Introduction to Prenatal genetic screening and diagnosis

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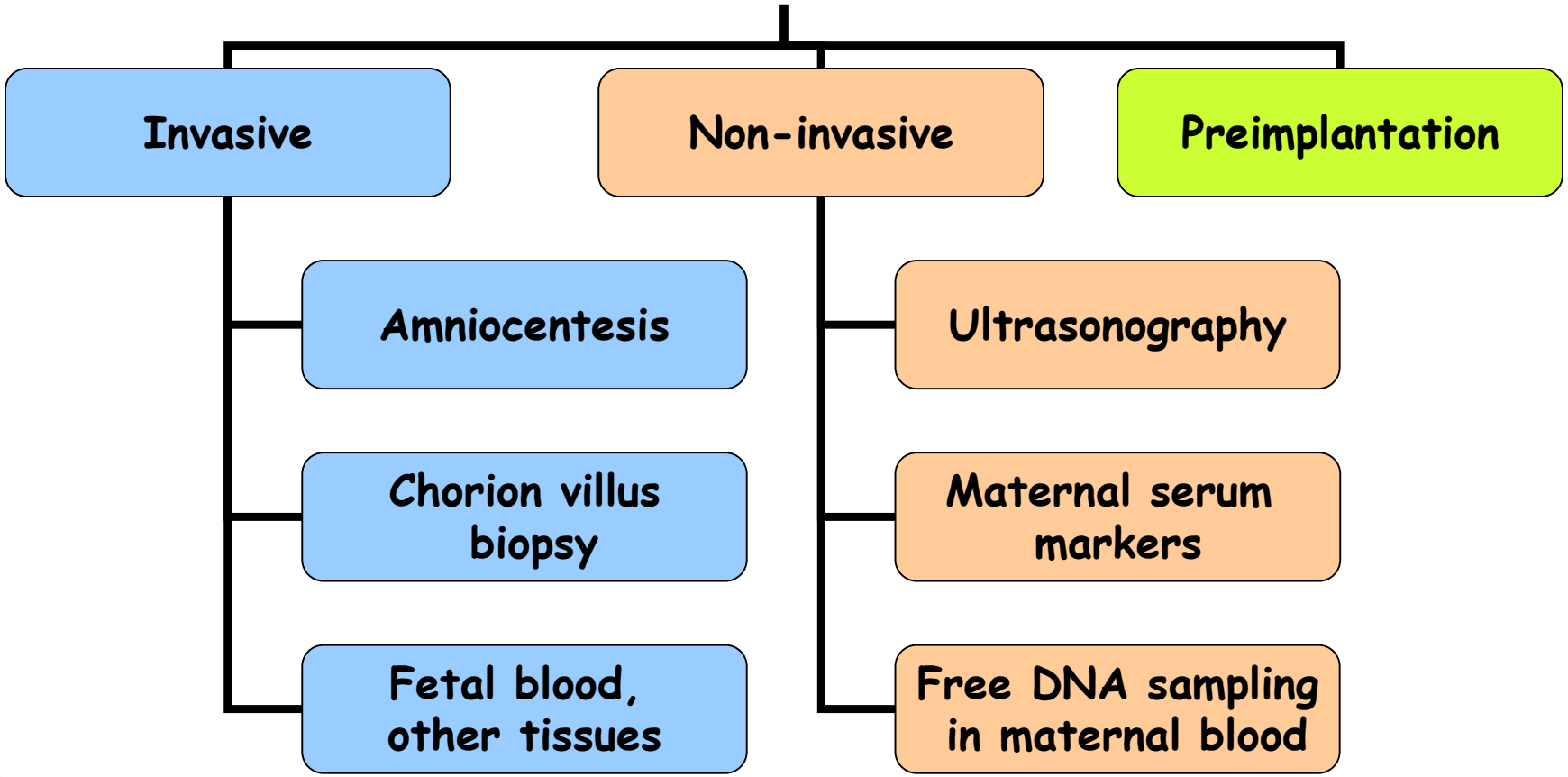
While it is never easy for a couple to decide to pursue prenatal diagnosis because of the possibility of subsequently having to consider termination of pregnancy, prenatal diagnosis is an option that could be chosen by couples at high risk of having a child with a serious congenital disorder.

