Diagnosing Congenital Abnormalities before Birth

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Most pregnancies are normal and uncomplicated. However, in approximately 2% - 3% of pregnancies, the foetus is affected with some form of congenital abnormalities. These abnormalities can be a physical structural abnormality (1%), a chromosomal abnormality (0.5%) or, a single gene disorder (1%).

Many of these conditions can now be diagnosed prenatally and appropriate advice and management options can be offered. The aim of antenatal diagnosis is to identify the affected foetus as early as possible, so that the couple has a choice of the full range of management options, including pregnancy termination. Modern standard of care demands that the physician caring for pregnant women, particularly in early pregnancy, is well aware of these diagnostic modalities.

Structural Abnormalities

This group of abnormalities can affect any organ systems of the body. Cardiac and central nervous system (CNS) abnormalities are the commonest. While some women are at increased risk than others, these abnormalities can affect any pregnancy. Women who have a past history of fetal abnormalities, with medical disorders like diabetes or epilepsy, using medications like anticonvulsants and ACE inhibitors are at an increased risk than others.

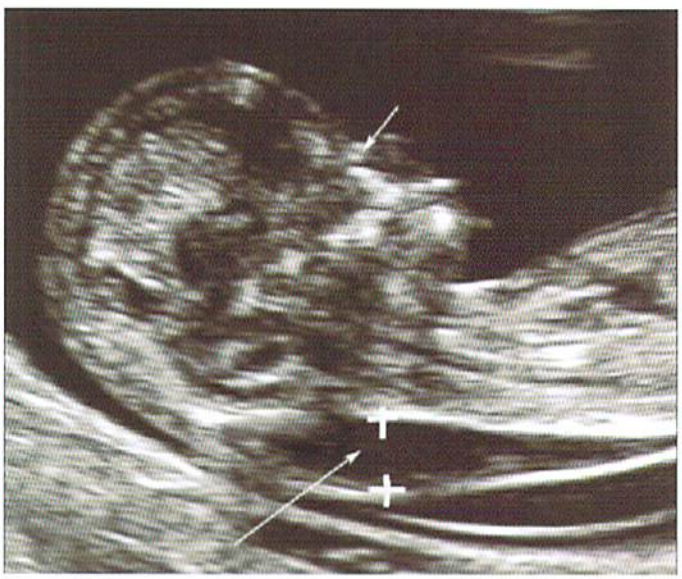
Most of these abnormalities can be diagnosed on a detailed prenatal ultrasound examination (Fetal Anomaly scan or FA scan) and the best time to perform such a scan is between 20-22 weeks. It has to be understood that ultrasound examination is an operator dependent procedure and the sensitivity is directly proportional to operator experience. Such detailed examinations are preferably done at referral centres. This is particularly true for the prenatal evaluation of fetal cardiac defects which needs considerable experience and expertise. Patients, at particularly higher risk of abnormalities, should have an early FA scan done at 16-18 weeks. However, the pregnant mother should be counselled that not every abnormality is detectable on a mid-trimester FA scan. Some abnormalities often present late in gestation e.g. coarctation of aorta, duodenal atresia, etc.; while some abnormalities evade detection because of various other factors like maternal habitus, previous abdominal scars and decreased amniotic fluid volume. Overall, a good ultrasound centre should be able to detect 80% - 85% of significant structural abnormalities.

Chromosomal Abnormaliites

The commonest chromosomal abnormalities are trisomies (3 copies of a particular chromosome instead of 2) involving chromosomes 21 (Down Syndrome), 18 (Edward Syndrome) and 13 (Patau Syndrome). Another relatively common abnormality is monosomy X (Turner Syndrome).

Of these, Down syndrome is by far the most common, occurring in 1 in 650 pregnancies. Trisomy 13 and 18 are uniformly lethal conditions – foetuses either die in utero or soon after birth, and both of these conditions have multiple structural abnormalities. Prenatal diagnostic efforts have focused mainly around the detection of Down syndrome. While the incidence of trisomies increases with maternal age, every pregnant woman has some risk. It is now recommended that every woman, irrespective of age, should be offered a screening test for Down syndrome early on in pregnancy.

The best screening test available now is the first trimester combined screen (FTS or OSCAR test). It involves an ultrasound scan performed between 11 - 14 weeks of pregnancy to measure Nuchal Translucency (echo-free area under the fetal neck skin) and visualisation of nasal bone. Risk assessment also includes measurement of serum levels of PAPP-A (Pregnancy Associated Plasma Protein-A) and beta-hCG at the same time. The result, as calculated by a special software, is given as a risk estimate and it is available within a few hours of the test.



