Sampling of the chorionic villi: a technique to complement amniocentesis

SAMPLING of the chorionic villi is a relatively new technique which complements amniocentesis and ultrasound in the field of antenatal genetic diagnosis. It involves the biopsy of fetal tissue from the chorionic plate at its site of attachment to the uterine wall and this can then be used for cytogenetic and biochemical investigations. Chorionic villi sampling is already in world-wide use. In the UK, 12 centres are known to be actively using it for clinical diagnosis.

Whereas amniocentesis cannot be performed until the second trimester of pregnancy, sampling of the chorionic villi is possible much earlier, typically at six to nine weeks of fetal life (eight to 11 weeks from last menstrual period). Because the technique provides large quantities of fetal tissue, cell culture is unnecessary before diagnostic procedures can begin. In comparison, amniocentesis yields only small numbers of cells, and cell culture is essential to increase the total cellular mass which can then be used for genetic or biochemical investigations.

The possibility of accurate genetic diagnosis during the first trimester means that should it be necessary to terminate the pregnancy then this early abortion may be less traumatic to the physical and mental health of the mother than are the late, mid-trimester abortions which necessarily follow amniocentesis.

Development of chorionic villi sampling

Chorionic villi sampling was first used in China for fetal sex determination and later in both China and the USSR for genetic diagnosis.[1-3] It began to be used in the West during the 1970s. While there are numerous variations on the basic technique, the three most common methods are: the insertion of a flexible catheter via the cervix and manipulation of the catheter to the site of the chorion from where a portion of zygotic tissue is removed;[4] the use of biopsy forceps in a similar manner;[3,5] or transabdominal puncture.[6] All three methods are performed under ultrasound control.

The main indications for chorionic villi sampling are to determine the karyotype of the fetus in older women where there is a significant risk of Down's syndrome and the other chromosomal nondisjunctions; for biochemical analysis and gene mapping in those genetic disorders with a high recurrence risk (for example, sickle cell anaemia, Tay-Sachs disease, some beta-thalassaemias); and in metabolic sex-linked chromosomal disorders.[7] The technique is of greatest use for the exclusion of chromosomal abnormalities in the pregnancies of older women. Chorion biopsy is not useful, however, for diagnosing neural tube defects (for example, spina bifida). In this case estimation of venous or amniotic alpha-fetoprotein is still necessary.

Risks and benefits

Before any new technique is adopted it must be shown that the benefits outweigh the disadvantages and that there are distinct advantages over the currently used technology. How does chorionic villi sampling compare with amniocentesis?

The risk of miscarriage attributable to amniocentesis has been estimated at around 0.5 per cent, but some studies have shown that this risk can be as high as 3 per cent.[8] There is evidence from studies on humans that the use of amniocentesis is associated with neonatal respiratory disorders[9] and animal studies have shown that this may be by affecting lung development.[10,11] Amniocentesis may predispose the fetus to minor compression abnormalities of the lower limbs.[9,12] But perhaps most significantly, the long delay between conception, investigation and diagnosis may have psychological and social consequences for the parents.[8,13,14]

An informal World Health Organization register of pregnancies investigated by chorionic villi sampling has been in operation since 1983 and currently comprises around 3000 cases from 43 centres. In 97 per cent of these, sufficient chorionic villi were obtained for the technique to be satisfactory; 10 per cent of pregnancies were aborted following diagnosis of an affected fetus. The risk of miscarriage was 4.1 per cent, although there was a slightly lower risk, around 3.4 per cent, in centres with more experience of the method.

Thus, even in expert hands, the fetal loss following sampling of the chorionic villi is higher than that following amniocentesis. In addition, the long-term consequences of the procedure are unknown. Disruption of the chorionic plate and amniotic sac, together with possible direct trauma to the fetus, might well have unknown long-term effects. Fetal growth retardation during the second trimester, antepartum haemorrhage, infection, premature rupture of the amniotic sac, lowered birth weight, and premature delivery have all been postulated as possible consequences. The prolonged ultrasound necessary during chorion biopsy may well have risks of its own. In addition there may be a psychological cost to the mother when a much wanted normal pregnancy miscarries, possibly felt by her to be a direct consequence of the procedure.

It is worth noting that the first attempts at chorionic villi sampling by doctors in the West in Scandanavia during the 1970s were abandoned in favour of amniocentesis because of the unacceptibly high risk of short-term complications.[15,16] But in retrospect this was probably because of the inadequacies of ultrasound control at that time.

