Prenatal diagnosis of genetic diseases

Ishraq Dhaifalah MD.
Introduction:

- Until the recent past, couples at high risk of genetic disorder have the choose of:
  - taking the risk
  - considering other reproductive options (long term contraception, sterilisation, termination of pregnancy or even adoption and artificial insemination (AID))
- until the 1966 when the relation of advanced maternal age and increase rate of Down syndrome was noticed and the prenatal diagnosis was developed
• The purpose of prenatal diagnosis is not simply to detect abnormalities in fetal life and allow termination. It rather have the following goals:
• Provide a range of informed choice to the couples at risk of having a child with abnormality
• Provide reassurance and reduce anxiety, especially among high-risk groups
• Allow couples at high risk to know that the presence or absence of the disorder could be confirmed by testing
• Allow the couples the option of appropriate management (psychological, pregnancy/delivery, postnatal)
• To enable prenatal treatment of the affected foetus
Indications for prenatal diagnosis:

- advanced maternal age
- previous child with a chromosome abnormality
- family history of a chromosome abnormality
- family history of a neural tube defect
- family history of other congenital structural abnormalities
- abnormalities identified in pregnancy
- other high risk factors (consanguinity, poor obst., history, maternal illnesses
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Advanced maternal age

- Is the commonest indication for prenatal diagnosis
- No standard criterion exists at what age women should be investigated
- Most centres offer AMC or CVS to women aged 37 or over 35. (risk 1: 35)
- Figures differ for the risk of Down’s sy. Because a proportion of this pregnancy abort spontaneously
Previous child with a chromosome abnormality

- Previous child with Down’s syndrome due to non-disjunction or unbalanced translocation will give a risk in subsequent pregnancy as, of mother’s age related risk plus 5%.

- If one of parents have balanced chromosomal rearrangement (translocation, inversion) causing serious problems for a previous child due to unbalanced rearrangement, then recurrence risk is between 1-2% and 15-20%. The risk will depend on nature of rearrangement and segment involved.
Family history of a chromosomal abnormality

- Usually no increase in risk compared to general population since most chromosomal disorders will arise as a result of disjunction than familial rearrangement.
- A history of Down’s sy
- However each situation should be confirmed by nature of chromosome abnormality in affected individual or urgent chromosome analysis from blood of related parents if normal, no invasive tests...
Family history of a single gene disorder

- A previous affected child
- Affection of one of the parents
- Positive family history

- Have a 25-50% recurrence and prenatal diagnosis should be offered as many can be diagnosed by DNA analysis or biochemical testing (Achondroplasia, Huntington disease, Neurofibromatosis,....)
Family history of a neural tube defect

• In first and second-degree relatives the risk should be determined
• High risks were diagnosed by amniocentesis and AFP assessment
• Ultrasound with MSAFP is the method of diagnosis nowadays
• Small closed neural tube defects can be missed even with the most skilled person (fortunately are not associated with serious problems)
Family history of other congenital structural abnormalities

- Evaluation of family pedigree
- Calculation of the risk
- If increased risk, detailed ultrasound can be offered between 16-18 weeks of pregnancy. It will detect most of serious defects (cranial, cardiac, renal and limb deformation)
Abnormalities identified in pregnancy

- Uncertainty of maternal serum screening and fetal anomaly scanning can make invasive procedure for the diagnosis more necessary
- Poor fetal growth can be an indication for prenatal chromosome analysis as well as for confirmation of a serious and non-viable abnormality
Other high risk factors

- Parental consanguinity leading to hereditary disorder or congenital anomalies (offer a detailed ultrasound)
- Poor obst. history as recurrent miscarriage or still birth indicating high risk in future preg. (offer ultrasound of fetous and chromosome analysis of parents)
- Maternal illnesses as poorly controlled DM or maternal epilepsy treated with some drugs as sodium valproate (offer detailed ultrasound)
Methods of prenatal diagnosis

