

Cross-trimester repeated measures testing for Down's syndrome screening: an assessment

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Executive summary

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Executive summary

Objective

To provide estimates and confidence intervals (CIs) for the performance (detection and false-positive rates) of screening for Down's syndrome using repeated measures of biochemical markers from first and second trimester maternal serum samples taken from the same woman.

Design

Stored serum on Down's syndrome cases and controls was used to provide independent test data for the assessment of screening performance of published risk algorithms and for the development and testing of new risk assessment algorithms.

Setting

Two independent test data sets, including data on a total of 121 cases of Down's syndrome, were used in the study:

- The First and Second Trimester Evaluation of Risk (FaSTER) repeated measures study, in which samples were obtained from 15 screening centres across the USA between October 1999 and December 2002.
- The North York repeated measures study, in which samples were obtained from women who received integrated prenatal screening at the North York General Hospital, Toronto, Canada between December 1999 and November 2007.

Measurements

Repeated measurements (first and second trimester) of maternal serum levels of human chorionic gonadotrophin (hCG), unconjugated estriol (uE3) and pregnancy-associated plasma protein A (PAPP-A) together with alpha-fetoprotein (AFP) in the second trimester.

Outcomes

1. Detection and false-positive rates for screening with a threshold risk of 1 in 200 at term.
2. Detection rate achieved for a false-positive rate of 2%.

Rates were standardised to the distribution of maternal ages in England and Wales for the 3-year period from 2000 to 2002.

Results

Published distributional models for Down's syndrome cases were inconsistent with the test data. When these test data were classified using these models, screening performance deteriorated substantially through the addition of repeated measures. This contradicts the very optimistic results obtained from predictive modelling of performance. Simplified distributional assumptions, based on the principles of linear discriminant analysis, improved model fit and showed some evidence of benefit from the use of repeated measures of PAPP-A but not for repeated measures of uE3 or hCG.

Each of the two test data sets was used to create new parameter estimates against which screening test performance was assessed using the other data set. The results were equivocal, but there was suggestive evidence of improvement in screening performance through the use of repeated measures of PAPP-A when the first trimester sample was collected before 13 weeks' gestation.

A Bayesian analysis of the combined data from the two test data sets showed that adding a second trimester repeated measurement of PAPP-A to the base test (PAPP-A in the first trimester with AFP, hCG and uE3 in the second) increased detection rates and reduced false-positive rates. The benefit decreased with increasing gestational age at the time of the first sample. At 11 weeks' gestation,

the repeated measurement of PAPP-A reduced the false-positive rate by an estimated 1% (95% CI 0.6% to 1.5%) from 3.5% to 2.5%, and increases the detection rate by an estimated 3% (95% CI 1% to 6%) from 89% to 92%. There was no evidence of any benefit from repeated measures of hCG or uE3.

Conclusions

If realised, a reduction of 1% in false-positive rate with no loss in detection rate would give important benefits in terms of health service provision and the large number of invasive tests avoided. The Bayesian analysis, which showed evidence of benefit, was based on strong distributional assumptions and should not be regarded as confirmatory. The evidence of potential benefit suggests the need for a prospective study of repeated measurements of PAPP-A with samples from early in the first trimester. A formal clinical effectiveness and cost-effectiveness analysis should be undertaken. A secondary objective of this prospective study should be to investigate the potential value of other repeated measures markers including ADAM metalloproteinase domain

12 (ADAM-12) and Inhibin-A. The additional complexity arising from the need to obtain serum samples in the first and second trimester should be assessed in terms of its cost-effectiveness and impact on screening services.

This study has shown that the established modelling methodology for assessing screening performance may be optimistically biased and should be interpreted with caution. Multivariate methods for assessment of goodness of fit and Bayesian methods for inference have been used in the analysis presented in this report and should be used more widely in the field of screening. Guidance on the use of these methods should be produced and software should be made available for their implementation.

Publication

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NIHR Health Technology Assessment programme

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