PRENATAL DIAGNOSIS

Helen M Kingston

Techniques for prenatal diagnosis

• Ultrasonography	—safe —performed in second trimester
• Amniocentesis	—procedure risk 0·5% —performed in second trimester —widely available
• Chorionic villus sampling	—procedure risk 2% —performed in first trimester —specialised technique
• Fetoscopy	—procedure risk 3% —performed in second trimester —very specialised technique
• Embryo biopsy	—future technique

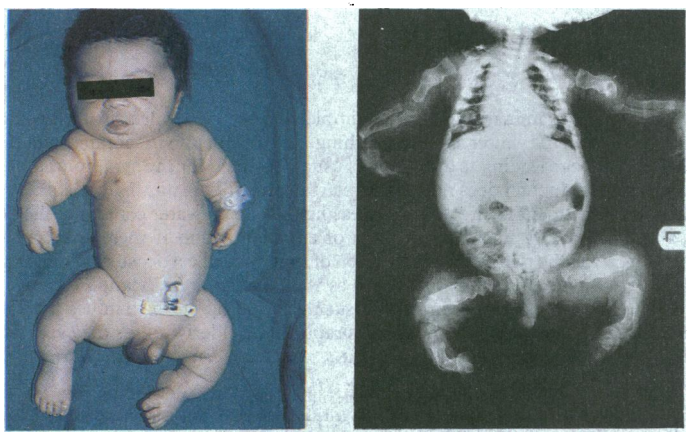
Prenatal diagnosis is important in detecting and preventing genetic disease. Two main advances in recent years have been the development of chorionic villus sampling procedures in the first trimester and the application of recombinant DNA techniques to the diagnosis of many mendelian disorders. Various prenatal procedures are available, generally being performed between eight and 20 weeks' gestation. The timing, safety, and accuracy of prenatal tests are important factors that must be considered. Having prenatal tests and waiting for results is stressful for couples, and they must be supported during this time and given the results as soon as possible. Many couples who face a high risk of a serious genetic disorder in their children will consider embarking on a pregnancy only if reliable prenatal diagnosis is available. Prenatal testing may also be appropriate for couples in whom the pregnancies are at fairly low risk, often allowing a pregnancy to continue with less anxiety.

Indications for prenatal diagnosis

General criteria for prenatal diagnosis

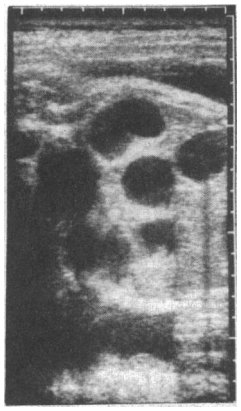
- High genetic risk
- Severe disorder
- Treatment not available
- Reliable prenatal test
- Termination of pregnancy acceptable

Prenatal diagnosis occasionally allows prenatal treatment to be instituted but is generally performed to permit termination of pregnancy when a fetal abnormality is detected or to reassure parents when a fetus is unaffected. Pregnancies at risk of fetal abnormality may be identified in various ways. A pregnancy may be at increased risk because of advanced maternal age, because the couple already have an affected child, or because of a family history of a mendelian disorder or an inherited chromosomal rearrangement. Occasionally couples from certain ethnic groups whose pregnancies are at high risk of particular autosomal recessive disorders can be identified before the birth of an affected child by population screening programmes. In many mendelian disorders, particularly autosomal dominant disorders of late onset and X linked recessive disorders, family studies may be needed to assess the risk to the pregnancy and to determine the feasibility of prenatal diagnosis.



Osteogenesis imperfecta type II (perinatally lethal) can be detected by ultrasonography in second trimester.

Several important factors must be carefully considered before prenatal testing, one of which is the severity of the disorder. For many genetic diseases this is beyond doubt; some disorders lead inevitably to stillbirth or death in infancy or childhood. Perhaps more important, however, are conditions that result in children surviving with severe, multiple, and often progressive, physical and mental handicaps, such as Down's syndrome, neural tube defects, muscular dystrophy, and many of the multiple congenital malformation syndromes.



Prenatal detection of jejunal atresia indicating need for neonatal surgery.

The availability of treatment is also important to consider. When treatment is effective termination may not be appropriate and prenatal diagnosis is generally not indicated, unless early diagnosis permits more rapid institution of treatment, reducing illness, complications, and deaths. Phenylketonuria, for example, can be effectively treated after diagnosis in the neonatal period, and prenatal diagnosis, although possible for parents who already have an affected child, may be inappropriate. On the other hand, prenatal diagnosis of congenital malformations amenable to surgical correction is important as it allows the baby to be delivered in a unit with facilities for neonatal surgery and intensive care.

