Health technology
The study examined nine strategies for prenatal screening for Down syndrome (DS). These were no screening, nuchal translucency (NT) alone and with first-trimester serum screening (NTSS), first-trimester serum screening (FSS), quadruple test screen (QUAD), integrated screening (ICS), integrated serum screening (ISS), sequential screening (SEQ) and maternal age (diagnostic test offered only to women aged 35 years or older).

With FSS, free beta-human chorionic gonadotropin (hCG) and pregnancy associated plasma protein-A levels were assessed. NTSS consisted of a combination of both serum and sonographic screening.

QUAD evaluated alpha-foetoprotein, unconjugated estriol, beta-hCG and dimeric inhibin-A.

ICS consisted of a combination of NTSS and QUAD, with combined results given once in the second trimester.

ISS was a combination of FSS and QUAD.

SEQ consisted of NTSS and QUAD, with combined results given serially in the first and second trimesters, respectively.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of pregnant women in the first and second trimesters of pregnancy.

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

Dates to which data relate
The clinical data were derived from studies published between 1990 and 2004. Some costs and much of the resource use data were derived from studies published between 2000 and 2004. The price year was 2004.

Source of effectiveness data
The clinical and epidemiological model inputs used in the decision model were:

the sensitivity and specificity of the screening strategies,
the prevalence of DS,

the loss rates,

the acceptance rates for invasive procedures,

the age distribution of the women, and

the pregnancy termination rate.

**Modelling**
A decision analytic model was used in a hypothetical cohort of 1 million pregnant women presenting before 11 weeks' gestation. The pathways depended on the screening test results. It was assumed that patients with negative genetic screen results, regardless of whether these were true or false negatives, did not undergo invasive prenatal testing and would therefore have rates of a normal neonate or a DS neonate as potential outcomes. Patients with positive screening results, regardless of whether they were true or false, accepted invasive genetic testing at a constant acceptance rate. However, further details of the model were not given.

**Sources searched to identify primary studies**
The clinical data were derived from published studies that were not described. The authors stated that the level of evidence used to derive data on screening accuracy was medium and worst. No best level evidence was included as a source of data. Some assumptions were also made.

**Methods used to judge relevance and validity, and for extracting data**
A systematic review of the English literature was performed to identify relevant sources of data. Details of this review were not given. The authors did not provide extensive information about the methods used to combine the published evidence, but said that average values were generally used.

**Measure of benefits used in the economic analysis**
The summary benefit measure used in the economic modelling was the number of DS cases. This was estimated using a modelling approach. Other model outputs, which were not combined with the costs, included the number of DS live births, procedure-related euploid losses, and the ratio of DS cases averted and euploid losses.

**Direct costs**
The viewpoint of the analysis was not clear. The cost categories included in the study were the costs of screening options, chorionic villus sampling, amniocentesis, pregnancy termination, genetic sonogram and management of DS. A breakdown of the cost items was not given for all categories. The costs were mainly derived from local sources or published studies. Some Medicare reimbursement rates were also used. Hospital charges were adjusted by a cost-to-charge ratio for the Commonwealth of Pennsylvania. Patterns of resource consumption were presumably based on published studies and authors' assumptions. Discounting was relevant, as the long-term costs were evaluated, and an annual rate of 3% was used. The price year was 2004. Previous costs were inflated to 2004 values using annual inflation rates.

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

**Indirect Costs**
Productivity costs do not appear to have been included.
Currency
US dollars ($).

Sensitivity analysis
A deterministic sensitivity analysis was performed to assess the robustness of the base-case results of the decision model to variations in the clinical and economic parameters. The parameters were varied around estimates found in the literature. Both one- and multi-way sensitivity analyses were carried out. In an alternative scenario, the cost of a genetic sonogram was incorporated into second-trimester screening.

Estimated benefits used in the economic analysis
In the hypothetical cohort of 1 million pregnant women, the expected number of DS cases detected was 0 with no screening, 906 with NT alone, 706 with FSS, 965 with NTSS, 824 with QUAD, 1,000 with ISS, 1,106 with ICS, 1,118 with SEQ, and 353 with maternal age.

The expected number of DS live births averted was 0 with no screening, 634 with NT alone, 494 with FSS, 675 with NTSS, 577 with QUAD, 700 with ISS, 774 with ICS, 783 with SEQ, and 247 with maternal age.

The expected number of procedure-related euploid losses was 0 with no screening, 588 with NT alone, 490 with FSS, 490 with NTSS, 263 with QUAD, 158 with ISS, 263 with ICS, 980 with SEQ, and 490 with maternal age.

