Prenatal Diagnosis of Congenital Anomalies

Chapter 55

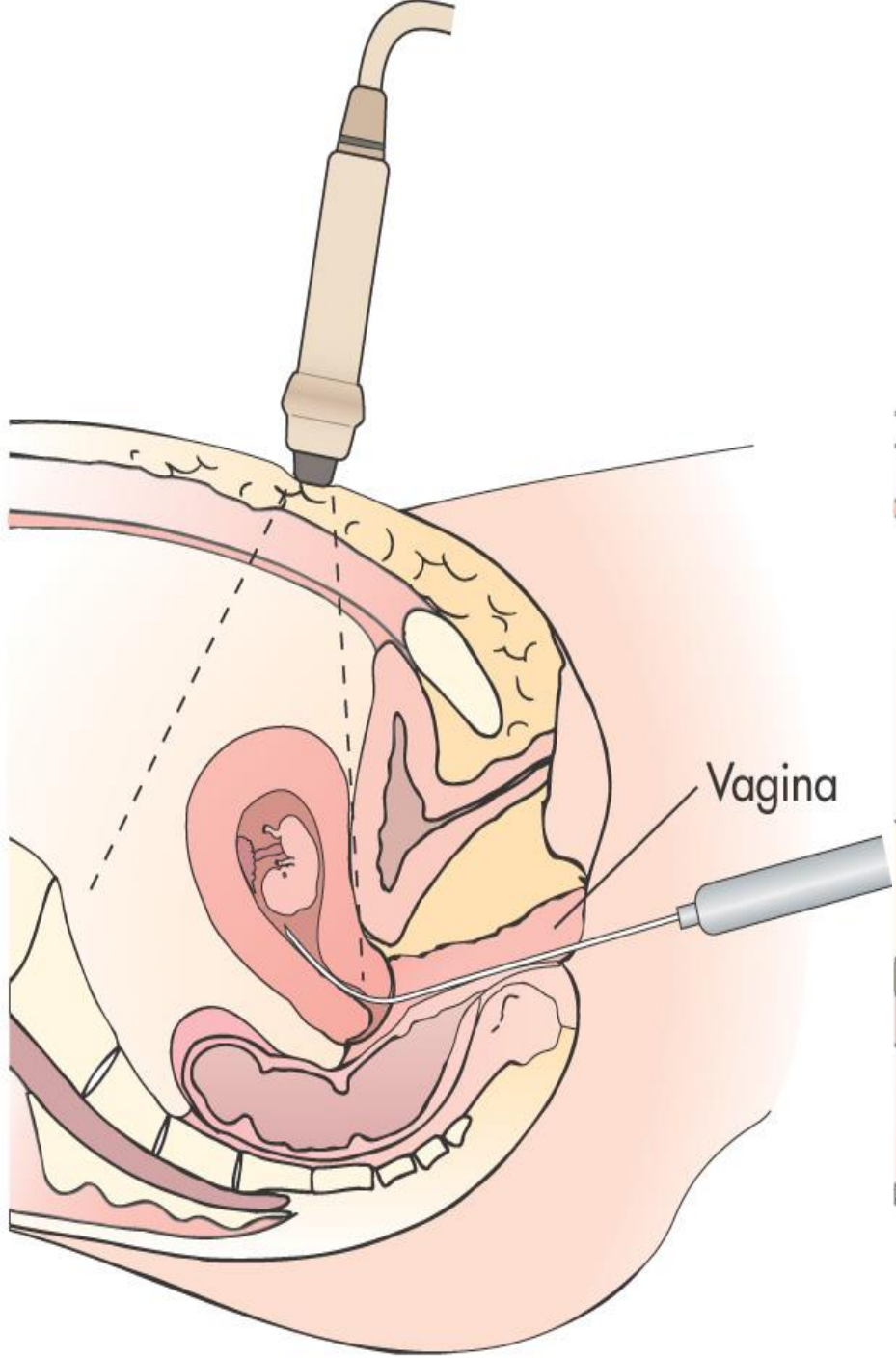
Alpha-Fetoprotein and Chromosomal Disorders

