New maternal serum markers and a better utilisation of existing ones can help improve risk assessment for foetal abnormalities. On-going work on the development of markers to screen for conditions such as pre-eclampsia also provides hope for reducing morbidity and mortality in pregnancy.

The growing importance of maternal serum markers

by Dr P. Mottram

In the 1970s it was established that elevated levels of maternal serum human alpha-foetoprotein (hAFP) were associated with neural tube defects in the foetus. Later it was found that hAFP in combination with other markers was also useful in assessing the risk of Down syndrome and other chromosomal abnormalities. In recent years both academia and diagnostic companies have searched for better screening tools for chromosomal abnormalities. At the same time it has been realised that there is a major need for serum markers that will help in the prediction of problems during pregnancy, including intra-uterine growth restriction (IUGR), pre-eclampsia (PE) and prematurity.

Better performance in Down screening to reduce amniocenteses

In the screening programmes that have been established in many countries, the risk of chromosomal abnormality is calculated for every pregnancy. Women deemed at high-risk of giving birth to affected babies are then offered a definitive diagnostic test based on cytogenetic analysis following amniocentesis or chorionic villous sampling (CVS). These diagnostic tests are expensive, and the invasive sampling procedures required are associated with the risk of damage to the foetus and possible miscarriage. The potential danger to unaffected foetuses is an especially strong incentive for avoiding amniocentesis or CVS wherever possible. There is thus considerable interest in improving screening procedures.

Traditionally, screening for chromosomal abnormalities has been performed in the second trimester of pregnancy, with determinations of some or all of the serum markers, hAFP, intact human chorionic gonadotropin (hCG), unconjugated oestriol (uE3) and inhibin A obtained between 14-18 weeks of gestation. Ultrasound examination, with measurement of the nuchal fold (NF) at 20-24 weeks, is sometimes carried out to complement serum tests.

Interest in bringing screening forward to the first trimester of pregnancy has been based on the perceived benefit of more time being available for relevant retesting, counselling, diagnostic testing and the possible termination that may be a consequence of a positive screening result. A number of studies have indicated that pregnant women prefer screening and its possible consequences to take place in the first trimester [5, 8]. The usual serum markers for first trimester testing are free hCGB and pregnancy-associated plasma protein A (PAPP-A). The preferred ultrasound marker for measurement at 11-13 weeks in addition to serum marker measurements is m nuchal translucency (NT).

OSCAR - a practical and popular screening solution

OSCAR stands for One Stop Clinic for Assessment of Risk. Within the context of screening for Down syndrome, it includes the coordination of a range of healthcare personnel and services to provide testing, risk calculation and counselling, all within a single visit of the pregnant woman to the antenatal clinic during the first trimester of pregnancy. The approach allows more efficient use of clinical time as well as improved diagnostic efficiency. By measuring PAPP-A and free hCG, together with NT at a one-stop clinic, detection rates of 90% per cent may be achieved with a false positive rate of only 5% [2]. The approach also provides improved patient satisfaction by reducing the number of patient visits, thus minimising patients’ time and travel costs, as well as their anxiety and stress.

Naturally the clinic wishing to implement OSCAR is faced with practical problems. Scheduling of tests and personnel time has to be well co-ordinated, and all individual events need to be of defined and reasonably short duration. The development of compact and rapid testing systems makes it possible to acquire the serum biochemistry test results required for first trimester Down syndrome risk assessment within a sufficiently narrow time window. As an example, PerkinElmer’s DELFIA Xpress random access platform integrated with LifeCycle with Elipse risk calculation software represents an ideal solution, being fast, flexible and easy to use.

Multi-marker strategies

Many attempts to improve the performance of Down screening have focused on finding the best ways to use existing markers, i.e. the optimum combinations of markers and the timing of the tests. Proposed strategies are typically compared to integrated screening, which in terms of performance represents an established standard. In integrated screening both first and second trimester markers are measured, and risk is assessed after all marker results are available. The widespread adoption of integrated screening itself has, however, been hindered by practical and economic considerations as well as the central problem that the benefit of early detection enabled by the use of first trimester markers is removed. It has been remarked in this context that if a model supports an 85% detection rate (DR) for a 1% false positive rate (FPR), then first trimester markers alone can detect roughly 60% of affected pregnancies, while the addition of the second trimester tests makes it possible to detect another 25%.