Methods used for prenatal diagnosis of congenital disorders



Prenatal genetic screening

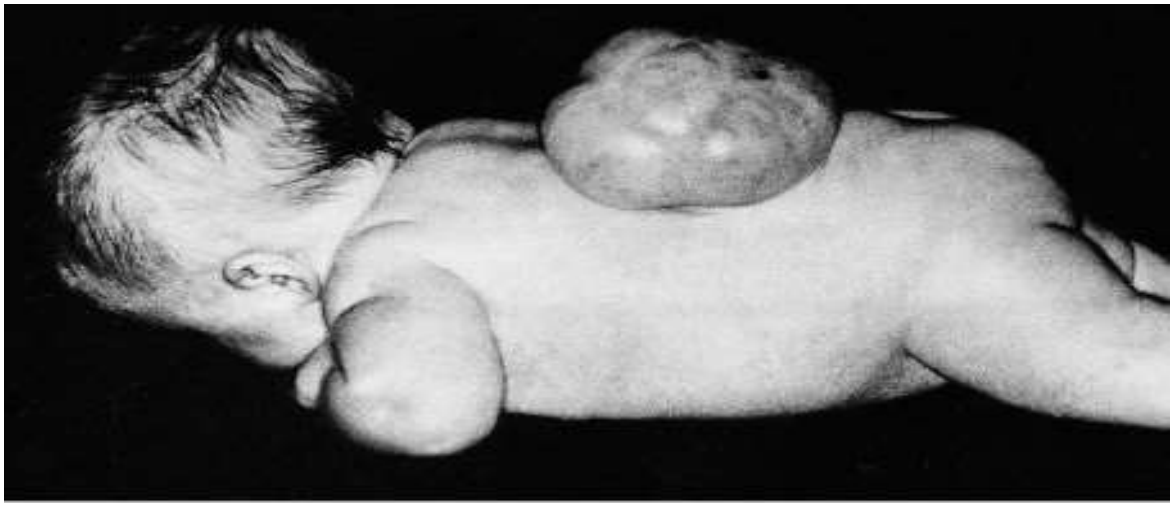
- For most women, prenatal genetic screening involves a blood test for maternal serum markers and a special ultrasound done early in pregnancy.
- Abnormal results could point to the possibility that the fetus has:
  1. Down syndrome
  2. Other chromosomal abnormalities such as Trisomy 18 and Turner syndrome
  3. Open neural tube defect (ONTD)
  4. Other conditions

Ultrasound offers a valuable means of prenatal diagnosis. It can be used not only for obstetric indications, such as placental localization and the diagnosis of multiple pregnancies, but also for the prenatal diagnosis of structural abnormalities that are not associated with known chromosomal, biochemical or molecular defects.

Ultrasound is particularly valuable because it is non-invasive and conveys no known risk to the fetus or to the mother. It does, however, require specialized expensive equipment and a skilled and experienced operator.

Neural tube defect

Spina bifida indicates a defect in the closure of the vertebral column leading to protrusion of the meninges/spinal cord. Severe conditions lead to lower limb paralysis and incontinence.



- The observation that increased nuchal translucency (NT) is seen in fetuses who are subsequently born with Down syndrome, has resulted in the introduction of measurements of nuchal pad thickness in the first trimester as a screening test for Down syndrome.

First trimester risk assessment using the double test (pregnancy-associated plasma protein A (PAPP-A) and free beta-human chorionic gonadotropin (HcG) and nuchal translucency thickness in combination with maternal age has been shown to be very efficient giving a detection rate of 90% for Down syndrome and for a 5% false-positive rate.

