Prenatal screening for Down's syndrome

The prevention of non-disjunctional trisomy 21 ('regular' Down's syndrome) depends on offering amniocentesis to older women, and this is not a particularly sensitive screening procedure as the following illustration shows.¹ In 1985 if all pregnancies in England and Wales in women of 35 years or more had been screened (slightly more than 7% of all pregnancies), only 36% of fetuses with Down's syndrome would have been diagnosed prenatally. Fifty one thousand, three hundred and sixty eight amniocenteses would have been performed and about 250 normal fetuses lost, assuming a mortality rate from the procedure of only 0.5%. If one aimed at diagnosing 50% of all fetuses with Down's syndrome one would have to screen all pregnancies in women of 31 and over. This would be unrealistically expensive and too many normal pregnancies would be put at procedural risk.

In practice the uptake of screening because of advanced maternal age falls far short of 100%. For example, in 1984 in the United Kingdom there were only 24 222 prenatal diagnostic chromosome analyses for 705 456 live and stillbirths, or 34.3/1000. Of these 66% were performed because of maternal age of 35 or more, representing only about one third of women in this age group.²

More sensitive screening tests are clearly required and may now be available since the publication of studies of the association between fetal Down's syndrome and low maternal serum α fetoprotein concentrations.^{3–4} This was confirmed by Wald *et al*⁵ in a review of 19 published reports that described a total of 405 pregnancies in which the fetuses had Down's syndrome. More recently there have been similar reports concerning serum unconjugated oestriol concentrations.^{6–7} Unconjugated oestriol is a screening test that is said to be independent of maternal age,⁶ and largely independent of α fetoprotein concentration, so permitting greater sensitivity. For different combinations of maternal age, maternal α fetoprotein, and oestriol concentrations, a single estimate of risk of Down's syndrome ('isorisk') can be derived. This allows decisions to be taken about the degree of risk judged to be sufficient to warrant offering amniocentesis. For example, to achieve about a 35% detection rate of Down's syndrome (equivalent to amniocentesis for all mothers aged 35 and over) the false positive amniocentesis rate (proportion of unaffected pregnancies having amniocentesis) would be 7.5% if age

alone was the criterion, 5.3% using age plus maternal α fetoprotein, but only 2.8% using the combination of oestriol, age, and maternal α fetoprotein. Alternatively, one might decide on a strategy by which a standard investment is made corresponding to a 5% amniocentesis rate. This investment if made in age alone would yield slightly less than 30% detection of Down's syndrome, if made in age and maternal α fetoprotein the yield would be 30–35%, and the best return would be 40–45% from the combination of oestriol, age, and maternal α fetoprotein. Wald *et al*⁶ argue the economic advantages of combined screening at a detection rate of 40% because the addition of oestriol to maternal age and maternal α fetoprotein screening would mean that, of every 1000 women screened, 34 (3.4%) would avoid unnecessary amniocentesis resulting in savings greater than the cost of the extra 1000 serum oestriol estimations. Even greater savings would be possible if a simultaneous combined α fetoprotein concentration-oestriol assay were to be developed.

These are important claims, particularly as the impact of maternal α fetoprotein on screening for Down's syndrome has not yet gained general acceptance, and they suggest that there is a need for a review of strategies as more extensive prospective data are accumulated from pilot studies. There will still be false positive results with some unnecessary amniocenteses, although these would be compensated for by the reduction in the number of amniocenteses performed on older women no longer thought to be at high risk. Continuing the existing policy and introducing combined screening would raise amniocentesis rates unacceptably, and a new screening policy not based exclusively on maternal age would exclude some older women. Will obstetricians and patients accept what will seem to be a withdrawal of services when inevitably some older women who would expect amniocentesis on present criteria are found to have low composite risks and nevertheless produce children with Down's syndrome? It will be important to avoid confusion and possible medicolegal problems by clear explanations of new screening criteria. Obstetric teams will have to cope with these problems of re-education, and will need the help of professional counsellors to deal with the greatly increased expectations for patient participation in decisions concerning screening for fetal defects.⁸

