Trisomy 18

Seeking other disorders within antenatal serum screening programmes for Down's syndrome

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Case example: Trisomy 18

It is accepted that certain requirements need to be met before a screening test is judged to be ethical and worthwhile.[1] Antenatal screening for Down's syndrome and spina bifida meet these conditions. They are serious disorders that lead to prolonged disability. Screening can identify most of these pregnancies with an acceptably low amniocentesis rate.

A difficulty arises when the method of screening for one disorder also identifies others that would not warrant screening in their own right. This can lead to further intervention which poses risks and incurs costs.

Identifying trisomy 18 as part of antenatal screening programmes for Down's syndrome is one such example. Trisomy 18 occurs with a birth prevalence about one tenth that of Down's syndrome. It is the second most common aneuploidy surviving to birth, but in spite of this, most cases result in a miscarriage or stillbirth and of those that survive about 50% die within a month. About 10% live longer than one year with severe disability.[2] So in 100 000 pregnancies, about 16 will result in a liveborn infant with trisomy 18 of which one or two will survive beyond one year, if no steps are taken to identify affected pregnancies.

For cases of trisomy 18 identified in women who are screen positive for Down's syndrome there is no problem. There is no increase in the amniocentesis rate, no additional risk to the pregnancy, and little additional cost. However, fetal trisomy 18 is usually not identified in pregnancies that are screen-positive for Down's syndrome. While the markers used to identify a high risk of trisomy 18 are the same as those used in screening for Down's syndrome, a different pattern is seen and a different algorithm used, so that some women will have a high risk for trisomy 18 but not for Down's syndrome. The amniocentesis rate is therefore increased with an associated increase in fetal loss and cost.

Figure 1 shows the effect of adding a separate trisomy 18 algorithm using the triple test (AFP, uE_3, and hCG), with a second trimester trisomy 18 risk cut off of 1 in 100. About 60% of trisomy 18 term pregnancies are detected with an estimated amniocentesis rate of about 0.2% and odds of being affected given a positive result (OAPR) of 1:20. With a fetal loss rate from amniocentesis of 1% there would be one unaffected fetal loss for five affected term pregnancies diagnosed. This is probably an acceptable balance of risk and benefit, even though most affected infants die within one year. If the risk cut off level were lowered the balance becomes less acceptable. At a risk cut off of 1 in 400, about 75% of trisomy 18 term pregnancies are detected with an amniocentesis rate of about 1%. The OAPR in this case would be 1:83 and the ratio of affected fetuses detected to healthy fetuses lost would be almost 1:1 (fig 2). Any further reduction in the risk cut off would mean that there would be more healthy fetuses lost than affected ones detected, which most would regard as unacceptable.

The estimates in figures 1 and 2 take no account of women who are also screen-positive for Down's syndrome and would be offered an amniocentesis anyway. However, since the percentage of trisomy 18 in this category is small (10–20%, personal communication) this would have little effect on the estimates shown. While it will be rare for women to be both at increased risk of trisomy 18 and screen-positive for Down's syndrome, when this happens the odds of having a trisomy 18 pregnancy are very high (1:2).[5]

The strategy designed to identify some pregnancies with trisomy 18 with only a modest increase in the amniocentesis rate is sensible but it has led some to expect that all pregnancies screened should have a risk estimate reported for trisomy 18. Some may think it is even appropriate to use the same risk cut off level for the two disorders, even though the OAPRs would be different. Routine trisomy 18 risk reporting is liable to alert physicians and patients to pregnancies with a risk well above the background risk but still well below a cut off selected to ensure a low additional amniocentesis rate. This may encourage patients to have an amniocentesis when otherwise they

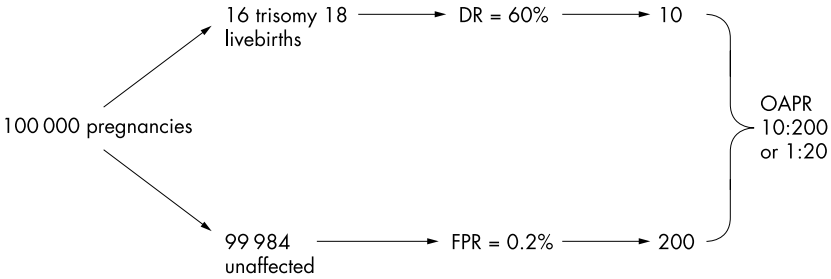

Figure 1 Detection of pregnancies with trisomy 18 in screening programmes for Down's syndrome using the triple test* with a mid trimester risk cut off of 1 in 100 (adapted from Hackshaw and Wald [3–4]). DR, Detection rate; FPR, false positive rate; OAPR, odds of being affected given a positive result. *Triple test: measurement of alphafetoprotein, unconjugated oestriol, and human chorionic gonadotrophin at about 16 weeks of pregnancy, interpreted with maternal age.

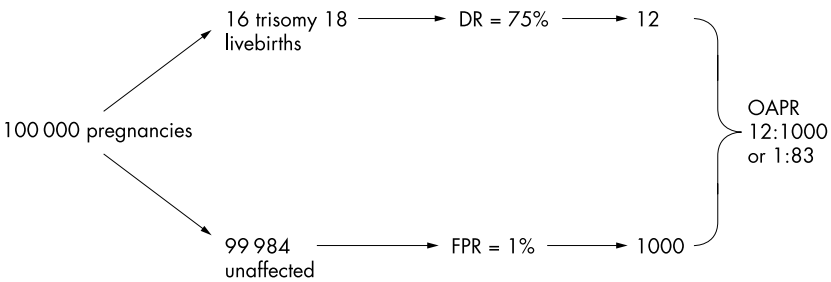

Figure 2 Detection of pregnancies with trisomy 18 in screening programmes for Down's syndrome using the triple test* (adapted from Hackshaw and Wald [3–4]). DR, Detection rate; FPR, false positive rate; OAPR, odds of being affected given a positive result).*Triple test: measurement of alphafetoprotein, unconjugated oestriol, and human chorionic gonadotrophin at about 16 weeks of pregnancy, interpreted with maternal age. with a mid trimester risk cut off of 1 in 400

would have no reason to consider one, leading to an unacceptable loss of healthy fetuses for each with trisomy 18 detected.

Seeking to identify pregnancies with trisomy 18 is an example of a general issue that can arise in medical screening, that is, using screening programmes for one disorder as an opportunity to identify others. This may be worthwhile, but only if the consequences are known, quantified, and judged to be acceptable. The case for seeking other disorders within screening programmes needs to be evaluated as rigorously as the primary programme. Even if adding a new element in this way is easy for those performing the test, the consequential effects can be significant both to the individuals screened and their medical advisers.

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