PRENATAL DIAGNOSIS

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OUTLINE

• Introduction
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• Screening tests
• Genetic counselling
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Introduction

“In recent years, the feeling has grown in both the professional and general public that we must be concerned not simply with insuring the birth of the baby but of one that will not be a liability to society, to its parent and to itself” – Dancis 1969
“THE FETUS AS A PATIENT”
Rapid Evolution of Prenatal Diagnosis as Result of:

- Developments in Human Cytogenetics
- Molecular Techniques
- Biochemical Techniques
- Developments/Improvements in Obstetric & Gynaecology and Human Embryology
- Significant Progress in Foetal Therapy
- New legal theories-wrongful birth, wrongful life
PRENATAL DIAGNOSIS

DEFINITION

It is the science of identifying structural and functional abnormalities in the developing fetus through invasive and non-invasive techniques for diagnostic or therapeutic purposes.
INTRODUCTION

SIGNIFICANCE

• About 2-3% of all live born infants have abnormalities (structural or functional).

• These anomalies account for majority of perinatal deaths.
INTRODUCTION

- Genetic counselling can be provided.
- Multidisciplinary management involving the obstetrician, geneticist, paediatrician, clinical psychologist and other specialists can discuss with the parents on the following:
  - The therapeutic options;
  - The optimal time, mode and place of delivery;
  - Plan the postnatal management.
ETHICAL / LEGAL CONSIDERATIONS

• The pregnant woman has an ethical obligation to accept fetal therapy for a fetus if the following conditions are met:
  • If treatment to prevent a serious disease or handicap would benefit or save the life of the fetus.
  • If mortality or injury to the fetus is unlikely.
  • If mortality or morbidity in the mother is unlikely.
  • If Maternal and fetal benefits is considered.
CLASSIFICATION OF FETAL DISORDERS

- disorders untreatable and incompatible with prolonged life
- disorders that might benefit from prenatal treatment
- disorders that benefit from mode and timing of delivery
- disorders best treated after delivery

NOTE- some fetal disorders might involve more than one class
→ Early Intervention = to apply therapeutic interventions to those conditions for which postnatal treatment would be too late

Options for Management:

- Non Intervention (Downs Syndrome)
- Termination of Pregnancy (Anencephaly)
- Prenatal Treatment (Diaphragmatic Hernia, Rhesus Isoimmunisation)
- Modifying Delivery (Mode & Place) Conjoint twin
- Postnatal Treatment (Certain Cardiac Defects)
MILE STONE IN THE HISTORY OF PRENATAL DIAGNOSIS.

• 1958 1st practical Ultrasound use-Ian Donald
• 1963 intraperitoneal fetal transfusion for severe rhesus disease-Liley et al
• 1967 Amniocentesis used for Rhesus disease to make cytogenetic diagnosis-Jacobson et al.
• 1972 Anencephaly with subsequent TOP, steroid use to enhance fetal lung maturity.
milestones

• 1974- high amniotic AFP->anencephaly/spina bifida- Brock&Sutcliffe
• 1975-uss disease of spina bifida- Campbell
• 1982-Transcervical CVS under uss-Kazy
• 1982-uss-guided intravenous transfusion for rhesus disease-Bang
• 1982- in utero treatment of obstructive uropathy by vesico-amniotic shunt- Golbus
• 1983- transabdominal ultrasound cordocentesis-Daffos
milestones

• 1989 –maternal serum AFP for Down’s syndrome-Wald
• 1990- first successful in utero operation for diaphragmatic hernia- Harrison et al
• 1992- nuchal translucency as a 1st trimester screening test for chromosomal abnormalities- Nicolaides et al
milestones

from 1994 till date improvements have been made in cytogenetic analysis

1. CYTOGENETIC INVESTIGATIONS
   a) Detections of chromosomal aberrations
   b) Fluorescent in-situ hybridization (FISH)

2. MOLECULAR GENETIC TECHNIQUES
   a) Linkage analysis using microsatellite markers
   b) Restriction fragment length polymorphisms (RFLPs)
   c) Single nucleotide polymorphisms (SNPs)
   d) DNA chip
   e) Dynamic allele-specific hybridization (DASH)
SCREENING TESTS

• DEFINITION-Tests that do not provide a diagnosis but rather identify individuals with risk high enough to benefit from a definitive diagnostic test.

