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Current topic

Prenatal diagnosis of skin diseases

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The possibility of prenatal diagnosis and abortion of abnormal fetuses reassures many couples considering a pregnancy. Some children are conceived only because the pregnancy can be terminated if a serious uncorrectable abnormality carried in the family is passed on. This paper reviews how skin diseases can be diagnosed prenatally. Space does not permit reference to most of the original papers but there are full recent reviews on this subject.[1–3]

Techniques of prenatal diagnosis

(1) STUDIES OF MATERNAL BLOOD

Maternal serum α fetoprotein concentration is used to screen for fetal defects which involve a break in fetal surface, such as spina bifida or exomphalos. It was hoped that this test would detect fetuses with blistering skin conditions such as epidermolysis bullosa. This technique has not proved useful for these conditions, however, and couples at risk of a severe skin disorder should not be over-reassured by a normal α fetoprotein concentration.

A possibility for the future is to use cell separating techniques to isolate the small number of fetal cells found in maternal blood. This would allow prenatal diagnosis by the techniques described in section 3 without instrumenting the uterus.

(2) ULTRASOUND IMAGING

The skin itself is not an organ easily examined by ultrasound scanning. Syndromes that include skeletal or other structural defects, however, can be diagnosed by ultrasound scanning alone. For example, severely affected fetuses with Goltz's syndrome (focal dermal hypoplasia), X linked chondrodysplasia punctata, and Ellis-van Creveld syndrome (chondroectodermal dysplasia) will manifest limb abnormalities, which can be diagnosed by ultrasound examination at about 18 weeks' gestation. Fetal sexing is often possible by ultrasound and if this shows a fetus is female, invasive diagnostic tests for X linked conditions may be unnecessary.

Ultrasound scanning plays an important part in all invasive prenatal diagnostic procedures. Although successful fetal sampling has been described using endoscopic or 'blind' techniques, transabdominal ultrasound guided needling has replaced these methods.[4–6] By holding the ultrasound transducer parallel to the proposed path of the needle, it is possible to identify the target, observe the needle enter the skin, and then guide the needle to the target through a safe route.[6] This technique is used to obtain amniotic fluid (amniocentesis), chorionic villi (placental biopsy), fetal blood (cordocentesis), and biopsies of fetal tissues. For fetal skin biopsy, cupped biopsy forceps (figure) are passed down the needle, opened, pressed on to the fetal skin, closed, and the forceps are then withdrawn through the needle. All of these tests are done as outpatient procedures in an ultrasound clinic under local anaesthetic and without maternal sedation.

As these tests are all done in the same way, they are thought to have a similar procedure related risk of causing fetal death, which in experienced hands is about 1%.[5 7 8] The risk of a pregnancy miscarrying after an invasive test, however, is also determined by the spontaneous abortion rate, which depends on the gestational age, obstetric history, indication for prenatal diagnosis, and many other factors but can be much greater than 1%. In those fetuses surviving to delivery at term a fetal skin biopsy site is either not detectable at birth or perhaps a very small scar is occasionally produced.

Ultrasound guided needling of the pregnant uterus is associated with almost no serious maternal complications. Fetomaternal haemorrhage does sometimes occur and so rhesus negative mothers are given an injection of human anti-D immunoglobulin. Despite this precaution maternal red cell isoimmunisation to D or other red cell antigens will occasionally be produced.

(3) STUDIES OF FETAL CELLS (AMNIOCYTES OR CHORIONIC VILLI)

Fetal cells are usually obtained for prenatal diagnosis by amniocentesis or placental biopsy (see above).