- Invasive:
  - Amniocentesis
  - Chorionic villus sampling
  - Cordocentesis
  - Preimplantation genetic diagnosis
  - Fetoscopy

- Non-invasive testing:
  - Maternal serum AFP
  - Maternal serum screen
  - Ultrasonography
  - Isolation of fetal cells from maternal circulation
Invasive methods of prenatal diagnosis

Amniocentesis

- Aspiration of 10-20 ml of amniotic fluid through the abdominal wall under ultrasound guidance around the 16 weeks of gestation.
- In about 14 days there will be enough cells for chromosome analysis for biochemical or DNA studies; some time a longer time is needed for growth of more cells.
- Couples should be informed of the risk of abortions (0.5-1%) and the possibility of termination if wished.
Figure 18–2. A, Amniocentesis. A needle is inserted transabdominally into the amniotic cavity, and a sample of amniotic fluid (usually about 20 ml) is withdrawn by syringe for diagnostic studies (e.g., chromosome studies, enzyme measurements, or DNA analysis). Ultrasonography is routinely performed before or during the procedure. B, Chorionic villus sampling. Two alternative approaches are drawn: transcervical (by means of a flexible cannula) and transabdominal (with a spinal needle). In both approaches, success and safety depends on use of ultrasound imaging (scanner). (From Moore KL and Persaud TVN [1998] The Developing Human: Clinically Oriented Embryology, 6th ed. WB Saunders, Philadelphia.)
Chorionic villus sampling

- It enables diagnosis in first trimester (10-11 week of gest.) under ultrasound guidance by transcervical or transabdominal aspiration of chorionic villi.
- These are fetal cells derived from the outer layer of trophoblast.
- Results can be obtained in one to three days, so a diagnosis in first trimester in addition that villi provide a rich source of DNA.
- Disadvantage is in higher risk of abortion (2-3%) and limb abnormalities if carried before the 9 weeks of gestation.
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Figure 18–3. Development of the tertiary chorionic villi and placenta. A, Diagrammatic cross-section of an implanted embryo and placenta at about 21 days. B, Cross-section of a tertiary villus showing establishment of circulation in mesenchymal core, cytotrophoblast, and syncytiotrophoblast. (From Moore KL [1988] The Developing Human: Clinically Oriented Embryology, 4th ed. WB Saunders, Philadelphia.)
Cordocentesis

- Visualisation of the umbilical vessels by transabdominal ultrasound and enabling fetal blood sampling.
- It is usually used in the management of Rhesus isoimmunization and in some cases to solve the problem of mozaicism.
Cordocentesis
Fetoscopy

- Visualisation of foetus by means of endoscope (it has been suppressed by modern US)
- It can be undertaken to diagnose a subtle structural abnormalities pointing to a serious diagnosis
- Can also be used to obtain fetal samples for some diagnosis as inherited skin disorders (epidermolysis bullosa) and some metabolic disorders in which enzymes are only in specific organs
Fetoscopy
Non-invasive methods of prenatal diagnosis
Maternal serum AFP

• Mostly done around the 16 weeks of gestation.
• More specific for the diagnosis of NTD (95% of NTD can occur without a history)
• Amniocentesis was used to confirm the diagnosis but with a good detailed ultrasound first and second degree can be diagnosed
• It has been found that by periconceptional supplementation with folic acid decrease the rate of occurrence of NTD and other abnormalities
Maternal screening test

- It is now a standard practice to offer screening for NTD, Down’s sy. and Edward sy. Using a blood sample obtained from the mother at the 16 (15-20) weeks of gestation.
- It can diagnose up to 75% of NTD and 60-70% of Down’s sy.
<table>
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<th>Condition</th>
<th>AFP</th>
<th>UE3</th>
<th>HCG</th>
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<td>Increased risk of</td>
<td>Inc.</td>
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<tr>
<td>NTD</td>
<td>Inc.</td>
<td>Not applicable</td>
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Ultrasonography

