

Recurrent false-positives in antenatal screening for Down's syndrome

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We recently showed that adjusting marker values in a current pregnancy for those in a previous unaffected pregnancy improves screening performance; it reduces the recurrent false positive rate without reducing the detection rate [1]. It has been asserted that there are two reasons to be cautious about using this adjustment [2].

The first reason stated for caution is that our estimates of screening performance are based on a "series of assumptions" as data are lacking on marker values from pregnancy to pregnancy when the first is unaffected and the second affected. We made one assumption in our paper, which we believe to be reasonable. We assumed that the regression slope of current affected pregnancies on previous unaffected pregnancies is the same as that for pairs of unaffected pregnancies.

What is not stated is that two assumptions are implicitly made when marker values are not adjusted for values in a previous pregnancy. The first is that there is no correlation between marker values in a current affected pregnancy and a previous unaffected pregnancy. Although this assumption is implausible, we examined its effect on screening performance. The results, shown in Table 1, indicate that adjustment still improves screening performance. Table 2, reproduced from our paper, is shown for comparison. The second assumption, that there is no association between marker values in a pair of unaffected pregnancies, has been shown to be incorrect [2,3].

The second reason stated for caution is that the adjustment may be invalid in certain situations, for example when the previous pregnancy was a twin pregnancy, a woman changed her smoking habits between pregnancies, a spontaneous fetal loss, or extremely high or extremely low marker values which will tend to be associated with pathological conditions. As stated in our paper, information on whether a previous pregnancy was a twin pregnancy and on whether a woman's smoking habits had changed would be available in the screening database in which case no adjustment would be made. We also stated that adjustment should not be performed if the woman were screened within the last ten months as her previous pregnancy is likely to have ended in a miscarriage or a termination of pregnancy. We recommended that marker values in a previous pregnancy be truncated before they are used to adjust values in a current pregnancy, to minimize the over-correction of marker values because of extreme values in a previous pregnancy.

These exclusions from the general policy of adjustment are rare, probably representing no more than about 2 or 3% of all pregnancies. To make no adjustment to all pregnancies because there is no need to adjust this small group would be a disservice to the majority of women who would benefit from the adjustment. There is, therefore, a clear benefit in adjusting marker values for those in a previous pregnancy increasing screening performance at minimal extra inconvenience and cost. The practice is better than making no adjustment and there is no basis for being cautious about using the adjustment.

References

1. Wald N, Barnes I, Birger R, Huttly, W. 2006. Effect on Down syndrome screening of adjusting for marker levels in a previous pregnancy. *Prenatal Diagnosis*; **26**: 539-44.
2. Autumn 2006. Allowing for previous MoMs. *Down's Screening News*; **13**: 45.
3. Holding S, Cuckle H. 1994. Maternal serum screening for Down's syndrome taking account of the result in a previous pregnancy. *Prenatal Diagnosis*; **15**: 321-4.
4. Wald NJ, Cuckle HS. 1981. Raised maternal serum AFP levels in subsequent pregnancies. *Lancet*; **1**: 1103.

Table 1 Screening performance in women who have had a previously screened pregnancy according to whether serum marker levels are adjusted for those in the previous pregnancy; assuming the no correlation between serum markers in a current affected pregnancy and a previous unaffected pregnancy.

| Screening test | Adjustment | DR(%) for a FPR of | | | FPR(%) for a DR of | |
|------------------|------------|--------------------|----|----|--------------------|-----|
| | | 1% | 3% | 5% | 75% | 85% |
| Triple | No | 54 | 69 | 75 | 4.9 | 10 |
| | Yes | 58 | 71 | 77 | 4.2 | 9.8 |
| Quadruple | No | 63 | 76 | 81 | 2.9 | 7.1 |
| | Yes | 67 | 78 | 83 | 2.2 | 6.2 |
| Combined | No | 71 | 81 | 85 | 1.5 | 4.9 |
| | Yes | 73 | 82 | 86 | 1.3 | 4.4 |
| Serum Integrated | No | 70 | 81 | 86 | 1.7 | 4.7 |
| | Yes | 74 | 83 | 87 | 1.2 | 3.9 |
| Integrated | No | 85 | 91 | 94 | 0.3 | 1.0 |
| | Yes | 86 | 92 | 94 | 0.2 | 0.8 |

DR: Detection rate

FPR: False positive rate

Table 2 Screening performance in women who have had a previously screened pregnancy according to whether serum marker levels are adjusted for those in the previous pregnancy; assuming that the regression slope of current affected pregnancies on previous unaffected pregnancies is the same as that for pairs of unaffected pregnancies

| Screening test | Adjustment | DR(%) for a FPR of | | | FPR(%) for a DR of | |
|------------------|------------|--------------------|----|----|--------------------|-----|
| | | 1% | 3% | 5% | 75% | 85% |
| Triple | No | 54 | 69 | 75 | 4.9 | 10 |
| | Yes | 59 | 73 | 80 | 3.5 | 7.9 |
| Quadruple | No | 63 | 76 | 81 | 2.9 | 7.1 |
| | Yes | 68 | 80 | 85 | 1.9 | 4.9 |
| Combined | No | 71 | 81 | 85 | 1.5 | 4.9 |
| | Yes | 75 | 83 | 87 | 1.1 | 3.7 |
| Serum Integrated | No | 70 | 81 | 86 | 1.7 | 4.7 |
| | Yes | 76 | 85 | 89 | 0.9 | 2.9 |
| Integrated | No | 85 | 91 | 94 | 0.3 | 1.1 |
| | Yes | 88 | 93 | 95 | 0.2 | 0.7 |

DR: Detection rate

FPR: False positive rate