An outcomes analysis of five prenatal screening strategies for trisomy 21 in women younger than 35 years

Biggio J R, Morris T C, Owen J, Stringer J S

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
Five prenatal screening strategies for foetal aneuplody (trisomy 21) in women under 35 years of age were examined. The strategies were as follows. Triple screen: midtrimester maternal serum alpha-fetoprotein, chorionic gonadotropin (hCG), and unconjugated estriol.

Quad screen: triple screen plus maternal serum dimeric inhibin A.

First-trimester screen: sonographic measurement of foetal nuchal translucency combined with maternal serum pregnancy associated plasma protein A and free beta-subunit of hCG (free beta-hCG) levels at 10 to 14 weeks’ gestation.

Integrated screen: a combination of first-trimester and quad screens, but the first-trimester results were withheld until the quad screen was completed. A composite result was provided, and if the screen was positive, prenatal diagnosis was available.

Sequential screen: a combination of first-trimester and quad screens, except that the results of the first-trimester screen were provided immediately and prenatal diagnosis was available if the screen was positive. Later prenatal diagnosis was available if the mid-trimester screen was positive.

Alternatively, the performance of a genetic sonogram (GS) was considered after a screen-positive triple or quad screen.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of pregnant women younger than 35 years.

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 studies published between 1986 and 2003. Some costs and resource use data were derived from sources published between 1995 and 2003. The price year was 2002.

Source of effectiveness data
NHS Economic Evaluation Database (NHS EED)
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The effectiveness evidence was derived from a synthesis of completed studies and authors’ assumptions.

**Modelling**
A decision model was constructed to examine the clinical and economic impact of the alternative prenatal screening strategies in a hypothetical cohort of 1,000,000 women who were younger than 35 years at the time of delivery. The entire cohort presented for prenatal care before 10 weeks’ gestation and accepted prenatal screening for foetal trisomy 21 (T21). Other details of the decision model were not reported.

**Outcomes assessed in the review**
The outcomes estimated from the literature were:

- the prevalence of T21 at 10 weeks,
- foetal demise for aneuploid or euploid,
- the rate of acceptance of the diagnostic test,
- the rate of women who elect termination of T21,
- postamniocentesis loss,
- foetal loss after chorionic villus sampling (CVS), and
- the sensitivity and specificity of the 5 screening strategies and GS.

**Study designs and other criteria for inclusion in the review**
It was not stated whether the review of the literature was systematic. The information on the sources used to identify primary studies was limited.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
Not stated.

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

**Number of primary studies included**
Thirty-four primary studies provided the evidence.

**Methods of combining primary studies**
The primary estimates appear to have been combined using narrative methods.

**Investigation of differences between primary studies**
Not stated.
Results of the review
The prevalence of T21 at 10 weeks was 0.0016806 (1 of 595).

The rate of foetal demise for aneuploid was 25% at 10 to 14 weeks and 23% from week 15 to term.

The rate of foetal demise for euploid was 1% at 10 to 14 weeks and 1% from week 15 to term.

The rate of acceptance of the diagnostic test was 70% (range: 30 - 70).

The rate of women who elect termination of T21 was 90% (range: 50 - 100).

The rate of postamniocentesis loss was 0.9% (range: 0.3 - 1).

The rate of foetal loss after CVS was 1.6% (range: 0.3 - 2).

The sensitivity and specificity were, respectively:

- 60% (range: 55 - 65) and 95% with triple screen,
- 70% (range: 60 - 80) and 95% with quad screen,
- 80% and 85% with first-trimester screen,
- 85% and 99% with integrated screen,
- 94% (range: 86 - 96) and 90% with sequential screen, and
- 69% (range: 30 - 90) and 92% with GS.

Methods used to derive estimates of effectiveness
The authors estimated the rate of acceptance of amniocentesis after an abnormal genetic ultrasound, owing to the lack of published evidence.

Estimates of effectiveness and key assumptions
The rate of acceptance of amniocentesis after an abnormal ultrasound was 70% (range: 50 - 99).

Measure of benefits used in the economic analysis
The benefit measures used were the number of T21 cases detected, the number of T21 live births averted in comparison with no screening, and the number of procedural-related euploid losses. All measures were model outputs.

Direct costs
The unit costs were presented separately from the quantities of resources used for some items, because some costs were given as macro-categories. The health services included in the economic evaluation were screening tests, amniocentesis (procedure and ultrasound), CVS (procedure and ultrasound), counselling, karyotype, GS, curettage, midtrimester pregnancy termination (medication and hospital services), and the lifetime cost of T21. Only counselling given to patients with a positive screen test was considered. In fact, counselling was given to all patients before the screening test and was not taken into consideration in the analysis.

The cost/resource boundary of the patient and the third-party payer was adopted. The costs were estimated from multiples sources, including Physicians' Fee References, two published studies, and local charges (these were multiplied by a factor of 0.6, which represented the local cost-to-charge ratio). Discounting was relevant only for the lifetime costs of T21. However, such a cost was derived from a published study and it was not stated whether any discounting had

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been performed in the primary source. Resource use was based on published data and model assumptions. All the costs were presented in 2002 values using the Consumer Price Index for Medical Care.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
US dollars ($).

