Course :Medical Genetics

Screening of Diseases

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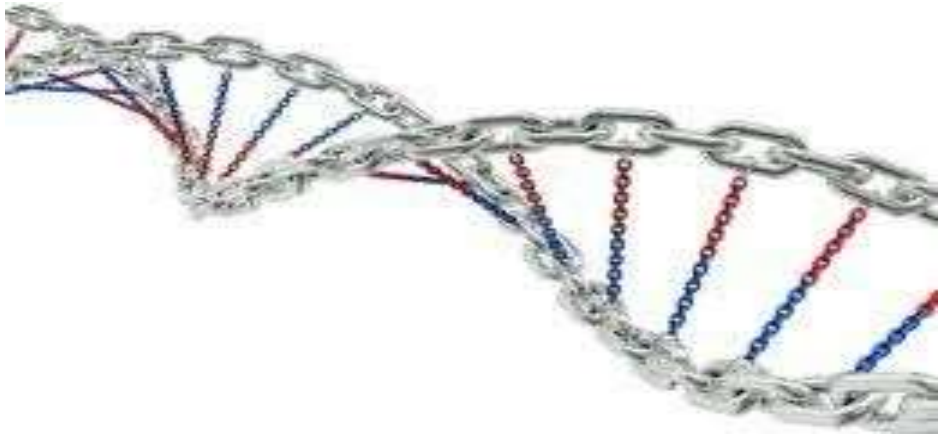
SCREENING OF DISEASE CARRIER TESTING

- Genetic carrier screening determines whether you and your partner carry one or more gene mutations in common that could put you at risk of having children with a particular genetic disorder.
- If both you and your partner are carriers for the same recessive genetic disorder, you have a 1 in 4 or 25% chance (with each pregnancy) of having an affected child. While all people carry a small number of recessive gene mutations that could cause a genetic disorder in their children, recessive diseases only occur when both parents are carriers for the same condition and both pass on the mutation to their offspring.
- Carriers are typically healthy and have no symptoms. Most people only become aware that they are carriers after having a child with a genetic disorder, or through carrier screening.

GENETIC CARRIER SCREENING TECHNOLOGY

- Recent technology advances now allow laboratories to screen for multiple diseases at the same time for a relatively low cost. screening
- There are many testing panels available for genetic, called by a number of names, including „multi-disease“, „universal“, or „all-in-one“ genetic carrier screening.



POPULATION SCREENING

- Population genetic screening programs give rise to a range of ethical, privacy and discrimination-related concerns.
- Individuals can experience anxiety on receiving test results, particularly if the information means they will be faced with difficult choices, such as the possible termination of pregnancy.
- Consent and counselling issues are important. Screening may reveal the genetic status of family members who have not chosen to be screened, raising concerns about privacy and the „right not to know".
- Screening may result in stigmatisation of certain genetic disorders. Those who refuse to be screened may also suffer social stigmatisation.
- The information generated may have implications in contexts other than health, for example in employment and insurance.

GENETIC REGISTERS

- In 1972, a World Health Organization Scientific Group recommended that medical genetics centres should set up registers of genetically determined disorders specifically for the purpose of prevention.

- It was recognised that registers are the most effective way of identifying members of families who are at significantly increased risk of developing an inherited disorder or of having affected children,and that performance of such activities goes beyond the responsibilities and resources of individual doctors.

- Subsequently, genetic registers were established in many countries, including Australia.

- Genetic registers will have the greatest impact on the prevalence and burden of disorders that are serious and relatively common, for which the risk to relatives is high, for which prevention and/or improved outcome are possible as a result of surveillance, and for which there are reproductive choices which will enable couples to avoid the occurrence of severe genetic disorders in their children

- genetic registers have focussed on disorders caused by mutations in a single gene (monogenic, Mendelian disorders).

- These include dominant disorders such as Huntington disease or familial adenomatous polyposis and X-linked disorders such as Duchenne muscular dystrophy or fragile X mental retardation.

- Registers have also addressed heritable chromosome abnormalities.

CHARACTERISTICS OF A GENETIC REGISTER

- The following are the key characteristics of genetic registers:

- (i) Genetic registers address heritable disorders. Each genetic register usually addresses one disorder, or a closely related group of disorders.

- (ii) Genetic register staff contribute to the provision of care to family members, both affected and unaffected, either directly or through health professionals. They do so by

- Undertaking the systematic collection of accurate and up-to-date information over a long period, aiming at complete ascertainment offamily members at risk and the collection of all relevant informationabout them.
- Ensuring that family members have an opportunity to becomeaware of their risk, and of any genetic testing, prevention,surveillance, treatment or reproductive options that may beavailable to them.
- Working closely with health professionals to facilitate, coordinateand, in some cases, to provide aspects of care.– Bringing together pedigree and medical information relating toindividuals, nuclear families and branches of the family in order toconstruct a single large pedigree.
- This aggregation of family information may improve assessments of risk, assist with identifying and contacting those at risk, provide information about disorder severity and manifestations in the particular family, prevent duplication of genetic testing, help validate genetic test results and facilitate research.

