Cost-effectiveness model for first-trimester versus second-trimester ultrasound 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
Three screening strategies for Down syndrome (DS) were examined.

First-trimester screening: pregnant women were screened with first-trimester nuchal translucency measurements and the serum analytes pregnancy-associated plasma protein A (PAPP-A) and free b sub-unit of human chorionic gonadotropin (free b-hCG). All positive results underwent further diagnostic evaluation with chorionic villous sampling (CVS).

Second-trimester screening: women were screened with second-trimester genetic sonograms and the serum analytes alpha fetoprotein, HCG and estriol. All positive results underwent further diagnostic investigation with amniocentesis.

Combined first- and second-trimester screening: women were initially screened with first-trimester nuchal translucency measurement and serum analytes, with all positive results undergoing further diagnostic evaluation with CVS. All negative results were subsequently screened again using second-trimester genetic sonograms and serum analytes, with all positive results undergoing further diagnostic investigation with amniocentesis.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of women carrying singleton pregnancies (living intrauterine gestation).

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

Dates to which data relate
The clinical data came from studies published between 1994 and 1999. No dates for the resource use data were explicitly reported. The price year was presumably 2002.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' opinions.

Modelling
Three decision tree models were constructed to assess the economic impact of the three screening algorithms for a hypothetical cohort of 1,000,000 pregnant women. The structure of the trees reflected the pathways described for each screening strategy. The models took the potential impact of foetal death associated with invasive screening tests into consideration, as well as the probability of abortion in case of trisomy 21.

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

- the prevalence of DS,
- the sensitivity of US in the first and second trimesters,
- the mortality rates for CVS and amniocentesis, and
- the false-positive rates for US in the first and second trimesters.

Study designs and other criteria for inclusion in the review
It was not stated whether a systematic review of the literature was undertaken to identify the primary studies. No information on the inclusion or exclusion criteria was provided. The primary studies were not described.

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
Three primary studies appear to have provided clinical data.

Methods of combining primary studies
Not stated.

Investigation of differences between primary studies
Not stated.

Results of the review
The prevalence of DS ranged from 1 in 1,000 to 1 in 10.

The sensitivity of US for DS was 80% in the first trimester and 70% in the second trimester.

The mortality rate was 1% for CVS and 0.5% for amniocentesis.

False-positive rates for first- and second-trimester US varied from 0 to 5%.
Methods used to derive estimates of effectiveness
Authors’ opinions were used to derive some estimates of effectiveness used in the decision model.

Estimates of effectiveness and key assumptions
The following assumptions were made:

- all women with trisomy 21 foetuses would abort;
- all pregnancies were carried to term, except for those lost to complications related to either CVS or amniocentesis and those diagnosed with trisomy 21 terminated by either first- or second-trimester abortion;
- all patients with positive results from first-trimester or second-trimester screening US agreed to undergo either CVS or amniocentesis, respectively.

Measure of benefits used in the economic analysis
It was unclear whether a summary benefit measure was used in the economic analysis and combined with the costs. The model outputs reported were the number of false positives, cases of trisomy 21, iatrogenic deaths and trisomy deaths.

Direct costs
The cost analysis was carried out from the perspective of the third-party payer. The health services included in the economic evaluation were US, PAPP-A and free b-hCG, CVS, abortion, other serum analyses and amniocentesis.

The unit costs were reported separately from the quantities of resources used for some items. The costs were estimated using Medicare reimbursement rates for Washington State using Current Procedural Terminology codes, relative value units including professional and institutional components, and payments for first-trimester and second-trimester US, CVS, amniocentesis and serum analyses. The tests were performed sequentially, until either a diagnosis was made or the algorithm was complete. Some assumptions were made to derive resource use data. It was assumed that the cost for foetal losses secondary to CVS and amniocentesis was the same as the cost for first- or second-trimester miscarriages or abortions. The costs for maternal complications from CVS and amniocentesis, predominately infections and bleeding, were assumed to be have been equal. Discounting was not relevant since the costs were incurred during a short timeframe. The price year might have been 2002.

Statistical analysis of costs
No statistical analyses of the costs were performed.

Indirect Costs
The indirect costs were not considered in the economic evaluation.

Currency
US dollars ($).

Sensitivity analysis
The use of sensitivity analyses was not explicitly stated, but the authors investigated the impact of changes in prevalence rates and the sensitivity of initial screening US on model outputs. The authors appear to have set the ranges of values used.

Estimated benefits used in the economic analysis
In a hypothetical cohort of 1,000,000 pregnant women and at a prevalence rate of 0.001, there were 50,000 false positives, 800 cases of trisomy 21, 1,000 iatrogenic deaths and 16 trisomy deaths with first-trimester screening. When second-trimester screening was added there were 47,460 false positives, 140 cases of trisomy 21, 237 iatrogenic deaths and 1 trisomy death. The outcomes associated with different prevalence rates were only reported graphically. In general, the number of iatrogenic foetal deaths decreased for all screening strategies as the prevalence of DS increased and the number of false positives decreased.

