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Antenatal diagnosis and management of life-limiting conditions

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SUMMARY

Whereas structural fetal abnormalities are relatively frequent occurrences, many of these do not impact measurably on future life and/or are amenable to postnatal therapy. A small minority are considered to be potentially lethal or life-limiting. Examples include specific skeletal dysplasias, urinary tract abnormalities – typically those which lead to anhydramnios and pulmonary hypoplasia, some disorders of the central nervous system and trisomies 13 and 18. Without seeking to compile an exhaustive list of such conditions, we discuss the principles and new considerations in relation to antenatal diagnosis and perinatal management of such disorders.

1. Introduction

Congenital structural anomalies and chromosomal abnormalities are among the leading causes of perinatal death and long-term morbidity.[1,2] Advances in prenatal diagnosis, in particular fetal ultrasound, mean that many such abnormalities are diagnosed in the mid-trimester, and increasingly the first trimester of pregnancy.

The diagnosis of a structural anomaly in the fetus allows prenatal parental counselling and plans to be made for postnatal assessment and management. For a small minority of structural anomalies – for example congenital diaphragmatic hernia,[3] bladder outflow obstruction[4] and spina bifida[5] – prenatal (fetal) therapy may be considered, particularly when there is considered to be a high risk of neonatal death without such an intervention.[4,6,7]

For some fetal anomalies, the anticipated outcome is so poor that the parents should be advised about a high risk of intrauterine, neonatal or infant death. In these circumstances, many parents may wish to pursue termination of the pregnancy, whereas others may decide to continue with the pregnancy and choose a bespoke 'package' of ongoing care, often referred to as perinatal palliative care.[8]

In this review we discuss some of the more common disorders that may be considered 'life-limiting' or potentially 'lethal' and some of the options that parents and clinicians may wish to consider.

2. Methods of diagnosis

2.1. Ultrasound (two- and three-dimensional)

In most developed and many developing countries, prenatal 2D ultrasound examination has become established care for a number of purposes: (i) confirmation of viability and number of fetuses; (ii) accurate dating of the pregnancy; (iii) assessment of placenta location; (iv) screening for and identification of structural and chromosomal abnormalities. Furthermore, other ultrasound techniques such as uterine artery Doppler and cervical length can identify the small but significant group of women whose pregnancies are at increased risk of pre-eclampsia, fetal growth restriction, and spontaneous preterm birth.[9,10] While 3D ultrasound may aid in the diagnosis of suspected facial clefting, as well as central nervous system (CNS), cardiac and limb defects, its place in the routine screening and detection of fetal anomalies remains undefined.

In the UK, the National Screening Committee has issued guidance on the proportion of cases of structural and chromosomal abnormalities it expects to be detected (Table 1)[11] and the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) provides guidelines on the conduct of both a 'screening' and more targeted fetal ultrasound examination in order to detect structural fetal anomalies.[12]

Most lethal structural abnormalities may be detected at 18–22 weeks. However, the ultrasound appearances of some abnormalities, for example the acrania/anencephaly sequence, are usually diagnostic in all cases by 11–12 weeks.[13] Whereas first trimester screening identifies almost twice as many cases of chromosomal

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Table 1
UK National Screening Committee recommendations of fetal disorders to be screened for, and to be subject to audit.[11]

Condition	Expected detection rate
Anencephaly	98%
Open spina bifida	90%
Cleft lip	75%
Diaphragmatic hernia	60%
Gastroschisis	98%
Exomphalos	80%
Serious cardiac abnormalities	50%
Bilateral renal agenesis	84%
Lethal skeletal dysplasia	60%
Edwards syndrome (trisomy 18)	95%
Patau syndrome (trisomy 13)	95%

abnormalities as are detected in the second trimester, the converse is true for structural abnormalities.[14] Approximately 90% of lethal abnormalities are identified following either first or second trimester screening (Table 2).

Multi-modality imaging is now frequently the standard of care in corroborating and confirming the diagnoses that previously might have been made only by grey-scale ultrasound. Clinicians, and increasingly parents, might seek further reassurance from a 'second opinion' imaging modality before making irrevocable decisions about the pregnancy. For example, the great majority of fetuses with potentially lethal renal tract pathology can be identified at the mid-trimester ultrasound scan. Use of colour or power Doppler sonography to check for the presence of the renal arteries will often clarify the diagnosis in the case of bilateral renal agenesis, particularly if doubt remains about possible differential diagnoses (such as severe placental insufficiency, or pre-viable membrane rupture). As the lack of amniotic fluid may make ultrasound imaging difficult, fetal MRI has been used selectively to corroborate ultrasound findings.[15]