• Genetic screening tests should meet criteria generally accepted for other types of screening tests:
  1. The disease is well defined and serious.
  2. Treatment or prevention is available but not possible without the screening test.
  3. The screening test is cost effective and reliable.
  4. The subsequent diagnostic test is reliable.
GENETIC COUNSELLING

• Aims at helping the individual or couple to understand risk of having a child with a chromosomal abnormality, genetic disorder or congenital malformation.

GENETIC COUNSELLING involves the provision of The medical facts including Disease, prognosis and possible treatment options, the risks of recurrence and the reproductive options available.

• Complications of counselling might include Anxiety and other psychological problems, poor belief of facts & figures, higher risk of miscarriage and stillborn.
INDICATIONS FOR GENETIC COUNSELLING

• Advanced maternal age (≥ 35yrs)
• Previous child or parent with chromosomal abnormality
• Previous child with congenital malformation
• One of the couples with balanced chromosomal translocation
• Mother with X-linked abnormal gene
• Both parents with same recessive abnormal gene (e.g. sickling gene)
• Recurrent miscarriages or stillbirth
• Teratogen exposure
• Consanguinity (e.g. first cousins)
TECHNIQUES FOR PRENATAL DIAGNOSIS

A. NON-INVASIVE TECHNIQUES


2. Triple-panel test
   Screening for fetal Down syndrome
   a) MSAFP ↓
   b) Maternal unconjugated estriol ↓
   c) Maternal serum β-hCG ↑
   d) Inhibin A is included in Quadriple test
TECHNIQUES FOR PREGNATAL DIAGNOSIS

A. NON-INVASIVE TECHNIQUES

3. Separation of fetal cells from maternal blood.
   • Virtually all pregnant mothers have fetal cells in their bloodstream through the placental villi.
   • Isolation of these cells for analysis may obviate the need for more invasive procedures.
   • Done ideally from 18 weeks but can be successfully from 12 weeks.
   • Has been used to diagnose disorders such as cystic fibrosis, sickle cell disease and thalassaemia.
4. Pre-implantation biopsy of blastocysts obtained by in vitro fertilization.

5. Fetal visualization
   a) Ultrasound
   b) Fetal echocardiography
   c) Magnetic Resonance Imaging (MRI)
   d) CT scan (radiography)
GENETIC TECHNIQUES
PREIMPLANTATION GENETIC DIAGNOSIS

Identification of certain genes responsible for certain hereditary diseases prior to implantation during IVF

- Indication:
  - Used to diagnose single gene disorders such as cystic fibrosis and sickle cell disease.

- Timing:
  - From the 3-day-old embryo at the 6- to 10-cell stage.

- Procedure:
  - Requires the polar body or blastocyst
  - Technique is still under development and is currently quite complex.

- Advantage:
  - The main advantages are that only healthy embryos are selected for implantation and pregnancy termination can be avoided.
TECHNIQUES FOR PRENATAL DIAGNOSIS

B. INVASIVE TECHNIQUES

1. FETAL VISUALIZATION
   a) Embroscopy
   b) Fetoscopy.

2. FETAL TISSUE SAMPLING
   a) Amniocentesis
   b) Chorionic villus sampling (CVS)
   c) Percutaneous umbilical blood sampling (PUBS)
   d) Percutaneous skin biopsy
   e) Other organ biopsies, including muscle and liver.
A. NON-INVASIVE TECHNIQUES
5. NON INVASIVE - FETAL VISUALIZATION

A. ULTRASONOGRAPHY

• Single most valuable tool in identifying fetal structural anomalies.

• USS could be STANDARD, LIMITED, SPECIALIZED

• Useful in detecting abnormal growth patterns and assessing fetal well-being; this is particularly important in Antenatal fetal surveillance.

• Early second-trimester USS for structural abnormalities in women at low risk is controversial. (RCOG justifies routine USS, whereas routine USS is questionable by ACOG)
• STANDARD USS- provides information on fetal number, fetal viability, assessment of gestational age, amniotic fluid volume, placental location, anatomic survey

• LIMITED USS-is a goal directed search for a suspected problem e.g nuchal translucency, ultrasound guided amniocentesis

• SPECIALIZED USS-is performed when an anomaly is suspected based on history, biochemical abnormalities, or due to results obtained from either limited or standard scan e.g doppler ultrasonographic scan, biophysical profile, fetal echocardiogram.
STANDARD USS

Fetus at 9 weeks
LIMITED USS

measurement of the nuchal translucency
SPECIALIZED USS-for detection of umbilical cord insertion
5. NON INVASIVE - FETAL VISUALIZATION

B. FETAL ECHOCARDIOGRAPHY

• When used with duplex or colour flow Doppler, it can identify a number of major structural cardiac defects and rhythm disturbances.

