Cost of Integrated, sequential and contingent prenatal screening for Down's syndrome.

Gekas and colleagues, in their paper comparing prenatal Down's syndrome screening strategies (contingent, sequential, Integrated and triple test screening)[1] conclude that the contingent screening strategy was the most cost-effective, had the least number of procedure related unaffected fetal losses and the least number of unnecessary pregnancy terminations and is therefore the preferred option for prenatal screening for Down's syndrome.

According to Gekas et al. contingent screening is about 31% less expensive than Integrated screening and sequential screening is about 8% less expensive without second trimester alphafetoprotein (AFP) testing for neural tube defects (NTD's). In a similar analysis we reported that without AFP testing for NTD's contingent screening was 15% less expensive than Integrated screening per Down's syndrome pregnancy diagnosed but no less expensive if AFP testing for NTD's is included, and Sequential screening was 21% more expensive than Integrated screening[2]. Given that the modelled population Gekas et al. used in their cost analysis was the same as the one we used apart from the maternal age distribution, the results in the two analyses should not be materially different. It seems that the explanations for the different estimates are as follows.

1) The termination of some Down's syndrome pregnancies in the first trimester of pregnancy would be unnecessary because they would have miscarried before second trimester testing had they had the Integrated test. The cost of diagnoses and termination of these pregnancies should be included in the global costs but the number of these pregnancies should not be included in the cost effectiveness ratio (cost per Down's syndrome pregnancy diagnosed). Including them as Gekas et al. did

overestimates the cost effectiveness of Sequential and Contingent screening relative to Integrated screening.

2) The false-positive rate of the Integrated test used in the modelling of Gekas et al (2.60%) was taken from the SURUSS report[3], which applied to screening at 10 completed weeks of gestation and did not take into account that NT MoM values in Down's syndrome pregnancies decrease with gestational age, whilst the corresponding false-positive rates for sequential and contingent screening were taken from Wald et al[2] which related to screening applied at 11 completed weeks and did take into account the gestational age decrease in NT MoM values in Down's syndrome pregnancies[4]. The correct Integrated test false-positive rate that should have been used to achieve a 90% detection rate in the Gekas et al cost analysis was 2.15% not 2.60%[2]. Using the correct false-positive rate would decrease the cost of Integrated screening (fewer diagnostic tests).
3) Given point 2 above, the risk cut-off that should have been used to yield a 90% detection rate for the Integrated test was 1 in 198[2] not 1 in 245[3] (which incidentally was corrected to 1 in 250[5]). Again the cost of Integrated screening would be lower because of the reduced number of diagnostic tests.
4) Gekas et al. define the first trimester stage of contingent and sequential screening as risk estimation based on NT and PAPP-A, however the false-positive rates for a 90% detection rate that were used in their analyses were taken from Wald et al[2] and these apply to risk estimation based on free β-hCG as well as NT and PAPP-A in the first trimester. Using the proposed 1 in 9 first trimester test risk cut-off (0.1% false-positive rate) the first trimester test detection rate for NT and PAPP-A was estimated at 38%, but is 51% for NT, free β-hCG and PAPP-A. The overall false-positive rate for sequential screening is slightly higher using NT and PAPP-A (2.18% without first trimester free β-hCG and 2.12% with it) and at 2.64% instead of 2.29%[2] for contingent

screening. By using the performance figures for the three markers instead of two, Gekas et al underestimated the costs for Sequential and Contingent screening.

5) In the first trimester of pregnancy, Gekas et al. estimate there to be 290 affected pregnancies. This represents a fetal loss rate to term of 55%, much higher than the 43% estimated by Morris et al.[6] and 30% estimated by Snijders[7]. In the second trimester of pregnancy Gekas et al. estimate there to be 190 affected pregnancies. This represents a fetal loss rate of 31% from this period to term, also higher than the 23% estimated by Morris et al.[6]. With such a high prevalence of Down's syndrome pregnancies in the first trimester, and given that Down's syndrome pregnancies diagnosed in the first trimester that would have miscarried before second trimester testing were included in the cost effectiveness ratio, the cost-effectiveness ratios for Sequential and Contingent screening are overestimated.

All the above points contribute to either the overestimation of the costs of Integrated screening or the underestimation of the costs of Sequential or Contingent screening. There are a number of other issues that may indicate problems with the modelling performed by Gekas et al. They are as follows

1) Using the simplest screening method of amniocentesis for women aged 35 or more they calculate the global cost of screening 100,000 women to be 4.15 million Canadian dollars. This appears too low; in their population 14.6% or 14,600 women per 100,000 women are aged 35 or more. The cost of a consultation with a genetic counsellor is $C73.90 and the cost of amniocentesis is $C500 per woman. With their assumed probability of 90% amniocentesis uptake the cost of diagnosis for 100,000 women is (14,600×73.90) + (14,600×90%×500) = $C7.65 million, 84% more than

their estimate of $C4.15M. Including the cost of affected pregnancy terminations would further inflate this cost.

