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Screening for Down's syndrome: effects, safety, and cost effectiveness of first and second trimester strategies

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Objective

To compare the effects, safety, and cost effectiveness of antenatal screening strategies for Down's syndrome.

Design

Analysis of incremental cost effectiveness.

Setting

United Kingdom.

Main outcome measures

Number of liveborn babies with Down's syndrome, miscarriages due to chorionic villus sampling or amniocentesis, healthcare costs of screening programme, and additional costs and additional miscarriages per additional affected live birth prevented by adopting a more effective strategy.

Results

Compared with no screening, the additional cost per additional liveborn baby with Down's syndrome prevented was £22 000 for measurement of nuchal translucency. The cost of the integrated test was £51 000 compared with measurement of nuchal translucency. All other strategies were more costly and less effective, or cost more per additional affected baby prevented. Depending on the cost of the screening test, the first trimester combined test

and the quadruple test would also be cost effective options.

Conclusions

The choice of screening strategy should be between the integrated test, first trimester combined test, quadruple test, or nuchal translucency measurement depending on how much service providers are willing to pay, the total budget available, and values on safety. Screening based on maternal age, the second trimester double test, and the first trimester serum test was less effective, less safe, and more costly than these four options.

What is already known on this topic

Screening strategies that combine nuchal translucency measurement with serum testing perform better than either of these tests used alone

Serum testing in the second trimester using the triple test is cost effective compared with screening based on maternal age

What this study adds

The integrated test is the most effective, safest, and most expensive strategy

The choice of screening strategy should be between the integrated test, first trimester combined test, quadruple test, or measurement of nuchal translucency

Screening based on maternal age, the second trimester double test, and the first trimester serum test is less effective, less safe, and more costly than the above options

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Introduction

The provision of screening services in the NHS lags far behind advances in performance of screening tests over the past decade.¹ In 1998, 57% of antenatal care providers offered the second trimester double test for Down's syndrome and 8% offered screening based only on maternal age.² Few NHS providers offered the more effective nuchal translucency measurement (7%) or quadruple test (3%). The integrated test, which is the most effective screening test and involves testing in the first and second trimesters,³ is available only privately.

The main considerations for providers of screening for Down's syndrome should be minimising the risk of babies with Down's syndrome being missed by the test, reducing miscarriage due to amniocentesis or chorionic villus sampling, and costs. We therefore compared the effects, safety, and cost effectiveness of nine strategies currently available for screening for Down's syndrome in the United Kingdom.

Methods

Decision model

We compared no screening with nine screening strategies offered in the first or second trimesters (table 1). Prenatal diagnosis included abdominal chorionic villus sampling before 15 weeks' gestation or amniocentesis thereafter if screening indicated a greater than 1 in 300 risk of Down's syndrome. We determined the number of liveborn children with and without Down's syndrome, pregnancy losses (including terminations, spontaneous losses, and miscarriages due to chorionic villus sampling or amniocentesis), and the healthcare cost of the screening programme in 10 000 women with the age distribution of women delivering in England and Wales in 1995.

Model estimates

Estimates used in the model are based on a systematic review,¹ other published sources, and discussions with a reference group of UK service providers and users (see acknowledgements). We assumed that 100% of women

attend antenatal clinic between 10 and 14 completed weeks of gestation (median 12 weeks gestation) and are offered tests in the first trimester or between 15 and 19 weeks (median 15 weeks) for tests in the second trimester. Table 1 gives the time required for counselling and for processing of screening and diagnostic tests and the proportion of women accepting procedures.

