Cost utility of prenatal diagnosis and the risk-based threshold
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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 authors compared chorionic villus sampling (CVS) and amniocentesis with no invasive testing for the screening of Down's syndrome, or another chromosomal abnormality, in pregnant women of all ages and risk levels.

Type of intervention
Diagnosis.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of pregnant women of all ages and risk levels.

Setting
The study 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 1983 and 2000. The cost data were mainly derived from studies published between 1994 and 1995. The price year was 2003.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies.

Modelling
A decision analytic tree model was built to assess the cost-utility of CVS and amniocentesis, compared with no diagnostic testing, for pregnant women of all ages and risk levels. The time horizon of the model covered the life expectancy of the pregnant women starting from the tenth week of pregnancy. Six possible health states were considered, including:

- birth of a baby not affected by chromosomal disorder,
- birth of a baby affected by chromosomal disorder,
- miscarriage,
- elective abortion after positive test results, and
- future birth after a pregnancy loss.
The model considered three hypothetical cohorts of women of 20, 35 and 44 years of age.

**Outcomes assessed in the review**
The outcomes assessed were:

- trisomy risk at week 10 of pregnancy;
- miscarriage excess risk of amniocentesis compared with no testing;
- miscarriage risk of CVS compared with amniocentesis;
- the sensitivity and specificity of amniocentesis and CVS;
- the probabilities of future birth after amniocentesis and miscarriage, CVS and miscarriage, amniocentesis and elective abortion, and CVS and elective abortion;
- the probability of requiring amniocentesis due to CVS diagnostic uncertainty;
- the probability of elective abortion after abnormal results;
- the probability of limb abnormality after CVS, and

the utilities of: unaffected birth after testing and having normal results, unaffected birth after no test, future unaffected birth after testing and miscarriage, no future birth after testing and miscarriage, future unaffected birth after testing and elective abortion, no future birth after testing and effective abortion, affected by limb abnormality after testing and normal results, and trisomy.

**Study designs and other criteria for inclusion in the review**
The authors reported that they primarily relied on randomised controlled trials (RCTs) to provide data where possible. Otherwise, case series, case-control and observational studies were considered for inclusion in the review.

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

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

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

**Number of primary studies included**
Approximately 14 primary studies were included in the review.

**Methods of combining primary studies**
The method used to combine the primary studies was not explicitly reported. However, the authors reported that where trials were combined, they used a broad range consisting of the upper and lower 95% confidence intervals from the contributing studies. For test performance parameters, the authors reported that they had weighted the estimates by the number of patients tested.
Investigation of differences between primary studies
It was unclear whether the authors investigated any differences between the primary studies.

Results of the review
The trisomy risk at week 10 of pregnancy was 0.58% (range: 0.19 to 22).

The miscarriage excess risk of amniocentesis compared with no testing was 0.75% (range: 0.27 to 1.47).

The miscarriage risk of CVS compared with amniocentesis was 1.4% (range: 0.5 to 4.44).

The sensitivity of amniocentesis was 99.32% (range: 98.6 to 100) and the specificity was 99.86% (range: 99.8 to 100).

The sensitivity of CVS was 98.47% (range: 97.5 to 100) and the specificity was 99.83% (range: 99.5 to 100).

The probability of future birth was 40.9% (range: 20 to 60) after amniocentesis and miscarriage, 50.0% (range: 30 to 70) for CVS and miscarriage, 32.8% (range: 20 to 60) for amniocentesis and elective abortion, and 27.9% (range: 15 to 55) for CVS and elective abortion.

The probability of requiring amniocentesis due to CVS diagnostic uncertainty was 6.48% (range: 2.95 to 8.6).

The probability of elective abortion after abnormal results was 92.9% (range: 60.0 to 95).

The probability of limb abnormality after CVS was 0.0058% (range: 0 to 0.096).

The utilities were:

- 0.923 (range: 0.62 to 1) for unaffected birth after testing and having normal results;
- 0.918 (range: 0.63 to 1) for unaffected birth after no test;
- 0.870 (range: 0.51 to 1) for future unaffected birth after testing and miscarriage;
- 0.700 (range: 0.18 to 1) for no future birth after testing and miscarriage;
- 0.836 (range: 0.40 to 1) for future unaffected birth after testing and elective abortion;
- 0.692 (range: 0.13 to 1) for no future birth after testing and elective abortion;
- 0.900 (range: 0.41 to 1) for affected by limb abnormality after testing and normal results; and
- 0.672 (range: 0.13 to 1) for trisomy.

Measure of benefits used in the economic analysis
The measure of benefits used was the quality-adjusted life-years (QALYs) gained. The utility data were derived from a time trade-off utility assessment of 534 English-, Spanish-, or Chinese-speaking pregnant women, aged 16 to 47 years. Using this approach, the utilities were derived for seven health states (see ‘Results of the Review’ section).

Direct costs
The direct costs included in the analysis were those of the health care system. These included laboratory costs, physician fees, inpatient costs, the costs of the diagnostic test (i.e. CVS and amniocentesis), and all future health care costs for the pregnant women. The authors did not include the costs associated with Down's syndrome in the base-case. However, these costs were included in the sensitivity analysis. Laboratory costs and physician fees were derived from Medicare schedules. Inpatient costs were derived from hospital charges, which were then converted into costs using appropriate cost-to-charge ratios. As the costs could be incurred over the lifetime of a woman, they were appropriately
discounted using an annual rate of 3%. The study reported the average costs. The price year was 2003.

