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Editorial

Current state of second trimester screening for Down's syndrome

The era of biochemical screening for fetal Down's syndrome began just 15 years ago with the observation that maternal serum α fetoprotein (AFP) levels, measured in the second trimester, tended to be low in Down's syndrome pregnancies.[1] With that observation and the description of how AFP levels could be combined with maternal age as independent predictors of risk, the prospect of identifying more than a fraction of affected pregnancies became a reality.[2] New biochemical analytes, measured in maternal serum, have been added to the original single marker to improve the efficiency of screening. In 1988 the triple test (AFP, human chorionic gonadotrophin (hCG), and unconjugated oestriol (uE_3) with maternal age) was described,[3] and this and its double test variant (without uE_3) are most commonly used in screening. More recently, the addition of a fourth biochemical marker, inhibin A, has been proposed and has been implemented in several screening programmes. The so-called quad test has been estimated to have a detection rate of about 75% at 5% amniocentesis rates.[4 5]

In this issue of the *Journal of Medical Screening*,[6] Haddow and colleagues provide further evidence of the effectiveness of inhibin A as a second trimester screening marker. The median inhibin A level in the pregnancies with Down's syndrome was 2.10 times that among unaffected pregnancies of the same gestational age, similar to the estimate of 2.05 for the 460 Down's syndrome samples in the eight studies published to date.[6] Haddow and colleagues estimate that inhibin A measurement added to the triple test will lead to a detection rate of 75–78% at a 5% amniocentesis rate, remarkably similar to the estimates of previous studies. Research on inhibin A as a second trimester serum screening marker has produced notably consistent results.

A practical consideration is the specification of an appropriate screening policy that takes advantage of the improved screening performance that uses a new marker in combination with the established screening markers. For example, while showing that at a fixed 5% false positive rate inhibin A measurement adds about 8% to the detection achieved with standard triple marker screening, Haddow *et al* suggest that a better option would be to avoid increasing the detection rate but, instead, to decrease the false positive rate. In their example, triple marker screening generates a 70% detection rate at a 5.9% false positive rate. With the addition of inhibin A, the false positive rate would decrease by 4.4% to 3.3% while maintaining the same 70% detection rate. Put another way, almost half of the amniocentesis procedures and half the fetal losses caused by amniocentesis would be avoided without sacrificing detection.

Alternatively, an argument can be made for increasing detection above that obtained with triple marker screening. The question is are we doing well enough by detecting 60–70% of Down's syndrome pregnancies, the standard currently attained? If we can attain close to 80% detection at a comparable amniocentesis rate, shouldn't we do this? Most screening programmes today use a risk cut off for screen positive that generates a potential 5–8% amniocentesis rate. If a similar or even slightly lower amniocentesis rate were maintained, the addition of inhibin A to triple marker screening would achieve an approximate 80% detection rate (Haddow *et al* estimate an 80–82% detection rate at a 7% false positive rate).

Other, less optimal ways of incorporating inhibin A into current screening practice might be considered. Those programmes currently using double markers might add inhibin A as a third marker; detection in this case would be expected to increase by about 10%. Programmes currently using triple markers might consider substituting inhibin A for one of the other three. AFP, although the weakest of the triple markers in Down's syndrome screening, would not be dropped because of its use in screening for open neural tube defects. uE_3 would seem a likely candidate; substituting inhibin A for uE_3 would increase detection by 3–5% according to Haddow *et al*. However, uE_3 is the most effective marker in screening for Edwards' trisomy 18 syndrome and inhibin A is not an adequate substitute in that role.[7 8] Replacing hCG with inhibin A would not seem reasonable given that hCG and inhibin A each separately have similar

effectiveness. But, Haddow *et al* estimate that a triple marker panel of AFP, inhibin A, and uE_3 would in fact be slightly more effective than a panel consisting of AFP, inhibin A, and hCG, mostly because of the moderate correlation between hCG and inhibin A values in both cases and controls. In addition, screening programmes in the United States might avoid the economic burden of licensing with the hCG patent holders by substituting inhibin A for hCG.

Inhibin A is one of the latest in a series of placental secretory products whose levels in maternal serum have been shown to be raised in Down's syndrome pregnancy. It is also one of the best screening markers so far examined. At this point in the evolution of prenatal screening it is reasonable that measurement of inhibin A should be added to existing second trimester screening protocols and that four marker testing should be considered the standard by which all older screening methods are judged.

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