Second trimester screening for Down's syndrome using maternal serum dimeric inhibin A

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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 study compared maternal serum dimeric inhibin A, both alone and in combination with other serum markers, to existing screening methods (maternal age and serum measurements of alpha fetoprotein, unconjugated oestriol and human chorionic gonadotrophin) to detect second trimester Down's syndrome.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The authors did not report details of the study population. However, the aim of the evaluation implies that the study population whose treatment decisions would be affected comprised pregnant women in the second trimester.

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

Dates to which data relate
The dates of the effectiveness evidence, resources used and prices used were not reported.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
The authors apply unit costs of tests and diagnosis to the study sample to predict the allowable cost of adding the additional screen. The authors did not report whether the cost data used were derived from observations for the women included in the study sample.

Study sample
No power calculations were reported. The study sample comprised maternal serum samples from women with second trimester pregnancies (gestational age 14-21 completed weeks) and a diagnosis of Down's syndrome (cases). The patients were taken from those enrolled in a previous multi-centre cohort study of women having a scheduled second trimester amniocentesis and who provided serum samples. 5,385 women provided informed consent before a scheduled second trimester amniocentesis and serum samples were obtained and stored. A total of 52 cases and 256 control samples were selected for analysis. The authors did not report whether the samples comprised all available samples or a
The method of sample selection was not reported. Each case was matched with five serum samples from the pool of pregnancies with normal karyotype (controls). The following variables were used for matching: recruitment centre; completed week of gestation; month of enrolment; and maternal age. The authors noted that 4 of the control samples selected were not available. The authors reported that possible biases in sample selection were eliminated by the fact that all pregnancies were karyotyped in the second trimester, and that the indications for amniocentesis did not include abnormal screening results.

Study design
This was a multi-centre, case-control study. The number of centres involved was not reported. The duration of follow-up or loss to follow-up was not reported. The assessment of outcomes was blinded. Assays were performed without knowledge of whether the sample was from a case or control pregnancy.

Analysis of effectiveness
The method of analysis of the clinical study was not reported. The primary outcome used in the analysis was the screening performance of dimeric inhibin A (alone or in combination with other serum markers) to detect Down's syndrome. Dimeric inhibin A was measured in duplicate using a solid phase sandwich enzyme linked immunosorbent assay. The methods for measuring the other serum markers (alpha-fetoprotein, unconjugated oestriol, and human chorionic gonadotrophin and its free beta subunit) were not reported in this study. The case and control groups differed with respect to gestational age. Gestational age specific median values for dimeric inhibin A were computed using measurements from the controls. Individual assay measurements were then converted to multiples of the median (MOM) and adjusted for maternal weight using a published method. This method was not reported.

Effectiveness results
The effectiveness results were as follows:

At a 5% false positive rate, the combination of maternal age and dimeric inhibin A identified 52% of Down's syndrome pregnancies.

Adding alpha-fetoprotein increased the detection rate to 68%.

A triple test of alpha-fetoprotein, unconjugated oestriol and dimeric inhibin A increased the detection rate to 73%.

A four-marker test had the highest detection rate of 75%.

The false positive rate for the triple test at a 70% detection rate was 4.2%.

The four-marker test had a false positive rate of 3.4%.

Clinical conclusions
The authors concluded that this study confirmed the results of previous studies indicating that dimeric inhibin A is among the best second trimester maternal serum markers for the detection of Down's syndrome. In contrast with other serum markers the levels of dimeric inhibin A do not vary with gestational age during the second trimester.

Modelling
A published model, that was not described, was used to estimate the reliability of Down's syndrome screening performance for dimeric inhibin A, both alone and in combination with other serum markers.

Measure of benefits used in the economic analysis
No summary measure of benefit was reported in this study. The outcomes were reported in a disaggregated way and as such, a cost-consequence analysis was performed.
Direct costs
Quantities and costs were not reported separately and the types of costs included in this study were not clearly reported. The authors reported that they estimated the maximum cost at which the addition of dimeric inhibin A to a screening programme would be cost neutral. This was estimated as the savings in amniocentesis costs resulting from the reductions in false positives achieved by adding dimeric inhibin A while holding the detection rate constant. The cost of added screening costs was set equal to the savings made by reducing the number of diagnostic tests (310 fewer amniocenteses and karyotypes). The detection rate was set at 70% and a 6.5% false positive rate without and 3.4% with dimeric inhibin A. In the baseline analysis, diagnostic testing was assumed to cost $1,000. The authors did not report the methods or data used to estimate the quantities and costs; the source of quantity and cost data; the time horizon for the study; the dates when the quantity of resources were measured; or the price year. Discounting was not carried out due to the short time frame of the study (less than one-year).