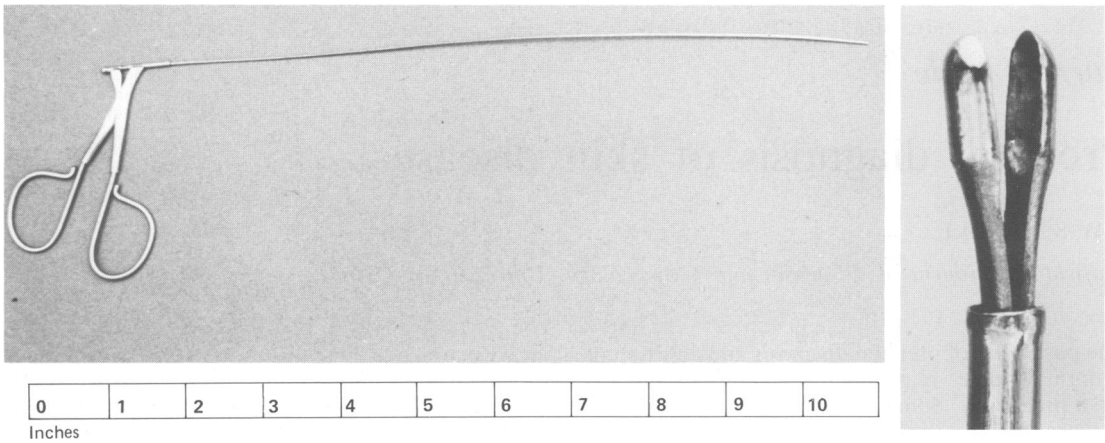

Figure *Fetal skin biopsy forceps. The cupped tip is drawn in or out of the sleeve by opening or closing the handles.*

Initially amniocentesis was done after 14 weeks' gestation and placental biopsy before 12 weeks but both these gestational age limits have been challenged and these tissues can be used over a wide range of gestational ages.[5 9] The great advantage of fetal cell techniques in prenatal diagnosis, however, is that they can be used earlier in pregnancy than the other approaches currently available.

(a) Cytogenetics

Structural abnormalities of chromosomes can be identified at the metaphase stage of cell division. The number of cells in metaphase can be increased by cell culture and by incubation with colchicine. These steps are usually needed with amniocytes, but the number of fetal cells obtained and the incidence of cell division is higher with chorionic villi so that a 'direct' cytogenetic preparation can be made and gross abnormalities like Down's syndrome can be excluded within a day.

Fetal sexing and abortion of male fetuses can be used in the case of X linked diseases for which there is as yet no specific diagnostic test (for example, incontinentia pigmenti). Alternatively, if the fetus is shown to be female further investigation—such as skin biopsy to diagnose X linked hypohidrotic ectodermal dysplasia—is unnecessary. More detailed cytogenetic analysis including chromosome banding, which usually requires a period of cell culture with both amniocytes and chorionic villi, can allow indentification of structural abnormalities of the chromosomes associated with clinical syndromes. Ataxia telangiectasia can be diagnosed by increased spontaneous chromosomal breakage especially at a particular site on chromosome 14. Bloom's syndrome features an increased sister chromatid exchange rate, xeroderma pigmentosum has defective DNA repair after ultraviolet irradiation, and Cockayne's syndrome cells are extremely sensitive to the cytotoxic effect of ultraviolet irradiation but show normal DNA repair.

(b) DNA analysis

Every nucleated cell contains the entire genome. Therefore, tests which involve study of the genome can be done using nucleated cells from any tissue. Some diseases are always produced by a known single base mutation so that fetal cells can be examined for this and no family studies are required. Usually, however, only the region of a chromosome that contains the mutation can be detected. This is done by studying each family requesting prenatal diagnosis to see whether inheritance of an identifiable region of DNA is associated with inheritance of the disease ('gene tracking'). When this is the case the family is described as informative and prenatal diagnosis is possible as soon as fetal cells are available (from eight to nine weeks' gestation onwards). Conditions with skin manifestations in which this can be done include Von Recklinghausen's neurofibromatosis, tuberous sclerosis, hypohidrotic ectodermal dysplasia, and dyskeratosis congenita.[10] X linked ichythyosis has been mapped and the mutation (a deletion) detected in many cases but it is unlikely that parents would want prenatal diagnosis for this condition.