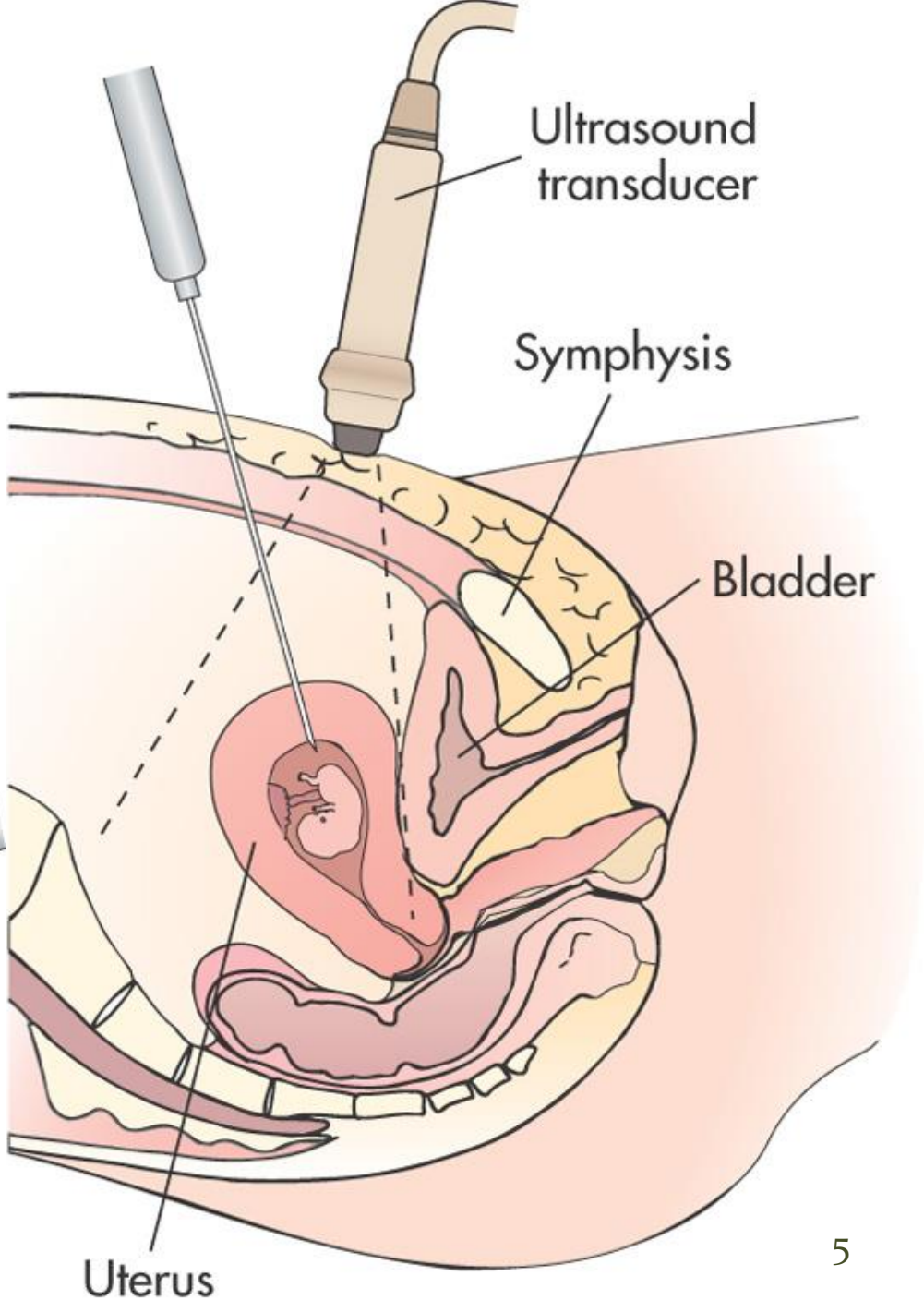
- Major congenital anomaly
  - 3 of every 100 births
- 10% to 15% of births are complicated by minor birth defects
- Prenatal ultrasound has become the investigative tool for the obstetrician to access the developing fetus
- Role of the sonographer is to screen for the unsuspected anomaly and study the fetus at risk for an anomaly

Genetic Testing

Chorionic Villus Sampling

- An ultrasound-directed biopsy of the placenta or chorionic villi (chorion frondosum)
- Alternative test used to obtain a fetal karyotype by the culturing of fetal cells, similar to amniocentesis
- Performed transcervically or transabdominally





Chorionic Villus Sampling

- Chorion frondosum is the active trophoblastic tissue that becomes the placenta
- Chorionic villi are fetal in origin
  - Chromosomal abnormalities may be detected when cells from the villi are grown and analyzed

