Cross-trimester marker ratios in prenatal screening for Down syndrome

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined a modified version of integrated Down syndrome (DS) screening (first- and second-trimester measurements integrated into a single screening test) in which ratios of the levels of the same serum markers measured in both these trimesters (i.e. cross-trimester, CT, ratios) are added as new screening markers. The analytes that were measured in both trimesters of pregnancy were alphafetoprotein (AFP), unconjugated oestriol (uE3), human chorionic gonadotrophin (hCG) (both total and free beta), pregnancy-associated plasma protein A (PAPP-A) and inhibin-A.

The concentrations of the analytes were expressed as multiples of the median (MoM) for unaffected pregnancies. The ratio of the same analyte level measured in the first and second trimesters of pregnancy (the CT ratio) was expressed as the MoM value in the second trimester divided by the MoM value in the first trimester. Measurements in the first trimester were performed at 10 to 13 weeks, and those in the second trimester at between 14 and 22 weeks.

The medians for CT ratios in DS pregnancies at 10, 11, 12 and 13 completed weeks were estimated by linear regression of the log_{10} CT ratio MoMs against the median gestational age within each week of gestation, weighted by the number of DS pregnancies in each week.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised pregnant women undergoing DS screening.

Setting
The setting was a hospital. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data were derived from studies published between 1999 and 2005. The costs and data on resource use were derived from a study published in 2003. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Outcomes assessed in the review
The outcomes estimated from the literature were analyte measurements, the maternal age distribution, and the maternal
age-specific odds of having an affected live birth. All these data were entered into a simulation model that aimed to determine the detection rate (DR) and the false-positive rate (FPR) for integrated DS screening with and without the CT ratio. The optimal risk cut-off level for DS pregnancies (i.e. the best cut-off to achieve a reasonable trade-off between DR and FPR) was estimated.

Study designs and other criteria for inclusion in the review
The authors did not state whether a systematic review of the literature was undertaken to identify the primary studies. Much of the evidence came from the Serum Urine and Ultrasound Screening Study (SURUSS), which involved 74 DS pregnancies with pairs of first- and second-trimester serum measurements and 492 unaffected pregnancies. Maternal age distribution was based on the distribution of maternities in England and Wales from 1996 to 1998. Other sources of clinical data were not described.

Sources searched to identify primary studies
Not applicable.

Criteria used to ensure the validity of primary studies
Not applicable.

Methods used to judge relevance and validity, and for extracting data
Not applicable.

Number of primary studies included
Seven primary studies provided the clinical evidence.

Methods of combining primary studies
The primary estimates appear to have been combined using a narrative approach.

Investigation of differences between primary studies
Not applicable.

Results of the review
A graphical analysis of the results suggested that all analytes, except AFP, showed a material discrimination between affected and unaffected pregnancies.

The screening performance of CT ratios was significantly better with the first trimester measurements at 11 weeks than at 12 or 13 weeks.

The performances of the conventional and new versions of integrated screening were expressed as the DR for a specific FPR and the FPR for a specific DR. For example, at a 90% DR, the integrated test (in which total hCG was used) yielded an FPR of 0.67% with CT ratios and 2.15% without CT ratios, a proportional reduction of 68%. The corresponding estimates for the serum integrated test (at a 90% DR) were 2.37% and 8.12%, respectively, a similar proportional reduction. A comparable reduction in FPR rate was also found when assuming an 85% and 95% DR.

The screening performances of the tests were influenced little by whether total or free beta-hCG was used. With the addition of CT ratios to the integrated test, and with first-trimester measurements performed at 12 rather than 11 completed weeks, the FPR for a 90% DR approximately doubled to 1.29%, and at 13 weeks it was 2.12%. 
A cumulative analysis showed that most of the gain in screening performance came from CT ratios for PAPP-A and uE3.

Other important results were as follows:

the integrated test with CT ratios had the best screening performance;

the serum integrated test with CT ratios had similar screening performance to the integrated test without CT ratios; and

the serum integrated test without CT ratios had the poorest screening performance.

Screening performance was reduced by dropping any of the markers. The loss was greatest when PAPP-A was dropped and least with inhibin-A. For example, after excluding the measurement of inhibin-A, the integrated test with uE3, hCG and PAPP-A CT ratios gave an FPR of 1.02% for a 90% DR, compared with an FPR of 0.67% if inhibin-A were retained as a marker.