**Sensitivity analysis**
Several univariate sensitivity analyses were performed to examine the impact of variations in model inputs on the estimated economic and clinical model outputs. The model inputs varied were:

- the proportion of women requesting an invasive diagnostic procedure after an abnormal screening test,
- the proportion of women choosing to terminate an affected pregnancy,
- the sensitivity of some screening options,
- the proportion of women who would elect to have an amniocentesis performed after an abnormal GS, and
- the procedural-related loss rate for CVS and amniocentesis.

The ranges of values used for the clinical estimates were derived from the literature.

**Estimated benefits used in the economic analysis**
In the cohort of 1,000,000 women, the number of T21 cases detected was 529 with triple screen (365 with GS), 618 with quad screen (426 with GS), 941 with first-trimester screen, 750 with integrated screen, and 1,213 with sequential screen.

The number of T21 live births averted was 366 with triple screen (253 with GS), 427 with quad screen (295 with GS), 490 with first-trimester screen, 520 with integrated screen, and 678 with sequential screen.

The number of number of procedural-related euploid losses was 311 with triple screen (25 with GS), 311 with quad screen (25 with GS), 559 with first-trimester screen, 62 with integrated screen, and 859 with sequential screen.

The analysis showed that, from the perspective of safety (ratio of live births to euploid losses and the inverse), the integrated screen had the most favourable ratios.

**Cost results**
In the cohort of 1,000,000 women, the estimated cost (in millions) was $662 with no screening, $497 with triple screen ($566 with GS), $472 with quad screen ($554 with GS), $486 with first-trimester screen, $521 with integrated screen, and $455 with sequential screen. Therefore, the sequential screen option was the cheapest.

**Synthesis of costs and benefits**
The costs and benefits of the alternative screening strategies were not combined because the sequential screen option
dominated the other options, which resulted in fewer T21 cases detected and fewer T21 live births averted. However, the safety profile for the sequential screen was unfavourable.

The results of the sensitivity analysis confirmed, in general, the dominance of the sequential test. The exceptions were that the quad screen was the preferred option (more cost-effective) if 30 to 69% of women with an affected pregnancy chose termination, or when the sensitivity of first-trimester screening was less than 68.5%.

Authors' conclusions
The sequential screen used for prenatal care before 10 weeks' gestation was the most cost-effective strategy for the identification of foetal aneuplody in women younger than 35 years of age. However, sequential screen was associated with the highest number of procedural-related euploid losses, due to the high false-positive rate, which increased the number of invasive procedures required. The conclusions of the analysis were robust to variations in most model inputs.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was appropriate because the authors covered all screening strategies offered to pregnant women under 35 years of age in the USA. No screening was used as the basic comparator for comparative purposes only. The impact of adding GS was also considered. Each screening option was described in detail. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness analysis came from a review of the literature. However, it was not stated whether the review was systematic. Further, since no information on the design of the primary studies was reported, it is not possible to assess the validity of primary studies. The methods used to extract and combine the primary estimates were unclear. It appears that the choice of some estimates among those reported in the literature was based on authors' opinion. Some assumptions were also made. The issue of uncertainty in the clinical data was explicitly addressed in the sensitivity analysis, where the most uncertain model inputs were varied.

Validity of estimate of measure of benefit
The benefit measures used in the analysis reflected typical outcomes of prenatal screening programmes aimed to identify foetal aneuploidy. Therefore, they are comparable only with the benefits of similar interventions.

Validity of estimate of costs
The authors stated explicitly which perspective was adopted in the study. As such, only the relevant categories of costs were included in the analysis. The unit costs were not presented separately from the quantities of resources used, as the lifetime cost of T21 was derived from a published study and a breakdown of the cost items associated with this category of cost was not reported. Similarly, the authors did not state whether discounting had been applied to the lifetime cost of T21 in the primary study. More detailed information was provided for other categories of costs, namely screening costs. The price year was reported, which aids reflation exercises in other settings. The source of the data was provided and a cost-to-charge ratio was applied when local charges were used. The costs were treated deterministically and were specific to the study setting. No sensitivity analyses were performed on the economic inputs.

Other issues
The authors reported the results of other economic evaluations of prenatal screening programmes and highlighted the differences across the studies. The issue of the generalisability of the study results to other settings was not addressed, which limits the external validity of the analysis. Moreover, sensitivity analyses were performed only on clinical inputs. The analysis was carried out using a modelling approach, but limited information on the decision model was provided. The study referred to women under 35 years of age before 10 weeks' gestation and this was reflected in the conclusions of the study. In particular, the authors noted that the conclusions of their analysis should not be extrapolated to women after 13 weeks' gestation, as they are no longer candidates for first-trimester screening modalities.
Implications of the study
The study results suggested that it was difficult to define an optimal screening approach for the prenatal care of women under 35 years of age before 10 weeks' gestation. From the payer perspective, the sequential screen could be the most cost-effective approach, but the high number of procedure-related euploid losses might affect patient preferences. The authors suggested that individualised screening could be preferable under some circumstances.

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Other publications of related interest


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