CVS

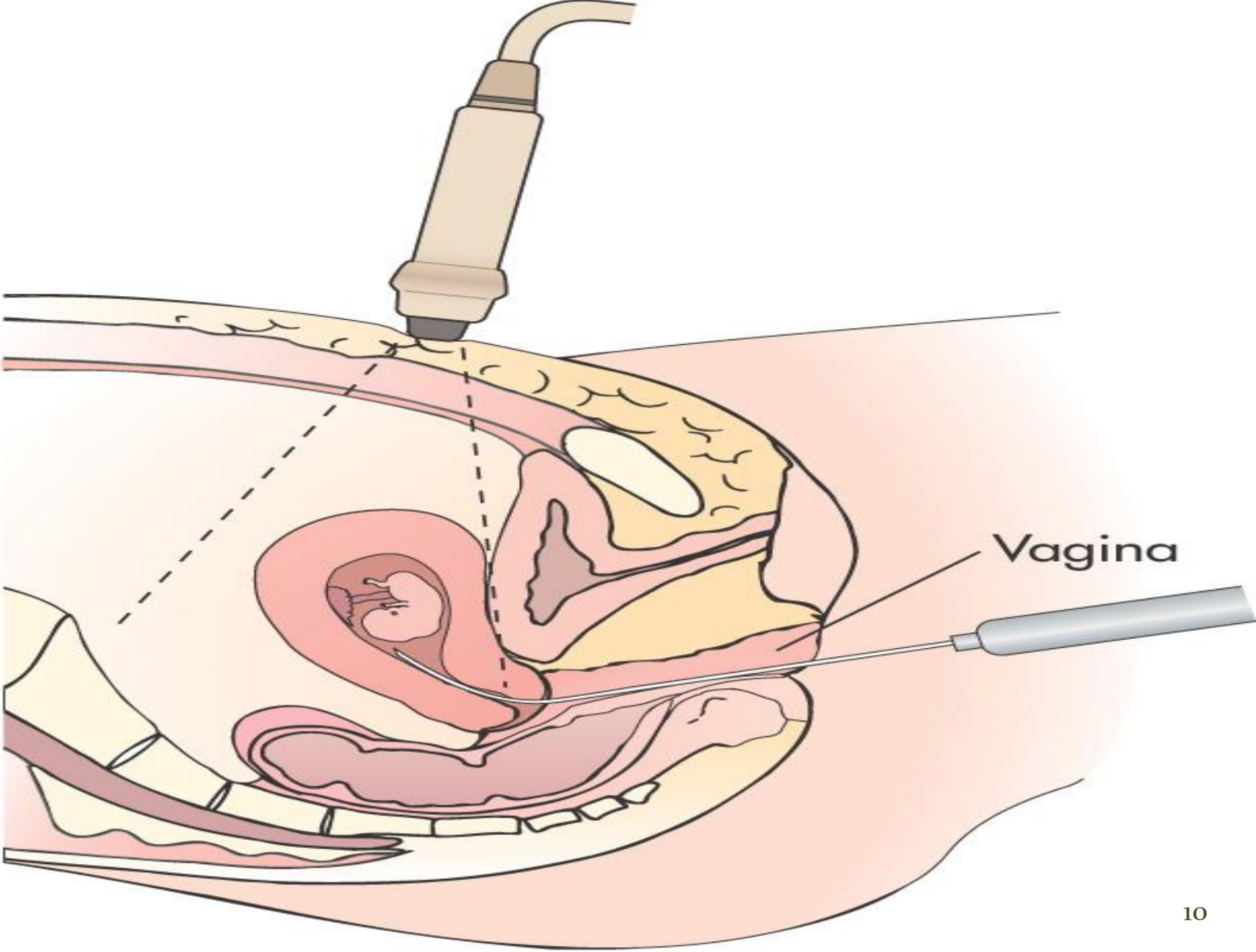
- Advantages
  - Performed early in pregnancy
    - 10 to 14 weeks
  - Results are available within 1 week
  - Earlier results allow more options for parents
- Risk of fetal loss is approximately 0.5% to 1%
- There has been some association with limb-reduction defects when CVS is performed before 8 weeks of gestation