Detailed 'fetal anomaly' scanning is being offered routinely to all pregnant women at around 18 weeks gestation as a screening procedure for structural abnormalities such as cardiac and other congenital malformations.

Cell free DNA testing in maternal blood

- Recently, a new screening test based on the analysis of cell free DNA (cfDNA) on maternal blood is introduced.
- cfDNA testing is a highly effective form of prenatal aneuploidy screening that can facilitate early detection as well as early reassurance.
- Currently, cfDNA testing is more expensive than conventional screening.

Cell free DNA testing in maternal blood

- This test has an excellent performance in screening for trisomy 21, with a detection rate above 99% and a false positive rate lower than 0.1%.

- A screening test does not give a yes or no answer but identifies increased risk for certain disorders so that definitive diagnostic tests can be offered.
- If the risk is considered high, then diagnostic tests could be done by obtaining fetal tissues either through chorion villus sampling or amniocentesis.

Progression of Prenatal screening

Termination or Continuation of pregnancy

Abnormal results

CVS
amniocentesis

Abnormal results

maternal serum markers
Ultrasound

A fundamental difference between prenatal and other types of screening is that when prenatal screening leads to the diagnosis of an abnormality in the fetus there is often no treatment available before birth. Women are left with the choice between continuing the pregnancy knowing the infant will be born with the condition identified or abortion to prevent the birth of an affected child.

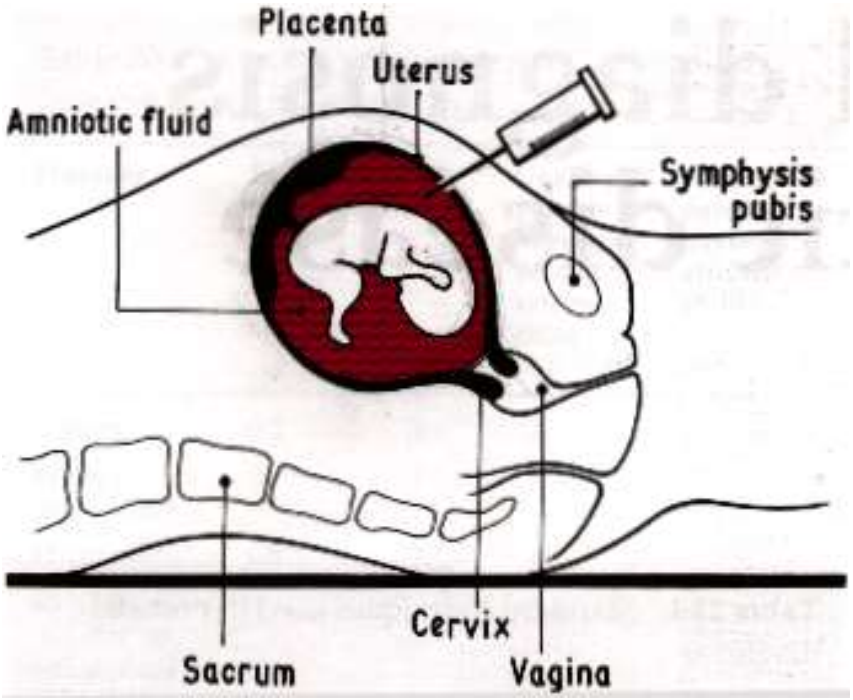
Termination of pregnancy when fetus is severely affected

- There is diversity of opinion among Islamic institutions on the issue of pregnancy termination, ranging from an absolute prohibition of abortion at any time to permission for pregnancy termination before the 120th day of gestation under specific circumstances.
- Ethical, legal and religious issues accepted in the country make the decision.

