

Retrospective audit of different antenatal screening policies for Down's syndrome in eight district general hospitals in one health region

Diana Wellesley, Tracy Boyle, John Barber, David T Howe

Abstract

Objective To compare the effectiveness of different screening policies for the antenatal detection of Down's syndrome.

Design Retrospective six year survey.

Setting Maternity units of eight districts.

Participants Women who completed their pregnancies between 1 January 1994 and 31 December 1999 (155 501 deliveries).

Main outcome measures Cases of Down's syndrome identified before 24 weeks' gestation.

Results 335 cases of Down's syndrome were identified, 323 in continuing pregnancies or liveborn children. Of these, 171 were identified antenatally. Seven different screening policies were used, in three principal groups: serum screening offered to all mothers, maternal age with serum screening or nuchal translucency available to limited groups, and maternal age combined with anomaly scans. The districts that used serum screening detected 57%, those using maternal age plus serum or nuchal translucency screening 52%, and those using a maternal age of ≥ 35 and anomaly scans detected 54%. The least successful district, which offered amniocentesis only to women aged over 37 years, detected only 31%. If amniocentesis had been offered from 35 years, as in all other districts, the detection rate would have risen to 54%. Across the region 15% (range 12-20%) of pregnant women were 35 years or more at delivery, and 58% (33-69%) of infants with Down's syndrome were born to women in this age range.

Conclusions Current additional serum or nuchal translucency screening techniques for antenatal detection of Down's syndrome are less advantageous than previously supposed. More pregnant women were aged over 35 than has been presumed in statistical models used in demonstration projects of serum screening and, as a result, the proportion of affected fetuses in this age group is much greater than predicted.

Introduction

Screening for Down's syndrome has become an accepted part of routine antenatal care, but there is wide variation between different districts in the policy used. On the advice of the antenatal subgroup of the National

Screening Committee in April 2001 the UK government announced that by 2004 all pregnant women should be offered serum screening in the second trimester to increase the antenatal detection of Down's syndrome and to reduce the amniocentesis rate.

Despite the large number of demonstration projects¹ there have been no controlled trials showing the effectiveness of such screening compared with screening by maternal age in units that offer routine anomaly scanning. We carried out a comparative audit of antenatal screening in adjacent health districts to determine whether serum screening is justified by an increase in the detection rate of Down's syndrome or by a reduction in the rate of invasive procedures.

Methods

We used the Wessex antenatally detected anomalies register to ascertain all cases of Down's syndrome detected in pregnancy (including deliveries, miscarriages, or terminations) or postnatally in the region in the six years from 1 January 1994 to 31 December 1999. These were confirmed with the only cytogenetics laboratory for the region. District D first began to contribute to the database in 1997 so the figures for this district cover only 1997-9 inclusive. We considered cases to have been successfully diagnosed antenatally if they were detected before 24 weeks' gestation, a stage in pregnancy when termination can still be offered.

We obtained the maternal age profiles of women who delivered in each district in 1998 through the Office for National Statistics and hand checked them by postcode to ensure that women were allocated to the correct district. Because of the difficulties of hand checking this was the only year for which we did this.

Results

In the six years studied, 155 501 babies were delivered in the region in the eight district hospitals, their associated community hospitals, or at home. In total 335 cases of Down's syndrome were detected during pregnancy or in newborn babies, giving an overall incidence of 2.1 per 1000 deliveries (95% confidence interval 1.87 to 2.33). In 1989 the national incidence was 1.4 per 1000 live births.² In 12 cases the pregnancies had already failed as a result of missed abortions

Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton SO16 5YA

Diana Wellesley
associate specialist in clinical genetics

Wessex Regional Genetics Laboratory, Salisbury District Hospital, Salisbury SP2 8BJ

Tracy Boyle
section head, prenatal diagnostics

Human Genetics Research Division, Duthie Building, Southampton General Hospital, Southampton SO16 6YD