Rapid extension of these techniques to the prenatal diagnosis of a wide range of severe skin disorders is expected. Gene mapping requires a large number of cases, however, especially to

exclude heterogeneity in the mutation locus, and many of the skin disorders for which prenatal diagnosis could be requested are rare. International collaboration is required to facilitate these advances.[10]

(c) Biochemical studies
Unlike the genome, biochemical functions are not always present in every cell. However, biochemical properties of fetal cells can sometimes be used for prenatal diagnosis. When it has been shown that an enzyme is normally produced by amniocytes or chorionic villi at the appropriate gestational age and the absence or reduction of enzyme activity in these tissues is associated with the disease, prenatal diagnosis is possible. Enzyme defects that can be diagnosed prenatally in this way include Ehlers-Danlos syndrome type VI (lysyl hydroxylase) and type VII (procollagen peptidase), X linked cutis laxa (lysyl oxidase), congenital erythropoietic porphyria (uroporphyrinogen III cosynthetase), Fabry's disease (α galactosidase), and α L fructose deficiency. Other metabolic disorders manifest in fetal cells that can be used for prenatal diagnosis include increased uptake of radiolabelled copper in Menkes' syndrome.

(d) Exfoliative cytology
As many amniotic fluid cells are desquamated skin cells, it was hoped that study of these would allow prenatal diagnosis of skin disorders. This may be possible in the diagnosis of bullous congenital ichthyosiform erythroderma but so far this technique has not been used because of problems with blood cell contamination, changes with gestational age and the large number of cell types found in amniotic fluid.[2]

(4) STUDIES OF FETAL BLOOD
Cordocentesis has a limited role for prenatal diagnosis of skin disorders. Syndromes which include skin manifestations that are diagnosable prenatally by studies of fetal blood include the Wiskott-Aldrich syndrome (abnormal platelets), the Chédiak-Higashi syndrome (ultrastructural abnormalities of neutrophils), and the Heamansky Pudlak syndrome (ultrastructural abnormalities of platelets and monocytes).

(5) FETAL SKIN STRUCTURE
Prenatal diagnosis of most skin disorders will eventually be done by the techniques described above rather than fetal skin biopsy. This is because fetal skin is not sufficiently mature for such diagnosis until an advanced gestational age for subsequent abortion should the fetus be found to be affected. Until earlier diagnosis is possible, however, these techniques will continue to prove extremely useful and acceptable to many families at risk of severe skin disease. It is essential that before undertaking prenatal diagnosis by fetal skin structure there should be good communication between the obstetrician and dermatologist and that during the biopsy procedure the skin samples should be confirmed as adequate by an experienced microscopist.

(a) Epidermal disorders
Keratinisation normally starts at 24–26 weeks. Fortunately, some keratinisation diseases can be recognised at 20–22 weeks' gestation because of characteristic skin structures (bullous ichthyosiform erythroderma) or because of an abnormally early onset of keratinisation (Harlequin ichthyosis, lamellar ichthyosis, and Sjogren-Larsson syndrome).

(b) Epidermolysis bullosa syndromes
The structural components of the dermoepidermal junction start to develop in the first trimester of pregnancy. Prenatal diagnosis is usually done from 18–22 weeks but diagnosis of some of these conditions as early as 15 weeks has been reported. Both junctional and dystrophic types of epidermolysis bullosa, and the Dowling variety of epidermolysis bullosa simplex can be diagnosed by their characteristic planes of separation with ultrastructural abnormalities and by the use of direct immunofluoresence using monoclonal antibodies specific for junctional antigens.

(c) Ectodermal dysplasias
X linked hypohidrotic ectodermal dysplasia can be detected by absence of pilosebaceous units in fetal skin at 20 weeks' gestation, but can now often be diagnosed by use of gene tracking.

(d) Albinism
Tyrosinase negative oculocutaneous albinism can be diagnosed by ultrastructural examination of hair bulb melanosomes in biopsy specimens of fetal scalp at 18–20 weeks' gestation.

Conclusion

The decisions as to whether the risk of having an affected child justifies prenatal diagnosis and whether the consequences of the disease indicate abortion of an affected fetus must be taken by the parents after obtaining as much information as possible about the disease and the procedures. Some of the conditions now diagnosed only in the second trimester will in the future be detectable in the first trimester, and the number of diseases for

which prenatal diagnosis can be offered will increase. Doctors advising couples at risk of having a child with a severe inherited disease should consider referral for investigations such as family DNA studies, which might allow a diagnosis earlier in the pregnancy. Information about these techniques might allow them to consider a pregnancy which they would otherwise not contemplate.

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