Based on the age specific prevalence of pregnancies affected by Down's syndrome at 10 and 16 weeks' gestation and at term,^{6,10} we took account of the weekly risk of spontaneous fetal loss in affected and unaffected pregnancies. Overall, we estimated that 45% of affected fetuses would be spontaneously lost between 10 weeks' gestation and term. The test characteristics for nuchal translucency measurements were derived from a study of 326 affected fetuses and 95 476 unaffected fetuses,^{4,11} adjusted for verification bias due to termination of affected fetuses who would otherwise have been spontaneously lost.⁴

The test characteristics for all serum tests were derived from the analysis of stored serum samples from 77 women with affected pregnancies and 385 with unaffected pregnancies, all of whom had amniocentesis.⁶ We selected combinations of serum analytes that, according to the systematic review,⁶ performed best. Alternative combinations of analytes—for example, substitution of free β human chorionic gonadotrophin for total human chorionic gonadotrophin or inhibin A for unconjugated oestriol, would not substantially affect test performance. We assumed that all women would have an ultrasound dating scan and that, for second trimester serum tests, maternal weight would be taken into account.

We estimated the risk of giving birth to a Down's syndrome baby for each woman, based on the screening test results and maternal age. Firstly, we calculated the distribution of likelihood ratios for the screening test separately for pregnancies affected and unaffected by Down's syndrome using Monte Carlo simulation¹² and assumed independence between the nuchal translucency measurement, first trimester serum test (PAPP-A), and quadruple test. We then calculated the distributions of risk of an affected pregnancy for each year of maternal age by multiplying likelihood ratios by the age specific risk of an affected live birth. Finally, we calculated a single, age specific distribution of risk after screening by taking account of the proportion of pregnant women at each maternal age and the age specific risk of Down's syndrome.

Cost

The costs of screening tests included laboratory expenses (consumables and staff), informing the women of the results (by telephone if positive, by post if negative), service costs (including processing results and monitoring the service), overheads, and (for nuchal translucency measurement) training (table 1). The costs of chorionic villus sampling and amniocentesis included counselling before the procedure, equipment and staff to do the procedure, laboratory expenses (consumables and staff, non-reagent and labour costs), and overheads. For all these costs, we assumed an existing infrastructure for antenatal screening and diagnosis of Down's syndrome. We also estimated costs of events arising from screening (table 2) All costs were adjusted to June 1998 prices (for full details see www.ich.ucl.ac.uk/srtu).

Sensitivity analyses

The sensitivity analyses examined the effect of a 50% increase and decrease in the costs of chorionic villus sampling, amniocentesis, the screening test, and nuchal translucency measurement. We also tested the effect of varying the cut-off point for a positive result.

Results

Effects and costs

Table 3 and the figure show the effects and costs of no screening and of the nine screening strategies.

Measurement of nuchal translucency would result in 7.6 fewer births of babies with Down's syndrome compared with no antenatal screening, at a total cost of £171 000 per 10 000 pregnant women. The incremental cost effectiveness ratio for nuchal translucency compared with no screening is £22 000 (171 000/7.6) per prevented birth of a baby with Down's syndrome. The integrated test results in 2.0 fewer births of babies with Down's syndrome than the nuchal translucency measurement at a total cost of £276 000. The incremental cost effectiveness ratio of the integrated test compared with nuchal translucency is £52 000 (276 000–171 000)/2.0) per affected baby prevented.

Service providers with an intermediate total budget should consider the first trimester combined test or the quadruple test. Compared with measuring nuchal translucency, the first trimester combined test costs an extra £57 000 per affected liveborn baby prevented (total cost £238 000). At a similar total cost (£241 000), the quadruple test costs an additional £75 000 per affected baby prevented compared with measuring nuchal translucency.

Effects and safety

The integrated test is the most effective and safest strategy. All other strategies result in more liveborn babies with Down's syndrome and more miscarriages of unaffected pregnancies due to amniocentesis or chorionic villus sampling. Compared with no screening, the integrated test results in 0.14 miscarriages due to chorionic villus sampling or amniocentesis per birth of a Down's syndrome baby prevented. The next safest strategies, compared with no screening, are the first trimester combined test (0.22 miscarriages), nuchal translucency measurement (0.34), and the quadruple test (0.42).

