Screening for Down syndrome – Maternal Serum Screening and Ultrasound Soft Markers

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EVOLUTION OF SCREENING FOR DOWN SYNDROME PREGNANCIES

Many advances in fetal Down syndrome (DS) screening have occurred since the National Institutes of Health advised maternal age-based screening in 1979 in the USA.[1] The pace has quickened over the past decade, with the introduction of second-trimester maternal serum and ultrasound-based screening methods for fetal DS and, more recently, with the development of first-trimester screening programs. In the United States, second-trimester maternal serum screening for fetal DS is still the current standard, whereas in parts of the United Kingdom and Europe, a first trimester screening approach that incorporates ultrasound and biochemical screening has been advocated. Implementation of National guidelines in the UK by the National Screening Committee[2] has been started.

Although all would agree that both methods are an improvement over age-based screening alone, controversy persists regarding which method, or a combination, is most efficacious and cost-effective. Several authors have reported on the economic evaluations of alternative prenatal DS screening programs[3-6] with differing conclusions. A similar comparison of second trimester serum screening with combined first trimester screening (nuchal translucency and biochemistry) for fetal DS is lacking and impossible to perform as an abnormal ultrasound would result in an intervention.

The first protein routinely measured in the maternal blood was AFP (alpha-fetoprotein). High AFP levels were originally used to identify fetuses at risk for neural tube defects. In 1984 it was discovered that low AFP levels may help identify fetuses with DS.[7] The blood test, sometimes still called the "AFP test",[8] evolved by 1990 into the so-called "triple test", since it tested two other analytes: human chorionic gonadotrophin (hCG) and unconjugated oestriol (uE3).[9] Later the maternal blood screen evolved into the "quad screen" because a fourth marker (inhibin A) was also reported to be useful.[10] These maternal serum screening tests were performed at 15-20 weeks of pregnancy. The "triple test" which measures the amount of AFP, hCG and uE3 or the "double test", which consists of measuring AFP and hCG have slightly differing detection rates but should detect around 60 - 70% of DS pregnancies for a 5% false-positive rate.[10-17]

Nuchal translucency (NT) screening for DS between 11 and 14 weeks of pregnancy gained credence in the mid 1990's as an equally if not more efficient method of screening for DS compared to second trimester serum screening with a estimated detection rate of 70 – 80% for a 5% false-positive rate.[18,19] First trimester serum screening using PAPP-A and free beta hCG was used in combination with NT would increase its detection to around 90% at the same false-positive rate.[19] Recently it would appear that the presence or absence of nasal bone is a very powerful risk predictor of DS to enable an even higher screening efficiency.[20] Despite the impressive gains, there is sustained interest in further improving detection rates while maintaining or even reducing the number of false-positive diagnoses.[21]

LIMITATIONS OF VARIOUS STUDIES IN REPORTING THE DETECTION RATES IN THE LITERATURE

The best way of comparing various screening tests of DS would be by comparing their receiver-operator curves on a standardized maternal population.[22] As age is a major component in deriving the risks, a predominantly older maternal population would give higher detection rates for the same false-positive rate. The incidence of DS is also relatively uncommon and large numbers would be needed in order to accurately reflect the performance of a screening test. An under-acknowledged limitation of many studies is the underestimation of the denominator for DS pregnancies which were not identified and miscarried before term. This verification bias would result in over

estimation of the detection rate[23]. Another confounding factor is the natural loss rate of DS pregnancies throughout the pregnancy resulting in assumptions and modelling needed when comparing first and second trimester screening programmes. Although there are now prospective "non-interventional" first trimester DS screening programmes that attempt to compare the effectiveness with second-trimester screening program, fetuses with thickened NT were excluded from the study.[24,25] It is often overlooked that the uptake rates of these screening tests may vary widely.[23,26]

Nuchal Translucency

In 1990, researchers at the Kings College Hospital, London noted that increased NT at 10 to 14 weeks of gestation is associated with chromosomal abnormalities. Several studies have reported that measurement of nuchal translucency, as recommended by the Fetal Medicine Foundation, is a sensitive marker for DS with a detection rate of 75 to 80% for a false-positive rate of 5%.[18,19,27] However, it does appear that the success of the test relies very much on accurate, reproducible measurements of NT being done in a standardized and consistent fashion.[27] Just as laboratory assays participate in quality assurance schemes, measurement of NT which is an operator-dependent clinical screening service requires an equivalent clinical quality assurance program to ensure consistency in screening results.