• Timing:
  • Performed at 15 weeks and beyond
5. NON INVASIVE - FETAL VISUALIZATION

B. FETAL ECHOCARDIOGRAPHY

• **Indication:** Fetal echocardiography is recommended in cases where cardiac defects are suspected, including:
  • Identification of an extracardiac malformation on routine USG
  • Suspected genetic disease or fetal chromosome abnormality associated with heart defects
  • Exposure to potentially teratogenic agents
  • Family history of congenital heart defects
  • Maternal diseases such as diabetes or phenylketonuria associated with heart defects, in particular heart blocks, such as lupus or other immune disorders
  • Alcohol or drug consumption by the mother
  • Maternal rubella infection during pregnancy
5. NON INVASIVE - FETAL VISUALIZATION

C. MRI

• It is an important adjunct to USS
• Used mainly in assessment of cases with inconclusive USS findings
• Used when prenatal USS is not reliable such as maternal obesity and or oligohydramnios.

BUT...

• Spatial resolution inferior to USS
• Poor depiction prior to 20 weeks gestation
5. NON INVASIVE - FETAL VISUALIZATION

C. MRI..

• **Indication:**
  • Amniotic band syndrome
  • Fetal cerebral anomalies
  • Volumetric analysis of fetal size or individual fetal organs.
  • Congenital high airway obstruction syndrome
  • Congenital haemochromatosis:
5. NON INVASIVE - FETAL VISUALIZATION

C. MRI...

• **Advantages:**
  - Absence of ionizing radiations
  - Large field of view
  - More precise volumetric measurement
  - Good image quality in oligohydramnios
  - Superior soft tissue contrast enhancement
  - Better intracranial delineation
  - Multiplanar capability
5. NON INVASIVE - FETAL VISUALIZATION

D. CT SCAN

- Has limited applications.
- It is used mainly when MRI is contraindicated in the mother (e.g. she has a pacemaker or an intraocular foreign body.
- Used if USS provides inconclusive data.

- **Advantage:**
  - Delineates fetal bony anatomy better.

- **Limitation:**
  - Risk of teratogenesis due to ionizing radiations in the 1st trimester
  - May increase risk of cancer induction e.g. leukemia
B. INVASIVE TECHNIQUES
1. INVASIVE- VISUALIZATION

A. EMBRYOSCOPY

• Indication:
  • The embryo is visualized for the diagnosis of structural malformations.

• Timing: first trimester up to 12 weeks.

• Procedure:
  • Sterile procedure
  • Ultrasound guidance.
  • A rigid endoscope is inserted via the cervix into the space between the amnion and the chorion.
1. INVASIVE- VISUALIZATION

B. FETOSCOPY

• Indication:
  • For the visualization of the embryo to detect the presence of subtle structural abnormalities.
  • Can be used for fetal blood sampling and tissue sampling.

• Timing:
  • Performed in the 2nd trimester after 16 weeks.

• Procedure:
  • Under sterile conditions and ultrasound guidance,
  • A fine-calibre endoscope is inserted into the amniotic cavity through a Minilaparotomy,

• Complication:
  • Associated with a 3-5% risk of miscarriage; therefore it is superseded by the detailed ultrasound scanning.
2. FETAL TISSUE SAMPLING

A. CHORIONIC VILLUS SAMPLING (CVS)

• Route for obtaining villi: (under Ultrasound guidance)
  • Transcervically (TC) or
  • Transabdominally (TA)

• Timing: Performed at 10 to 13 weeks.
Fig. 10.7 Transabdominal chorionic villus sampling.
Fig. 10.6 Transcervical chorionic villus sampling.
2. FETAL TISSUE SAMPLING

A. CHORIONIC VILLUS SAMPLING.

• Indications:
  • Singleton pregnancy at age over 35 years at delivery
  • Autosomal trisomy birth
  • Previous 47, XXX or 47, XXY birth
  • Patient or partner is carrier of chromosome translocation
  • Patient or partner is carrier of chromosomal inversion
  • History of triploidy
  • Some cases with repetitive early pregnancy losses
  • Patient or partner has aneuploidy
  • Major fetal structural defect identified by ultrasound.
2. FETAL TISSUE SAMPLING

A. CHORIONIC VILLUS SAMPLING.

• Advantages:
  • Earlier timing.
  • Short culture time with results obtained earlier than amniocentesis (24-48 hours).
  • Decreased medical risk associated with early termination of pregnancy.