Sensitivity analyses

A 50% increase or decrease in the unit costs of chorionic villus sampling and amniocentesis would hardly alter the cost effectiveness. If the cost of amniocentesis fell by 50%, the quadruple test would enter the efficiency frontier (cost effectiveness ratio compared with nuchal translucency £39 000 and for the integrated test compared with the quadruple test £51 000).

The cost effectiveness of the screening strategies is most susceptible to variation in the costs of the screening test. A 50% decrease in the unit costs of all screening tests would increase the cost effectiveness ratio of all strategies above that of the integrated test (£19 000 compared with no screening), although the cost effectiveness ratios would be close for nuchal translucency measurement and the first trimester combined test. A 50% increase in the unit costs of measuring nuchal translucency would increase the cost effectiveness ratio for nuchal translucency compared with no screening to £25 000. The cost effectiveness ratios for the first trimester combined, quadruple, and integrated tests would be similar (£51 000-£56 000). The second trimester double test, triple test, maternal age, and first trimester serum test were not cost effective at any of the assumptions tested.

Varying the cut-off point for doing amniocentesis or chorionic villus sampling between risks of 1 in 100 and 1 in 400 did not alter the cost effectiveness ranking of the screening strategies. Similarly, varying the risk cut-off point corresponding to a 5% false positive rate for the screening test did not alter the ranking (see www.ich.ucl.ac.uk/srtu).

Discussion

The nuchal translucency measurement, quadruple test, first trimester combined, and integrated tests represent the best options in terms of effectiveness, cost effectiveness, and safety. All other strategies would be less effective, cost more per additional birth of an affected baby prevented, and be less safe. This finding was robust in the sensitivity analyses.

The choice between the four options depends on how much service providers are willing to pay to prevent one affected liveborn baby, on the total budget available for antenatal screening, and on how much service providers value safety. We would expect service providers to be willing to spend at least £30 000 to £40 000 per additional affected baby prevented, as this reflects the incremental costs paid by most service providers that offer screening to all women.¹⁴

Implications for practice

These findings contrast with current practice in the United Kingdom, where the second trimester double test is most commonly offered.² Moving from the double test to the first trimester combined test or quadruple test would not cost any more and would result in 1.5 (for the first trimester combined) or 1.2 (for the quadruple test) fewer affected liveborn babies for every 10 000 pregnancies (table 2). Alternatively, the nuchal translucency measurement would be more effective than the double test (0.3 fewer affected babies) at a total cost saving of £70 000. Finally, moving from the double test to the integrated test would result in 2.3 fewer affected babies and cost £13 000 per additional affected baby prevented.

Limited research on women's preferences suggests that the choice of screening strategy should be based primarily

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on minimising the number of affected pregnancies that are missed and miscarriages due to chorionic villus sampling or amniocentesis.^{15,16} Timing of test results and termination seem to be a secondary consideration. Nevertheless, given the realistic distribution of gestation at attendance for antenatal screening that we used in our analysis, only 31% of women would be in time for a surgical termination (before 13 weeks gestation) after nuchal translucency or age based screening and none after the first trimester combined test (see www.ich.ucl.ac.uk/srto).

Implementation issues

Our results are susceptible to variation in performance of screening tests. The performance of serum markers in pregnancies affected by Down's syndrome is highly consistent across different studies,¹ whereas performance of nuchal translucency measurement varies widely.^{17,18} Such variation may be explained by verification bias, chance, referral patterns, variation in test reliability,¹⁹ and the use of repeated measurements. We used performance characteristics for nuchal translucency measurement derived from routine screening of 95 000 pregnancies, which were then adjusted for verification bias.⁴ However, we do not know how much test performance was optimised by repeated measurements or referral for a second opinion. In addition, the performance of the integrated test, which was derived by combining test characteristics for serum tests and the nuchal translucency measurement from different datasets, needs to be evaluated in a study of pregnant women.

