INVITED ARTICLE

ANTENATAL DIAGNOSIS OF FETAL ABNORMALITIES

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ABSTRACT

Fetal abnormalities may be strongly inherited e.g. in the Mendelian diseases. Some of the abnormalities are due to detectable chromosome anomalies, while the majority of fetal abnormalities arise as a result of the interaction of polygenes and environmental factors. The process of fetal abnormality diagnosis depends on a careful taking of the history and its evaluation. The clinical examination of the fetus by real time ultrasound, if relevant and finally special investigations which are to some extent invasive such as chorionic villus sampling, amniocentesis and fetal blood sampling. The fetal tissue so obtained may be assessed for their genetic structure by DNA recombinant methods, or the disease may be diagnosed by analysis of the genic products. The commoner hereditary diseases probing fetal abnormalities in S. E. Asia are described and the diagnosis of these diseases discussed. Fetal diagnosis, at the moment, is still labour intensive and costly and must be applied in a discriminate fashion.

Key Words: Fetal abnormalities: antenatal diagnosis: mendalian diseases: chromosome abnormalities.

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INTRODUCTION

The objective of fetal diagnosis for abnormalities is to offer termination of the pregnancy, if the parents so desire, for these diseases which are fatal or potentially fatal and for which there is still no adequate nor specific therapy.

Fetal abnormalities can be classified into 3 categories (Table 1): (1).

Mendelian diseases are totally inherited, and when the Mendelian disease occurs as a result of inheritance of one mutated gene, it is autosomal dominant when it involves the non-sex chromosomes, or it is sex-linked when it involves a mutated gene residing on the X-sex chromosome. When disease occurs only with mutation of both alleles of a non-sex gene, it is termed an autosomal recessive disease. In the case of an autosomal dominant disease, an affected fetus will have one of his parents also being affected but often this parent's phenotype may be minimal because of variability in expression. The mother of a fetus afflicted with a sex-linked disease is often the carrier in that she is usually asymptomatic because of lyonisation (2). The parents of a fetus suffering from an autosomal recessive disease are carriers and do not suffer from the disease, because the normal unaffected allelic gene can produce sufficient of the genic product for normal living but the fetus inheriting the mutated gene from each parent, has no normal gene and hence no genic produce (3). By simple mathematics, it can be seen that 50% of the offspring of a parent with an autosomal dominant disease will be affected; and 50% of male offspring oa a carrier mother of a sex-linked disease will suffer from the disease and 50% of a female offspring will themselves be carriers: 25% of fetuses with both parents who are carriers of an autosomal recessive disease will be affected. Hence, risk figures for Mendelian diseases can be very precise.

Chromosome disease can be inherited or can be sporadic. The majority are sporadic and are examples of abnormalities in chromosome number arising from non-disjunction of normal parental chromosomes during segregation at meiosis of their gametes, or non-disjunction of the chromosomes of the zygote (4). Inherited chromosome disorders usually arise because one of the parents carries a balanced chromosome translocation (5).

The commonest diseases of the fetus are those arising from inheritance of parental polygenes reacting with environmental factors such as neural tube defects, intra-uterine infections, Vater syndrome, congenital heart diseases etc.

The commonest significant fetal abnormalities seen in Singapore are shown in Table II: (6).

The figures for incidence of Mendelian diseases in other S. E. Asian countries exceed those for Singapore, e.g. HbE carriers in Vietnam border on 50% and so on.

PREREQUISITES FOR DIAGNOSIS OF FETAL ABNORMALITIES

Fetal disease diagnosis, like diagnosis in medicine, relies essentially on the history, clinical examination and investigations, and like post-natal diagnosis, the history is still paramount. It is the taking of the family genetic history of the parents and their family members (i.e. the pedigree history) and the ability to interpret such a history that will allow in many cases the diagnosis of the 'first' case even before affected family members have been born. If affected members have been born, it is mandatory for the

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doctor to examine these cases himself and obtain the correct diagnosis, e.g. a chronic hemolytic anaemia may be strongly inherited as in thalassemia or hereditary spherocytosis, or it may be sporadic as in paroxysmal nocturnal hemoglobinuria or systemic lupus. Clinical examination for fetal diagnosis is not as clear cut as for post-natal patients but real time fetal ultrasound examination may be extremely useful when the history has pinpointed the possible diagnosis. A 'routine' fetal ultrasound is often unrewarding in elucidating fetal abnormalities. It is in the field of investigations that fetal diagnosis have made great strides in recent years and have brought great rewards but it is not surprising that the technology can be very labour intensive, i.e. they are cost-effective for the individual family but less so when applied indiscriminately to the whole society in the form of universal screening. Therefore, family and fetal investigations are most effective when they are applied with careful discrimination.