PRENATAL DIAGNOSIS

- **Genetic Testing** → Analysis of chromosomes, RNA, DNA or proteins to detect abnormalities that may cause a genetic disease

- **Prenatal Genetic Diagnosis** → ***Diagnosis of genetic disorders in established pregnancies*** → ***guides the family in reproductive decision-making***
  - **Terminating Pregnancy**
  - **Facilitate planning of medical, surgical, psychological support**

- **Timing, Safety, Accuracy**

- Maternal Age > 35 yrs → Scanning at 12 weeks, fetal physical anomaly at 18-20 weeks

BENEFITS

- Reassures at-risk families (normal result)
- Risk information to couples (who may not choose pregnancy when no info available)
- Psychological preparation of a couple for an affected baby
- Help healthcare personnel to plan management
- Risk info provided to couple for whom termination could be an option

NON-INVASIVE

- Ultrasound scanning
- X-ray analysis
- Magnetic Resonance Imaging
- Alpha-fetoprotein measurement in amniotic fluid and in maternal serum

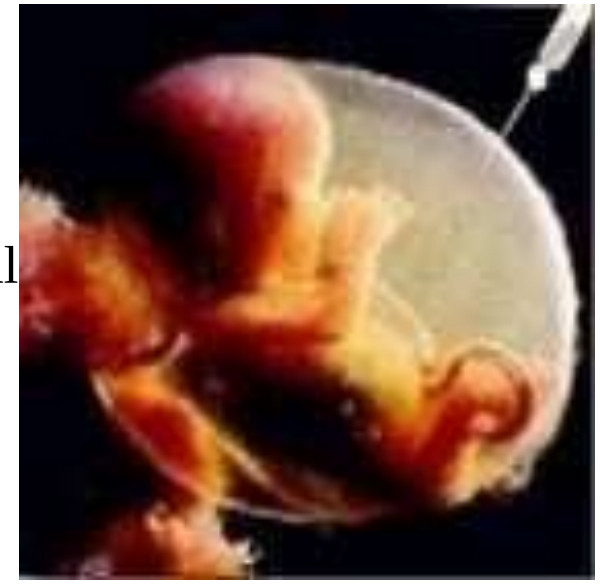
INVASIVE

- Aminocentesis
- Chorionic Villus Sampling (CVS)
- Cordocentesis (Percutaneous Umbilical Blood Sampling)
- Fetoscopy
- Embryo Biopsy

AMNIOCENTESIS

15-17 weeks post LMP

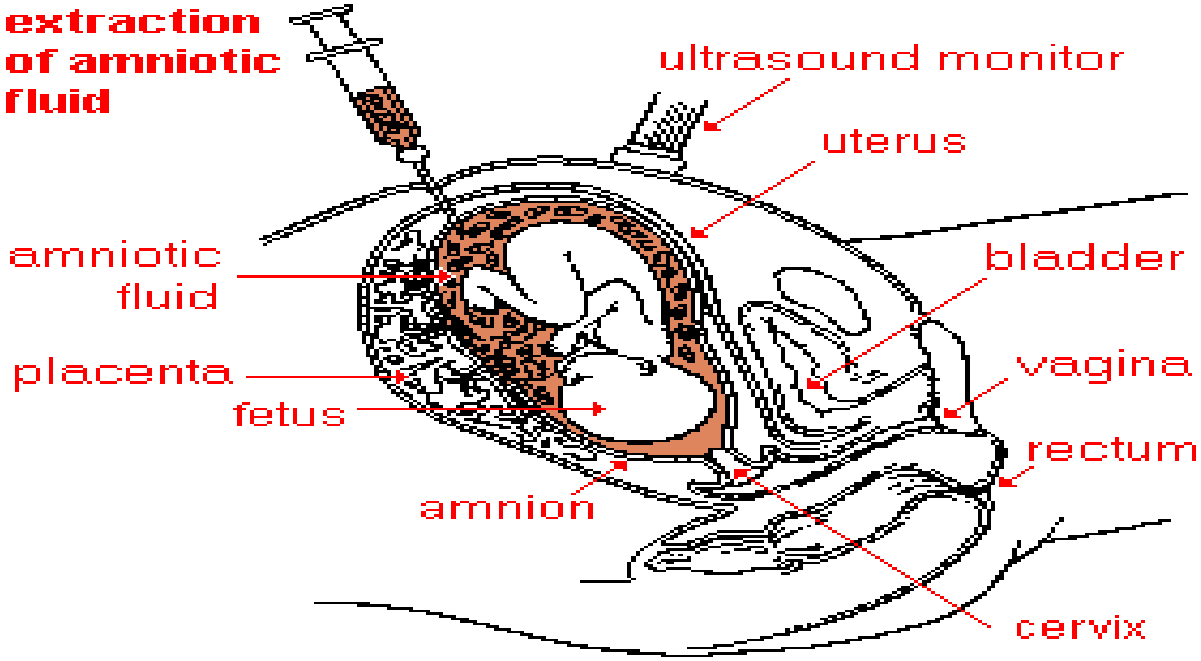
- Needle inserted through abdominal wall into the amniotic sac
- 20-30 ml of amniotic fluid (*amniocytes shed by the fetus*) is withdrawn
- Culture of amniocytes → cytogenetics, biochemical assays, FISH, DNA diagnosis
- AFP measurement (for NTD)



<u>Safety & Accuracy</u>: → Transient fluid leakage(1%)