Indications for prenatal diagnosis

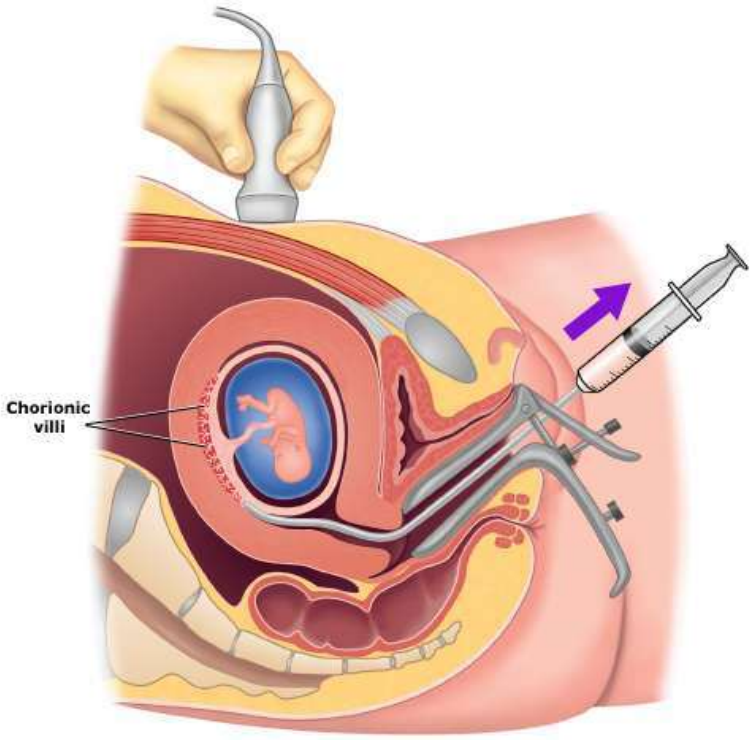
- Abnormal results in prenatal screening
- Previous child with a chromosome abnormality (probability of translocation carrier in parents)
- Family history of a chromosome abnormality
- Family history of a single gene disorder
- Family history of neural tube defect or other congenital abnormalities

Amniocentesis



- Done around the 16th week of gestation
- Aspiration of 20 ml of amniotic fluid through the abdominal wall under ultrasound guidance
- 0.5-1% risk of miscarriage

Chorion villus sampling



- Usually performed at 11-12 weeks gestation
- Transcervical aspiration of chorionic villi under ultrasound guidance
- Around 1% risk of miscarriage

Fetal risks following amniocentesis

- The earlier the amniocentesis is performed, the higher the risk of amniotic fluid leakage and the higher the risk for foot deformities.
- It is advisable not to perform amniocentesis before 15 weeks gestation.

Fetal risks following Chorion villus sampling

CVS should not be performed before 10 weeks due to the risk of limb reduction defects.

Experienced operators have a higher success rate and a lower complication rate.

Following the prenatal diagnosis of a fetal congenital disorder

- The couple should be counseled by a genetic counselor to inform them of the test results and the risks to the fetus.
- The couple should take an informed decision about termination or continuation of pregnancy.
- Autonomy of decision is crucial.
- The ethical, legal, and religious issues should be respected.

Amniocentesis, chorionic villus sampling and genetic diagnosis

- Many cytogenetic laboratories are capable of diagnosing chromosome aberrations in fetal cell cultures whether obtained through amniocentesis or chorionic villus sampling.

- The diagnosis of single gene disorders in fetal cells is more difficult and requires specialized laboratories and advanced technology. For less common and rare disorders, samples have to be sent abroad.

Selective termination of pregnancy when fetus is affected???

How can congenital disorders be categorized???