2) The number of cases of Down's syndrome detected in table 3 (termed effectiveness) appears too low. Given that, according to table 2, there are 190 Down's syndrome pregnancies at the second trimester, uptake of screening is 70% and the cost figures are given for an overall 90% detection rate, 120 Down's syndrome pregnancies should be detected by the Integrated test, not the 87 reported. The number detected by the other screening options are similarly too low.
3) The number of Down's syndrome pregnancies detected by contingent screening for all but two of the fixed first trimester test risk cut-offs are slightly higher than the number detected by sequential screening. This cannot be true since the same number of affected pregnancies must be detected in the first trimester test (same test and same risk cut-off) but fewer affected pregnancies will be detected in the second trimester with a contingent screening policy since some affected pregnancies will be determined low risk (risk less than 1 in 2000) after the first trimester test and not be screened further. Gekas et al. also state that the proportion of affected pregnancies detected by the first trimester test range from 44.1% to 86.1% for sequential screening, and, using exactly the same test and risk cut-offs, range from 43.7% to 86.3% for contingent screening. These estimates should be identical.
4) Gekas et al. report that with Contingent screening using a 1 in 175 first trimester test risk cut-off the number of Down's syndrome pregnancies detected is 111.69, but at a lower risk cut-off of 1 in 237 the number detected is 111.61. Whilst the difference is small, this is impossible, the number of Down's syndrome pregnancies can only increase as the first trimester test risk cut-off decreases.

We were unable to replicate the cost figures reported by Gekas et al. and therefore unable to correct their figures taking into account the points above. We were also unable to estimate the cost of Sequential or Contingent screening for women that only receive first trimester testing and women that proceed to second trimester testing (a single figure is given for each screening method). Therefore, we show in the tables a cost analysis in the same format as Gekas et al. based on our previous unit cost and screening parameters[2,3] We include the extra costs associated with a higher prevalence of Down's syndrome pregnancies in the first trimester of pregnancy, which we previously did not (although the extra cost is relatively small).

Table 1 a shows that the cost of screening 100,000 women (assuming all women accept screening) is £2.88million for programmes based on the Integrated test. A programme based on Contingent screening is 15% less expensive (£2.46million, 1 in 9 first trimester test risk cut-off) and a programme based on Sequential screening is more 15% more expensive (£3.32million, 1 in 9 first trimester test risk cut-off). Per Down's syndrome pregnancy diagnosed, Integrated screening costs about £2,300 more than Contingent screening (much less than the $C12,000, about £6,750 at the current exchange rate, estimated by Gekas et al.) Relative to programmes based on the Integrated test, in both Contingent and Sequential screening programmes, up to 27 Down's syndrome pregnancies detected in the first trimester (1 in 9 risk cut-off) would be unnecessarily terminated because they would have miscarried before the early second trimester. Table 1b shows that with the inclusion of an AFP test for open neural tube defects a Contingent screening programme is more expensive than a programme based on Integrated screening (contrary to the previously published no difference in cost due to the first trimester test here being NT and PAPP-A rather than the Combined test[2]).

In determining the preferred strategy for Down's syndrome screening Gekas et al. rightly state that the screening test should have the lowest false-positive rate, the highest detection rate and the best cost effectiveness ratio (cost per Down's syndrome pregnancy diagnosed). However the authors ignore that consideration be given to the anxiety of giving some women two risk estimates during the same pregnancy, apart from stating that health care providers would have to be prepared and able to use very high first trimester test risk cut-off levels. They rightly state that it would be difficult to refuse a first trimester diagnostic test to a woman given a risk estimate close to their preferred 1 in 9 cut-off. There would also be women with high first trimester test risk estimates, say 1 in 50 who would be confused in receiving a second risk estimate of, say 1 in 5,000 in the second trimester. They may not be reassured by the lower estimate in the second trimester and still request a diagnostic test because of their first result.

The Integrated test for all women avoids such issues, does not cost much more than contingent screening (the difference being much lower than estimated by Gekas et al.), has the highest detection rate, the lowest false-positive rate, the lowest number of diagnostic procedure-related unaffected fetal losses and the lowest number of unnecessary pregnancy terminations. On this basis, screening using the Integrated test for all women is the method of choice.

