First- and second-trimester evaluation of risk for Down syndrome

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
Seven strategies for screening for Down syndrome (DS) during the first and second trimester of pregnancy were examined. The screening strategies were as follows.

Triple Screen: maternal serum alpha foetoprotein (AFP), estriol and human chorionic gonadotrophin (hCG).
Quad Screen: maternal serum AFP, estriol, hCG, plus inhibin A.
Combined First: nuchal translucency, pregnancy-associated plasma protein A (PAPP-A) and free beta-hCG.
Integrated: nuchal translucency, PAPP-A plus Quad, with result provided after all tests completed.
Serum Integrated: PAPP-A plus Quad without nuchal translucency.
Stepwise Sequential: Combined First plus Quad with the results given after each test.
Contingent Sequential: Combined First triple screen, and only those with a risk between 1:30 and 1:1,500 undergo Quad Screen.

Specifically, in the Stepwise Sequential screening strategy, the results were provided to patients after both the first and second trimester components of the tests. Contingent Sequential screening also began with first-trimester screening, but second-trimester screening was performed on the basis of the level of risk obtained with the previous tests (moderate- and high-risk women had a second-trimester test, whereas low-risk women did not have further tests).

Type of intervention
Screening.

Economic study type
Cost-utility analysis.

Study population
The study population comprised pregnant women.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from a study published in 2005. The resource use and cost data were derived from studies published between 1994 and 2004. The price year was 2006.
Link between effectiveness and cost data
The costing was carried out retrospectively on the same sample of women enrolled in the clinical trial.

Study sample
The FASTER study included a sample of 38,033 pregnant women. Other details of sample selection were not reported.

Study design
This was a prospective, multi-centre, non-randomised study. The length of follow-up appears to have been the duration of pregnancy. No other details were given.

Analysis of effectiveness
The clinical data used in the analysis were:

- the risk of DS;
- the proportion of DS surviving to live birth;
- the proportion of women who obtained second-trimester screening;
- the accuracy of screening (sensitivity and false-positive rates);
- the proportion of women receiving nuchal translucency where appropriate images failed to be obtained or were subsequently rejected;
- the rate of women who accepted amniocentesis with screen positive;
- the proportion of women younger than age 35 years who accepted amniocentesis with a positive screening test;
- the rate of loss from amniocentesis; and
- the proportion of women with DS who terminated the pregnancy.

Effectiveness results
The risk of DS was 0.002419 in the first trimester (92 cases out of 38,033 pregnancies), 0.002497 in the second trimester (88 cases out of 35,236 pregnancies), and 0.002185 in the third trimester (77 cases out of 35,236 pregnancies).

The proportion of DS surviving to live birth was 0.7027 (26 cases of 37).

The proportion of women who obtained second-trimester screening was 87.9% (92.8% of first-trimester screens).

The sensitivity was 0.85 for nuchal translucency plus serum screen, 0.6 for second-trimester Triple Screen, 0.81 second-trimester Quad Screen, 0.86 for Serum Integrated Screen, 0.95 for Fully Integrated Screen, 0.93 for Contingent Screen, and 0.95 for Sequential Screen.

The false-positive rate was 0.05 with nuchal translucency plus serum screen, 0.05 with second-trimester Triple Screen, 0.05 with second-trimester Quad Screen, 0.05 with Serum Integrated Screen, 0.05 with Fully Integrated Screen, 0.043 with Contingent Screen, and 0.049 with Sequential Screen.

The proportion of women receiving nuchal translucency where appropriate images failed to be obtained was 3.1% at week 10, 2.6% at week 11, 3.2% at week 12, and 5.5% at week 13.
The proportion of women receiving nuchal translucency where appropriate images were subsequently rejected was 7.4% at week 10, 3.1% at week 11, 2.3% at week 12, and 2.9% at week 13.

The rate of women who accepted amniocentesis with screen positive was 0.571.

The proportion of women younger than 35 years who accepted amniocentesis was 0.518, while the proportion of women aged 35 years or older who accepted amniocentesis was 0.616.

The rate of loss from amniocentesis was 0.0006.

The proportion of women with DS who terminated their pregnancy was 0.981.

Clinical conclusions
The clinical data were used to populate the decision model.

Modelling
The authors stated that a decision analytic model was used to model the clinical and economic impact of the seven screening strategies. However, no further information on the model was given.

Measure of benefits used in the economic analysis
The summary benefit measure used in the cost-utility analysis was the number of quality-adjusted life-years (QALYs). These were estimated using utility weights derived from the literature and applied to expected survival. The authors stated that utilities associated with a procedural-related loss and the birth of a DS child were derived from a study that used the standard gamble metric. Limited information on the other values was given. The QALYs were discounted at an annual rate of 3%.