Statistical analysis of costs
There was no statistical analysis of costs.

Indirect Costs
No indirect costs were reported in this study and, as the study perspective was not reported, it is not possible to assess whether their omission was justified.

Currency
US dollars ($). No conversion rate was reported.

Sensitivity analysis
A one-way sensitivity analysis on the cost of diagnostic testing, uptake of amniocentesis and number of serum markers was reported.

Estimated benefits used in the economic analysis
See effectiveness results above.

Cost results
The authors reported that the allowable additional cost of adding dimeric inhibin A to a screening programme was $31 per woman tested. The allowable cost varied according to the detection rate, method of dating and serum markers chosen and ranged between $16 and $39. No total intervention costs or comparator costs were reported.

Synthesis of costs and benefits
The estimated benefits and costs were not combined.

Authors’ conclusions
The authors concluded that adding dimeric inhibin A measurements to existing multiple marker screening programmes would be cost-effective if the added expense of the test were less than $31 per pregnancy tested.

CRD COMMENTARY - Selection of comparators
The selection of comparators was supported by published evidence from the USA and seemed to reflect clinical practice in this health care setting. However, at the time of this paper being published (1998) there were no assays for dimeric inhibin A licensed for use in the USA. Furthermore, decision-makers should consider carefully whether
dimeric inhibin A, either alone or in combination with other serum markers, does reflect screening options for the detection of Down's syndrome in the UK.

**Validity of estimate of measure of effectiveness**

The study assessed the effectiveness of dimeric inhibin A in terms of detecting Down's syndrome in maternal serum samples from Down's syndrome pregnancies. These were compared with serum samples from unaffected pregnancies. The serum samples for the study were selected from a dataset of samples collected for a different multi-centre cohort study. The authors reported the advantages of the dataset to be:

- all pregnancies were karyotyped in the second trimester, eliminating the possibility of biased sampling;
- the indications for diagnostic testing in the original study did not include abnormal screening test results (which would have biased the sample and estimation of analyte levels in the cases and controls);
- the other serum marker measurements were made on fresh samples over the a two year period when the samples were collected; and
- gestational dating based on last menstrual period and biparietal diameter data allowed accurate direct comparison of screening performance.

However, the authors did not report sufficient information about the study sample, method of selection, the power to detect statistically significant differences with the sample size used or methods of measurement and analysis. This means that it is not possible to assess either the level of uncertainty of the results or whether the study sample was representative of the study population.

**Validity of estimate of measure of benefit**

This study made no assessment of benefit from adding dimeric inhibin A to patient health gain. The analysis was therefore a cost-consequences study.

**Validity of estimate of costs**

No information was provided on the types or quantities of resource use or the data source for unit costs. This study presented an exploratory analysis of costs to determine the maximum acceptable cost of additional testing. This was set equal to the savings from reduced costs of diagnosis using amniocentesis.

**Other issues**

The authors reported that the results of the study confirmed previous results. However, the economic evaluation did not report adequate details about the study perspective, time horizon, costing methods or synthesis of costs and outcomes. These omissions limit the extent to which the generalisability of the findings of this study to other clinical settings and the NHS can be assessed. However, the stated aim of this study did not include formal economic evaluation. The cost analysis reported in this study was only referred to in the results and did not feature in the methods section of the paper. Therefore, the cost data presented seem to be additional information that was not part of the original study design.

**Implications of the study**

The authors recommend that dimeric inhibin A should be added to, or possibly could be substituted for, an existing serum marker in prenatal screening programmes for Down's syndrome. However, the unavailability of kits with Food and Drug Administration approval is one barrier to the implementation of this assay in the USA. You, as a user of this database should consider the authors' conclusions about cost-effectiveness in the context of practice in your own setting and the limitations of the study outlined above.