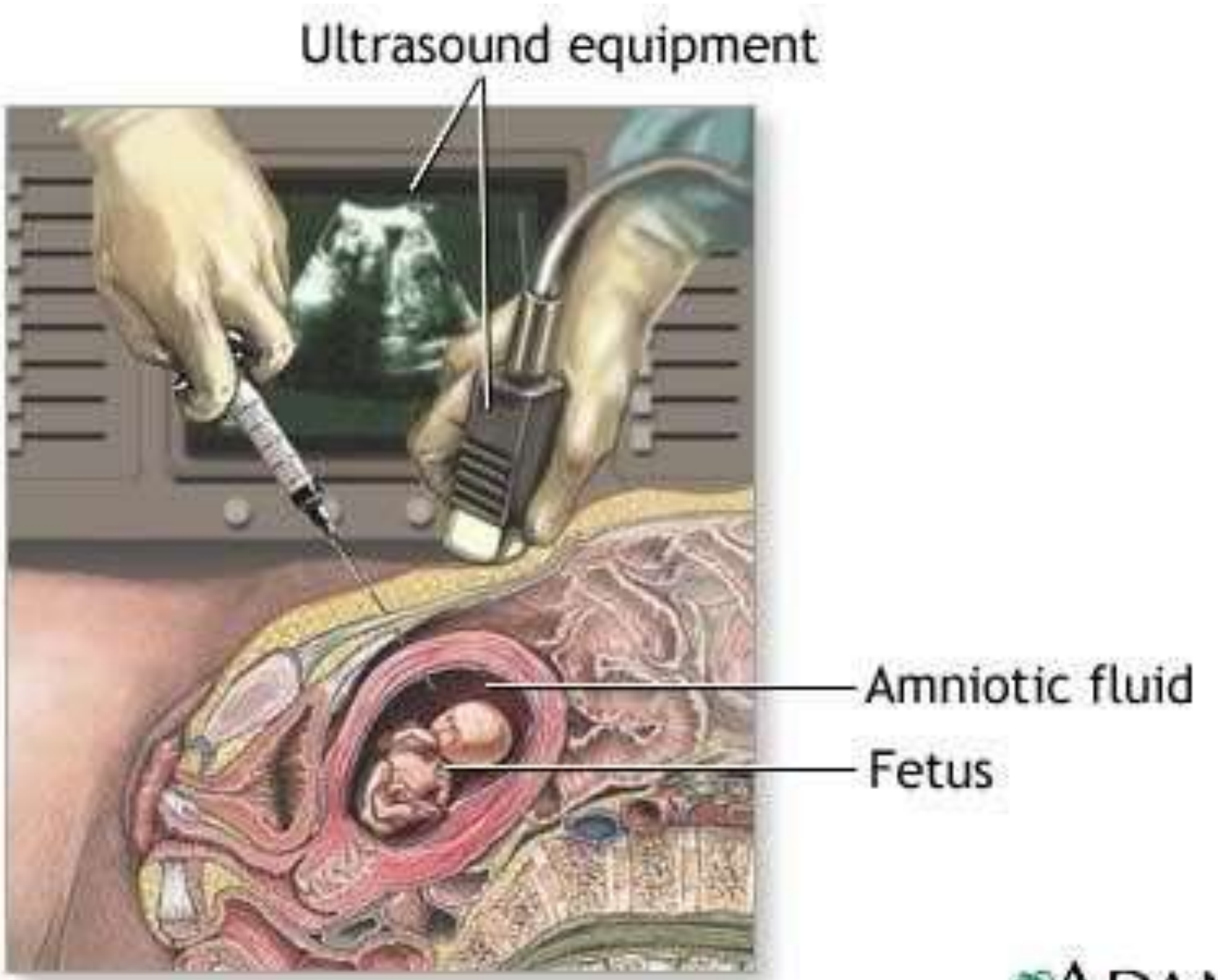
→ Maternal infections very rare

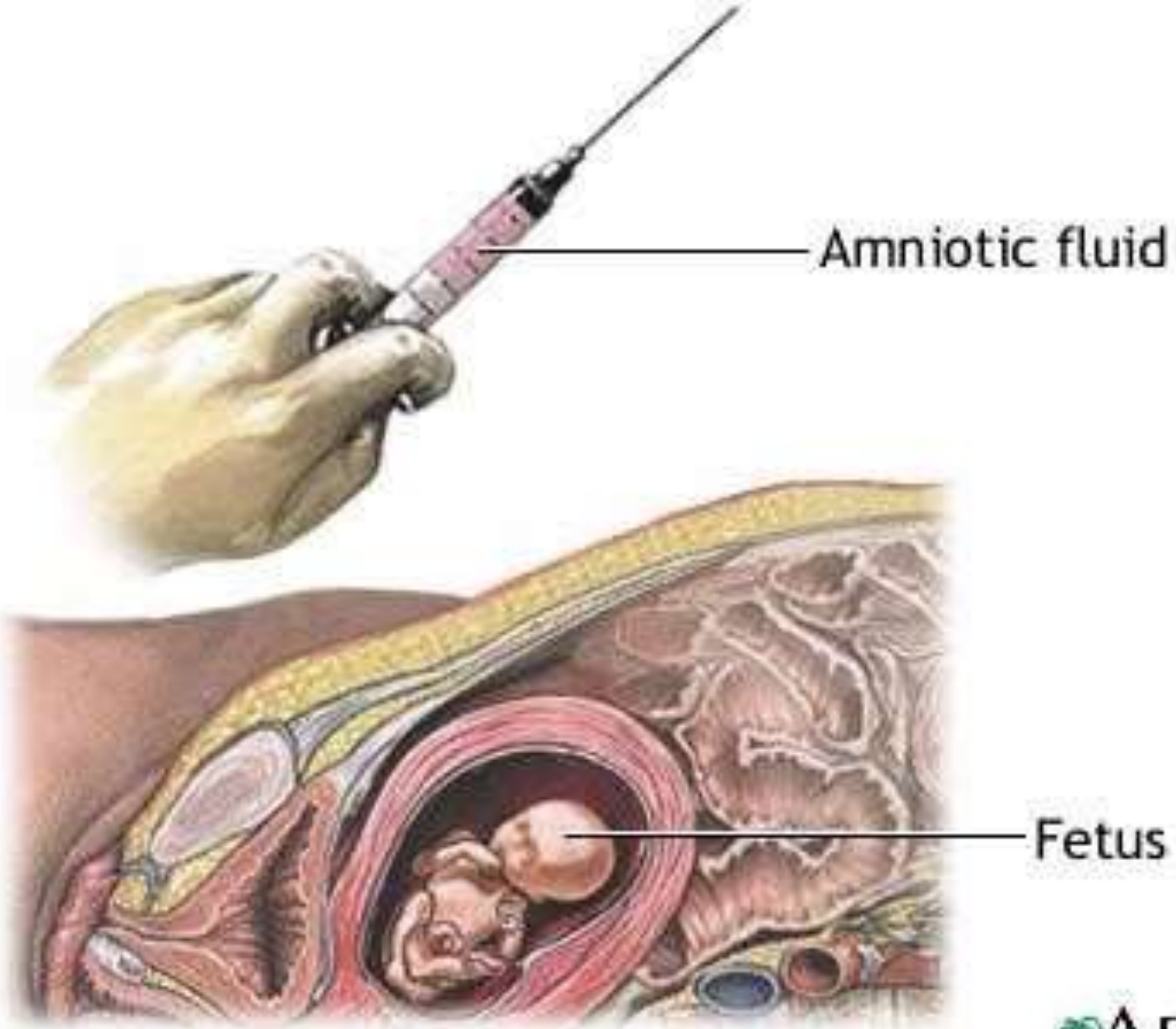
→ Increases the risk of fetal loss (3.5% compared to the normal 3%)



Indications

- ***Will be 35 or older when they deliver.***
- **Have a close relative with a disorder.**
- **Had a previous pregnancy or baby affected by a disorder.**
- **Have test results (such as a high or low alpha-fetoprotein count) that may indicate an abnormality.**


Ultrasound equipment
Amniotic fluid
Fetus
A.D.A.M.



MISDIAGNOSIS DUE TO CHROMOSOMAL MOSAICISM

- Most of it due to generation of extra chromosome during in vitro cell culture → **Pseudomosaicism** (only some cells in the colony have extra chromosome)
- Consistent aneuploidy in multiple colonies → **True mosaicism**

CHORIONIC VILLUS SAMPLING

–Aspirating fetal trophoblast tissue

–10-11 weeks post LMP

Advantages: 1) Early diagnosis.