• Disadvantages
  • Rhesus isoimmunization
  • False diagnosis due to chromosomal mosaicism
  • Fetal loss rate of about 1/100.
2. FETAL TISSUE SAMPLING

B. AMNIOCENTESIS

• Indication: same as for CHORINIC VILLUS SAMPLING

• Timing: between 14 – 20 weeks of pregnancy.

• Procedure:
  • A gauge 20-22 needle is passed through the mother’s lower abdomen into the amniotic cavity inside.

• Advantages:
  • It is preferred to CVS in situations where CVS is not reliable such as twin pregnancy with fused placentae and in certain biochemical disorders.
  • Safer than CVS.
2. FETAL TISSUE SAMPLING

B. AMNIOCENTESIS
• Complications:
  • Uterine bleeding
  • Rhesus isoimmunization
  • Leakage of amniotic fluid
  • Uterine cramping
  • Increased risk of club foot when performed prior to 12 weeks
  • Fetal loss 0.3-1.0 %
  • Failed procedure due to tenting of the membranes ahead of the needle
  • Culture failure rates: 1% overall and 5% if the procedure is performed prior to 12 weeks'.
2. FETAL TISSUE SAMPLING

C. CORDOCENTESIS
(PERCUTANEOUS UMBILICAL BLOOD SAMPLING – PUBS)

• Indication:
  • Used to obtain fetal blood cells for genetic analysis when CVS or amniocentesis results are confusing or when rapid diagnosis is necessary.
  • Currently performed primarily for the assessment and treatment of confirmed red cell or platelet alloimmunization and
  • For analysis of non-immune hydrops.

• Timing: After 16 weeks.

• Procedure:
  • A 20-22 spinal needle is inserted under ultrasound guidance into the umbilical vein usually at or near its placental origin.
Figure 3: Percutaneous Umbilical Cord Blood Sampling
2. FETAL TISSUE SAMPLING

C. CORDOCENTESIS

• Complications:
  • Choriamnionitis
  • Preterm labour
  • Haematoma of the umbilical cord
  • Abruptio Placenta
  • Rhesus isoimmunization
  • Fetal exsanguination from the procedure site
  • Fetal loss
2. FETAL TISSUE SAMPLING

D. PERCUTANEOUS SKIN BIOPSY

• Indications:
  • Anhidrotic ectodermal dysplasia
  • Epidermolysis bullosa letalis
  • Epidermolysis bullosa dystrophica
  • Genetic forms of ichthyosis
  • Hydrotic ectodermal dysplasia
  • Occulocutaneous albinism

• Timing: 17-20 weeks gestation

• Procedure:
  • Percutaneous fetal skin biopsies are taken under ultrasound guidance between.
2. FETAL TISSUE SAMPLING

E. FETAL MUSCLE AND LIVER BIOPSY

- Indication:
  - Muscle biopsy - rare cases of Duchenne muscular dystrophy in which findings from all previous investigations are nondiagnostic.

- Fetal liver biopsies performed to measure enzyme levels
  - Glucose -6-phosphatase in patients with suspected glycogenesis disorders
  - Ornithine transcarbamylase in those suspected to have urea cycle disorders.
FETAL SURGERY
INTRODUCTION

• Fetal surgery is now an accepted modality for treatment of a variety of lethal and non-lethal congenital conditions.

• It represents a new, fast-moving frontier of medicine in which cooperative multidisciplinary efforts and inputs are required to assure both fetal and maternal welfare.