The ratio of DS cases averted and euploid losses was 0 with no screening, 1.1 with NT alone, 1.0 with FSS, 1.9 with NTSS, 2.2 with QUAD, 4.4 with ISS, 2.9 with ICS, 0.80 with SEQ, and 0.50 with maternal age.

Thus, SEQ and maternal age screening were associated with a higher number of euploid losses than DS cases averted, while ISS was associated with a higher number of DS live births averted with respect to euploid losses.

Cost results
The total population cost (in millions) of the different strategies in a hypothetical cohort of 1 million pregnant women was $1,029 with no screening, $175 with NT alone, $183 with FSS, $242 with NTSS, $256 with QUAD, $312 with ISS, $389 with ICS, $429 with SEQ, and $78 with maternal age.

Synthesis of costs and benefits
The costs and benefits were combined by calculating an average cost-effectiveness ratio (ACER). This was defined as the cost per DS case (live birth) averted.

Under base-case assumptions, the ACER was $27,603 with NT alone, $37,045 with FSS, $35,851 with NTSS, $44,367 with QUAD, $44,571 with ISS, $50,258 with ICS, $54,789 with SEQ, and $315,789 with maternal age.

All screening strategies were dominant in comparison with no screening.

When an incremental analysis was performed (data not shown), the cost-effectiveness results suggested that the preferred strategy was ISS because cheaper options such as NT alone, FSS or NTSS had lower DS detection rates and higher numbers of procedure-related losses.

The sensitivity analysis showed that the base-case results were stable over plausible variations of model inputs. Only when the cost of NT fell below $57 did the NTSS strategy become the most cost-effective. Also, in a scenario in which the cost of genetic sonogram was incorporated into the second trimester, NTSS became the preferred option.

Authors' conclusions
Integrated serum screening (ISS) was the most cost-effective screening strategy for Down syndrome (DS) when
considering costs, DS cases detected and rates of procedure-related euploid losses. This conclusion was robust. The authors pointed out that an advantage of ISS was that it avoids the technical and logistical difficulties of nuchal translucency (NT) measurements. However, a drawback of ISS was that "results are held until the second trimester (an average of 3-4 weeks), which may be unacceptable to some women”.

CRD COMMENTARY - Selection of comparators
This study considered a wide range of screening tests order to cover all possible strategies for prenatal assessment of DS. All of the strategies were described. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The authors stated that a systematic search for data was undertaken to identify relevant studies with which to populate the decision model. However, the methods and conduct of the review were not reported. It was only stated that average values were selected from amongst those found in the literature. Further, the level of evidence extracted from the studies was generally low, which limits the validity of the clinical estimates. The authors conducted sensitivity analyses on key model parameters (test accuracy, termination rate, acceptance rate for invasive test etc.) to take account of the variability around point estimates.

Validity of estimate of measure of benefit
The benefit measure was modelled using published data. The number of cases of DS avoided represents a natural outcome of screening strategies and is commonly used in screening studies. However, it cannot be compared with the benefits of other health care interventions.

Validity of estimate of costs
The costs analysis appears to have been restricted to the inclusion of direct medical costs, although the authors stated that a societal perspective was adopted. The unit costs and resource quantities used were presented separately only for screening tests. Other costs, especially the cost of DS, were reported as macro-categories. Thus, a breakdown of the cost items was not given. Most of the costs came from published studies, which were not described. However, the authors stated that Medicare costs were used whenever possible, and these costs are an accurate estimate of service costs. Discounting was relevant and was appropriately performed. The authors reported the price year, which has implications for the generalisability of the study results in other time periods. Statistical analyses were not carried out, but the impact of variations of some cost items was investigated in the sensitivity analysis.

Other issues
The authors reported the findings from other studies that had reported contrasting results. Some possible explanations for these discrepancies were discussed. The issue of the generalisability of the study results to other settings was implicitly addressed in the sensitivity analysis, in which alternative estimates were considered. The authors noted that one key limitation of the analysis was the uncertainty surrounding some estimates of accuracy of tests such as FSS, ISS, ICS, and SEQ, given the fact that these are novel tests. However, plausible ranges of variations were considered in the sensitivity analysis. Another issue arising from the analysis was the fact that the study focused on DS, thus the results of the study cannot be extrapolated to all trisomies.

Implications of the study
The study results support the use of ISS as the most cost-effective screening strategy for DS.

Source of funding
None stated.

Bibliographic details

PubMedID
Other publications of related interest

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