A further concern, examined in the sensitivity analysis, is the possibility of an increased relative risk of spontaneous miscarriage in women with a positive test result (>1 in 300 risk of Down's syndrome) compared with those with a negative result. Reports of an increased relative risk range from 1.6 to 2.8 for nuchal translucency measurements ≥ 3 mm and would diminish the detection rate of nuchal translucency measurement.^{20,21} In our analysis, a relative risk of 2.8 would result in 1.3 more liveborn babies with Down's syndrome per 10 000 pregnancies after measuring nuchal translucency, but the strategy would still be cost effective.

The choice of screening strategy may be affected by several factors that were beyond the scope of our analysis. Firstly, we did not adopt a societal perspective,¹³ which would seek to maximise health gain for a given cost. Such analyses are problematic in terms of measures of effect—for example, should the outcome measure be prevented liveborn baby with Down's syndrome or quality adjusted life years.²² There are also difficult decisions about which costs to include. Some previous cost effectiveness analyses included direct and indirect lifetime incremental costs per liveborn baby with Down's syndrome (including education, health, and lost productivity). These ranged from £85 000 in 1990²³ to £340 000 in 1996.²⁴ The studies avoided including other indirect costs attributable to fetal losses by assuming a replacement pregnancy.

If the lowest estimate (£85 000) for the incremental lifetime costs associated with a Down's syndrome child is included in our analysis the net saving compared with no screening would be largest for the integrated test. The net saving would be £548 000 (costs avoided (9.7 Down's syndrome babies prevented \times £85 000)—screening programme costs (£276 000)).

Factors that could affect results

Three factors that we did not consider may affect our results. Firstly, capital costs for additional laboratory or clinical capacity may be incurred for use of the enzyme linked immunosorbent assay (ELISA) test for inhibin A (the fourth serum marker in the quadruple test), implementation of routine nuchal translucency measurement, or the creation of additional facilities for chorionic villus sampling. Secondly, uptake of all screening tests and termination may not be the same for all strategies and may be lower for the integrated test, which requires two visits. Decreased uptake of termination in later pregnancy is likely and would mean that our analysis overestimates the effectiveness of the integrated and quadruple tests. Thirdly, service providers need to provide for women who attend antenatal booking clinic after the first trimester (up to 35% based on results from 21 000 women in six inner London maternity units²⁵). Alternative strategies for late attenders include no screening, the quadruple test, or strategies to encourage earlier attendance at antenatal booking clinic—for example, by speeding up referrals from primary care.

Conclusions

The choice of screening strategy should be between the integrated test, first trimester combined test, quadruple test, or nuchal translucency measurement. Screening based on maternal age, the second trimester double test, and the first trimester serum test would be less effective, less safe, and more costly than these four options.

Commentary: Results may not be widely applicable

Wallace, Euan M; Mulvey, Sheila (Centre for Women's Health Research, Department of Obstetrics and Gynaecology, Monash University, Monash Medical Centre, Clayton, Victoria 3168, Australia).

The average age at which women in Western countries choose to have children continues to increase. Although this trend has several important implications for the outcome of pregnancy, one of the most obvious effects is an increase in the incidence of Down's syndrome.¹⁻¹ Prenatal screening for Down's syndrome has become an established part of antenatal care in many centres, resulting in a reduction in the number of babies born with Down's syndrome in the populations screened.¹⁻¹

Several serum markers of Down's syndrome have been described, and different screening programmes use different combinations of markers, making it difficult to compare their results.¹⁻² The recent introduction of first trimester serum and ultrasound screening has further complicated such comparisons. Therefore, it is often unclear which screening strategy is the most effective, the most cost effective, or the most appropriate for a given setting. Gilbert and her colleagues summarise various approaches to screening and describe the most cost effective strategies. Such information will be invaluable to all those providing antenatal care.

