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

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Abstract

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.

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

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Table 1 Detection rate and estimated uptake, process time, and cost of screening strategies for Down's syndrome

Procedure	Detection rate	Reported rate	Uptake	Process time* (weeks)	Unit cost†
First trimester screening (10 to 14 weeks)‡:					
Maternal age	32%§		80%	0	£0
Nuchal translucency measurement	74%§	73%[4]	80%	0	£4.40
First trimester double test (PAPP-A, HCG)	63%§	62%[5]	80%	1	£11
First trimester combined test (nuchal translucency, PAPP-A, HCG)	86%§	80% [3] 85% [6]	80%	1	£15
Second trimester screening (15 to 19 weeks)‡:					
Maternal age	32%§		80%	0	
Second trimester double test (AFP, HCG)	60%§	58%,[7] 59%[3]	80%	1	£10
Triple test (AFP, HCG, uE3)	68%§	67%,[8] 69%[3]	80%	1	£11
Quadruple test (AFP, HCG, uE3, inhibin A)	79%§	76%,[3] 79%[9]	80%	1	£13
Integrated test (first trimester: nuchal translucency, PAPP-A; second trimester: quadruple test)	95%§	94%[3]	80%	1	£22
Prenatal diagnosis:					
Amniocentesis (≥15 weeks)	100%	100%[1]	80% unaffected, 90% affected	2 (+1)¶**	£208
Chorionic villus sampling (11-14 weeks)‡	100%	100%[1]		0 (+1)¶**	£249
Termination					
Surgical dilatation, evacuation (11 to 13 weeks)‡			90%	1¶	£495
Medical with mifepristone (≥14 weeks)			90%	1¶	£495

AFP=α fetoprotein, HCG=β human chorionic gonadotrophin, PAPP-A=pregnancy associated plasma protein A, uE3=unconjugated oestriol.
*Time between procedure and date results given to the woman.
†For details of derivation see technical report.
‡Refers to completed weeks.
§Detection rate for a 5% false positive rate.
¶1 week allowed before procedure for administration and counselling.
**Culture of amniotic fluid takes 2 weeks, preparation of chorionic villus sample takes 2 days.

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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. Details of estimates used in the model are given on the *BMJ*'s website.

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)

Results

Effects and costs

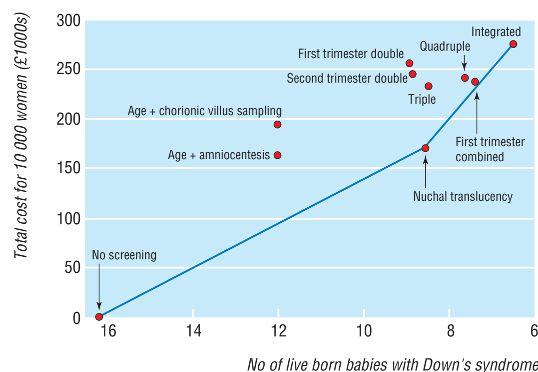
The figure shows the effects and costs of no screening and of the nine screening strategies. Measurement of nuchal translucency would result in 7.6 fewer births of babies with Down's syndrome compared with no antenatal screening, at a total cost of £171 000 per 10 000 pregnant women. The incremental 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.

Table 2 Risk and costs of events after screening for Down's syndrome

Event	Risk	Reported range	Unit cost
Miscarriage due to the procedure			
Amniocentesis	0.9%	0.0 to 1.9%[1]	£408
Chorionic villus sampling	0.9%	–2.2% to 2.0%* [1]	£408
Sample failure and repeat procedure in all			
Amniocentesis	0.8%	0.5 to 1.0%[1]	£181
Chorionic villus sampling	1.3%	1.0 to 1.6%[1]	£181
Spontaneous loss in unaffected pregnancies (10 weeks to term)†	2.1%		£408
Spontaneous loss in Down's syndrome pregnancies (10 weeks to term)†	45%		£408
Live birth			£597

*Difference compared with second trimester amniocentesis.
†Costs incurred because dilatation and evacuation assumed for all losses.