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Declaration of Interests

NJ Wald holds a patent for the Integrated test. He is also a Director of Logical Medical Systems Ltd, which produces software for the interpretation of Down's syndrome screening tests.

Table 1 Cost effectiveness analysis of screening 100,000 women (including 305 Down's syndrome pregnancies at the first trimester of pregnancy, 226 at the second trimester) for an overall 90% detection rate of affected pregnancies viable in the second trimester.

1a Cost without including separate AFP tests for open neural tube defects

Screening options	Cost of screening 100,000 women (£millions)	Down's syndrome pregnancies diagnosed†	Cost per Down's syndrome pregnancy diagnosed (£thousands)	Additional savings per additional Down's syndrome pregnancy detected* (£thousands)
Amniocentesis for women ≥35 years old	3.7197	101.29	36,723	Reference
Contingent screening, cut-off values for first trimester test				
1 in 6	2.4478	183.06 (22.45)	13,371	15,555
1 in 9	2.4560	183.06 (27.38)	13,416	15,454
1 in 28	2.5094	183.06 (40.01)	13,708	14,801
Sequential screening, cut-off values for first trimester test				
1 in 6	3.3046	183.06 (22.45)	18,052	5,076
1 in 9	3.3152	183.06 (27.38)	18,110	4,947
1 in 28	3.3735	183.06 (40.01)	18,428	4,234
Integrated test	2.8829	183.06	15,749	10,234

1b Cost including separate AFP tests for open neural tube defects.

Screening options	Cost of screening 100,000 women (£millions)	Down's syndrome pregnancies diagnosed†	Cost per Down's syndrome pregnancy diagnosed (£thousands)	Additional savings per additional Down's syndrome pregnancy detected* (£thousands)
Amniocentesis for women ≥35 years old	4.6197	101.29	45,609	Reference
Contingent screening, cut-off values for first trimester test				
1 in 6	3.0960	183.06 (22.45)	16,912	18,634
1 in 9	3.1047	183.06 (27.38)	16,960	18,528
1 in 28	3.1621	183.06 (40.01)	17,274	17,826
Sequential screening, cut-off values for first trimester test				
1 in 6	3.3057	183.06 (22.45)	18,058	16,069
1 in 9	3.3169	183.06 (27.38)	18,119	15,932
1 in 28	3.3791	183.06 (40.01)	18,459	15,172
Integrated test	2.8829	183.06	15,749	21,240

†Number of Down's syndrome pregnancies diagnosed that are viable in the second trimester of pregnancy, numbers in parentheses are affected pregnancies diagnosed in the first trimester that would have miscarried before second trimester testing.
*Compared to amniocentesis for women ≥35
FPR=false-positive rate.
Cost of Contingent and Sequential screening tests=£13.50 for women that do not proceed to second trimester testing , £28.50 for women that do. Cost of Integrated screening test=£23.
Cost of CVS=£350, cost of amniocentesis=£300, cost of termination=£500, cost of medical evacuation of products of conception=£400, cost of delivery=£600 (some Down's syndrome pregnancies that were terminated would have gone to term so the cost of delivering there pregnancies is saved and subtracted from overall costs).
Assumed probabilities: 90% of screen positive women with Down's syndrome pregnancy accept offer of diagnostic test, 80% of screen positive women with unaffected pregnancy accept offer, 0.9% fetal loss rate attributable to CVS and amniocentesis, 90% of Down's syndrome pregnancies diagnosed are terminated.
Spontaneous fetal loss rate in Down's syndrome pregnancies: 43% from first trimester to term, 23% from second trimester to term, 26% from first to second trimester.

References

1 Gekas J, Gagne G, Bujold E, Douillard D, Forest J, Reinharz D, Rousseaeu F. Comparison of different strategies in prenatal screening for Down's syndrome: cost effectives analysis of computer simulation. *BMJ*; 2009

2 Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Study (SURUSS). *J Med Screen* 2003; 10:56-104

3 Wald NJ, Rudnicka AR, Bestwick JP. Sequential and contingent prenatal screening for Down syndrome. *Prenat Diagn* 2006; 26(9):769-777

4 Wald NJ, Rodeck C, Rudnicka AR, Hackshaw AK. Nuchal translucency and gestational age. *Prenat Diagn* 2004; 24:150-153

5 Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM, Bestwick JP. Correction to SURUSS report. *J Med Screen* 2006; 13:51-52

6 Morris JK, Wald NJ, Watt HC. Fetal Loss in Down Syndrome Pregnancies. *Prenat Diagn* 1999; 19:142-145

7 Snijders R. Fetal Loss in Down Syndrome Pregnancies. *Prenat Diagn* 1999; 19:1180