John Barber
deputy director, cytogenetics laboratory

Wessex Fetal Medicine Unit, Princess Anne Hospital, Southampton SO16 5YA

David T Howe
consultant in fetomaternal medicine

Correspondence to: D Wellesley
dgw@soton.ac.uk

bmj.com 2002;325:15

Table 1 Maternal age (years) distribution (%) by district for 1998

District	<20	20-24	25-29	30-34	35-39	≥40
A	8	18	33	29	11	1
B	6	18	29	32	13	2
C	5	16	31	32	13	3
D	9	21	31	26	11	2
E	5	13	29	34	17	3
F	7	17	31	30	13	2
G	5	15	31	33	14	2
H	7	17	31	30	12	3
Total	6	17	31	31	13	2

Table 2 Age distribution of mothers with fetuses affected with Down's syndrome and incidence per 1000 births, 1994-9

District	No (%) of mothers		Total	Rate per 1000 deliveries (95% CI)
	<35 years	≥35 years		
A	27 (47)	31 (53)	58	1.55 (1.15 to 1.95)
B	16 (48)	17 (52)	33	2.67 (1.76 to 3.58)
C	28 (40)	42 (60)	70	2.56 (1.97 to 3.15)
D*	8 (67)	4 (33)	12	3.38 (1.47 to 5.29)
E	11 (31)	24 (69)	35	2.19 (1.47 to 2.91)
F	22 (36)	39 (64)	61	2.0 (1.5 to 2.5)
G	19 (50)	19 (50)	38	2.28 (1.56 to 3.0)
H	6 (37)	10 (63)	16	1.45 (0.74 to 2.16)
Total	137 (42)	186 (58)	323	2.1 (1.87 to 2.33)

*Data for 1997-9.

or miscarriage and so would not have led to a live child. We confined the analysis to the 323 continuing pregnancies.

Maternal age profile and age distribution

Table 1 shows the age distribution of women delivering in 1998 for the eight health districts. Across the region 15% of pregnant women were aged 35 or more. Table 2 shows the proportion of affected pregnancies in women according to age. Overall, 186 (58%, 53% to 63%) affected pregnancies were in women aged 35 years and over, suggesting that if maternal age was the only indication for offering invasive testing a high proportion of cases would be detected.

Screening procedures

Among the eight districts, there were seven different screening policies for Down's syndrome (table 3). These policies fell into three groups. The first group (districts A and B) offered serum screening to all women with free β human chorionic gonadotrophin and α fetoprotein. Invasive testing was offered to women with risks above 1:250 and 1:300 respectively. District A carried out a 16 week dating scan before serum screening but no routine anomaly scan at 20

Table 3 Screening methods for Down's syndrome and local scanning policies

District	Serum screening	Nuchal thickening	Dating scan	Anomaly scan	Maternal age*
A	Yes	No	16 wks	No	No
B	Yes	No	12 wks	Yes	No
C	No	Yes (for ≥34 years)	No	Yes	Yes
D	No	Yes	No	Yes	Yes
E	Offered privately	Offered privately	No	Yes	Yes
F	No	No	No	Yes	Yes
G	No	No	No	Yes	Yes
H	No	No	No	Yes	Yes (for ≥37 years)

*Offered at 35 years unless specified.

weeks. District B carried out a dating scan at 12 weeks and an anomaly scan at 20 weeks.

The second group (F, G, and H) used maternal age as the principal indication for offering invasive testing but also offered routine 19 to 20 week anomaly scans. The age threshold for testing was 35 years at the estimated date of delivery in F and G but 37 years in district H.

In the third group (C, D, and E) invasive testing was offered to women aged 35 and over but additional screening methods were also offered. District C offered nuchal translucency testing to women aged 34 and over and to younger women who specifically requested it. District D offered nuchal translucency measurement to all women. District E provided a leaflet to all pregnant women, which gave contact details for private nuchal translucency and serum screening. Although women in any district may elect to have private testing this was the only area in which it was actively offered. This is reflected in the number of cases of Down's syndrome in district E that were detected after serum screening (table 4). We were unable to establish how many women in district E opt for serum screening.

Detection rates of Down's syndrome—all ages

The overall antenatal detection rate was 171/323 (53%, 48% to 58%). Table 4 shows the proportion detected antenatally in each district and the screening methods that prompted an offer of an invasive procedure.