Ultrasound does not allow direct diagnosis of a fetal chromosomal anomaly, but it does allow identification of those structural anomalies[1] and 'markers of aneuploidy' that raise suspicions of an underlying chromosomal abnormality such as trisomies 21, 18 or 13. Such markers for aneuploidy may include increased nuchal translucency, nasal bone hypoplasia, abnormal ductus venosus blood flow, and tricuspid regurgitation.[9] The UK National Screening Committee has published recommendations on fetal disorders to be screened for, and to be subject to audit (Table 1).[11]

2.2. Invasive testing: karyotype, rapid aneuploidy testing, and array comparative genomic hybridization (array-CGH)

Prenatal determination of the fetal chromosome arrangement is achieved by invasive diagnostic procedures, most commonly amniocentesis, and chorionic villus sampling (CVS). In the UK, it is estimated that around 5% of the pregnant population are offered invasive testing each year[16]; these tests are associated with maternal discomfort, anxiety and procedure-related miscarriage. Although some reports have raised uncertainty about the risk of miscarriage due to invasive testing,[17,18] this is usually considered to be around 1% for amniocentesis and CVS. Systematic reviews and the national registry from Denmark suggest that these statistics hold true.[19,20]

Table 2
Comparison of first and second trimester ultrasound screening policies for detection of fetal anomalies in the south-east region of Sweden.

Detection of:	1st trimester	2nd trimester
All anomalies	13%	29%
Lethal anomalies	88%	92%
Chromosomal anomalies	71%	42%

$N = 21\,189$; five centres: one screening in first trimester, four in second trimester. Source: Hildebrand et al.[14]

The 'gold standard' test for determination of whether a fetus has a major chromosome abnormality is the karyotype, based on either direct preparation of uncultured villi or more commonly metaphase G-banding following culture of placental mesenchyme or amniocytes. Fetal blood sampling (e.g. by cordocentesis) is now infrequently used with the advent of rapid testing for trisomy such as fluorescence in-situ hybridization (FISH) and quantitative fluorescence polymerase chain reaction (QF-PCR).

Karyotype of cultured amniocytes or placental mesenchyme has typically meant that results are not available for an interval of around two weeks after an invasive test, which inevitably means a delay in providing reassurance to parents or to inform decision-making about a pregnancy.

In the last decade, rapid targeted testing for the commoner trisomies or for specific microdeletion disorders (such as 22q11, particularly in the context of cardiac outflow tract abnormalities[21]) has become commonplace. Such technologies can provide rapid turnaround of results, often on a large-scale automated basis.[22] While there has been concern that use of rapid tests alone might lead to clinically significant karyotypic abnormalities going undetected,[23,24] use of rapid tests alone has now largely replaced full karyotype in the screening programme for trisomy 21 in the UK. Full karyotype analysis is still usually requested when structural anomalies are detected on ultrasound, or when the nuchal translucency is noted to be significantly increased (>3.5 mm).[25]

Although interphase FISH was the first rapid test to be offered for detection of trisomy in prenatal samples, and has been demonstrated to be a robust and sensitive technique, it may be less suitable as a 'stand alone' test for the detection of trisomy because of the costs and time-consuming procedures involved in performing it.[22,26] By contrast, it has a well-defined role in the detection of particular chromosomal deletions and duplications, for example in the context of structural fetal abnormalities which raise suspicions of such syndromes (e.g. structural heart abnormalities[21]). Some of these deletions may fall below the resolution of G-band karyotyping (typically ~ 5 megabases or higher) and are therefore not amenable to detection by karyotyping alone, particularly as the resolution of prenatal karyotypes from CVS or amniocyte samples is usually poorer than from lymphocyte preparations.[27]

A normal karyotype by no means excludes a potentially significant chromosomal abnormality. In this context many children with developmental delay or dysmorphism will have an apparently normal karyotype. In the postnatal investigation of the child with developmental delay or dysmorphism, the shortcomings of G-band karyotype have been apparent for some time. Increasingly, the value of technologies such as subtelomeric FISH and array-CGH has been realized[28] to the point where these latter technologies have largely replaced the karyotype in some centres for the investigation of developmental delay.

As such, there has been increasing interest in the potential value of using array CGH technology in the investigation of structural fetal anomaly. Conceivably, this could allow a rapid and largely automated method of performing a high-resolution whole genome screen for chromosomal abnormalities more sensitive than conventional G-band karyotype. There is a small but significant additional yield in the detection of chromosomal imbalance when array-CGH technology is employed in the investigation of structural fetal anomalies. A systematic review has suggested that array-CGH identifies genomic imbalances in around 5% more cases than conventional G-band karyotype when structural anomalies are