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Title **Cross-Trimester Repeated Measures Testing for Down's Syndrome Screening: An Assessment**

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Aim

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

Conclusions and results

Using data on maternal serum samples taken between 11 and 13 weeks gestation and again in the second trimester, the study shows evidence of benefit from repeated measures of pregnancy-associated plasma protein-A (PAPP-A). If realized, the reduction of around 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 benefit of using repeated measures decreased with increasing gestational age at the time of the first sample and was gone by 13 weeks gestation. More evidence is needed on earlier gestations (9 to 10 weeks) where repeated measures of PAPP-A may have very substantial benefits. The study showed little evidence of benefit from repeated measurements of unconjugated estriol (uE3) or human chorionic gonadotrophin (hCG).

Published distributional models for Down syndrome were inconsistent with the test data used for this study. Consequently, when these test data were classified using the published models, screening performance deteriorated substantially through the addition of repeated measures. This contradicts the optimistic results obtained from predictive modeling.

Recommendations

The evidence of potential benefit suggests the need for a prospective study of repeated measurements of PAPP-A with the first trimester serum sample taken between 9 and 11 weeks gestation. A formal clinical- and cost-effectiveness analysis should be undertaken.

Methods

Two independent test data sets including 121 pregnancies with Down syndrome and 605 controls were analyzed. These data had measurements of PAPP-A, uE3, and hCG taken in the first trimester and again in the second. Three prespecified analyses were undertaken: 1) independent tests of existing algorithms, 2) each of the two data sets was used to create a risk assessment algorithm that was tested on the other data set, and 3) an algorithm that used a pooled covariance matrix was fitted to the two data sets and assessed using a Bayesian approach, taking account of the uncertainty in parameter estimation.

Further research/reviews required

See Executive Summary link www.hta.ac.uk/project/1620.asp.

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