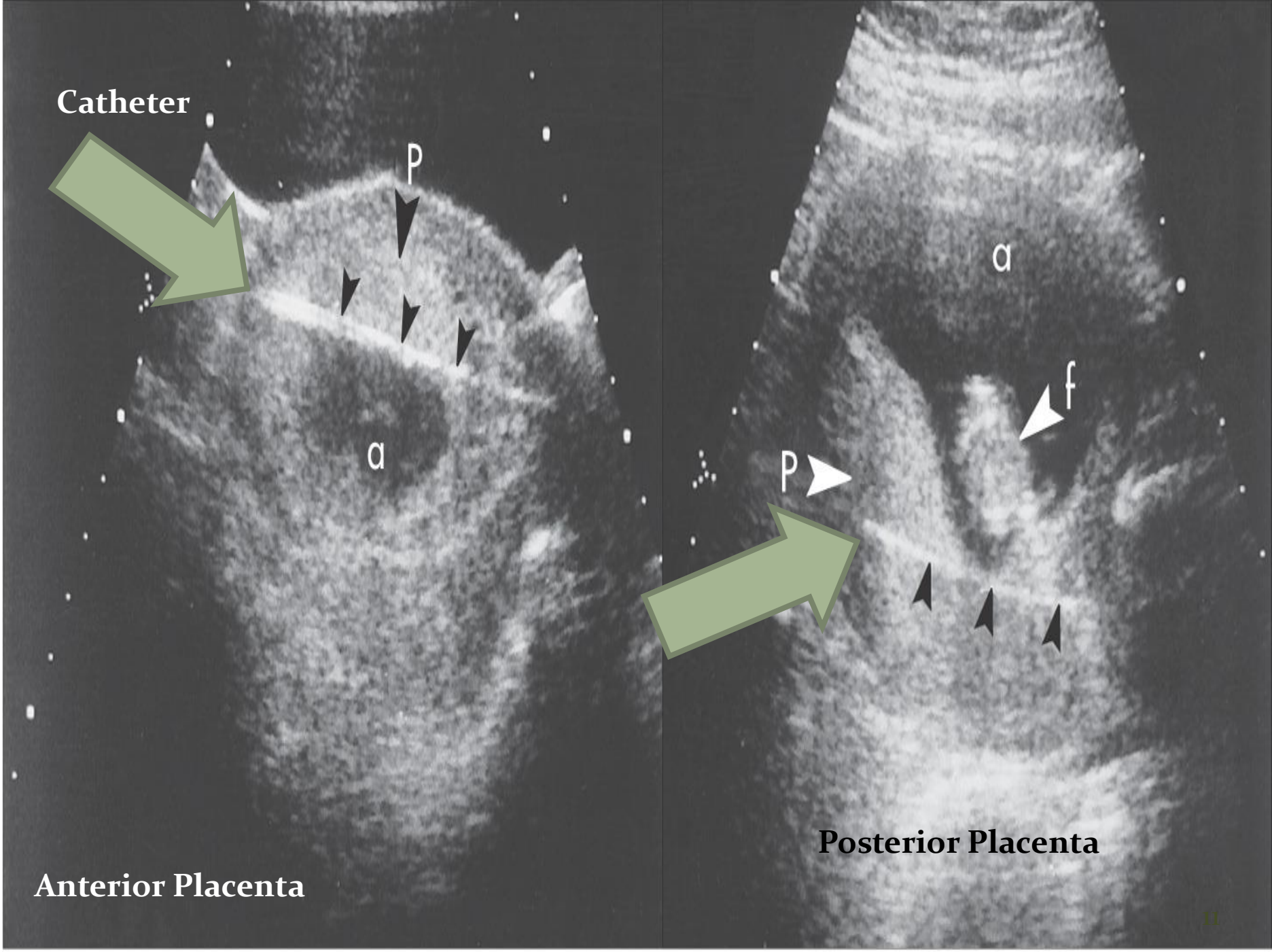
CVS

- **Ultrasound performed before the actual procedure should aid in the following ways:**
  - **Determining the relationship between the lie of the uterus and cervix and path of the catheter**
    - **Filling or emptying of the bladder may be necessary to facilitate the catheter route**
  - **Assess the fetus in terms of life, normal morphology, and age**
  - **Identify uterine masses or potential problems that may interfere with passage of the catheter**