The publicity associated with new screening strategies may well increase demand and a 'positive' screening result will lead to greater patient compliance. This will in turn produce more clinical, ultrasonography, laboratory, and counselling work. Facilities available in the United Kingdom for screening for Down's syndrome are patchy, and it is already difficult for most cytogenetic laboratories to meet demand when cash limits are so tight. Biochemistry laboratories will also have to consider the implications on resources as they modify their techniques to make the measurement of low maternal α fetoprotein concentrations more accurate (currently screening concentrates on high maternal α fetoprotein for NTD) and develop assays for unconjugated oestriol concentrations that are suitable for large scale rapid application. Efficient data management and combined estimations of risk are demanding and will include consideration of age, α fetoprotein concentration and oestriol concentrations, and may require further modification for gestational age, maternal weight, and fetal sex. No doubt other screening techniques will be reported and will require assessment, for example fetal femur length.^{9 10} Recently Bogart *et al* have shown that second trimester maternal serum human chorionic gonadotrophin concentrations in pregnancies associated with Down's syndrome may be twice normal.¹¹ Combining this new marker with maternal age, serum α fetoprotein, and unconjugated oestriol could lead to a Down's syndrome detection rate of 60% for an amniocentesis rate of 5%. Ultimately the use of molecular genetic techniques may permit early prenatal diagnosis by chromosome 21 specific gene probes.

Though there is evidence that a conscientious objection to abortion on the grounds of fetal abnormality is the view of only a minority in our society,⁸ personal views must be respected and adequate provision made for survivors with Down's syndrome. These developments and others in fetal screening justify careful and detailed national planning as pilot studies are mounted and before large

scale implementation is attempted. The Department of Health and Social Security (DHSS) has been quick to respond to other genetic investigations, and has recently published a favourable report on the work of three centres it funded to evaluate DNA screening.¹² Surely the time has come to establish some form of central forum to advise the DHSS and the research councils on the multidisciplinary problems created by screening for fetal and genetic defects.

References

- 1 Brock DJH. Screening for Down's syndrome. *Lancet* 1987;ii:1083-4.
- 2 ACC Review of Clinical Cytogenetics 1984 England and Wales. London: Association of Clinical Cytogeneticists, 1986.
- 3 Merkatz IR, Nitowsky HM, Macri JN, Johnson WE. *Am J Obstet Gynecol* 1984;148:886-94.
- 4 Cuckle HS, Wald NJ, Lindenbaum RH. Maternal serum alpha-fetoprotein measurement: a screening test for Down's syndrome. *Lancet* 1984;i:926-9.
- 5 Wald NJ, Cuckle HS. Recent advances in screening for neural tube defects and Down's syndrome. *Obstetrics* 1988 (in press).
- 6 Wald NJ, Cuckle HS, Denselm IW, *et al*. Maternal serum unconjugated oestriol as an antenatal screening test for Down's syndrome. *Br J Obstet Gynaecol* 1988 (in press).
- 7 Canick JA, Knight GJ, Palomaki GE, Haddow JE, Cuckle HS, Wald NJ. Low second trimester maternal serum unconjugated oestriol in pregnancies with Down's syndrome. *Br J Obstet Gynaecol* 1988 (in press).
- 8 King's Fund Forum: screening for fetal and genetic abnormality. *Br Med J* 1987;292:1551-3.
- 9 Benacerraf BR, Gelman R, Frigoletto FD. Sonographic identification of second trimester fetuses with Down's syndrome. *N Engl J Med* 1987;317:1371-6.
- 10 Lockwood C, Benacerraf BR, Krinsky A, *et al*. A sonographic screening method for Down's syndrome *Am J Obstet Gynecol* 1987;157:803-8.
- 11 Bogart MH, Pandian MR, Jones OW. Abnormal maternal serum chorionic gonadotrophin levels in pregnancies with fetal chromosome abnormalities. *Prenat Diagn* 1987;7:623-30.
- 12 Department of Health and Social Security. Special medical development in clinical genetics, interim report: clinical effectiveness in the service context. *Medical Division CDPNM* London: DHSS, 1987.

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