Stepwise screening and contingent screening are approaches that represent possible
solutions to the problem. They do not unnecessarily delay the reporting of high risk cases in the first trimester, but at the same time the confirmed benefits of the second trimester markers are still made available. The principles of stepwise and contingent screening are illustrated in comparison to integrated screening in Figure 1. Contingent screening also offers the benefit that, compared with integrated screening, it supports better use of resources since typically 85% of pregnant women do not require the second stage tests [Figure 2].

ADAM12: a potential early marker for chromosomal abnormalities

ADAM metallopeptidase domain 12 (ADAM12) is a new marker with exciting potential in screening for a number of indications relating to foetal development. The protein has been suggested as an additional marker in screening programmes for chromosomal abnormalities such as Down syndrome [6] and may also have potential in future programmes for early detection of intrauterine growth restriction, premature birth and pre-eclampsia [7]. ADAM12 was discovered at the University of Copenhagen and is licensed to PerkinElmer, Inc., which is developing assay kits.

In Down screening, ADAM12 appears to be especially useful as a very early marker. Affected pregnancies are characterised by low levels at weeks 8 to 10. The levels then typically rise, so that by week 12 they are indistinguishable in affected and non-affected pregnancies. Later, in the 2nd trimester, the marker is encountered at high levels in affected pregnancies. These characteristics of ADAM12 suggest its likely utility in contingent screening strategies, repeated measurement strategies and others.

PP13 in early detection of pre-eclampsia

Pre-eclampsia (PE) is a condition of pregnant women. It is defined as increased blood pressure (hypertension) and protein in the urine (proteinuria), which can lead to eclampsia with life-threatening convulsions. PE is estimated to affect 8,370,000 woman worldwide every year and is a major cause of maternal, foetal and neonatal morbidity and mortality.

There is no effective preventive therapy for PE. Although some of the symptoms, for example hypertension, may be reduced using conventional therapies, the only accepted treatment for PE itself is delivery. Due to the serious consequences of the disorder, multiple efforts are being made to combat the condition through the identification of effective markers for risk assessment, and selection of suitable medication to reduce the anticipated risks. Cases categorised as early onset PE are associated with the risk of severe complications, and though they represent only 30% of the total PE cases, they currently absorb 80% of the total PE health care costs. The focus is thus on finding early markers. Early detection means increased likelihood of better outcomes, in terms of severity, complete recovery, or severity reduction.

The new maternal serum marker, Placental Protein 13 (PP13) shows potential for early detection of PE in low risk groups [4]. Initially isolated in 1983 [3], PP13 has been cloned by Diagnostic Technologies Ltd (DTL), which is collaborating with PerkinElmer, Inc. on the development of assays. The use of PP13 as a screening tool to define pregnancies at high risk of developing PE would not only help to plan the monitoring of a high risk pregnancy and avoid unnecessary healthcare visits for a low risk pregnancy, but also would help in designing more efficient clinical trials for prevention of PE.

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in early pregnancy appears to be lower than in women who do not develop PE. The subsequent rise in level of serum PP13 is steeper in women who later suffer from PE [Figure 3].

An ultrasound detection method, uterine artery Doppler, used at 20-24 weeks can achieve acceptable PE detection, but may provide results too late to allow much time for intervention. When the method is used on its own in the first trimester, the false-positive rate is unacceptably high.

It has been shown that first trimester screening involving both Doppler ultrasound and maternal serum PP13 detection may provide the specificity which is lacking with Doppler ultrasound alone [9]. As with screening for chromosomal abnormalities, contingent screening may also indicate the path forward for PE screening. It is estimated that a contingent screening strategy for PE could achieve a detection rate of 90% with all pregnancies tested for PP13, and on the basis of the results for PP13, only the 6% of results which are questionable should be submitted for Doppler ultrasound. A big advantage of this approach is that PP13 can be determined relatively easily, whereas Doppler assessment of the uterine arteries is less easily accessible and currently confined to specialist centres.

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References

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