Endovaginal CVS

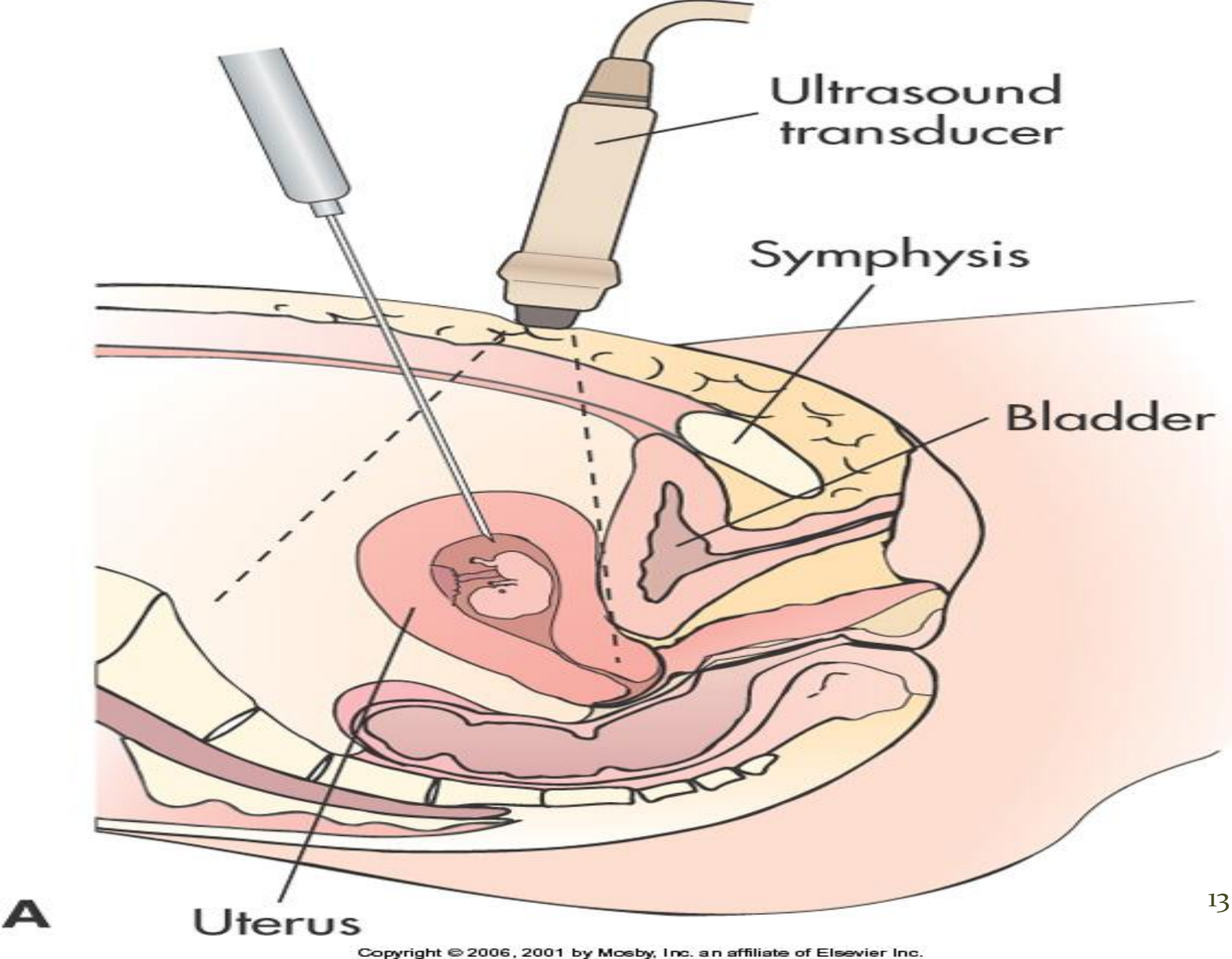
- Sonographer aids the obstetrician in determining the correct route to pass the catheter through the cervix to the placenta
- Guiding stylet is initially introduced to check uterine and placental position
- Flexible catheter is then introduced and directed into the placental tissue
- Placental cells are aspirated through the catheter
- Villi are collected in media-prepared syringes and immediately transported to the cytogenetics for analysis
- Sonographer should monitor the fetal heart rate and check for procedural bleeding





Transabdominal CVS

- Entails using a special apparatus attached to the needle hub to permit adequate suction to withdraw the villi
- Procedure is performed in a manner similar to amniocentesis



Amniocentesis

- First used as a technique to
  - Relieve polyhydramnios
  - Predict Rh isoimmunization
  - Document fetal lung maturity
- In the mid-1960s
  - Used to study fetal cells from amniotic fluid
    - Allowed the analysis of fetal chromosomes