- It offers a valuable means for prenatal diagnosis
- It is used for obst. diagnosis as placental localisation and multiple preg. As well as for prenatal diagnosis of structural abnormalities which are not associated with known chromosome, biochemical, or molecular defects.
- It is a non invasive with no risk to the foetus or mother
- A specialised expensive equipment and a skilled experienced operator are needed
• It is offered to those with a history of genetic disease

• Detailed fetal anomaly scanning is offered also to all pregnant women around the 18 weeks of gest. as a screening procedure for structural anomalies (NTD and cardiac anomalies)

• It can identify features which suggest underlying chromosomal abnormality indicating amniocentesis.
New prenatal diagnostic techniques under development:

- Preimplantation genetic diagnosis
- Detection of fetal cells in the maternal circulation
Preimplantation genetic diagnosis

FISH at embryo in the two cells stage
probe LSI 21 (Vysis)
Isolation of fetal cells from maternal circulation

Fig. 1. ChemScan®RDI laser scanning concept.

Fig. 5. Purified trophoblast cell (47,XX+18) in PBMCs (XY) by immuno-FISH labeling.
Isolation of fetal cells from maternal circulation
Problems in prenatal diagnosis:

- Failure to obtain a sample or culture failure
- An ambiguous chromosome result
- An unexpected chromosome result
- Ultrasound soft markers
Prenatal treatment

• In the most situations the diagnosis of prenatal abnormalities has a subsequent option of termination of the pregnancy.

• While this applies in most situations, there is cautious optimism that with the advent of gene therapy prenatal diagnosis will, in time, lead to effective treatment in utero.
Examples of gene therapy

• Treatment of the autosomal recessive disorder - congenital adrenal hyperplasia (CAH). Affected females are born with virilisation of the external genitalia. There is evidence that this can be prevented by powerful steroid therapy at early gestational age.
### Gene therapy

**Combined immunodeficiency**
- deficiency of the adenosine deaminase
- bone marrow
- retrovirus

**Cystic fibrosis**
- deficiency of the transmembrane reg. gene
- liposomes
- fusing with epithelial cells

**Haemophilia A**
- gene for factor VIII
- liver tissue
- application into portal vein

**Lung carcinoma**
- K - ras (onkogene) at 30-40% adenocarcinomas
- instillation of the mirror gene coding transfer of RNA
- block of the decoding
- p53 tum. suppressor gene at 50-70% of all carcinomas
- instillation of good work. gene’s copy
- retrovirus - into tumour deposit
• Treatment of a foetus affected with severe combined immunodeficiency have been reported. Transfused stem cells are recognised as „self“ with the prospect of good long term results. So immunological tolerance of the foetus should make it easier to commence such therapy before birth than afterwards.
Summary of prenatal diagnosis (elements)

- It can be carried out by non-invasive procedures (MS-AFP for NTD, triple test for Down’s sy., and US for structural abnormalities)
- Invasive procedures as amniocentesis or CVS is usually requires for diagnosis of chromosome and single gene disorders
- Invasive procedures convey small risk for miscarriage (0.5-1% for amniocentesis, 2-3% for CVS, and 3-5% for fetoscopy)
• The commonest indication of prenatal diagnosis is advanced maternal age, family history of chromosome single gene or structural abnormality and a positive screening test in pregnancy.

• While the significance of most prenatal diagnostic findings is clear, situations can arise in which the implications for the foetus are very difficult to predict. When this occurs the parents should be offered specialised genetic counselling.
Figure 18-7. The different types of mosaicism that may be detected by prenatal diagnosis. A, Generalized mosaicism affecting both the fetus and placenta. B, Confined placental mosaicism with normal and abnormal cell lineages present. C, Confined placental mosaicism with only an abnormal cell lineage present. D, Mosaicism confined to the embryo. (Adapted from Kalousek DK [1994] Current topic: Confined placental mosaicism and intrauterine fetal development. Placenta 15: 219-230.)