DETECTION AND MANAGEMENT OF CONGENITAL ABNORMALITIES—II

Geoffrey Chamberlain

Testing in mid-pregnancy

Maternal serum α fetoprotein concentration by weeks of gestation. The upper line is taken as the boundary of the normal group, so it is important to date the pregnancy precisely—that is, by ultrasound measurement of the biparietal diameter.

Structural abnormalities

Open neural tube defects such as anencephaly and open spina bifida allow α fetoprotein to escape from cerebral spinal fluid into the amniotic fluid, whence it is absorbed into the maternal blood, producing higher than normal concentrations. This is the basis of α fetoprotein screening performed between 14 and 16 weeks. It is virtually non-invasive, entailing only taking a blood sample, and has a high predictive value. Fetal gestational age must be estimated by ultrasonography. False positive results can be caused by multiple pregnancy, a dead fetus, bleeding behind the placenta (which may manifest as a threatened abortion), and a few rather rarer abnormalities of the fetus such as gastroschisis.

If the serum α fetoprotein concentration is high either an amniotic fluid sample can be obtained by amniocentesis or a special ultrasound scan is performed to examine the spine and head carefully at 18-19 weeks of gestation.

By 20 weeks the fetus can be seen clearly on ultrasonography and many neural tube defects will have been determined. A little later the heart can be examined and the four chambers identified so that major cardiac abnormalities can be excluded. Limbs can be seen to exclude any shortening and, if relevant, the sex of the child may be determined by presence of the external genitalia in the male.

Top: Ultrasound scan of a fetus with a sacral meningocele taken at 19 weeks. Middle: Scan of a fetus with anencephaly taken at 17 weeks. Bottom: Ultrasound scan of the heart of a fetus with mitral atresia taken at 23 weeks' gestation.

Ultrasound scan showing male genitalia resting on the section of the thigh in a fetus of 30 weeks.

Double bubble effect of duodenal atresia, with the lower bubble in the stomach and the upper bubble in the duodenum. Normally continuity can be traced between these two bubbles.

Hydrocephalus showing enlarged posterior horn of the ventricle (between single arrows) and anterior horn (between double arrows).

Amniotic fluid estimation. (a) The largest pool has the longest column of 5.3 cm (between the arrows). (b) In polyhydramnios the longest pool between the arrows has a column of 9.1 cm. Generally 8.0 cm is taken as the upper limit of normal.

Later still the kidneys may be visualised for cysts or damming back of urine, producing hydronephrosis, while blockage in the intestinal tract can be checked by the presence of bubbles of fluid in the duodenal or large bowel area. The cerebral cortex and ventricles can be easily visualised and measured.

The volume of amniotic fluid can be calculated from measurements inside the uterine cavity or more pragmatically by measuring the longest column at the maximum diameter of the largest fluid pool. The placenta can be seen and its function assessed from the degree of degenerative changes occurring in the last weeks of pregnancy.

These investigations permit a thorough knowledge of the unborn child. Most of the skills are available in the ultrasound departments of district general hospitals, but there is usually more expert back up at the special obstetric ultrasound clinics of regional teaching hospitals.

Amniocentesis under local anaesthesia. The fluid withdrawn (about 10 ml) is spun down and either the cells are used for culture or the supernatant is used to estimate concentrations of α fetoprotein.

Chromosomal abnormalities

In mid-pregnancy the chromosomal state of the fetus may be checked from cells removed at amniocentesis. It is difficult but not impossible to get enough fetal cells before 16 weeks, but with new techniques of DNA amplification fewer cells will suffice so amniocentesis could be possible two to four weeks earlier. It takes three weeks to culture cells in the laboratory and so no chromosomal results can be given after amniocentesis for at least 21 days.

Metaphase spread of chromosome material from a nucleus after culture. The chromosomes are photographed and the print cut out and arranged in pairs to show the normal arrangement for a female, two X chromosomes at the end of the bottom grouping.

Chromosomes of a woman with trisomy 21. The last but one grouping (position 21) has three chromosomes instead of two.