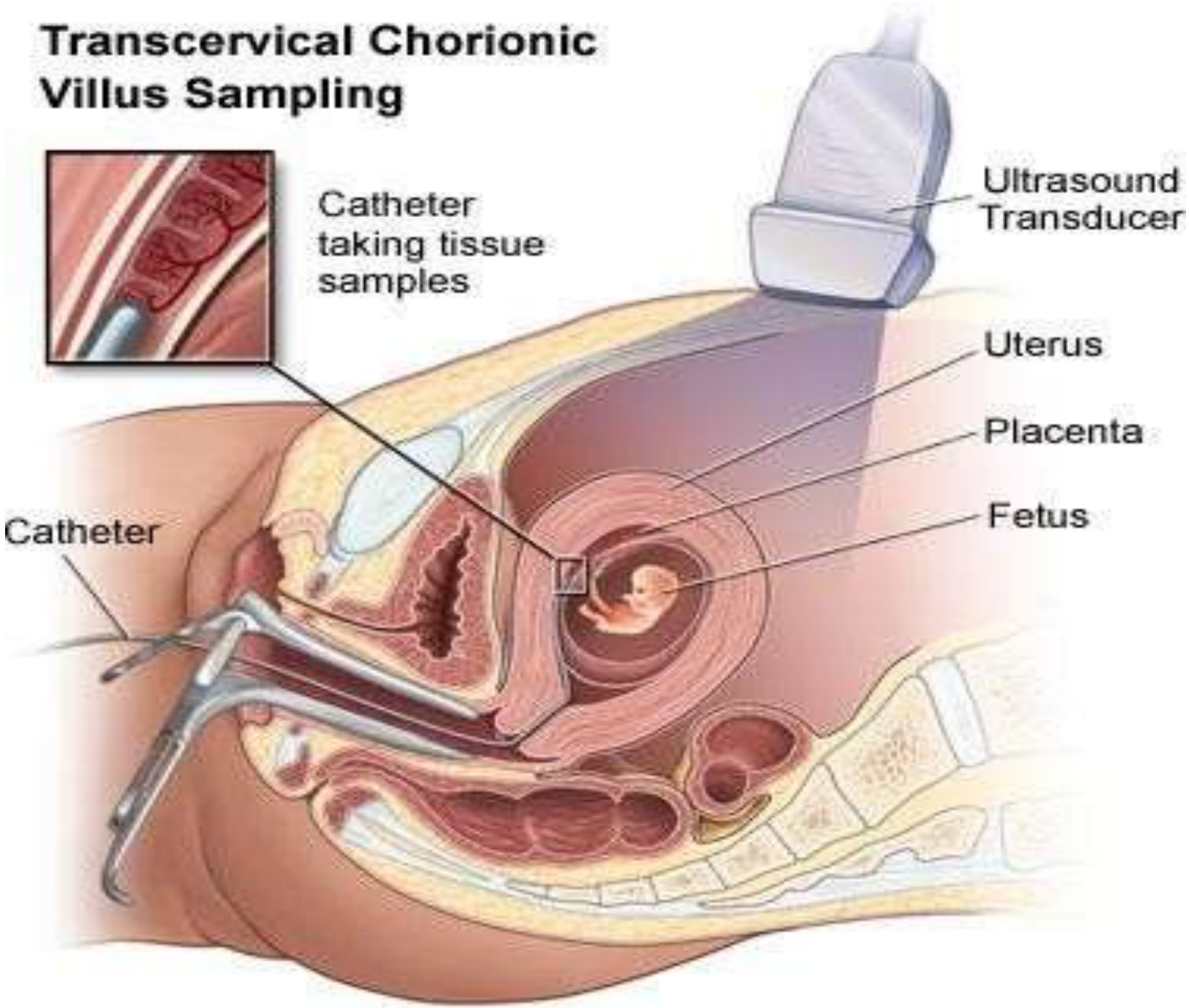
2) 99% successful results

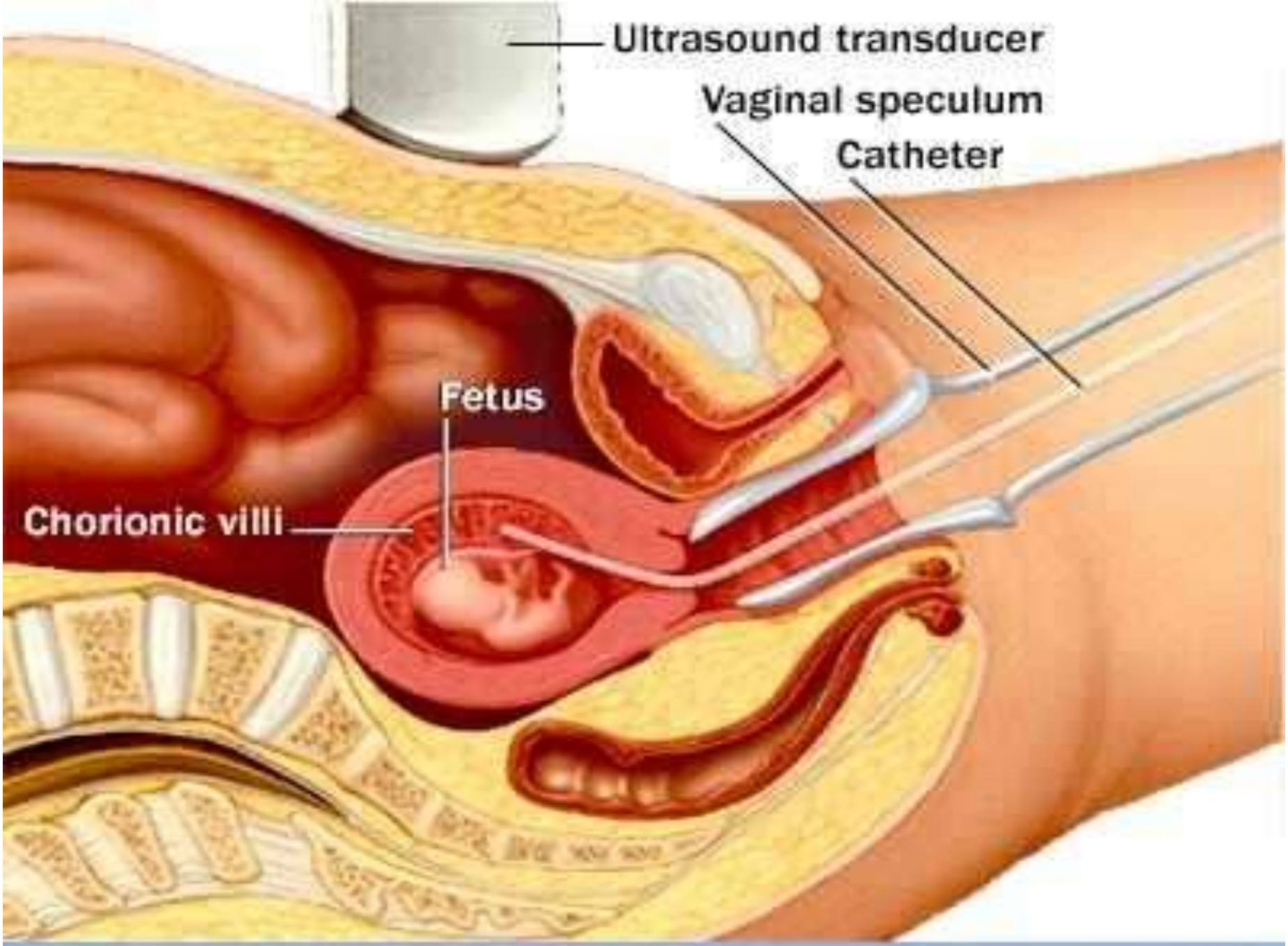
Disadvantages: 1) Amniotic fluid AFP cannot be determined. 2) Confined placental mosaics (1-2% cases) confuse diagnosis