There was no significant advantage to any screening policy, and the addition of more screening tests did not produce an additive effect. The district with the highest detection rate (F) offered invasive testing on the basis of maternal age and abnormal results on anomaly scans. The same policy was used by districts G and H, who had lower than average detection rates. District H offered amniocentesis only to women aged over 37, but if they had used an age cut off of 35 years, in common with other districts, they could have improved detection to 54%. This district also adopted a conservative approach to offering amniocentesis on the basis of ultrasound findings and was the only district where no cases were detected after an abnormal scan result. District G recently updated their ultrasound equipment and in 1999 detected 80% of cases antenatally, half after abnormal findings on ultrasonography.

The three districts that used maternal age with anomaly scans and additional methods, (C, D, and E) did not achieve higher antenatal detection rates than district F, which relied on maternal age and anomaly scans alone.

The two districts (A and B) that used serum screening as their mainstay detected 57% (47% to 67%) of affected fetuses, a figure in keeping with previously published demonstration projects. There was no significant difference between the detection rates in these two districts combined compared with districts F and G ($P > 0.65$). Even in these districts the contribution of serum screening to antenatal detection rates was less than anticipated. In 1993, when serum screening was introduced to these two districts, the uptake was about 85%, but by 1999 this had dropped to 55% in district A and 65% in district B. As a result, only 24% of affected fetuses were detected after serum screen results that indicated a high risk (table 4). The remainder were detected as a result of other

Table 4 Indication for invasive test that resulted in antenatal diagnosis of Down's syndrome before 24 weeks' gestation by district for 1994-9

District	Detected antenatally				Total	Detected at/after birth	Proportion detected antenatally % (95% CI)	Total cases
	Serum screen	Nuchal thickening	Anomaly Scan	Maternal age/ previous affected pregnancy				
A	16	0	11	6	33	25	57 (44 to 70)	58
B	6	5	4	4	19	14	58 (41 to 75)	33
A&B serum screen combined	22	5	15	10	52	39	57 (47 to 67)	91
C	1	20	8	8	37	33	53 (41 to 65)	70
D*	0	2	1	2	5	7	42 (14 to 70)	12
E	6	1	6	6	19	16	54 (38 to 71)	35
C,D,&E ≥35 years, nuchal thickening, serum screen	7	23	15	16	61	56	52 (42 to 62)	117
F	1	7	10	20	38	23	62 (50 to 74)	61
G	2	1	2	10	15	23	40 (24 to 56)	38
F&G ≥35 years scan	3	8	12	30	53	46	54 (44 to 64)	99
H	0	0	0	5	5	11	31 (8 to 54)	16
Total	32 (10%)	36 (11%)	42 (13%)	61 (19%)	171 (53%)	152 (47%)	53 (48 to 58)	323

*Data for 1997-9.

indications for invasive testing. Some women aged over 35 years opted directly for amniocentesis, and in others an abnormal scan result led to the diagnosis of Down's syndrome. In these districts, among women who accepted serum screening its sensitivity was 43% in women aged under 35 years and 80% in women over 35 years.

Detection rates in women aged under 35 years

One of the arguments advanced for methods such as nuchal translucency and serum screening is that they would increase the detection rate of Down's syndrome in young women. The overall detection rate in women aged under 35 was 48/138 (35%, 27% to 43%, table 5). Only districts A, B, and D offer routine screening to younger women, and they might be expected to have a higher rate of detection in this age range. Although district A had the highest detection rate of Down's syndrome in young women, districts B and D performed less well than other districts. The combination of districts A and B, which use serum screening, resulted in a detection rate in young women of 44% (29% to 59%). This was higher than in districts F and G combined, where a maternal age of 35 and over was used as the indicator for invasive testing and the detection rate was 34% (19% to 49%), but the difference was not significant ($P > 0.8$).

There were 90 cases that were not diagnosed before 24 weeks' gestation in women under 35 years. In 57 there was no indication for invasive testing under

the local policy, though nine fetuses had unrecognised heart abnormalities that were detected postnatally. In the 33 other cases, seven women refused serum screening; 15 had false negative results on serum screening and six had false negative results on nuchal scanning; three declined invasive testing after nuchal or serum screens that indicated high risk; and two arose in twin pregnancies with one affected fetus.