It is against this background that in 1984, the Medical Research Council set up a working party to debate the possibility of constructing a randomized trial to compare the benefits and costs of first trimester chorionic villi sampling with those of second trimester amniocentesis. The desirability of studying new techniques prior to their introduction into clinical practice has long been recognized, but chorionic villi sampling is rapidly growing in popularity, and unless such a trial is initiated soon, it may well prove impossible to study the technique properly. The United Kingdom has lagged somewhat behind other European countries and the USA in adopting this technique but as a consequence we are now in an excellent position to initiate such a study. Randomized trials have already been commissioned in the USA and Canada. In Canada it is impossible to obtain chorionic villi sampling at a collaborating centre except through random allocation. For success, however, such a study is likely to need international cooperation because the numbers of pregnancies which must be studied to enable significant differences to become apparent is likely to be in the order of many thousands.

There are several problems which must be considered. First, the difficulty of estimating excess fetal loss in the first trimester, a time when the rate of spontaneous miscarriage is high and ill-defined, should not be underestimated. The currently quoted figure for spontaneous abortion in the first trimester is 10 per cent, but this figure rises with age to become as high as 33 per cent in women aged over 40 years.[17] The main indication for chorion biopsy is likely to be maternal age, so the majority of

women involved will be aged over 35 years. For this reason it is difficult to predict the background level of miscarriage. Secondly, whereas chorionic villi sampling is a first trimester procedure, amniocentesis is performed in the second trimester and simple comparisons will exclude the background rate of first trimester miscarriages which have already occurred. Finally, there are ethical difficulties in setting up two randomized cohorts of women with much wanted pregnancies who may well already have formed opinions regarding which of the two methods they prefer.

Nevertheless, it is obviously desirable that some sort of randomized comparison of the two techniques should be made and that the two cohorts of mothers and progeny should be followed up for many years. Should such a study become reality, general practitioners will be actively involved in counselling mothers who are at risk and referring patients to participating gynaecologists early in their pregnancy. They will also be asked to collaborate in the long-term follow-up of the progeny.

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What sort of doctor?

> '. . . . The Board of Censors of the Royal College of General Practitioners has set up a working party to advise on "a method of assessing the performance of established general practitioners in the setting of their own practices".'[1]

Once a clinical discipline defines its work, it follows that some aspects of the work come to be regarded as better or more desirable and other parts worse or less desirable. Thus it is inevitable that emphasis is placed on quality. This immediately raises the questions: How does one recognize and measure quality? How can it be assessed? Pressure to assess the quality of general practice is coming from the profession itself, the consumers (the patients) and, because British general practice is rooted in a National Health Service, from Government as well.

General practice is responding to this pressure by introducing a series of assessment methods, three of which have been developed so far.[2] First came the MRCGP examination, developed in the 1960s, which became the normal entry requirement for College membership in 1968. Secondly, in 1973 a new system of assessment for the selection and reselection of trainers in general practice was introduced and was based on a visit to the practice. Then, in the early 1980s, a working party of the Royal College of General Practitioners advocated a third approach to assessment.[3] This led to another working party and a synthesis of their two reports with accompanying documentation is published today.[1]

The first method of assessment, the MRCGP examination, has been continually refined since it was introduced and a huge amount of theoretical analysis and study and many examiners' meetings have led it to its current format. Its introduction helped to underline general practice as a clinical specialty and to define the content of general practice more clearly. The examination is now taken by about 1700 doctors each year, of whom over 1000 pass. It has become the natural end-point assessment of vocational training.

The second method of assessment, that of trainer selection, is aimed by definition at principals in general practice. Normally, these principals have been in practice for at least three years and are voluntarily seeking the additional responsibility of teaching their discipline. The assessment process has been greatly influenced by the Joint Committee on Postgraduate Training for General Practice whose booklet *Criteria for the selection and reselection of trainers* has provided guidelines.[4] Some of the principles are also contained in the *Statement of fees and allowances.*[5] One essential point is that the applicant is always visited in the practice and, in the great majority of regions, revisited on subsequent applications. The historical importance of the trainer selection system was to move assessment into the practice.

The third method of assessment, popularly known as 'What sort of doctor?', also focuses on principals but it is not aimed either at achieving membership of the College or at the selection of trainers. It represents an attempt to identify the fundamental values on which good general practice rests. It does not lead to a degree or diploma, but offers applicants the opportunity to learn about their own performance and discover ways in which they can improve. The essence of this method is a visit to the applicants in their own practices by peers who, operating within an agreed framework, comment on what they find.