Safety & Accuracy: → Risk for limb deficiencies

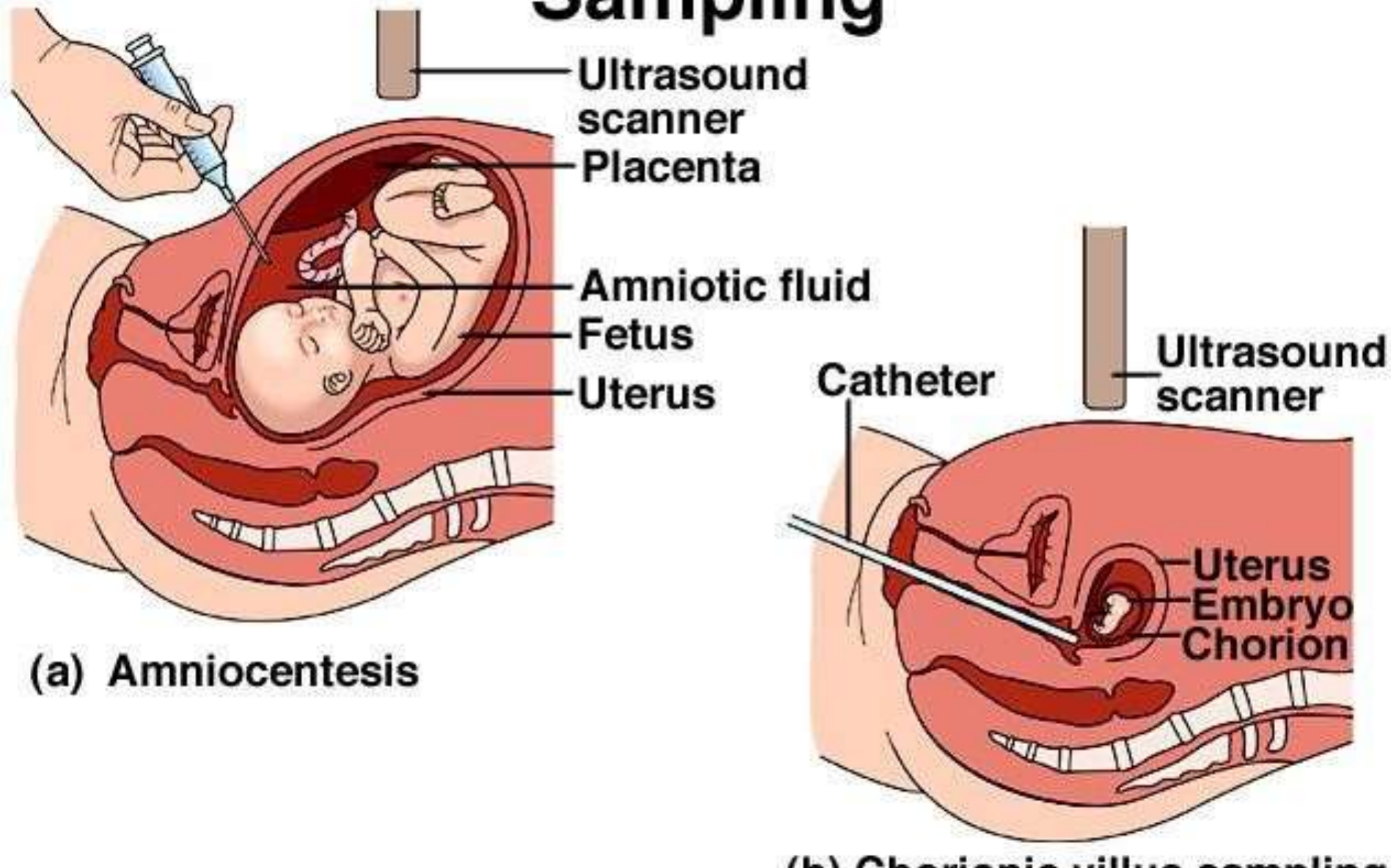
→ Inborn errors of metabolism detected (if amniocytes do not suffice)

→ Increases the risk of fetal loss (1.5% compared to the normal 1%)


Transcervical Chorionic Villus Sampling
Catheter taking tissue samples
Ultrasound Transducer
Uterus
Placenta
Fetus
Catheter