**Cost results**
The total costs of first-trimester screening, second-trimester screening and combined first- and second-trimester screening were, respectively:

- $398,665 (first), $560,236 (second) and $3,056,788 (combined) at a prevalence rate of 0.001;
- $40,142 (first), $56,223 (second) and $304,150 (combined) at a prevalence rate of 0.01; and
- $4,290 (first), $5,821 (second) and $28,886 (combined) at a prevalence rate of 0.1.

The cost per diagnosis associated with different prevalence rates of DS was only reported graphically. In general, the cost per diagnosis decreased for all strategies as the prevalence of DS increased.

**Synthesis of costs and benefits**
It was unclear whether the costs and benefits were combined.

The sensitivity analysis showed that, regardless of the sensitivity of initial screening US, first-trimester screening remained the cheapest strategy. Even assuming a 100% sensitivity of second-trimester US, the sensitivity of first-trimester US would have to fall below an unrealistic 55% before second-trimester US would become more cost effective than first-trimester US screening.

At a prevalence below 0.1, iatrogenic foetal deaths per diagnosis of DS and total iatrogenic foetal deaths were substantially higher for first-trimester screening and combined screening than for second-trimester screening. At a prevalence of 0.001, iatrogenic foetal deaths exceeded total diagnosed cases of DS within first-trimester screening and combined screening. In general, regardless of prevalence, second-trimester screening always had substantially lower iatrogenic foetal deaths than total diagnosed cases of DS.

**Authors' conclusions**
The use of a combination of first- and second-trimester ultrasound (US) screening led to substantially increased numbers of iatrogenic foetal deaths per diagnosis of Down syndrome (DS). However, it was unclear which strategy was optimal since first-trimester US screening could not completely replace second-trimester US, which is useful also for the detection of major abnormalities. The authors noted that a possible solution could be contingency testing, whereby US is offered only to women with abnormal serum pregnancy-associated plasma protein A (PAPP-A) and free b subunit of human chorionic gonadotropin (free b-hCG). Overall, the authors pointed out that second-trimester US, although possibly more expensive, could "be more applicable to women under the age of 45 years because of what would appear to be the overall increased sensitivity for detecting both genetically and nongenetically associated abnormalities and because of the overall reduced normal fetal death rate compared with first-trimester screening".

**CRD COMMENTARY - Selection of comparators**
The authors justified their choice of the comparators, which represented actual and proposed screening strategies for the detection of DS. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence came from the literature. However, the methods and conduct of the review were not...
reported. No information on the search and inclusion or exclusion criteria was provided. The number of studies included in the review was reported, but the primary studies were not described. Thus, it was not possible to assess the validity of the primary sources of data. Some assumptions were also made to derive clinical data that were not available from the literature. The issue of uncertainty was not extensively addressed in the sensitivity analysis since only a few clinical parameters were varied.

Validity of estimate of measure of benefit
It was unclear whether a summary benefit measure was used. However, if one of the model outputs was used (i.e. cases of trisomy 21 detected), it would have been specific to the disease considered in the study and, therefore, not comparable with the benefits of other health care interventions.

Validity of estimate of costs
The categories of costs included in the analysis were consistent with the perspective adopted in the study. A detailed breakdown of the cost items was provided, but there was limited information on the quantities of resources used. The authors justified their exclusion of some costs. The unit costs were reported for most items. The sources of the data were given. The price year was reported, which aids reflation exercises in other time periods. The costs were treated deterministically and no sensitivity analyses were carried out on the cost estimates. Discounting was not relevant and was not applied.

Other issues
The authors stated that their findings were consistent with those from published studies. In particular, the authors noted that a prior analysis had included the cost for the care of surviving trisomy 21 foetuses. The inclusion of such costs could bias the results of the analysis since the lifetime care of an individual with DS costs proportionately too much in comparison with the cost associated with the screening programme. Further, such models should also account for the potential positive contributions of individuals with DS to society. In terms of the generalisability of the study results to other settings, the authors stated that the cost data reflected US rates, and thus should be transferable to settings comparable with those considered in the current study.

The authors noted some limitations to the validity of their study. For example, the analysis did not take the diagnosis of chromosomal abnormalities not related to trisomy 21 into consideration. Similarly, the costs associated with morbidity from CVS and amniocentesis were not considered. The impact of practitioner expertise was also not considered.

Implications of the study
The study results suggested that second-trimester screening should be regarded as the optimal screening option for pregnant women, although the results of ongoing trials (i.e. the National Institutes of Health-funded First and Second Trimester Estimate of Risk multicenter trial) would affect the cost-effectiveness of first-trimester screening in comparison with second-trimester screening. The authors stated that patients should be informed about the risks of foetal loss associated with each screening option, as this piece of information could influence the choice of the optimal screening strategy.

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Other publications of related interest


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