ORIGINAL ARTICLE

The Role of Maternal Serum Alpha-Fetoprotein, Human Chorionic Gonadotrophin and Oestriol in the Antenatal Screening of Down's Syndrome

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Summary

The use of maternal age alone to identify pregnant mothers at risk of a fetus with Down's syndrome has recently been supplemented by maternal serum screening using biochemical markers such as alpha-protein, human chorionic gonadotrophin and oestriol. These tests have been reported to increase the sensitivity of antenatal detection of such fetuses from 35% to 67% with a false positive rate of 5%. However, these maternal serum markers may be affected by maternal weight, the smoking history of mothers and diabetes mellitus. Furthermore, such sensitivities are achieved only when gestational age is assessed accurately by ultrasound. Many further studies need to be carried out before the introduction of maternal serum screening into routine obstetric practice in Singapore. These include studies on the incidence of Down's syndrome in the local population, studies on the distribution of these serum markers in the second trimester of pregnancy, sensitivities and positive predictive values of such a test in the local population as well as the socio-economic implications of implementing such a screening test in the local obstetric population.

Key Words: Trisomy 21, Obstetric, Biochemical markers

Introduction

For many years, it has been common obstetric practice to use maternal age to identify mothers at risk of having a Down's affected pregnancy. The risk for Down's syndrome increases exponentially for expecting mothers from 35 years of age and above. However, only 35% of the children with Down's syndrome are born to mothers of that age group, whilst the rest of the 65% are born to mothers less than 35 years of age[1]. Maternal serum alpha-fetoprotein (MSAFP) screening was introduced into routine obstetric practice to improve the identification of mothers at risk of Down's syndrome in all age groups. Progress has also been made in the development of additional maternal biochemical markers for trisomy 21 such as human chorionic gonadotrophin (hCG) and oestriol to improve the sensitivity of screening[1-4]. Computer-assisted test interpretations have also been used recently to assign a risk to each mother[5-6]. Should such a test be made available locally?

Biochemical markers of Down's syndrome

In the second trimester, MSAFP and oestriol levels rise progressively and maternal serum hCG concentrations decrease in normal pregnancies. Between 15 and 20 weeks, each of these biochemical markers, when expressed as a log multiple of median (MOM), has been reported to be independent of gestational age and

fit a normal Gaussian distribution[1]. Pregnancies with Down's syndrome demonstrate a characteristic pattern: low MSAFP and oestriol levels and high hCG levels (triple test).

Low levels of MSAFP are due to reduced fetal production, mainly by the fetal liver and yolk sac. In the three largest studies to date, low MOM values of 0.72, 0.72 and 0.64 for MSAFP were reported based on 114, 68 and 86 affected pregnancies respectively[7-9]. Human chorionic gonadotrophin is a glycoprotein hormone secreted by the syncytiotrophoblast, appears in maternal blood after implantation of the fertilised ovum and rises until 10 weeks gestation. Between 10 and 18 weeks, levels decline at a steady rate. In the three largest studies, MOM values of 2.04, 1.79 and 2.39 were reported based on 77, 54 and 50 affected pregnancies respectively[1,2,10]. Recent studies have suggested that measuring the beta-subunit may improve the sensitivity of the test[11,12]. Oestriol is a steroid hormone produced by the syncytiotrophoblast from fetal precursors. Reduced maternal levels of this hormone (MOM levels of between 0.71 to 0.77) have been reported in pregnancies with Down's syndrome[1,2,6,13]. However, a recent study by Macri *et al*[14] of 41 Down's affected pregnancies reported a MOM value of 0.99, casting doubt on the usefulness of serum oestriol levels in screening for such pregnancies.

Other biochemical markers in maternal serum such as pregnancy specific beta-1 glycoprotein (SP-l)[15,16] and human placental lactogen (Knight *et al.* 1990) are also reported to be raised in Down's affected pregnancies. Recently, Cuckle *et al*[17] reported the usefulness of maternal urea-resistant neutrophil alkaline phosphatase. However, this is presently very labour intensive and further improvements in technology are needed.