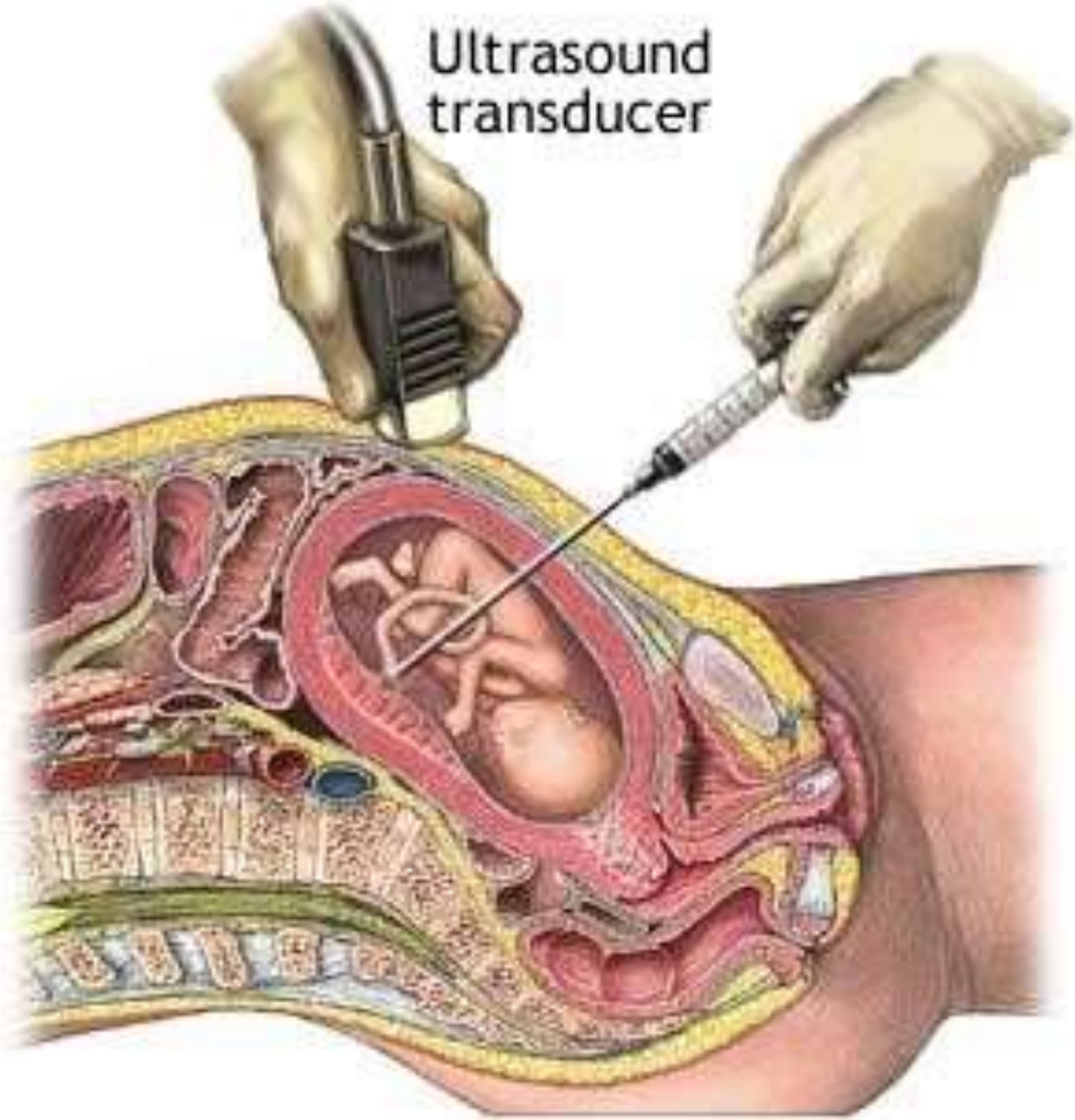


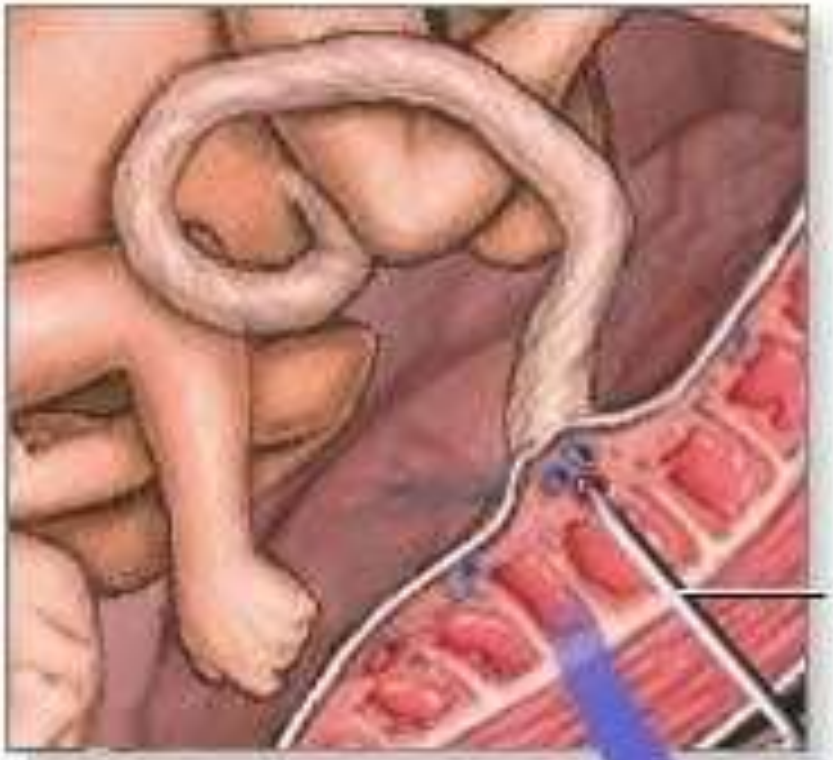
Amniocentesis & Chorionic Villus Sampling