1. Severity of disease
2. Survival
3. Impact on family
4. Impact on affected
5. Impact on society and government

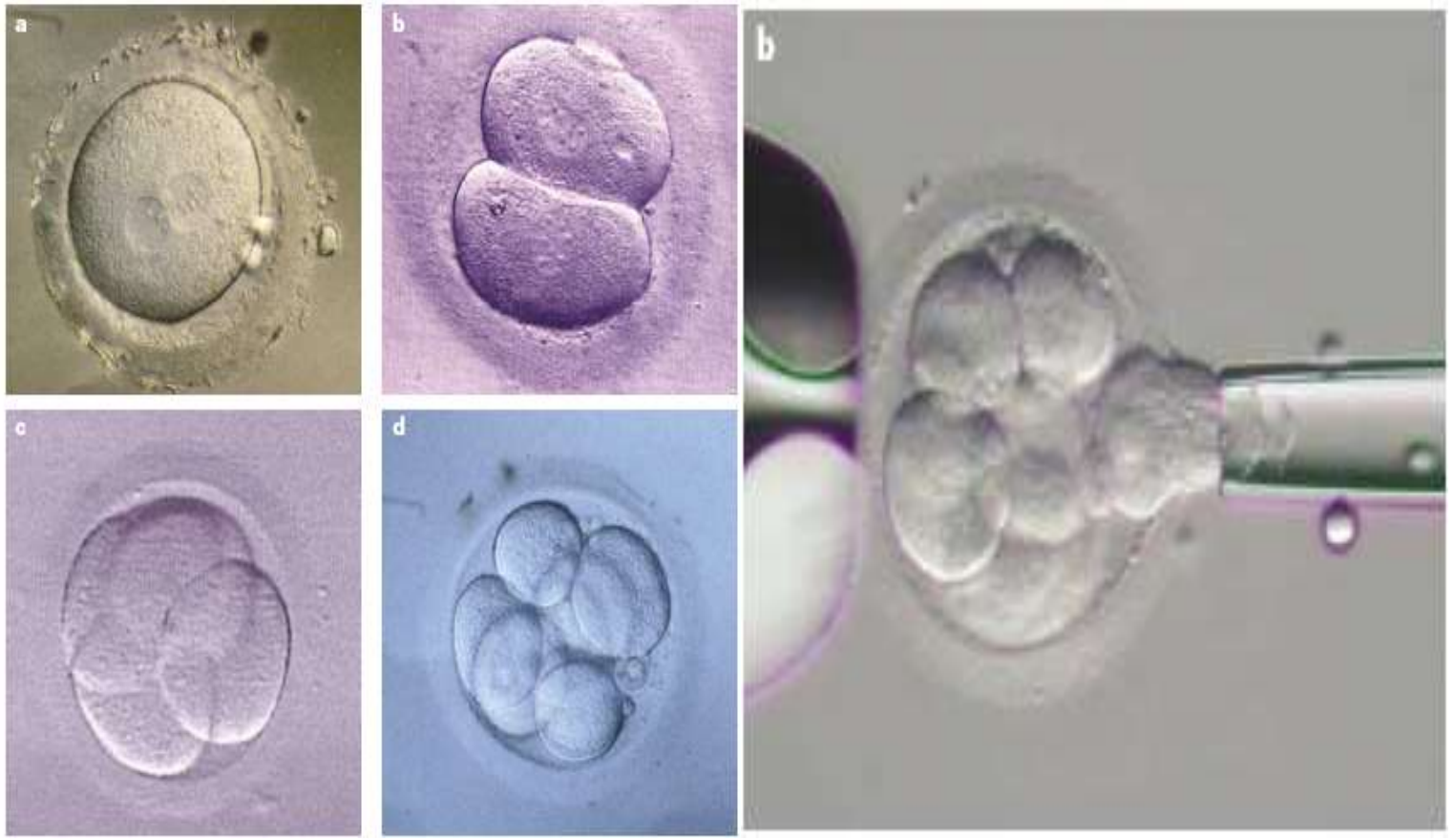
Preimplantation Genetic Diagnosis (PGD)

- Preimplantation Genetic Diagnosis (PGD) uses in vitro fertilisation (IVF) to create embryos.
- Tests one or two cells from each embryo for a specific genetic abnormality.
- Identifies unaffected embryos for transfer to the uterus.
- The approach through PGD assists couples at risk of an inherited disorder to avoid the birth of an affected child without going through selective pregnancy termination.