The commonest use of amniocentesis is for the diagnosis of Down's syndrome (trisomy 21), and in most parts of England and Wales women over the age of 35 are offered this screening test. Amniocentesis is an invasive procedure with a small risk of spontaneous abortion, 0.3-1.0% of women miscarrying within a few days afterwards. This risk is very much less if the procedure is done under ultrasound guidance by an experienced obstetrician, being 0.3-0.5%. There is a very small risk of infection, which is avoided by proper antiseptic techniques.

Cordocentesis.

Occasionally at about 20 weeks of pregnancy it is necessary to be certain that the fetus has normal chromosomes if a high risk pregnancy under adverse circumstances is to be continued. It is wise to know that the baby is normal before putting the mother through many weeks of often unpleasant treatment. The white cells of fetal blood can be obtained at cordocentesis by penetrating the umbilical cord where the vessels are held firmest, close to the placenta. Chromosome examination of the white blood cells gives a result fairly speedily (four days).

Availability of tests

Birth prevalence of spina bifida in England and Wales. A slight reduction has occurred from the mid-1960s, becoming sharper from 1973. Testing for α fetoprotein, although described in the early 1970s, was not widespread in its use until the late 1970s and so there may be a coincident factor in this reduction as well as the effect of screening. Many would think this is due to an improved diet for the women of the country.

Detection rates of Down's syndrome comparing age as the only criterion with the results of triple biochemistry screening to indicate amniocentesis.

Biochemical screening for abnormalities of the central nervous system and for Down's syndrome is patchy and varies from one district health authority to another. The reasons lie not just in the whims of economic dictate but with variations in the interpretation of epidemiological data.

Abnormalities of the central nervous system

The total number of abnormalities of the central nervous system in England and Wales has fallen since the early 1970s. Data are based on three sources:

- Notification of termination of pregnancy for abnormalities of the central nervous system
- Death certification of stillbirths and neonatal deaths because of abnormalities
- Notifications of abnormalities of babies who live.

There is a differential in the south of Britain, where the proportional decrease is even greater. In many parts of England, particularly in the home counties, the rate of abnormalities of the central nervous system is less than one per 1000. At this level a screening programme that used α fetoprotein might do more harm than good because of action that might be taken on false positive results. Many authorities have abandoned screening for these reasons. Ultrasonography as a screening test for anencephaly has good results, and when modern, high resolution equipment is available spina bifida can be detected. Although the special skills and equipment are currently not always available in ultrasonography clinics, the state of affairs should improve.

Down's syndrome

As explained previously, the risks of Down's syndrome are greater in women over 35, but because most babies are born to women under this age about half of the babies with the syndrome will be missed if age is used as an indicator for fetal chromosome tests. The use of triple biochemical screening with ultrasonography may answer this, although costs will have to be considered. In one health district in south London it costs £38 000 a year to diagnose Down's syndrome in one fetus. Some health authorities would set this against the cost of maintaining a child born with Down's syndrome for the rest of his or her life in an institution, probably over £500 000. The cost of diagnosis, however, comes from one year's budget, whereas the cost of maintenance is spread over many years' budgets; local health authorities are forced into this philosophical financial juggling.

If triple biochemistry screening with ultrasonography is introduced some women considered to be at high risk by age alone will be reallocated to a lower risk group on the results of the triple biochemistry screening. Thus eventually the number of amniocenteses and chromosome examinations will be reduced, but there will be difficulty in persuading conservative groups such as patients and doctors to abandon the age indication for the newer biochemical screening of risk. This subject is full of promise, and new indices may add even further precision to the screening—for example, femur length, which is commonly shorter in fetuses with trisomy 21.

Conclusions

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Professor Geoffrey Chamberlain, FRCOG, is chairman of the department of obstetrics and gynaecology at St George's Hospital Medical School, London.

At first the antenatal detection of congenital abnormalities may seem to lead only to a nihilistic outcome, but the diagnosis can lead to other lines of management such as the preparation for early paediatric surgery or, in future, to genetic engineering. This is unlikely to be of any help once the embryo has started its development, but work done now on formed embryos can be extrapolated back to research on the oocyte. Here recombinant DNA technology may be used to change the affected part of a chromosome before cell development starts, thus producing a normal fetus. Such technology obviously needs to be controlled by society to help couples who previously had no chance of producing a normal baby.