Antenatal screening for Down's syndrome

The multivariate method of assigning a risk to the pregnant mother of a Down's affected fetus comprises the age-related risk and a risk modifier, the latter derived from the maternal serum markers[18,19]. A cut-off of 35 years of age results in a sensitivity of 30-35% with a false positive rate of 5%[1]. Assuming the same false positive rate, Wald *et al*[20] reported increased sensitivities of 35%, 54% and 58% respectively when MSAFP, hCG and oestriol were added to the screening programme. The use of MSAFP alone did not increase the sensitivity of screening appreciably. Conversely, the addition of hCG to MSAFP increased the sensitivity considerably.

The sensitivities and false positive rates of the serum markers are also dependent on maternal age[4,19]. For a given risk cut-off of one in 300, a sensitivity of 51.6% and false positive rate of 4.7% can be achieved in 28 year old women; comparable values for a similar risk cut-off in 36 year old women will be 78% and 19% respectively[19]. Therefore, such a screening programme will be less effective in a younger population.

The sensitivities of the maternal serum screening programme can be improved by accurate dating by ultrasound. Wald *et al*[20] reported increased sensitivity rates of 36, 58 and 67% respectively with the addition of MSAFP, hCG and oestriol when gestational age was adjusted by ultrasound. This increase by nearly 10% in sensitivity suggests that the maximum yield of such a screening programme necessitates concurrent ultrasound dating.

Other workers have suggested that further allowances have to be made for maternal weight, smokers and mothers with insulin-dependent diabetes. Wald *et al*[20] reported a decrease in the concentrations of the serum markers with increasing weight, related to a dilutional effect of increased interstitial fluid volume in heavier women. Maternal serum levels are also reported to be reduced in insulin-dependent diabetics[21] and increased in smokers[22].

Is a maternal serum screening programme justified for the local population?

Before the implementation of such a screening programme for the obstetric population at large, numerous questions have to be addressed. The incidence of Down's syndrome has been reported to be 1.3 per 1000 in England and Wales[23]. However, no comparable figures have been reported for the local population in Singapore. The prevalence of the condition locally has to be clearly documented before embarking on such a screening programme.

The sensitivity of the "triple test" in the detection of trisomy 21 fetuses has been reported to be up to 67% if ultrasound is used to assess gestational age[1]. This was achieved by simulating the effect of screening on laboratory results and correlating with pregnancy outcome[1,19,24]. It is unlikely that such results will be achievable in routine clinical practice. False positive rates have been reported to be as low as 5% in most major studies[1,6,12]. However, the most important statistic to the individual pregnant mother is the odds of being affected given a positive result. Reynolds *et al*[19] reported odds of between one in 26 and one in 111, depending on the age of the mother. The low positive predictive values are due to the low prevalence of the disease.

The concentrations of the three serum markers are expressed as MOM. However, some workers have reported daily variations in log MOM human chorionic gonadotrophin levels during the same period[25]. Further studies on the distribution of these serum markers in the local obstetric population should be performed as MSAFP levels may also vary with different races.

Although the cost of serum screening using the Triple Test is relatively cheap (about S$70 or RM120) many additional factors also need to be costed, including counselling time. Furthermore, the amniocenteses rates will be increased primarily due to older mothers requesting amniocentesis regardless of the results of serum screening.

Greater anxiety may be generated by a screening programme of this kind[29]. Maternal serum screening, introduced to the obstetric population at large, will also inevitably raise questions about the ethico-moral issues about Down's syndrome and termination of pregnancy. There remains the concern that public encouragement of screening will devalue the worth of the handicapped[30].

Conclusions

The introduction of the Triple Screening Test using maternal serum has increased the ability to detect more Down's syndrome fetuses antenatally. Numerous conceptual and methodological hurdles have to be overcome before this test can be introduced for widespread routine clinical practice. Its cost effectiveness has to be properly evaluated in terms of extra laboratory support, counselling support and extra manpower involved. The acceptance of this test within the local population must also be evaluated. These factors must be taken into consideration before the introduction of such a screening test into routine obstetric practice.

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