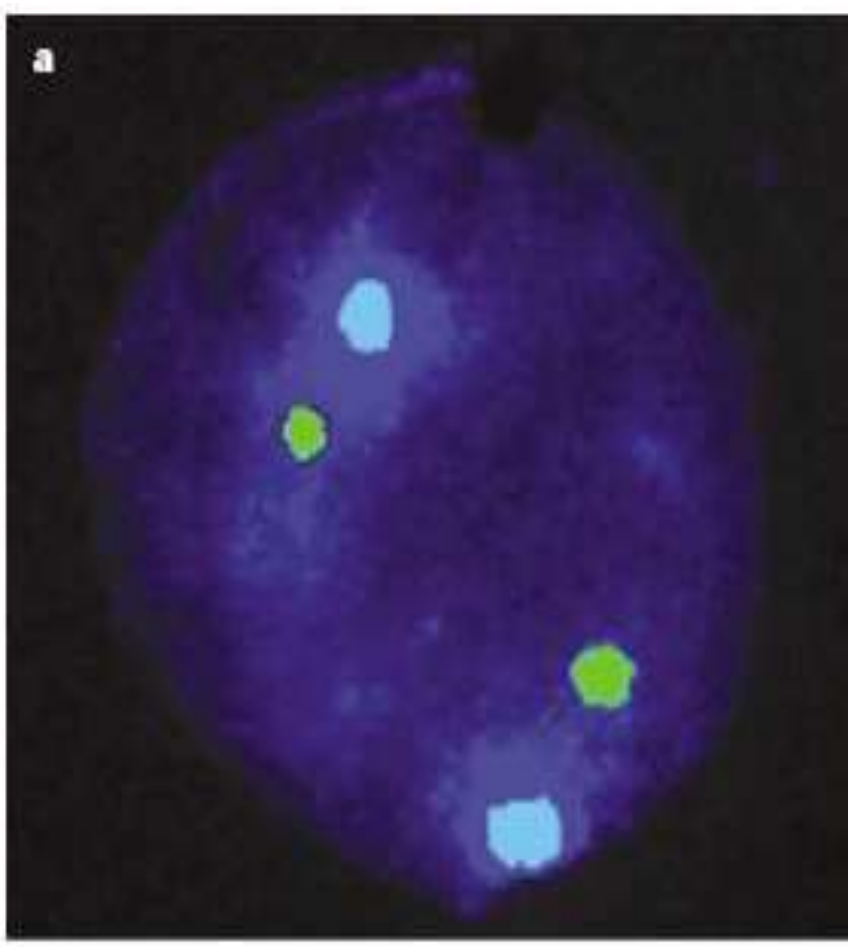
Indications for PGD

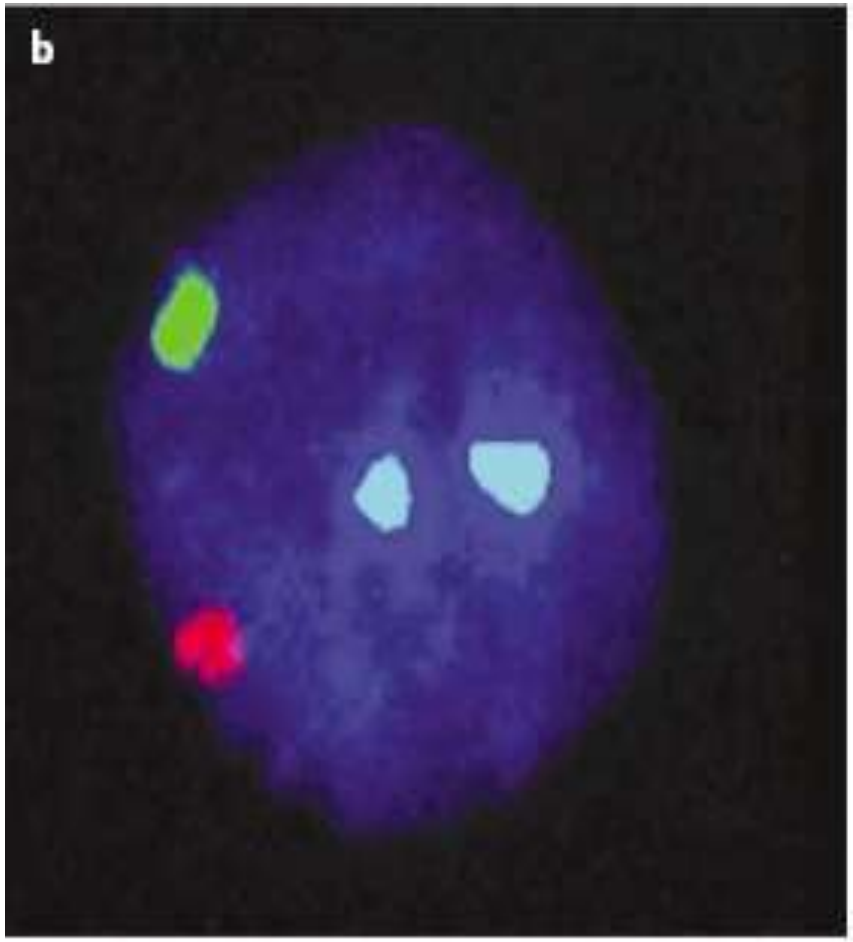
1. To detect chromosomal disorders by fluorescence in situ hybridisation (FISH).
2. To identify single gene defects such as cystic fibrosis, where the molecular abnormality is testable with molecular techniques after polymerase chain reaction (PCR) amplification of DNA extracted from single cells.
3. To determine the sex of the embryo for sex linked disorders where the specific genetic defect at a molecular level is unknown, highly variable, or unsuitable for testing on single cells.

Preimplantation genetic diagnosis (PGD)