The combined First Trimester Screen for Fetal Aneuploidy (10-14 weeks)

This evolved from NT screening and combines measurements of two hormones (free beta hCG and PAPP-A) from the maternal blood, together with the maternal age and ultrasound measurements (NT and crown-rump length) to calculate an overall risk for fetal DS. It has a reported detection rate of 80-90% or even higher for fetal DS.[20,24,28,29]

Integrated Screen or Sequential Screen

Recently, Wald et al[30] reported a new and highly sensitive and specific formulation, the integrated test. Based on mathematic modelling from previously published data sets, the combination of first trimester NT and pregnancy-associated plasma protein-A plus second trimester serum human chorionic gonadotrophin (hCG), alpha-fetoprotein (AFP), unconjugated oestriol, and inhibin A produced extremely high screening performance. At a 1% and 5% false-positive rate, corresponding detection rates were 85% and 94%, respectively. Despite its promise, some reservations have been expressed about this algorithm[31] and the delay between the first- and second-trimester components of the test. In addition, there is the obstetricians' discomfort about withholding information on the first trimester portion of the test, particularly because these markers by themselves are sensitive predictors of DS and could materially affect a family's choices. When NT measurement is combined with serum biochemical first-trimester markers (PAPP-A and free b-hCG), the DS detection rate rises to as high as 91%, at a 5% false-positive rate.[32]

These tests may be considered as combinations of the first trimester screen and second trimester screen. For the integrated screen, a single result (risk estimate) is given after both the first and 2nd trimester screens are completed.[33] For sequential screening, the patient is given one result after the first trimester screen and a second modified result after the 2nd trimester biochemical screen. The practicality of such a screening programme on a large scale needs to be addressed.

It should be noted that a first trimester serum screening would be highly correlated with a second trimester serum screening and any combinations would need to take this into account.[34]

ULTRASOUND SOFT MARKERS BETWEEN 15 AND 22 WEEKS GESTATION

How are likelihood ratios for soft markers derived?

The first sonographic marker of DS, the thickened nuchal fold (>= 6 mm), was first described in 1985.[35] Since that time, a number of ultrasound "markers" for detecting fetal DS have been observed during the second trimester. These markers should be distinguished from "structural" defects. If there is a structural malformation, such as duodenal atresia or exomphalos, the risk of aneuploidy is far higher. Using a panel of ultrasound markers in a systematic fashion as a part of screening has been referred to as a "genetic sonogram". These markers include nuchal fold thickening, renal pelvis dilation, shortened femur or humerus, echogenic bowel, absent middle phalanx of the fifth finger, sandal gap, and more recently absent or hypoplastic nasal bone.

The best estimates of both the positive and negative likelihood ratios for each of the common markers of DS are given in Table 1.[36,37] These estimates were derived from the combined data from 2 leading centres of obstetric ultrasound in the United States. Major or minor defects were identified in 74.3% of 350 fetuses with DS and in 13.5% of 9384 chromosomally normal fetuses. On the basis of these data, the likelihood ratio for trisomy 21, if there is no detectable defect or marker, is 0.30. In each case, the likelihood ratio is the quotient of the incidence of a given marker in DS pregnancies and its incidence in chromosomally normal pregnancies. For example, a thickened nuchal fold is found in 33.5% (107/319) of DS

Table 1. Incidence of major and minor defects or markers in the second-trimester scan in trisomy 21 and chromosomally normal fetuses in the combined data of 2 major series[36,37]

Sonographic Marker	Trisomy 21(n/N) (n/N)	Normal (n/N)	Positive likelihood ratio	Negative likelihood ratio	Likelihood ratio for isolated marker
Nuchal fold	107/319 (33.5%)	59/9331 (0.6%)	53.05 (39.37-71.26)	0.67 (0.61-0.72)	9.8
Short humerus	102/305 (33.4%)	136/9254 (1.5%)	22.76 (18.04-28.56)	0.68 (0.62-0.73)	4.1
Short femur	132/319 (41.4%)	486/9331 (5.2%)	7.94 (6.77-9.25)	0.62 (0.56-0.67)	1.6
Pyelectasis	56/319 (17.6%)	242/9331 (2.6%)	6.77 (5.16-8.80)	0.85 (5.16-8.80)	1.0
Echogenic focus	75/266 (28.2%)	401/9119 (4.4%)	6.41 (5.15-7.90)	0.75 (0.69-0.80)	1.1
Echogenic bowel	39/293 (13.3%)	58/927 (0.6%)	21.17 (14.34-31.06)	0.87 (0.83-0.91)	3.0

** From these data the positive and negative likelihood ratios (with 95% CI) for each marker can be calculated. In the last column, the likelihood ratio for each marker is found in isolation.[38]*

fetuses and 0.6% (59/9331) chromosomally normal fetuses, which results in a positive likelihood ratio of 53.05 (33.5/0.6). Consequently, the finding of a thickened nuchal fold increases the background risk by a factor of 53.05, but at the same time an absence of this marker should reduce the risk by 33%. The same logic applies to each 1 of the 6 markers shown in the table above.

When two or more markers are detected, there is a significant association with aneuploidy and therefore the management of such cases is more straightforward. However, risk assessment based on the presence of a single marker is difficult. The lack of clarity is primarily related to the initial reports of associations coming from fetal medicine centres catering for a high-risk population, with the strength of association usually weakened or indeed negated in studies of low-risk populations.

HOW ARE ESTIMATED RISKS CALCULATED?

The estimated risk can be derived by multiplying the *a priori* risks (age or serum screen) by the positive likelihood ratio of the specific marker. The use of ultrasound markers in this way is nearly identical to the use of biochemical markers as part of a panel. Although there are no prospective trials to test this form of sequential screening, many maternal-fetal medicine specialists assume that they are independent risk predictors from serum screening and use it to modify the *a priori* risks.