Applications of prenatal diagnosis

- Maternal serum screening — α fetoprotein estimation
- Ultrasonography — structural abnormalities
- Amniocentesis — α fetoprotein and acetylcholinesterase; chromosomal analysis; biochemical analysis
- Chorionic villus sampling — DNA analysis; chromosomal analysis; biochemical analysis
- Fetoscopy — direct examination; fetal sampling

A prenatal test must be sufficiently reliable to permit decisions about a pregnancy. Some conditions can be diagnosed with certainty, others cannot. For example, in mendelian disorders amenable to DNA analysis but for which specific gene probes are not available and the biochemical defect in the disorder is not known, the use of linked DNA markers allows a quantified risk to be given for a pregnancy.

As an abnormal result on prenatal testing may lead to termination this course of action must be acceptable to the couple. Careful assessment of their attitudes is important, and even those couples who clearly elect for termination need continued counselling and psychological support afterwards. Couples who do not contemplate termination may still request a prenatal diagnosis to help them to prepare for the outcome of the pregnancy, and these requests should not be dismissed.

Methods of prenatal diagnosis

Some causes of increased maternal serum α fetoprotein concentration

Underestimated gestational age

Threatened abortion

Multiple pregnancy

Fetal abnormality
- Anencephaly
- Open neural tube defect
- Anterior abdominal wall defect
- Turner's syndrome
- Bowel atresias
- Skin defects

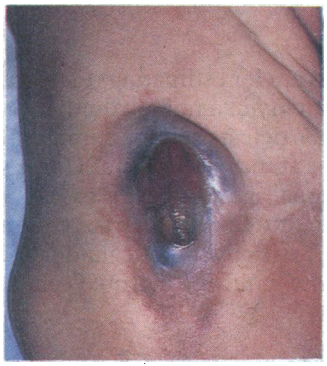
Maternal hereditary persistence of α fetoprotein

Placental haemangioma

Screening of maternal serum

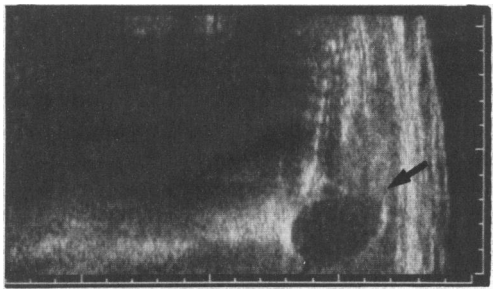
Testing of maternal serum has limited use for detecting genetic disease in the fetus but is valuable in screening for neural tube defects. About 80% of cases of open neural tube defects and over 90% of those of anencephaly can be detected by an increased maternal serum α fetoprotein concentration at 16-18 weeks' gestation. High concentrations indicate a need for further assessment. Screening of serum α fetoprotein alone is not sufficiently reliable in high risk cases in which a previous infant has been affected, and in these cases ultrasonography and amniocentesis should be offered.

A low serum α fetoprotein concentration indicates an increased risk of Down's syndrome. In future amniocentesis for chromosomal analysis may be offered on the basis of a composite risk estimated from the maternal age and the serum α fetoprotein, unconjugated oestriol, and human chorionic gonadotrophin concentrations. This would increase the detection rate of Down's syndrome without increasing the number of amniocenteses performed.



Lumbar meningomyelocele.

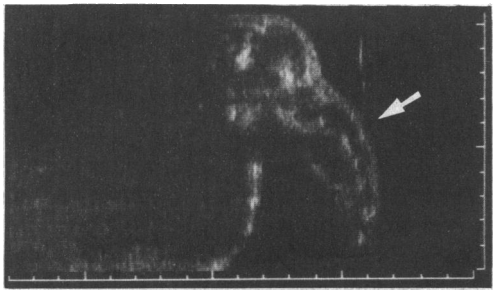
The possible identification of circulating trophoblast cells in maternal blood offers a potential method of detecting genetic disorders in the fetus. The application to prenatal diagnosis will, however, probably be limited as trophoblast cells are difficult to isolate and may represent cells arising from previous pregnancies.



Large lumbosacral meningomyelocele.

