**Point-of-Care Screening for Chromosomal Anomalies in the First Trimester of Pregnancy**

Since the serendipitous finding almost 20 years ago of a reduced concentration of maternal serum α-fetoprotein (MSAFP) in an index case of a second-trimester pregnancy complicated by trisomy 18 (1) and the subsequent confirmation of this finding in other pregnancies complicated by trisomy 21, there has been a gradual improvement in trisomy 21 screening efficiency as better markers have been identified. Screening using a combination of maternal age, MSAFP, and maternal serum free β-human chorionic gonadotropin (β-hCG) or total hCG has enabled trisomy 21 detection rates of 65–70% (for a 5% screen-positive rate) to be achieved in second-trimester prospective screening (2, 3). Although the use of additional markers such as unconjugated estriol and dimeric inhibin-A have been proposed, modeling predicts only an additional 5% detection (4), and no large-scale prospective data have been published with a four-marker combination.

In the past decade, research energies have largely focused on the first trimester of pregnancy. The identification of suitable maternal serum biochemical markers such as free β-hCG (5) and pregnancy-associated plasma protein A (PAPP-A) (6) led this advance. The development of improved ultrasound imaging techniques, however, allowed the identification of nuchal translucency thickness as the major marker of chromosomal anomalies in the first trimester. With measurements performed in a standardized way (defined by the Fetal Medicine Foundation; www.fetalmedicine.com) by suitably trained sonographers, trisomy 21 detection rates in combination with maternal age have reached 73% (for a 5% screen-positive rate) in multicenter prospective intervention studies (7). A combination of nuchal translucency and the two first-trimester serum markers has been shown to increase this detection rate to 89% for trisomy 21 (8) and to also allow the detection of 90% of other chromosomal anomalies (trisomies 13 and 18, Turners syndrome, and triploidy) using alternative algorithms (9).

The identification of pregnancies at increased risk in the first trimester has several advantages. These advantages include, for some women, an earlier diagnosis with a consequent safer and less traumatic therapeutic abortion and for the majority of women, an earlier reassurance. Although improvements in screening performance have in the past been measured by increased detection rates, little attention or research has focused on service delivery and counseling or how this affects maternal and family anxiety and stress at a time when families should be celebrating a new family addition.

With the advent of new diagnostic technologies, it has become possible to look at screening service delivery in a different way, which may lead to reduced family anxiety, a more informed choice, and a more efficient use of healthcare professionals’ time. Rapid immunoassays suitable for point-of-care testing (10) like the one described for PAPP-A by Qin et al. (11) are a further step that will allow the development of more widespread one-stop clinics for the assessment of risk for fetal anomalies (OSCAR). The concept of the OSCAR approach was developed in 1997 (12) when the first rapid assays for serum free β-hCG and PAPP-A became available on the CIS Kryptor platform (now available from Brahms Diagnostica GmbH). The 19-min homogeneous immunoassay technology (13), based on time-resolved amplified cryptate emission using chelates developed by Nobel Prize winner Jean-Marie Lehn, can be carried out in the same time that it takes a qualified sonographer to measure the fetal size (crown rump length) and nuchal translucency thickness and report a mini anomaly scan.

With rapid testing technology, it became possible to consider locating the testing within the antenatal clinic and organizing a clinic in such a way that the mother presents to the clinic at a specified appointment time for a 1-h visit. In the first step the mother has pretest counseling with a midwife counselor, and if she so wishes she can then (with informed consent) proceed to the clinic phlebotomy station to have blood collected, which is passed to the adjacent laboratory. The mother then proceeds to the ultrasound suite, and during the time of the ultrasound scan, the free β-hCG and PAPP-A are measured in her blood.

A potential advantage of the system outlined by Qin et al. (11) is the ability to measure these markers directly in whole blood, although the need for hematocrit correction will partially negate this advantage unless this measurement can be incorporated directly into the measurement device. After the ultrasound examination, a patient-specific multimarker risk assessment can be made, and within 45 min after the mother enters the clinic, a counselor can discuss this report with her in a posttest counseling session. If appropriate, diagnostic testing by chorionic villus sampling could be scheduled for the following day, with a quantitative PCR diagnostic result available within 48 h (14).

Such clinics have been in operation in two centers in the United Kingdom since 1998. The results of the first year of screening women of all maternal ages in one of these centers have been reported (15), with detection rates of 86% for trisomy 21 and 95% for all aneuploidies. Patient acceptance of offers of screening was high (97%), indicating that early one-stop screening was acceptable to women.

One-stop clinics have developed over the past decade in several clinical areas, ranging from breast cancer screening to cardiovascular risk clinics and one-stop surgical clinics. These services all have in common the integration of a range of clinical and diagnostic services that allow for a better use of clinical time and improved diagnostic efficiency. They aim to maximize patient satisfaction by reducing the number of patient visits and
minimizing patient travel costs, anxiety, and stress. In the context of prenatal screening for chromosomal anomalies, the integration of counseling, ultrasound, biochemistry, midwifery, and obstetrics in a one-stop clinic does seem to be acceptable to women and, while offering maximum utilization of hospital outpatient resources, provides a high diagnostic efficiency and potentially allows for a more informed choice.

New developments such as these that are made possible by innovative health technologies need to be assessed in a social context. One such program in the United Kingdom, the Innovative Health Technologies Program (www.york.ac.uk/res/ith), jointly sponsored by the Economic and Social Research Council and the Medical Research Council, has recently been announced. This program aims to bring together researchers with experience in social science, medicine, and health research to examine innovative health technologies, investigating the mutual shaping of science, technology, and society through theoretical and empirical research. The projects under investigation are focusing on new genetic screening programs and aim to evaluate and compare the existing and new models of service delivery (such as OSCAR) and to assess the impact on patient anxiety and stress and the social management of pregnancy.

Even before such studies begin, new technological advances may have a further impact in this area. One such development (16) is a perceived view that “integrating” prenatal screening across a 5-week period, measuring markers at 10, 11, and 15 weeks gestation with nondisclosure (rate), but at what cost to patient anxiety and stress, not to improved detection (92% detection at a 5% screen-positive rate), brings about the earlier screening test results, brings about the normal and abnormal development and growth. New York: Springer-Verlag, 1991:181–94.

The recent identification of a strong relationship of a one-stop clinic will play a part in further reducing the screen-positive rate requires further study.

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References


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