Amniocentesis

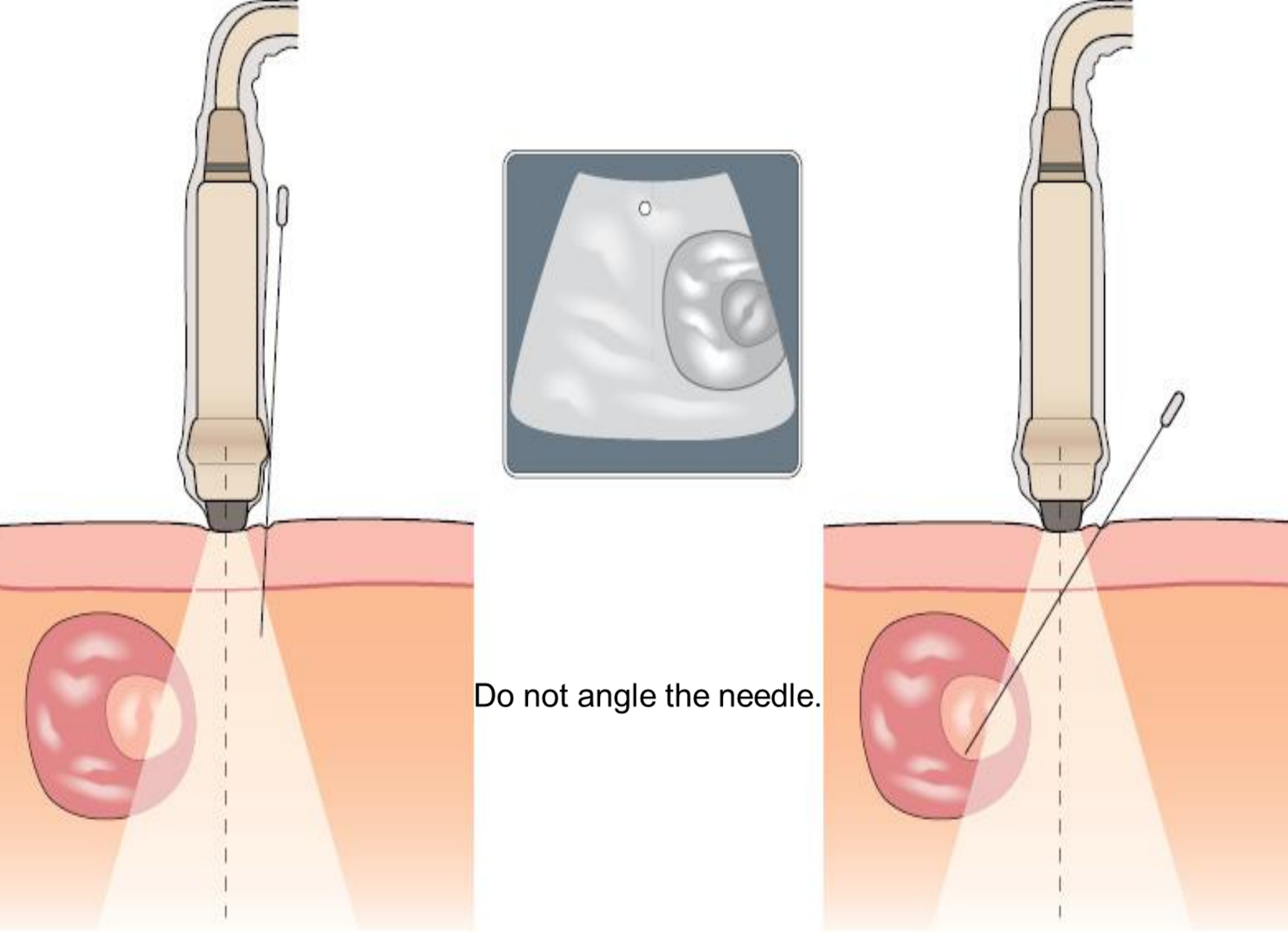
- Advanced maternal age is a common reason
- All pregnant women are at risk for having a child with a chromosomal defect
  - Risk is greater in a woman of advanced maternal age
- Risk of Down's syndrome is 1 in 365 in women 35 years of age
  - 1 in 2000 for women 21 years of age
- Risk of any chromosomal anomaly is 1 in 180 in women 35 years of age
  - 1 in 500 for the women 21 years of age