Limitations

Some authorities are likely to disagree with the conclusions reached by Gilbert et al. There is evidence that simple two marker protocols (such as α fetoprotein and free β human chorionic gonadotrophin) can achieve higher detection rates than those estimated by Gilbert et al for more complex combinations, even after correction for the high rate of spontaneous loss of pregnancies affected by Down's syndrome.^{1-2,1-3} How can this be?

A potential limitation of the analyses is that the effectiveness modelling is based on an archived set of serum samples derived from 77 women with pregnancies affected by Down's syndrome and 385 with unaffected pregnancies, rather than an analysis of published detection rates from prospective series, as was done for nuchal translucency. If the archived data set differs from the population being screened then the performance characteristics may not be the same in practice. This emphasises the importance of evaluating screening tests locally, where the expertise exists, rather than relying on a single archived serum bank.

It is also possible that marker combinations not analysed in this report will offer highly effective screening. For example, second trimester serum screening has better detection rates than first trimester tests.¹⁻⁴ The combination of nuchal translucency with second trimester serum markers may prove more effective than the first trimester test that Gilbert et al recommend. Several prospective comparative studies are underway worldwide that will investigate this possibility.

The cost comparisons of the various strategies highlight that more expensive approaches may be the most cost effective. Such insights will be extremely helpful to health planners. However, the costings used in the analyses are for a programme within a large public service such as the NHS and will not easily translate across healthcare systems. For example, the £4.40 allowed for measuring nuchal translucency is much less than the \$200 (£143) estimated in the United States.¹⁻⁵ Again, it will be important for local programmes to derive local costs before planning their service.

Women's views

What is not covered by these analyses, although the authors mention it, is patient preference. We have little information about what women prefer in screening, but there is some evidence that they want testing as early in pregnancy as possible, even if a later test performs slightly better.¹⁻⁶ Such information is surely fundamental to the development of future screening programmes. It would be unfortunate if the technical advances in screening were assessed and compared without considering women's wishes. Similarly, it is unacceptable that access to screening for Down's syndrome varies across the United Kingdom. Contributions such as that by Gilbert et al will inform relevant authorities, such as the UK National Screening Committee, and help ensure that appropriate and high quality screening is available to all women who want it.

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Wallace and Mulvey criticise our study for relying on a single archived serum bank. Instead, they advocate comparing detection rates from “prospective studies,” by which they mean routinely collected hospital data. We disagree. It is well known that data from routine practice may overestimate the performance of screen tests because positive results lead to interventions whereas affected pregnancies with negative results may not be counted (termed verification bias).²⁻¹ Such bias depends on the gestational age at testing and can be allowed for only indirectly. Differences in detection rates (assuming a constant false positive rate) may also relate to uptake of interventions and referral patterns. Finally, we required the test performance characteristics rather than the detection rate in order to standardise for age and cut-off point for positivity. The study based on an archived serum bank avoided biased detection of affected fetuses (all were karyotyped), took account of ultrasound pregnancy dating, and reported performance characteristics for all the serum tests.

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Footnotes

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Competing interests: None declared.

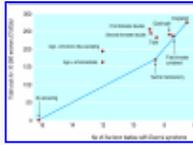
Competing interests: EMW holds the patent for use of inhibin A as a marker of Down's syndrome.

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Figures and Tables



Figure

Cost effectiveness of screening strategies for Down's syndrome with a risk of 1 in 300 as cut-off point for positive result. The continuous line is the efficiency frontier. Gradient represents the additional cost incurred per additional birth prevented ([more ...](#))

Table 1

Detection rate and estimated uptake, process time, and cost of screening strategies for Down's syndrome

Table 2

Risk and costs of events after screening for Down's syndrome

Table 3

Number of live births affected by Down's syndrome, miscarriages due to chorionic villus sampling or amniocentesis, and total costs per 10 000 pregnancies and incremental cost effectiveness ratios assuming risk of 1 in 300 as cut-off point for positive ([more ...](#))

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