**Statistical analysis of costs**
The costs were treated as point estimates (i.e. the data were deterministic).

**Indirect Costs**
Although the authors reported that a societal perspective was adopted, the indirect costs were not included in the analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
The authors performed one-way, multi-way and Monte Carlo sensitivity analyses on all model variables using the ranges reported in the literature. In the multi-way analysis, the authors varied two to eight related variables concurrently, and created relevant clinical scenarios.

**Estimated benefits used in the economic analysis**
The QALYs gained with each diagnostic intervention were as follows:

- for pregnant women aged 20 years, 24.13 with CVS, 24.16 with amniocentesis, and 24.08 with no testing;
- for pregnant women aged 35 years, 20.35 with CVS, 20.396 with amniocentesis, and 20.30 with no testing; and
- for pregnant women aged 44 years, 17.03 with CVS, 17.08 with amniocentesis, and 16.98 with no testing.

**Cost results**
The lifetime costs associated with giving each diagnostic intervention to pregnant women were as follows:

- for pregnant women aged 20 years, $54,180 with CVS, $54,080 with amniocentesis, and $52,940 with no testing;
- for pregnant women aged 35 years, $61,590 with CVS, $61,490 with amniocentesis, and $60,360 with no testing; and
- for pregnant women aged 44 years, $59,020 with CVS, $59,020 with amniocentesis, and $57,890 with no testing.

**Synthesis of costs and benefits**
The costs and benefits were combined using an incremental cost-utility ratio (i.e. the additional cost per QALY gained when one intervention is compared with another).

For pregnant women aged 20 years, when amniocentesis was compared with no testing, the additional cost per QALY gained was $14,200. Further, when CVS was compared with amniocentesis, CVS was dominated (i.e. it was both less effective and more costly than amniocentesis).

For pregnant women aged 35 years, when amniocentesis was compared with no testing, the additional cost per QALY gained was $12,600. When CVS was compared with amniocentesis, CVS was dominated.

For pregnant women aged 44 years, when amniocentesis was compared with no testing, the additional cost per QALY gained was $11,300. When CVS was compared with amniocentesis, CVS was dominated.
The results of the sensitivity analysis showed that the inclusion of the future costs of Down's syndrome had no effect on the results, nor did varying the discount rate. The analysis was, however, sensitive to small changes in the difference in women's utilities for the two most commonly experienced outcomes: undergoing diagnostic testing, obtaining normal results and giving birth to a chromosomally normal child; and not undergoing testing and then giving birth to a normal child.

Authors' conclusions
Prenatal testing for chromosomal disorders was cost-effective, irrespective of maternal age or risk of carrying an affected foetus.

CRD COMMENTARY - Selection of comparators
The authors reported that prenatal testing guidelines currently recommend either offering amniocentesis or CVS to women aged 35 years or older, or who at risk of giving birth to an infant with a chromosomal abnormality. Consequently, the authors compared these two diagnostic interventions, together with no testing, for women aged 20, 35 and 44 years old. The authors did not independently assess the cost-utility of maternal serum or ultrasonographic screening for Down's syndrome. You should decide if the diagnostic strategies considered in the study represent current practice in your own setting.

Validity of estimate of measure of effectiveness
The authors did not report that a systematic review of the literature was undertaken to identify all relevant research and minimise biases. Despite this, the authors conducted what appears to be a comprehensive and exhaustive review of the literature, as they included 14 primary studies in their review which were reported to be the best available evidence. The majority of these studies were RCTs, if well conducted, are considered to be the 'gold-standard' study design when comparing health interventions. One limitation reported by the authors was that, owing to the lack of RCTs to populate every parameter in the model, data from non-randomised studies had to be used to estimate some parameters. The authors appear to have combined some relevant parameters using a meta-analysis.

Validity of estimate of measure of benefit
The estimation of benefits was modelled using a decision analytic tree model, which was appropriate. The utility measures used to derive QALYs were derived from a study that considered a large sample of what appears to have been representative pregnant women.

Validity of estimate of costs
Although the authors reported that the costs were estimated from a societal perspective, the indirect costs (i.e. productivity losses due to early mortality or sickness) were not included in the analysis. Therefore, the perspective used in the analysis was effectively that of the health care system. The authors appear to have included most of the relevant costs in their analysis. Although they did not include the costs of Down's syndrome in the base-case, the authors included these costs in the sensitivity analysis and found that they did not affect their conclusions. The costs and the quantities were not reported separately, which will limit reflation exercises in other settings. The costs were derived from a number of published sources, but the majority were derived from Medicare schedules. All charges were appropriately converted to costs using cost-to-charge ratios, so as to estimate the true cost of providing each service. Since the costs were incurred over the lifetime of the women, all future costs were appropriately discounted. The price year was reported, which will ease any future inflation exercises.

Other issues
The authors reported that no prior economic analysis on prenatal testing has focused on assessing whether a population-based threshold for diagnosis should be used. The issue of generalisability to other settings was addressed in the exhaustive sensitivity analyses that the authors performed. The authors did not present their results selectively and their conclusions reflected the scope of the analysis. As a further limitation to their study, the authors reported that they only
considered autosomal trisomies in their analysis. According to the authors, the inclusion of other disorders in the analysis would make the diagnostic strategies even more cost-effective.

**Implications of the study**
The authors recommended that prenatal diagnostic testing should be offered to pregnant women of all ages and irrespective of risk. In addition, guidelines should also emphasise the important role of individual preference when making decisions about prenatal diagnostic testing.

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