The best risk cut-off level was estimated to be 1 in 150 with either the integrated or serum integrated test, achieving detection rates of about 93% and 89%, respectively, and FPRs of about 1.3% and 2.2%.

Measure of benefits used in the economic analysis
The summary benefit measure used was the number of DS pregnancies detected. This measure was obtained by combining data on DR and FPR for the integrated and serum integrated tests with and without CT ratios, using Monte Carlo simulations based on Gaussian distributions. Women were classified as screening positive if their risk estimate reached or exceeded a specified cut-off level.

Direct costs
The cost/resource boundary of the economic analysis was not stated as the cost analysis was derived from a published study. The health services included in the study were screening measurements, amniocentesis, karyotype, termination of pregnancy, and delivery. Details of the quantities of resources used and unit costs were not presented. Similarly, the price year was not given.

Statistical analysis of costs
No statistical analyses of the costs were carried out.

Indirect Costs
The indirect costs were not included in the economic analysis.

Currency
UK pounds sterling (€).

Sensitivity analysis
Sensitivity analyses were not carried out.

Estimated benefits used in the economic analysis
The DR for different levels of FPR was always higher for tests with a CT ratio than without a CT ratio.

Cost results
The total costs of screening 100,000 women were reported for different DRs and including different combinations of
analytes. For example, at a 90% DR, the total cost of screening 100,000 women was 3.16 million using the integrated test with all four CT ratios, compared with 2.96 million using the CT ratios for only uE3 and PAPP-A, or 2.96 million without CT ratios.

In general, the incremental cost of using CT ratios was relatively small. This was because the extra cost of performing more screening measurements was similar to the savings from having to carry out fewer amniocenteses and diagnostic tests in order to achieve the same DR.

**Synthesis of costs and benefits**
Average cost-effectiveness ratios (i.e. the cost per DS pregnancy diagnosed) were calculated in order to combine the costs and benefits of the alternative strategies.

The cost per DS case diagnosed was reported for the different DRs and analytes included. For example, at a 90% DR, the cost-effectiveness ratio was 15,500 using the integrated test with all four CT ratios, compared with 14,500 using the CT ratios for only uE3 and PAPP-A, and 14,600 without CT ratios.

The authors stated that the extra cost was likely to be worth the 35% reduction in the FPR (from 1.02% to 0.67%). Similar results were obtained with other DRs, and in some circumstances the average cost per case detected with CT ratios was even lower than without CT ratios.

The use of all four CT ratios was the most effective approach with serum integrated screening.

**Authors’ conclusions**
The addition of cross-trimester (CT) ratios to the integrated Down syndrome (DS) screening test improved test accuracy and was a cost-effective strategy.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparators was clear as the new integrated test was compared with the conventional approach. A clear description of the comparators was provided. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence was derived from the SURUSS study. The validity of the primary source does not appear to be a key issue for this study, which was based on solid methodological features. Sensitivity analyses were not carried out, but the authors considered different scenarios for accuracy rates.

**Validity of estimate of measure of benefit**
The proportion of detected cases of DS was an appropriate benefit measure, given that it reflects the most relevant effect of the interventions examined in the study. However, it will not be possible to compare a benefit measure such as this with the benefits of other health care interventions.

**Validity of estimate of costs**
The analysis of the costs was derived directly from a published study. Therefore, a detailed breakdown of the cost items was not provided. Similarly, the price year, unit costs and information on resource consumption was not given. This will limit the ability to replicate the analysis in other time periods and in different settings. The reader is therefore referred to the primary cost analysis.

**Other issues**
The authors compared their findings with those from a previous study that had used a different approach and generated very low risk estimates. The differences between the two approaches were discussed, the authors pointing out the advantages of their methodology. The issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were not carried out. However, the authors included many scenarios for DRs and FPRs, thereby increasing the external validity of the clinical analysis.

**Implications of the study**
The study results support the introduction of the modified integrated DS test into prenatal screening programmes.

**Source of funding**
None stated.

**Bibliographic details**

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**Other publications of related interest**
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**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Biomarkers; Down Syndrome /diagnosis /economics /embryology; False Positive Reactions; Female; Gestational Age; Humans; Predictive Value of Tests; Pregnancy; Pregnancy Trimester, First /blood /urine; Pregnancy Trimester, Second /blood /urine; Prenatal Diagnosis /economics /methods

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