Detection rates in women aged 35 years and over

Districts that screened by maternal age might be expected to detect all cases in women aged ≥35 years, whereas other screening methods would miss some of these cases. Across all districts, 186 cases of Down's syndrome occurred in older women and 124 (67%, 60% to 74%) were detected antenatally (table 6). Of the 62 missed antenatally, in 10 (16%) test results were falsely negative, in 43 (69%) women declined antenatal diagnosis, and in five (8%) invasive testing was declined as the pregnancy was twin. Finally four (7%) in women aged ≥35 were undetected in district H, where the policy was to offer invasive testing only to women over 37 years. Among all women ≥35 years who had affected fetuses, 23% (43/186) refused a diagnostic test.

Invasive procedure rates

Table 7 shows the rates of amniocentesis and chorionic villus sampling during this period for each district. They varied from 2.8% in the district with the youngest maternal population (D) and 4.2% in district H, where amnio-

Table 5 Detection of Down's syndrome in women aged <35 years by district 1994-9

District	Serum screen	Scan (weeks)		Amnio-CVS* for previous affected child	Total	Detected at/after birth	Total % (95% CI) detected antenatally	Total
		<14	≥14					
A	8	0	4	1	13	14	48 (19 to 67)	27
B	2	2	2	0	6	10	38 (21 to 55)	16
C	1	1	6	0	8	20	29 (13 to 46)	28
D†	0	1	1	0	2	6	25 (0 to 55)	8
E	3	0	1	0	4	7	36 (8 to 64)	11
F	1	3	7	1	12	11	52 (31 to 73)	23
G	1	1	0	1	3	16	16 (0 to 34)	19
H	0	0	0	0	0	6	0	6
Total	16	8	21	3	48	90	35 (27 to 43)	138

*Amniocentesis or chorionic villus sampling.

†Data for 1997-9.

Table 6 Detection rate of Down's syndrome in women ≥ 35 years and reason for those not detected

District	Detected antenatally (%)	Not detected antenatally		
		False negative screening test	Refused test	Other
A	20/31 (65)	2 serum screen	9	
B	13/17 (77)		4	
C	29/42 (69)	4 nuchal scan	9	
D*	3/4 (75)	1 nuchal scan	0	
E	15/24 (63)	1 serum screen	5	3 twins
F	27/39 (69)	1 nuchal scan	9	2 twins
G	12/19 (63)	1 nuchal scan	6	
H	5/10 (50)		1	4 (<37 years)
Total	124/186 (67)	3 serum screen; 7 nuchal scans	43	9

*Data for 1997-9.

centesis is offered to women aged 37 years and over, to 7.7% in district E, which had the oldest maternal population. District F is a referral centre and its rate is raised by having cases referred from other districts. We cannot adjust for this for all years but over the years 1997-9 the invasive procedure rate for local women in district F averaged 5.4%. Thus about 1.4% of invasive procedures were performed on women referred from elsewhere.

Discussion

Serum and nuchal translucency screening for the antenatal detection of Down's syndrome have been widely introduced without controlled trials of their effectiveness. We found no evidence that such screening improves the antenatal detection rates or reduces rates of invasive procedure. Although we are reporting only retrospective data this is the first study to compare different screening policies in contemporaneous groups of women. In this region there is uncertainty about the best way to screen for Down's syndrome because of the lack of clear evidence, with the eight districts using seven different policies.

We have also shown the disparity between predictions from mathematical modelling of the success of screening policies and their sensitivity in practice. In 2000 we reported an antenatal detection rate of Down's syndrome of 68% in a district that relied on maternal age screening and anomaly scans.³ This was partly due to an unexpectedly large proportion of women aged over 35 and a high proportion of affected fetuses in this age group. We have now confirmed the rise in the age of the antenatal population. Across the region 15% of pregnant women were aged 35 or more compared with the 5-7% assumed in statistical model-

ling in demonstration projects of serum screening.² Despite this high proportion the rate of invasive procedures was only 5-7%, even in districts that relied on maternal age screening. We speculate that the proportion of women who accept an offer of invasive testing rises with increasing age and risk.