METHODS OF INVESTIGATION

Real time ultrasound has been mentioned and is non-invasive. All the other methods of investigation are invasive to various degrees. The latter involve the obtaining of fetal tissue for fetal diagnosis. Fetal tissue can be obtained from fetal skin cells shed into amniotic fluid, i.e. via amniocentesis (7); or fetal cells can be obtained by fetal blood sampling (9). Chorionic villus sampling is possible in the first trimester while the other 2 procedures are carried out in the second trimester. Amniotic fluid itself can sometimes provide sufficient information for fetal diagnosis, and the fetal blood obtained provide cells as well as plasma for investigation. Hence, fetal tissues obtained can be investigated in the same manner as post-natal tissues obtained in the infant child or adult.

In the S. E. Asian context, the commonest invasive investigations on fetal tissue involve:

(a) Analysis of the globin chains of the hemoglobin molecule for hemoglobinopathies.
(b) Chromosome culture of fetal cells for exclusion of chromosome diseases.
(c) Detection of the abnormal gene by DNA recombinant techniques for diagnosis of Mendelian diseases (10).
(d) Biochemical analysis for enzymes etc. in fetal cells and amniotic fluid.

It is seen that 2 methods (b & c) detect abnormal genes and chromosomes, while the other 2 methods detect the products of these genes. Of these 4 methods, method c, i.e. the detection of the abnormal gene by DNA probes will ultimately supercede most of the other methods which deal with the diagnosis of Mendelian diseases. Note that DNA recombinant techniques are especially useful for the diagnosis of Mendelian diseases.

TABLE I
GROUPS OF FETAL ABNORMALITIES

GROUP	CAUSE
Mendelian disease	Mutation of 1 or 2 allelic genes
Chromosome diseases	Detectable abnormal chromosomes in structure or number (qualitative or quantitative)
Multifactorial diseases	Inherited polygenes and environmental factors

COST-EFFECTIVENESS OF ANTENATAL DIAGNOSIS IN S. E. ASIA:

Fetal diagnosis involves labour-intensive methods and priorities must be set for cost-effectiveness. The following investigations have been established in the Department of Paediatrics, National University of Singapore to deal with S. E. Asian patients:

(a) **Haemoglobinopathies:**

α thalassemia homozygosity leads to hydrops fetalis (Barts hydrops) resulting in stillbirth or death at birth. (4) It can be detected by the use of the α globin DNA probe, as the commonest abnormal gene in S.E. Asia is the deletion of the gene. It can be detected in the first trimester by chorionic villus sampling (CVS).

β thalassemia major in the fetus is detected by chain synthesis and separation of blood obtained by fetal cordocentesis during the second trimester but it will be possible to diagnose the condition in the first trimester utilising DNA recombinant methods on chorionic villi and multiplying the DNA available by the polymerase chain reaction (PCR) (12).

HbE-β thalassemia double heterozygote can also be detected during the second trimester by fetal blood globin chain synthesis and separation.

TABLE II
COMMONEST SIGNIFICANT FETAL ABNORMALITIES IN SINGAPORE

(A)	Mendelian diseases:	
	1. Erythrocytic glucose-6 phosphate dehydrogenase (G6PD) deficiency	3% of males
	2. Hemoglobinopathies:	
	(a) HbE disease:	5%
	(b) β thalassemia carriers:	3%
	(c) α thalassemia carriers:	6%
(B)	Chromosome diseases:	
	1. Sex chromosome abnormalities:	1 in 200 births
	2. Down's Syndrome:	1 in 800 births
(C)	Multifactorial diseases:	
	1. Congenital heart disease:	0.5 – 1%

(b) **Chromosome abnormalities**

The commonest significant chromosome abnormality anywhere in the world is Downs Anomaly (DA). Pregnant mothers aged 35 years and over should have routine amniocentesis during the second trimester and fetal cells cultured and analysed chromosomally for the diagnosis of DA as the percentage incidence rises precipitously after this age. However, this will only detect 20% of all DA as such fetuses are also seen in mothers below the age of 35 years. In order to detect more cases of DA and yet limit amniocentesis and chromosome culture to those more likely to produce DA fetuses, pregnant mothers can be pre-selected for amniocentesis by estimation of maternal alphafoetoprotein (AFP), human chorionic gonadotrophin (HCG) and conjugated oestradial (CE) (13). Families where inherited chromosome abnormalities are segregating must have routine amniocentesis if one of the parents is a translocation carrier.

(c) **Multifactorial diseases**

Many multifactorial diseases can be detected by fetal ultrasound, which can also detect some Mendelian disorders, e.g. the Mendelian skeletal dysplasias and so on. Examples of multifactorial diseases which

are detectable by ultrasound include neural tube defects such as spina bifida, anencephaly, encephalocoele. Congenital heart diseases can also be detected and in the future, it may be routine to use ultrasound to diagnose the more complex congenital heart diseases for which surgical treatment is still suboptimal.

CONCLUSION

The fetus is subject to abnormal developmental processes by virtue of genetic as well as environmental factors or both. When this occurs, many a time, the fetus is non-viable in utero, resulting in spontaneous abortions. For example, it is estimated that 60% of spontaneous abortuses reveal chromosomal disorders, so that this is Nature's way of getting rid of subnormal fetuses. However, not all such fetuses spontaneously abort, and antenatal diagnosis assists Nature and the family who wish to terminate the pregnancy, to do so.

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