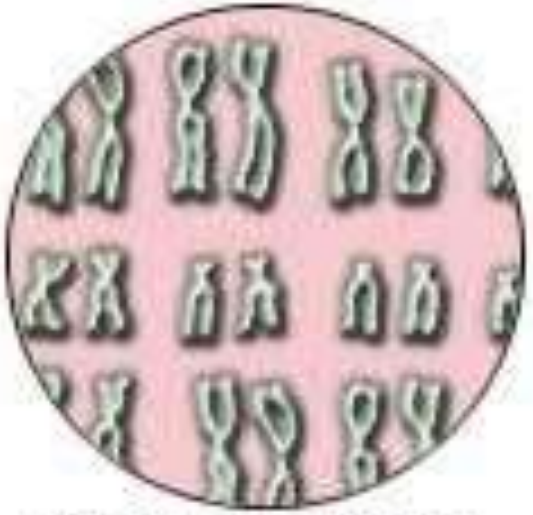
CORDOCENTESIS

- Access of fetal blood
- Percutaneous Umbilical Blood Sampling
- After 16 weeks, guided by ultrasound
- Low rate of fetal loss (but slightly higher than CVS)
- Applications:
  - Quick cytogenetic analysis (2-3 days) of fetal anomalies
  - Best analysis of hematological and immunological disorders (Lesch-Nyhan, Galactosemia)
  - Rapid distinction between true and false fetal mosaicism



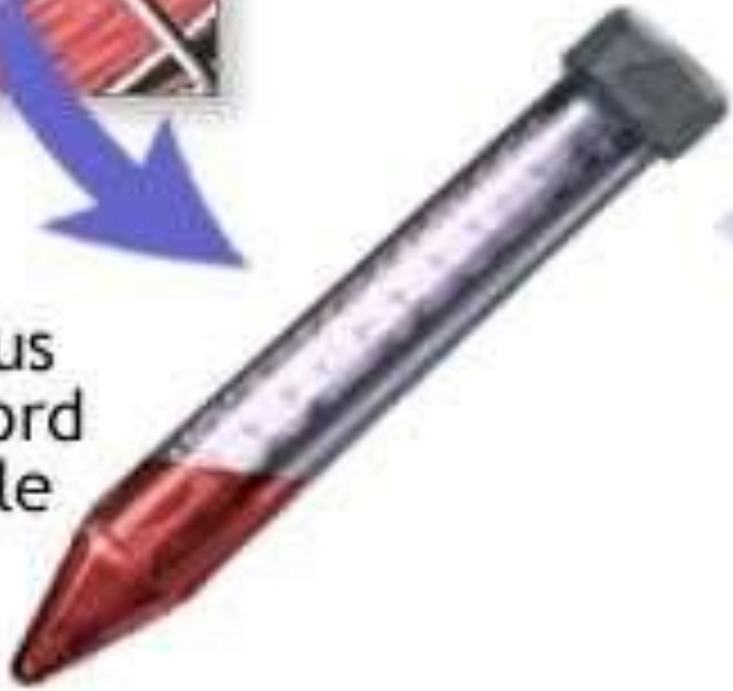


Needle tip



Chromosomes

Percutaneous
umbilical cord
blood sample



FETOSCOPY

- Viewing fetus through endoscope (optical fibre camera)
- 18 weeks
- Rate of fetal loss: 3%
- Applications:
  - To obtain fetal biopsy
  - Investigation of bladder obstruction

EMBRYO BIOPSY

- Biopsy collection ➔ skin and liver disorders

ULTRASONOGRAPHY

- Transducer → pulsed sound waves → pattern of sound waves corresponds to fetal tissue density
- Waves → Monitor: REAL TIME visualization
- Widely used method for fetal visualization
- Assists invasive techniques
- Tests for specific condition in at-risk fetus
- Obstetric indications
- Sensitivity: 30-50%; Specificity: 99%
- Anencephaly: 10-12 weeks; others: 18-20 weeks

- NTDs, Skeletal dysplasia, cleft lip & palate, microphthalmia, structural abnormality of brain, abdomen & heart
- 3rd trimester: hydrocephalus, microcephaly, duodenal atresia
- To identify a fetus with chromosomal abnormality by detecting malformation, IU growth retardation, hydrops or alteration of AFV
- Meningiomyelocele

X-RAYS

- Risk of mutagenic injury
- Sometimes used to assess fetal skeletal dysplasia
- “28-day rule”
- First 7 days: embryo is ultrasensitive; later on sensitivity decreses a bit
- Dosage-dependent exposure at 8-40 weeks → childhood leukemia.

MRI

Mainly for diagnosis of internal anomalies such as brain malformations

SCREENING OF MATERNAL BLOOD AND AMNIOTIC FLUID

Maternal serum has useful indicators: AFP, hCG, UE3 Increased AFP → NTDs

AFP: similar to albumin, from yolk sac and subsequently from liver; level increases in AF until 10-14 weeks then decreases steadily; Significantly higher level in pregnancies → fetal NTD;

AF assay + US ➔ 98% of embryos with spina bifida, anencephaly are detected (II trimester); along with aminiocentesis

AF-AFP increased in fetal death, twins, blood contamination

Accompanied with targeted US for specific malformations

- **MSAFP & NTD:** AFP diffuses across fetal membrane ➔ MSAFP---AFAFP
- Measurement of AFAFP with MS at 15-17 weeks.
- Safe, non-invasive population screening
- MSAFP: 2-2.5 times higher than normal median level is abnormal
- After all adjustments, about 1:15 will have high AF-AFP
- High sensitivity: 90% of anencephaly
- Though less than AFAFP, no risk of fetal loss
- **TRIPLE SCREEN:** T-21.
- Free beta hCG, PAPP-A, US ➔ DS
- T-18, T-13.