• A wide range of therapeutic strategies from percutaneous to open invasive techniques have led to a complex list of different procedures for different diseases.
Fetal surgery

- Hysterotomy (open fetal surgery)
- Fetendo (fetal endoscopic surgical techniques)
- Fetal image guided surgery (FIGS -IT)
- Stem cell transplant
- Gene transfer
1. OPEN FETAL SURGERY

- Most definitive and most invasive.
  - The mother is anesthetized,
  - An incision is made in the lower abdomen to expose the uterus.
  - The uterus is opened using a special stapling device to prevent bleeding,
  - The surgical repair of the fetus is completed,
  - The uterus followed by the maternal abdominal wall are closed.
  - Anaesthesia is reversed.
- The magnitude of the surgery is about the same as Cesarean section
- DR OLUYINKA OLUTOYE (TEXAS, USA)
- Operated on 23 weeks old fetus.
1. OPEN FETAL SURGERY

Post operative care:

- Requires hospitalization for 3 to 7 days,
- Requires Caesarean delivery for index and future pregnancies.
- Risk of preterm labour and preterm delivery.
- Requires close monitoring for preterm labour
- Requires tocolytics.
2. FETENDO

- Fetal endoscopic intervention
  - Developed in the 1990s to avoid making an incision in the uterus
- To avoid/prevent preterm labour.
- Fetendo routes:
  - Percutaneous (through the mother’s skin) or
  - Mini-laparotomy.
- It has replaced open fetal surgery for some fetal problems but not all.
- It has proven particularly useful for treating problems with the placenta, like twin-twin transfusion syndrome, and
- For looking inside the fetus, for example, to place a balloon in the fetal trachea or deal with obstruction of the fetal bladder.
2. FETENDO

- **Advantages:**
  - It is less invasive than open surgery.
  - Less risk of preterm labour
  - Less postoperative maternal morbidity.

- **Disadvantages:**
  - Still requires tocolytics and close monitoring.
  - Technically difficult
  - Requires the development of many new devices and techniques to see through the amniotic fluid, maintain the fetal position, and do delicate work within the fetus.
3. Fetal Image-Guided Surgery (FIGS-IT)

• Describes the method of manipulating the fetus without either an incision in the uterus or an endoscopic view inside the uterus.
• The manipulation is done entirely under real-time cross-sectional view provided by the sonogram.
• Advantage:
  • The least invasive of the fetal access techniques
  • Shorter hospitalization and maternal morbidity.
  • Less risk of preterm labour.
• Route: Percutaneous or in some cases, minilap.
• Anaesthesia: regional anaesthesia or even local anaesthesia.
FIGS-IT

- It is generally not useful for serious structural problems that require surgery.
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<th>Description</th>
<th>Indications</th>
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<td>• Balloon Dilation Aortic Stenosis</td>
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Complications

These vary with the invasiveness of the procedure;

- PROM/Oligohydramnios
- Preterm labour and delivery
- Excessive haemorrhage
- Anaesthetic complications.
- Infection of the incision
- Chorioamnionitis
- Caesarean delivery for all pregnancies.
- Infertility
STEM CELL/GENE THERAPY
STEM CELL/GENE THERAPY

- Immunocompetence in the human develops from 18 weeks.
- Thus, theoretically the fetus should tolerate foreign antigens introduced before 18 weeks.
- Fetal haemopoietic stem cell transplantation might treat a variety of diseases or serve as a vehicle for gene transfer for treatment of other genetic diseases.
- Research findings appear hopeful but still inconclusive.
- Stem cell research is on going.
In Utero Stem Cell Fetal Therapy

Indications:

1. Disorders affecting lymphocytes
   - Agammaglobinaemia
   - Bare lymphocyte syndrome
   - Ommen syndrome

2. Disorders affecting granulocytes
   - Chronic granulomatous diseases
   - Infantile agranulocytosis
   - Neutrophil membrane GP-180
3. Disorders affecting erythrocytes
   - Sickle cell disease
   - α-Thalassaemia
   - β-Thalassaemia
   - Hereditary spherocytosis
   - Mannosidosis
   - Mucolipidoses
   - Mucopolysaccharidoses
CONTROVERSIES

• Prenatal diagnosis in mentally challenged mothers
• Ethical consideration for the husband/father in prenatal diagnosis.
• Right of the fetus
• Right of the physician
• Right of the society
• Religious belief on termination of pregnancy
Summary

Prenatal Diagnosis is best performed within an integrated programme providing biochemical testing in conjunction with skilled ultrasonographers, knowledgeable counselors, and physicians in genetics, maternal – foetal medicine and neonatal care.
CONCLUSION

• Prenatal diagnosis and Fetal surgery are rapidly expanding frontiers to improve fetal outcome.
• Undoubtedly, as newer technologies evolve current fetal interventions may even become obsolete.
“WE WANT A HAPPY MOTHER AND CHILD”
THANK YOU!