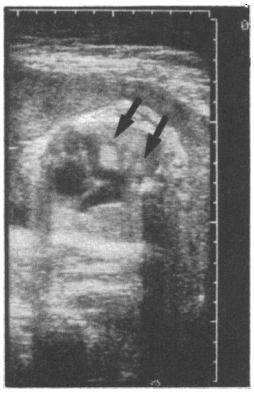
Ultrasonography

Obstetric indications for ultrasonography are well established and include confirmation of viable pregnancy, assessment of gestational age, location of the placenta, and monitoring fetal growth. Ultrasonography is an integral part of amniocentesis, chorionic villus sampling, and fetoscopy and has an increasingly important role in prenatal diagnosis of structural abnormalities in the fetus as skill develops and scanners give higher resolution.



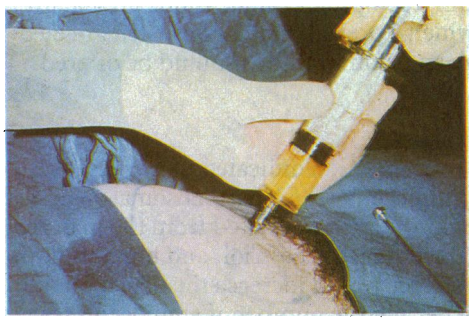
Shortened limb in Saldino-Noonan autosomal recessive bone dysplasia syndrome.

Disorders such as neural tube defects, severe skeletal dysplasias, and abnormalities of abdominal organs may all be detected by ultrasonography between 17 and 20 weeks' gestation, and hydrocephalus may be detected later in pregnancy. These abnormalities may be recognised during routine scanning of apparently normal pregnancies, and this allows the parents to be counselled about the abnormality and plans to be made for the neonatal management of disorders that are amenable to surgical correction. Centres specialising in high resolution ultrasonography can detect an increasing number of other abnormalities, such as structural abnormalities of the brain, various types of congenital heart disease, clefts of the lip and palate, and microphthalmia.



Cardiac leiomyomas in tuberous sclerosis.

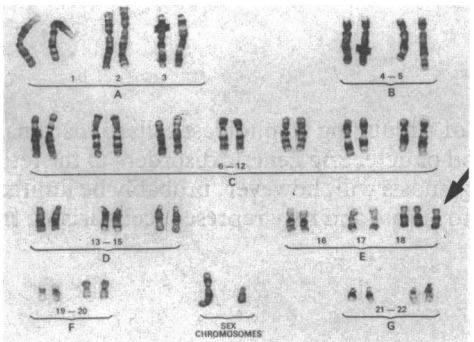
Most single congenital abnormalities follow multifactorial inheritance and carry a low risk of recurrence, but the safety of scanning provides an ideal method of screening subsequent pregnancies and usually gives reassurance about the normality of the fetus. Syndromes of multiple congenital abnormalities, however, may follow mendelian patterns of inheritance with high risks of recurrence; for many of these, ultrasonography is the only available method of prenatal diagnosis.



Amniocentesis procedure.

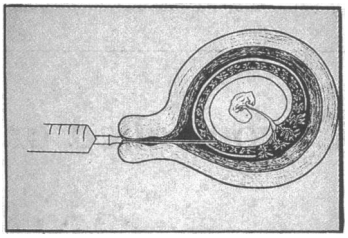
Amniocentesis

Amniocentesis—a well established and widely available method for prenatal diagnosis—is performed from 15 to 16 weeks' gestation. It is reliable and safe, causing an increased risk of miscarriage of around 0·5%. About 20 ml of amniotic fluid is aspirated directly, with or without local anaesthesia, after location of the placenta by ultrasonography. The fluid is normally clear and yellow and contains amniotic cells, which can be cultured. Contamination of the fluid with blood usually suggests puncture of the placenta and may hamper subsequent analysis. Discoloration of the fluid may suggest impending fetal death.

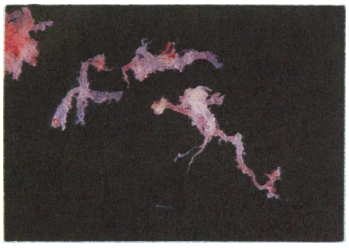


Trisomy 18 karyotype detected by analysis of cultured amniotic cells.