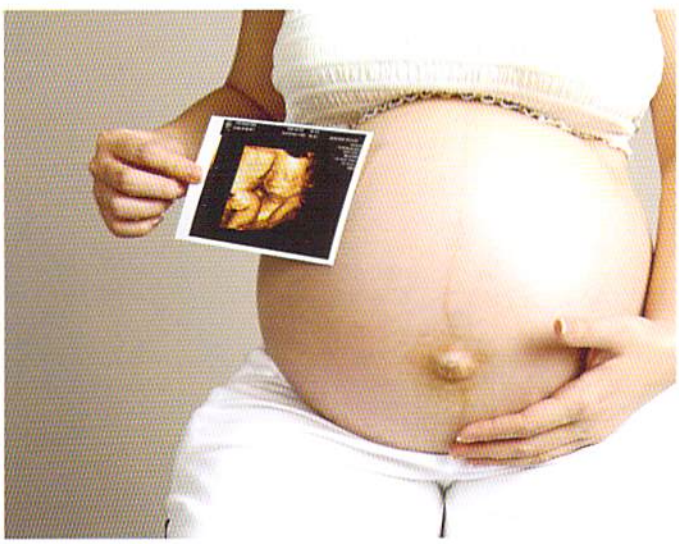
If the risk is assessed to be greater than 1 in 300, further diagnostic test (chorion villus sampling – CVS or amniocentesis) to assess the fetal karyotype can be offered. The diagnostic tests are ultrasound guided invasive tests and have a small associated risk of fetal loss (0.5% to 1%). This risk, again, is well known to be related to operator experience. If the FTS is performed at an accredited centre with an accredited laboratory, it can achieve a sensitivity of over 90% in the detection of Down syndrome with a false positive rate of 5%.

Pre-test counselling is extremely important to dispel misconceptions and anxiety. It should be explained to the woman that a high risk estimate on FTS does not necessarily mean that the foetus has a chromosomal abnormality. Only 1 out of 30 pregnant women going for a diagnostic test like CVS or amniocentesis, because of an abnormal FTS result, will actually have an affected foetus. The CVS test (11-13 weeks) can be performed at an earlier gestation than amniocentesis (15-20 weeks). The karyotype result takes about 12 days. However, rapid diagnostic tests are available now, e.g. FISH (Fluorescent In-situ Hybridisation) and QF-PCR, which can give a result for the common chromosomal abnormalities within 24 to 48 hours.

Single Gene Disorders

A single gene disorder is the result of a single mutated gene. There are estimated to be over 10,000 human diseases caused by single gene defects. Although rare, they collectively affect about 1% of pregnancies. They are distinct from the fetal structural abnormalities and syndromes, which are called multifactorial or polygenic disorders. Common single gene disorders are thalassaemias, cystic fibrosis and various congenital muscular dystrophies.

Since single gene disorders result from the presence of a single mutated or abnormal gene, they follow a predictable pattern of inheritance. Based on how they are inherited, these disorders are categorised into different groups. "Dominant" disorders like Huntington's chorea are caused by a single mutated allele and tend to appear in every generation. On the other hand, "recessive" disorders, like major thalassaemias, need the abnormal allele in both pair of chromosomes and hence, they tend to skip generations. While most single gene disorders affect both sexes equally, since the mutated gene is carried on autosomes, some disorders, like Duchenne muscular dystrophy, tend to be more common in males because the relevant mutated gene is carried on X-chromosomes ("sex-linked" inheritance).



Prenatal diagnosis of single gene disorders is usually offered when the parents are known carriers of the disease, when there is a relevant family history or, if there is a previous affected pregnancy. For some recessive disorders like thalassaemia or cystic fibrosis, carrier testing of parents for the recessive gene is possible. The most common single gene disorder in our population is thalassaemia, both alpha and beta. When both parents have the minor variety of a particular thalassaemia, the unborn child has a 25% chance of being affected by the major disease.

The simplest way to screen for thalassaemia is by doing a full blood count and checking for the MCV. A MCV value of <80 fl, in absence of iron deficiency, should prompt one to do a thalassaemia carrier testing. The MCV check should be done at the antenatal visit. If both parents are found to be a carrier of the same type of thalassaemia, prenatal diagnosis can be performed through CVS or amniocentesis. A CVS sample, performed at 11-13 weeks, is preferred for extracting fetal DNA and testing for the presence of the mutated gene. Hence, optimum antenatal care requires a timely referral of the "at-risk" pregnant woman for the diagnosis of these disorders.

Conclusion

While majority of pregnancies are normal, fetal abnormalities do occur. Majority of these conditions are now diagnosable well before birth and requires a clear understanding on the part of the care givers. Primary care physicians have a special role in this regard since they are the care providers for many women in early pregnancy.

DO's

- Detailed history at booking visit
- Dating ultrasound scan
- FBC at booking visit. Check MCV. If MCV <80fl, check for Iron deficiency. If normal, refer both partners for thalassaemia screen
- Offer First Trimester Screen (FTS) for chromosomal abnormalities (>11-<14 weeks). Should be done at an accredited centre.
- Book FA scan at 20-22 weeks at a referral centre. Early FA scan at 16-18 weeks for "high risk" patients

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A/Prof Biswas obtained his basic MBBS degree from Calcutta University, India where he was awarded the Gold Medal in aggregate as well as in Obstetrics & Gynaecology and Pathology. He started his postgraduate training in Obstetrics & Gynaecology at All India Institute of Medical Sciences (AIIMS), India in 1981 and continued further advanced specialist training in UK from 1987. He obtained his MD in 1986 and MRCOG (UK) in 1989. He obtained the FAMS in 1999 and became a Fellow of the Royal College in UK (FRCOG) in 2001.

His current practice at NUH includes all areas of general Obstetrics & Gynaecology, heading the Maternal-Fetal Medicine division of the Department. His special interest is in the areas of prenatal diagnosis, antenatal ultrasound and high-risk pregnancies. He is currently also the Clinical Director of the Department.

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