Consequently, in estimating the risk in a pregnancy with a marker, it is logical to take into account the results of previous screening tests. For example, in a 32-year-old woman at 20 weeks of gestation (background risk, 1 in 507) who had an NT screening that resulted in a 7-fold reduction in risk (to 1 in 3549), after the diagnosis of isolated echogenic bowel at the 20-week scan, the estimated risk would increase by a factor of 3 to 1 in 1183. However, for the same ultrasound finding in the absence of previous NT screening, the risk would increase from 1 in 507 to 1 in 169. There are some exceptions to this process of sequential screening, which assumes independence between the findings of different screening results. The findings of nuchal edema at the second trimester scan cannot be considered independently of NT screening in the first trimester. A recent study by Prefumo[39] also showed an association between NT and echogenic foci.

The presence of an isolated choroid plexus cyst or an echogenic left ventricular foci in the heart as a soft marker is controversial, with studies for[40,41] and against.[42-44] The various likelihood ratios may become less predictive in the future as most DS pregnancies would be "screened out" in the first and second trimesters through screening programs. In addition, there are reports emerging of associations between NT and soft markers on ultrasound.[39,45,46]

COUNSELLING ISSUES

The practice of recording or informing the mother of the demonstration of such markers varies considerably from one obstetric unit to another.[47] Whilst some units counsel an increased risk of aneuploidy and offer invasive karyotyping when a single marker is found, others do not even record the finding, deeming the risk of aneuploidy

insufficient to warrant the offer of karyotyping. In any event, if one such marker is identified, the sonographer must examine the fetus carefully to exclude the presence of any additional markers. Many soft markers will disappear or regress as gestation proceeds. The persistence or disappearance of a marker does not alter the risk of aneuploidy. For example, most choroid plexus cysts disappear with advancing gestation even when associated with trisomy 18.

There is paucity of hard data on which to estimate the increased risk of aneuploidy given the presence of a single soft marker. Population-based data are required to fully assess the true association between single markers and aneuploidy. Soft markers are generally common, and their appearance in a fetus with DS, which is a relatively common aneuploidy, may simply be a reflection of the prevalence in the whole population (e.g. mild pyelectasis occurs in 0.73% of an unselected population). Other confounding factors include observer bias (e.g. the RADIUS trial had a detection rate for fetal anomalies of just 35% in the screened group[48]), differing definitions, improvement in quality of ultrasound machines over the years the data was collected and the difficulty in collecting accurate denominator data.

However, the risk of miscarriage of 1:100[49] after any invasive diagnostic test for karyotyping also induces considerable anxiety. Counselling must aim to provide sufficient information to permit the parents to make an informed decision. It must also provide appropriate reassurance, whilst not creating false reassurance; a difficult balance to achieve. Women who wish to use risk assessment to decide whether to have an invasive test need to balance this risk against the procedure-related loss and the acceptability of the various methods for termination of pregnancy. Some women might decide that a risk for DS of 1:1000 is unacceptable, whereas others might feel that a 90% chance of having a healthy baby with the calculated risk of 1:10 is quite reassuring. If counselling is adequate and women truly understand what is at stake, the concept of false-positive and false-negative results becomes obsolete.

Women need to be reassured that in any given group of, say, 900 women with an estimated risk of 1:300, only 3 women will give birth to a baby with DS. One would be entitled to expect very tight confidence intervals around this estimate, i.e. 2-4 affected babies irrespective of what method of risk assessment is used. Apart from serum screening models,[50] there are no such first trimester study published. Also, it would be important to know to what extent such confidence intervals vary from method to method and from test to test.

The absence of markers on routine second-trimester scan has been shown to reduce the risk of aneuploidy in otherwise high-risk women, although in practical terms, women (or their obstetricians) given a high risk on one test might not accept a lowering of that risk based on another.

Whether the introduction of population screening with biochemistry and ultrasound examination has led to the potential benefits that are based on expected screening performance is unknown. The willingness of women to participate in different types of screening programs may depend on the gestational age when screening is offered, how long it takes to report results, and socio-demographic factors. Additionally, screening tests may not perform as well in clinical as compared with research settings, offers for screening may not be accepted, and women with screen-positive results may choose to forego invasive prenatal testing. Only a few relatively small studies have evaluated the outcomes of prenatal screening in population settings.

CONCLUSION

It is important to remember that the risk of DS derived from screening tests have to be weighed against the risk of miscarriage from ultrasound-guided diagnostic tests such as genetic amniocentesis between 16-20 weeks or chorionic villus sampling (CVS) between 11-13 weeks. Although the risk is small, the risk of genetic amniocentesis has been estimated as 1:200 to 400, and the risk of CVS has been estimated as 1 in 100 (surprisingly, these estimates are still controversial. The FASTER[24] study suggest that the risk of amniocentesis at referral centres may be significantly less than stated here). Appropriate counselling and risk communication should remain the cornerstone when offering any form of DS screening tests.

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