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 of an affected baby by adopting a more effective strategy (compared with next cheapest strategy). Strategies above the efficiency frontier are dominated (more costly and less effective than nuchal translucency measurement or integrated test) or ruled out by extended dominance (more costly or less effective and resulted in higher costs per prevented birth than a more effective option).[10]

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).

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 (see *BMJ*'s website for details).

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.[11]

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. 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 on minimising the number of affected pregnancies that are missed and miscarriages due to chorionic villus sampling or amniocentesis.[12 13] Timing of test results and termination seem to be a secondary consideration.

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.[14 15] 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.

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,[10] 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.[16] There are also difficult decisions about which costs to include.

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 units[17]). 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.

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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1 Wald NJ, Kennard A, Hackshaw A, McGuire A. Antenatal screening for Down's syndrome. *J Med Screen* 1997;4:181-246.
2 Wald NJ, Huttly WJ, Hennessy CF. Down's syndrome screening in the UK in 1998. *Lancet* 1999;354:1264.
3 Wald NJ, Watt HC, Hackshaw AK. Integrated screening for Down's syndrome based on tests performed during the first and second trimesters. *N Engl J Med* 1999;341:461-7.
4 Nicolaides KH, Snijders RJ, Cuckle HS. Correct estimation of parameters for ultrasound nuchal translucency screening. *Prenat Diagn* 1998;18:519-23.
5 Wald NJ, Hackshaw AK. Combining ultrasound and biochemistry in first-trimester screening for Down's syndrome. *Prenat Diagn* 1997;17:821-9.
6 Hecht CA, Hook EB. The imprecision in rates of Down syndrome by 1-year maternal age intervals: a critical analysis of rates used in biochemical screening. *Prenat Diagn* 1994;14:729-38.
7 Wald NJ, Cuckle HS, Densem JW, Nanchahal K, Royston P, Chard T, et al. Maternal serum screening for Down's syndrome in early pregnancy. *BMJ* 1988;297:883-7.
8 Wald NJ, Cuckle HS, Densem JW, Kennard A, Smith D. Maternal serum screening for Down's syndrome: the effect of routine ultrasound scan determination of gestational age and adjustment for maternal weight. *Br J Obstet Gynaecol* 1992;99:144-9.
9 Wald NJ, Densem JW, George L, Muttukrishna S, Knight PG. Prenatal screening for Down's syndrome using inhibin-A as a serum marker. *Prenat Diagn* 1996;16:143-53.
10 Siegel JE, Weinstein MC, Torrance GW. Reporting cost-effectiveness studies and results. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost effectiveness in health and medicine.* New York: Oxford University Press, 1996:276-312.
11 Torgerson DJ, Spencer A. Marginal costs and benefits. *BMJ* 1996;312:35-6.
12 Heckerling PS, Verp MS, Hadro TA. Preferences of pregnant women for amniocentesis or chorionic villus sampling for prenatal testing: comparison of patients' choices and those of a decision-analytic model. *J Clin Epidemiol* 1994;47:1215-28.
13 Kuppermann M, Feeny D, Gates E, Posner SF, Blumberg B, Washington AE. Preferences for women facing a prenatal diagnostic choice: long-term outcomes matter most. *Prenat Diagn* 1999;19:711-6.
14 Palomaki GE, Knight GJ, McCarthy JE, Haddow JE, Donhowe JM. TI-Screening of maternal serum for fetal Down's syndrome in the first trimester. *N Engl J Med* 1998;338:955-61.
15 Mol BW, Lijmer JG, van der Meulen JHP, Pajkrt E, Bilardo CM, Bossuy PM. Effect of study design on the association between nuchal translucency measurement and Down syndrome. *Obstet Gynecol* 1999;94:864-9.
16 Ganiats TG. Justifying prenatal screening and genetic amniocentesis programs by cost-effectiveness analyses: a re-evaluation. *Med Decis Making* 1996;16:45-50.
17 Gibb DM, MacDonagh SE, Gupta R, Tookey PA, Peckham CS, Ades AE. Factors affecting uptake of antenatal HIV testing in London: results of a multicentre study. *BMJ* 1998;316:259-61.

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