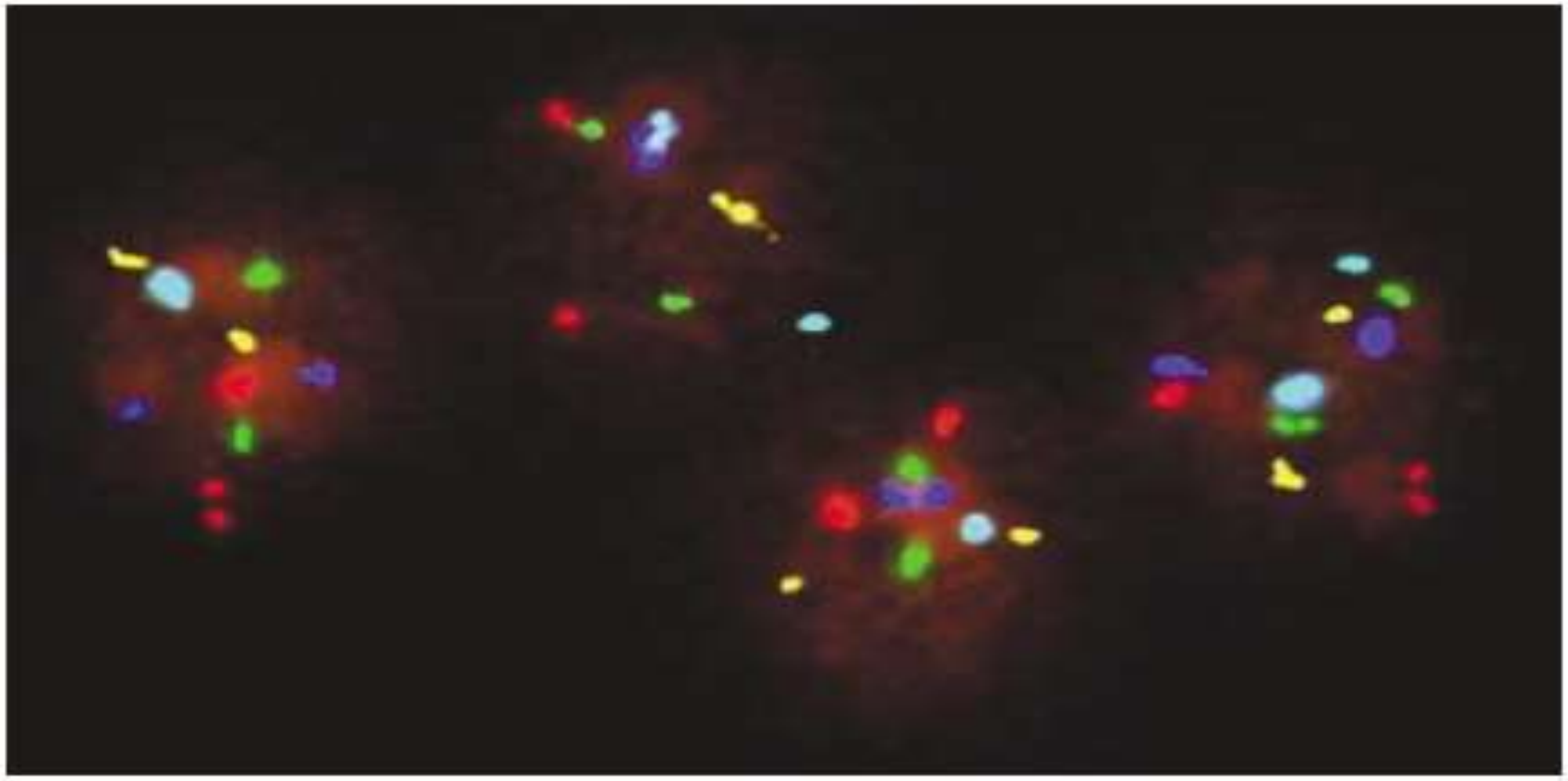
PGD of X-linked disorders or determination of sex by FISH





Aneuploidy screening using FISH.

The embryo has been hybridized with probes to chromosomes 13, 16, 18, 21 and 22. Interphase- FISH studies conducted on cell lines show an error rate of >5% per probe per cell



Things to keep in mind*:

*Reference Guide for Health Care Providers
Prenatal Screening Tests for the Detection of: Down Syndrome, Trisomy 18 and Open Neural Tube Defects
http://www.geneticresourcesontario.ca/Provider.pdf

- Informed choice - Before ordering the test, discuss benefits, risks and limitations.
- Autonomy - The patient should choose whether to have prenatal screening.
- What prenatal screening options are available in your area?
- What option is most suitable for your patient?
- Which test will provide the optimal care for your patient?
- A screening test is not diagnostic.

Prospects for the role of prenatal diagnosis in the future

- Prenatal diagnosis can be followed by intrauterine or neonatal surgery for the correction of certain congenital anomalies such as cardiac and renal defects.
- In utero gene therapy could become a practical therapeutic option in the future for the treatment of serious monogenetic diseases.
- Prenatal diagnosis with in-utero transplantation offers the potential to treat a large number of diseases by transplantation of healthy cells into a fetus with a birth defect.

Conclusions

- Detection rates for first trimester structural anomalies by ultrasound range from 30% in low risk, to about 60% in high risk groups.
- Screening for chromosomal disorders using biochemical markers, ultrasonography, and recently by non-invasive prenatal diagnosis based on cell-free fetal DNA in maternal plasma could be offered whenever feasible and acceptable.