

Medical genetics: advances in brief

Randomised study of risk of fetal loss related to early amniocentesis versus chorionic villus sampling

Sundberg K, Bang J, Smidt-Jensen S, *et al*. *Lancet* 1997;350:697-703.

Although there has been much interest in the possibility of early amniocentesis as an alternative to chorionic villus sampling (CVS), there are few controlled trials to compare the techniques. Potential advantages of early amniocentesis include a smaller risk of miscarriage and a result more accurately reflecting the fetal karyotype without the possibility of placental confined mosaicism. In this study amniocentesis at 11-13 weeks was compared to CVS at 10-12 weeks. A filter was used when collecting the amniotic fluid to enhance the number of cells in the sample. Allocation to procedure was randomised. Fetal loss was compared between the groups, midtrimester scanning was offered, and all pregnancies were followed to term. The women were similar in the two groups at baseline. There were more culture failures in the CVS group (7/555) than the early amniocentesis group (1/548). The results were also obtained quite quickly from the amniocentesis samples; the authors suggest that these positive outcomes are secondary to the use of a filter. Fetal loss rates were similar between the two groups (5.4 and 4.8%), but statistical conclusions could not be drawn. There were more abnormal results in the CVS group (2.5% to 0.7%) explained partly by placental confined mosaicism and partly by the earlier gestation at sampling (it was predicted that some abnormal pregnancies would have miscarried before early amniocentesis). The trial was stopped before completion because of clustering of cases of talipes equinovarus in the early amniocentesis group (1.7%). There seemed to be increased likelihood of talipes if the procedure was done early and if there was amniotic fluid leakage. Other studies have also found a similar incidence of talipes and the authors explain it as perhaps secondary to a disruption of amniotic fluid pressure affecting physiological development of the lower limb. Sundberg and colleagues still hope that early amniocentesis may be a good method of early prenatal diagnosis but make some suggestions for future trials, such as use of smaller bore needles to reduce risk of leakage and delaying amniocentesis until late in the first trimester.

ANGELA BARNICOAT

Mutations in GLUT2, the gene for the liver type glucose transporter, in patients with Fanconi-Bickel syndrome

Santer R, Schneppenheim R, Dombrowski A, *et al*. *Nat Genet* 1997;17.3:324-6.

Fanconi-Bickel syndrome (FBS) is an autosomal recessive condition characterised by hepatorenal glycogen accumulation, impaired glucose and galactose metabolism, low

insulin levels, and glucosuria. Previous suggestions that impaired monosaccharide transport across membranes may cause FBS prompted Santer *et al* to analyse the GLUT2 glucose transporter gene in three FBS families. Three mutations were found, all of which resulted in premature stop codons. As it is known that the distal segments of GLUT proteins are essential for glucose transport, then all three mutations should impair this function and the loss of GLUT2 activity is consistent with FBS symptoms. Patients exhibit hyperglycaemia in the fed state, which can be explained by impaired hepatic uptake of glucose. The observation of hypoglycaemia during fasting is compatible with reduced glucose transport out of the liver, the GLUT2 protein facilitating glucose transport in both directions, and resulting in glycogen accumulation. Impaired intestinal glucose absorption explains the symptoms of diarrhoea and malabsorption. Low insulin secretion can be accounted for by loss of the glucose sensing mechanism in pancreatic beta cells because of impaired glucose uptake. The authors note that heterozygosity for GLUT2 mutations may be a risk factor for the development of non-insulin dependent diabetes mellitus and suggest a systematic study of FBS families to answer this question. Furthermore this paper and a further article in the same issue of *Nature Genetics* describing mice which lack GLUT2 are the subjects of a "news and views" discussion as to the likelihood of GLUT2 playing a primary role in glucose sensing, the process which finely regulates the secretion of insulin in response to blood glucose levels.

DAVID O ROBINSON

Presence of fetal DNA in maternal plasma and serum

Lo YMD, Corbetta N, Chamberlain PF, *et al*. *Lancet* 1997;350:485-7.

The search for fetal material in the maternal circulation is not new, since the possibility of prenatal diagnostic tests without the risk of invasive procedures remains attractive. Lo *et al*, however, have approached the problem not by looking for fetal cells but by looking for fetal DNA in the maternal circulation. This follows reports of tumour DNA being measurable in the circulation of patients with malignancies. Blood was obtained from a number of pregnant women at different gestations, either before amniocentesis or at term. Non-pregnant women were used as controls. Great care was taken to ensure that no cells were in the plasma or serum samples before DNA extraction by a rapid boiling method. Samples were subjected to PCR to detect Y specific sequences. The male sex of the fetus was confirmed by detection of Y specific sequences in 24 of 30 samples. Male sex was most often (80%) correctly identified when plasma was used, compared to a 17% detection rate when nucleated cells from an equivalent volume of blood were used. None

of the women with female fetuses or the controls showed a positive result. The male sex was more likely to be correctly predicted if the sample was taken later in pregnancy. The source of free fetal DNA in maternal circulation is not well understood. The authors speculate that it may come from immunologically mediated cell lysis or developmentally regulated apoptosis. Although this is a preliminary report, it may be that detection of fetal DNA has much to offer, both in the detection of genetic disease where the detection of sequences which are exclusively paternally inherited can lead to diagnosis, and potentially in the understanding of conditions where the placental interface between mother and fetus is disrupted.

ANGELA BARNICOAT

Renal cystic disease in tuberous sclerosis: role of the polycystic kidney disease 1 gene

Sampson JR, Maheshwar MM, Aspinwall R, *et al*. *Am J Hum Genet* 1997;61:843-51.

Renal involvement in patients with tuberous sclerosis (TS) is common, and manifestations may include angiomyolipomas, cystic disease, and renal cell carcinoma. The radiological and macroscopic appearance of the kidneys in TS patients resemble those found in autosomal dominant polycystic kidney disease (ADPKD), but the clinical onset is often early. Major genes for TS (TSC2) and ADPKD (PKD1) lie adjacent to each other on chromosome 16 (p13.3) suggesting that PKD1 may be involved in TS patients with renal involvement. In this study, 27 unrelated patients with TS and renal cystic disease were studied clinically, radiologically, and at a molecular level. Twenty-two patients had contiguous deletions of TSC2 and PKD1. (No similar mutations were found in 81 TS patients with TS but normal renal ultrasound scans.) In 17 of the 22 patients with constitutional deletions, cystic disease was severe with early renal insufficiency, but the one patient with a deletion of TSC2 and of only the 3' UTR of PKD1 had few cysts. Four patients were somatic mosaics and the severity of their cystic disease varied considerably. Mosaicism and mild cystic disease were also found in parents of three of the constitutionally deleted patients. Five patients without a contiguous deletion had relatively mild cystic disease; of these, three had gross rearrangements of TSC2 and two had no identifiable mutation. Significant renal cystic disease in TS usually occurs when the PKD1 gene is involved and mosaicism for large deletions of TSC2 and PKD1 occur quite often. In future, knowledge of TS patients' underlying mutation may influence the type of renal surveillance and follow up recommended. It would also be interesting to review a population of patients with PKD1 to see how many have previously unsuspected involvement of the TSC2 gene.

FRANCES FLINTER