should focus on combinations of markers as predictors and combinations of tests such as serum screening markers and uterine artery Doppler to improve the accuracy of these tests.

**Funding**
Wellbeing of Women (NBTF626:03); NHS Health Technology Assessment UK (01/64).

**Bibliographic details**

**PubMedID**
18680570

**DOI**
10.1186/1471-2393-8-33

**Original Paper URL**
http://www.biomedcentral.com/content/pdf/1471-2393-8-33.pdf

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Aspirin /therapeutic use; Biomarkers /blood; Chorionic Gonadotropin /blood; Estriol /blood; Female; Fetal Growth Retardation /metabolism /prevention & control; Gestational Age; Humans; Inhibins /blood; Mass Screening /methods; Pre-Eclampsia /metabolism /prevention & control; Pregnancy; Pregnancy-Associated Plasma Protein-A /analysis; Prenatal Care /methods; alpha-Fetoproteins

**AccessionNumber**
12009100693

**Date bibliographic record published**
07/04/2009

**Date abstract record published**
05/08/2009

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.