Amniocentesis

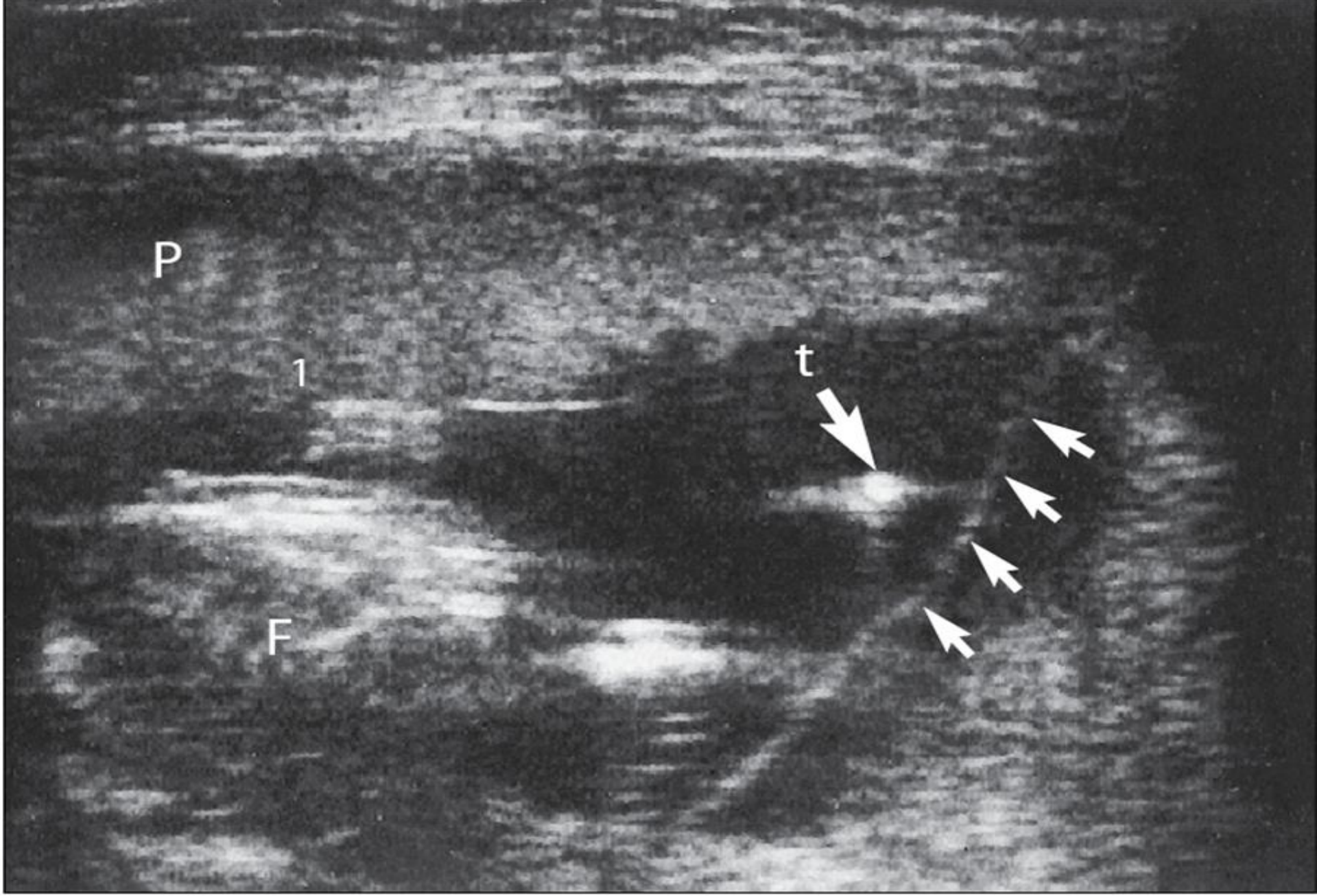
- For genetic reasons is ideally performed
  - At 15 to 20 weeks of gestation
- May be done as early as 12 weeks
  - May lead to the development of
    - Fetal scoliosis
    - Clubfoot
      - Secondary to the reduced amount of amniotic fluid
- Rate of miscarriage in early amniocentesis is unknown
- If performed beyond 20 weeks of gestation
  - May be associated with poor cell growth

Amniocentesis

- **Optimal collection site**
  - **Should be away from the fetus**
  - **Away from the central portion of the placenta**
  - **Away from the umbilical cord**
  - **Near the maternal midline to avoid the maternal uterine vessels**
- **Overall risk of miscarriage - 1 in 200**
  - **Important to weigh the risk of complication with the possible yield of identifying an abnormality**



Do not angle the needle.



B

Multiple Gestations

- Preliminary sonographic examination for each fetus should be performed to include survey of fetal anatomy and growth profiles
- Determine zygocity (mono- or di-)
- Determine if there are multiple sacs and the amount of fluid within each sac

Multiple Gestations

- Amniocentesis technique for multiple gestations similar to singleton
- Indigo carmine dye used
- Documentation of each amniocentesis and meticulous labeling of fluid samples important