The increased age at pregnancy increases both the incidence of Down's syndrome and the proportion of affected fetuses occurring in older women. The overall incidence was, at 2.1 per 1000 deliveries, 50% higher than in national figures.² Modelling of age related screening predicted that only 25-30% of affected cases would arise in older women.^{4,5} Our data show that the high proportion of cases in women over 35 is consistent across the region. This is predictable mathematically. Because in women aged over 35 there is a steep rise in the risk of having an infant with Down's syndrome a small rise in the proportion of women over this age causes a disproportionate increase in the number of affected fetuses born to them. It also accords with historical data. In six studies where over 13% of women were aged over 35, more than half of affected infants were born to this age group.⁶

Serum screening has the potential advantage for older women in that it can lower their individual risk, enabling them to avoid an invasive test. In practice in the districts offering routine serum screening the uptake of the test among older women was only 40%, and this has decreased progressively since it was introduced in 1993. In districts A and B, 40% of older women opted directly for amniocentesis rather than serum screening and 20% declined any test.

What is already known on this topic

Serum screening for Down's syndrome has been presumed to be more effective than screening by maternal age

There have been no controlled studies comparing serum screening with screening by maternal age, and its greater efficacy has been presumed from mathematical modelling, which assumed that only 5% of pregnant women were aged over 35 years

The modelling predicted that only 20-30% of cases of Down's syndrome would arise in women aged over 35 and made no allowance for the effects of routine anomaly scanning

What this study adds

15% of pregnant women were aged over 35 years, more than double the 5-7% presumed in statistical models of screening

58% of babies with Down's syndrome were born to women aged 35 years or more

Serum screening and nuchal scanning did not achieve significantly higher antenatal detection rates of Down's syndrome than the use of maternal age and routine anomaly scanning

Table 7 Invasive procedure rates in each district for 1994-9

District	No of procedures	Total No of births	Invasive procedure rate (%)
A	2217	37 298	5.9
B	833	12 375	6.7
C	1419	27 393	5.2
D	99*	3 547*	2.8
E	1227	15 953	7.7
F	2084	30 525	6.8
G	801	16 649	4.8
H	461	11 095	4.2
Total	9141	154 835	5.9

*Years 1997-9 only.

Conclusion

Our findings suggest that the recently announced government initiative to introduce universal serum screening from 2004 will not achieve its stated objectives. In districts with a higher proportion of older women the use of maternal age detects a high proportion of affected fetuses. The addition of routine anomaly scans, which are already offered in most UK health districts, also allows a large proportion of affected fetuses to be detected in younger women.

We have shown further evidence of the weakness of mathematical modelling and the need for controlled studies before new screening methods are introduced. Indeed, to avoid continuing the confusion that Down's screening currently causes in pregnant women, we believe that new screening methods should be offered only as part of a controlled study until their benefit is proved.

Contributors: The paper was a collaboration between the departments of clinical genetics and fetal medicine in Southampton and genetics in Salisbury. Data for analysis was

taken from the regional congenital anomaly database (WANDA) maintained by DW and from laboratory records obtained by JB. TB runs the prenatal section in which most of the cytogenetic analysis was carried out. DW and DTH performed most of the analyses of clinical data. All authors contributed to the final version of the paper. DW is guarantor for the paper.

Funding: None.

Competing interests: None declared.

- 1 Wald N, Kennard A, Hackshaw A, McGuire A. Antenatal screening for Down's syndrome. *Health Technol Assess* 1998;2:1-112.
- 2 Mutton DE, Alberman E, Ide R, Bobrow M. Results of first year (1989) of a national register of Down's syndrome in England and Wales. *BMJ* 1991;303:1295-7.
- 3 Howe DT, Gornall R, Wellesley D, Boyle T, Barber J. Six year survey of screening for Down's syndrome by maternal age and mid-trimester ultrasound scans. *BMJ* 2000;320:606-10.
- 4 Cheng EY, Luthy DA, Zebelman AM, Williams MA, Lieppman RE, Hickok DE. A prospective evaluation of a second-trimester screening test for fetal Down syndrome using maternal serum alpha-fetoprotein, hCG, and unconjugated estriol. *Obstet Gynecol* 1993;81:72-7.
- 5 Goodburn SF, Yates JRW, Raggatt PR, Carr C, Ferguson-Smith ME, Kershaw AJ, et al. Second-trimester maternal serum screening using alpha-fetoprotein, human chorionic gonadotrophin, and unconjugated oestriol: experience of a regional programme. *Prenatal Diag* 1994;14:391-402.
- 6 Adams MM, Erickson JD, Layde PM, Oakley GP. Down's syndrome. Recent trends in the United States. *JAMA* 1981;246:758-60.

(Accepted 3 December 2001)