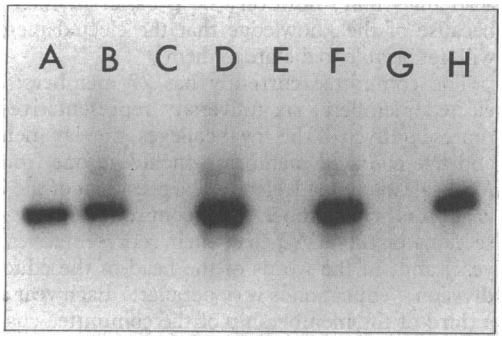
The main indications for amniocentesis are for estimating α fetoprotein concentration and acetylcholinesterase activity in amniotic fluid in pregnancies at increased risk of neural tube defects and for chromosomal analysis of cultured amniotic cells in those at increased risk of Down's syndrome associated with advanced maternal age. In specific cases biochemical analysis of amniotic fluid or cultured cells may be required for diagnosing inborn errors of metabolism. Tests on amniotic fluid usually yield results within 7-10 days whereas those requiring cultured cells may take around 3-4 weeks.



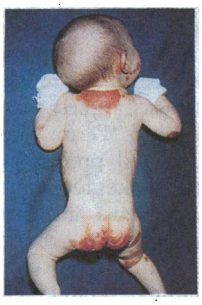
Procedure for transcervical chorionic villus sampling.



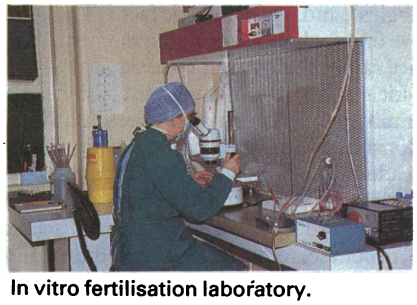
Chorionic villus material.



Fetal sexing by DNA analysis with a Y chromosome specific probe.
(Lanes A, B, H, control male; C, G, control female; E, mother; F, father; D, chorionic villus (male).)



Lethal form of autosomal recessive epidermolysis bullosa can be diagnosed by fetal skin biopsy.



In vitro fertilisation laboratory.

Chorionic villus sampling

Chorionic villus sampling is a recent technique in which fetally derived chorionic villus material is obtained transcervically with a flexible catheter between eight and 12 weeks' gestation or by transabdominal puncture and aspiration at any time up to term. Both methods are performed under ultrasonographic guidance, and fetal viability is checked before and after the procedure. The risk of miscarriage related to sampling in the first trimester in experienced hands is probably about 2% higher than the rate of spontaneous abortions at this time.

Dissection of fetal chorionic villus material from maternal decidua permits analysis of the fetal genotype. The main indications for chorionic villus sampling include the diagnosis of chromosomal disorders and an increasing number of inborn errors of metabolism and conditions amenable to DNA analysis. The advantage of this method of testing is the earlier timing of the procedure, which allows the result to be available by about 12 weeks' gestation, with earlier and easier termination of pregnancy, if required. These advantages are leading to an increased demand for the procedure in preference to amniocentesis, which has important consequences in planning services. If the availability of the procedure is limited, conditions that can be diagnosed only by this method must be given priority, together with high risk cases.

To obtain a prenatal diagnosis in the first trimester it is important to identify high risk situations and counsel couples before pregnancy so that appropriate arrangements can be made and, when necessary, supplementary family studies organised.

Fetoscopy

Fetoscopy is a highly specialised technique performed with a fibreoptic endoscope. The procedure is carried out in the second trimester in cases in which the fetus must be seen directly to identify dysmorphic features or to obtain fetal samples. It is possible to take fetal blood samples and skin biopsy specimens under direct ultrasonographic guidance without using an endoscope, and as the number of disorders amenable to DNA analysis increases and more tests can be performed on chorionic villus samples the indications for fetoscopy are decreasing.

Embryo biopsy

Preimplantation embryo biopsy is now technically feasible. In this method in vitro fertilisation and embryo culture would be followed by biopsy of one or two outer embryonal cells at the 8-16 cell stage of development. DNA analysis of a single cell and possibly chromosomal analysis of cultured cells could be performed so that only embryos free of a particular genetic defect would be reimplanted. This method may occasionally be more acceptable than other forms of prenatal diagnosis but the rate of successful pregnancies would be reduced.

Dr Helen M Kingston, MD, is consultant clinical geneticist at St Mary's Hospital, Manchester.

Illustrations produced by kind permission were: the ultrasonographic scans of jejunal atresia, meningomyelocele, Saldino-Noonan syndrome, and cardiac leiomyomas, Dr Sylvia Rimmer; meningomyelocele, Dr Dian Donnai; the trisomy 18 karyotype, Dr Lorraine Gaunt; the chorionic villus maternal, Dr A Andrews; and the autoradiograph of fetal sexing, Mr R Mountford, St Mary's Hospital, Manchester.

The ABC of Child Abuse continues next week. The 12th article in this series will appear on 3 June.