Direct costs
The viewpoint of the analysis was not explicitly stated, but it might have been that of society as the societal cost of a DS birth was included in the analysis. The health services considered in the study were the screening tests and the resources associated with pregnancy termination and care for a DS baby. The unit costs of the screening tests, but not the quantities of resources used, were reported. The costs and quantities were estimated using data derived from a review of the literature, no details of which were reported. The price year was 2006. All costs were inflated to 2006 values using the medical component of the Consumer Price Index.

Statistical analysis of costs
The costs appear to have been treated deterministically in the base-case analysis.

Indirect Costs
Productivity costs were not considered.

Currency
US dollars ($).

Sensitivity analysis
A univariate sensitivity analysis was carried out by varying different clinical inputs of the model across the ranges reported in the FASTER trial. A probabilistic Monte Carlo simulation was also performed, in which all of the input distributions were varied simultaneously. Finally, to examine the Stepwise Sequential screening strategy further, false-
positive rates of 2, 5 and 10% were considered separately in a deterministic analysis.

**Estimated benefits used in the economic analysis**
The expected QALYs in the sample of 38,033 women evaluated in the FASTER trial were 980,774 with Quad, 980,777 with Combined First, 980,820 with Integrated, 980,790 with Serum Integrated, 980,823 with Stepwise Sequential, and 980,832 with Contingent Sequential.

The highest QALYs obtained with the Contingent Sequential screening were mainly due to the lower rate of false positives and thus procedural-related miscarriages with amniocentesis.

**Cost results**
The expected costs ($ million) in the sample of 38,033 women evaluated in the FASTER trial were $37.5 with Triple Screen, $32.8 with Quad, $35.2 with Combined First, $34.5 with Integrated, $33.6 with Serum Integrated, $34.4 with Stepwise Sequential, and $32.3 with Contingent Sequential.

**Synthesis of costs and benefits**
Incremental cost-utility ratios were calculated in order to combine the costs and benefits of the alternative strategies.

The incremental analysis showed that the Contingent Sequential screening strategy dominated all other strategies, which were both less effective and more expensive.

When excluding the Contingent Sequential screening strategy, Triple Screen was dominated and Quad became the reference strategy. The incremental cost per QALY gained was $500,560 with Combined First, $33,385 with Integrated, $42,188 with Serum Integrated, and $29,524 with Stepwise Sequential.

The sensitivity analysis showed that the base-case results were robust to several variations in clinical inputs, although the analysis was sensitive to changes in the false-positive rate of the Stepwise sequential screening test.

**Authors' conclusions**
The analysis of data from the FASTER trial showed that the Contingent Sequential test was the preferred option for screening for Down Syndrome (DS).

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparators was clear and all relevant screening strategies appear to have been considered. Both individual and combined strategies were included. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness data came from a clinical trial, a type of study that is usually associated with a high internal validity. The multi-centre design and the large sample of women involved represent strengths of the analysis. However, there was very limited information on the other characteristics of the study since the trial had been published separately.

**Validity of estimate of measure of benefit**
The benefit measure (QALYs) was modelled, although details of the modelling were not given. The utility weights were derived from the literature and some details of these were reported. Discounting was applied in accordance with US recommendations. QALYs are appropriate, given the impact of the disease on quality of life and survival, and they can be directly compared with the benefits of other health care interventions.
Validity of estimate of costs
The viewpoint of the analysis was not stated clearly, but the societal costs of a DS birth were included. The unit costs and the quantities of resources used were not presented separately, which limits the possibility of replicating the analysis in other settings. The lifetime cost of caring for a DS child was reported as a macro-category and a breakdown of the cost items was not provided. All costs came from published studies. The cost estimates were treated deterministically and the impact of changes in the cost estimates was not investigated in the sensitivity analysis. The price year was reported, which will facilitate reflation exercises in other time periods.

Other issues
The authors did not compare their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other settings. However, the use of sensitivity analyses should have enhanced the external validity of the analysis. The authors noted some limitations of their analysis. First, the sensitivity rates observed in the FASTER trial might not be achieved in a national screening programme, thus the accuracy of screening might have been overestimated. Second, the costs considered in the analysis did not reflect those faced by patients, especially those without any insurance coverage.

Implications of the study
The study results support the use of the Contingent Sequential test for DS screening in first- and second-trimester pregnancies. The authors suggested that new guidelines should be created in order to take more accurate screening strategies into consideration.

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