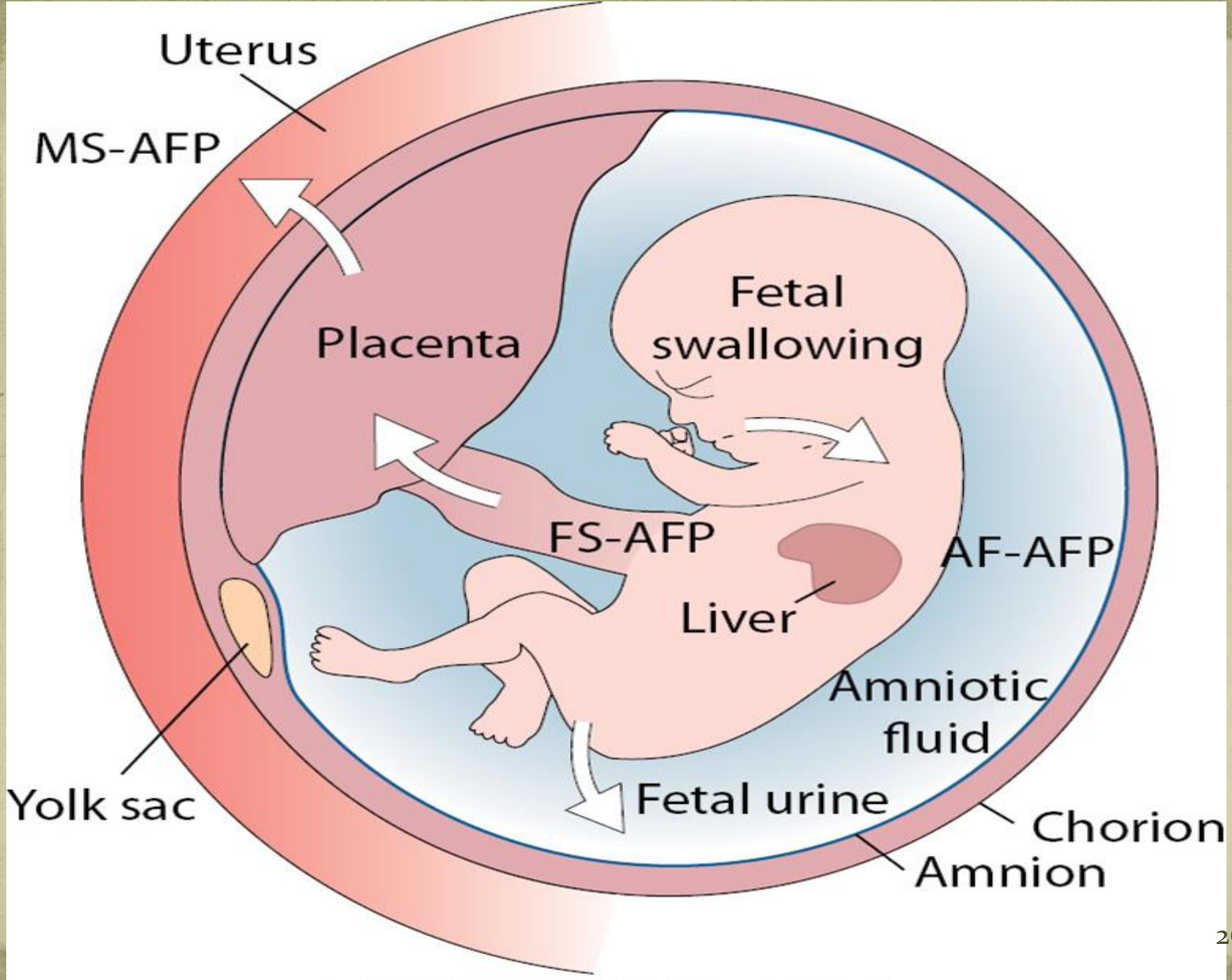
Cordocentesis

- Another method in which chromosomes are analyzed
  - Fetal blood is obtained through needle aspiration of the umbilical cord
  - Karyotype results can be processed within 2 to 3 days
- Commonly used for guidance for transfusions to treat fetal isoimmunization

Maternal Serum Markers

Alpha-fetoprotein (AFP)

- Major protein in fetal serum
- Produced by the yolk sac in early gestation and later by the fetal liver
- Found in the fetal spine, gastrointestinal tract, liver, and kidneys
- Transported into the amniotic fluid by fetal urination
  - Reaches maternal circulation or blood through the fetal membranes
- May be measured in the maternal serum (MSAFP) or from amniotic fluid (AFAFP)



- **Levels are considered abnormal**
  - **Elevated**
    - **Neural tube defects**
      - **Anencephaly**
      - **Open spina bifida**
        - **In both instances, AFP leaks from the defect to enter the amniotic fluid and then diffuses into the maternal bloodstream**
  - **Low**
- **Elevations are not found when there is closed spina bifida (occulta)**
  - **There is no opening to allow leakage**

- MSAFP levels increase with advancing gestational age and peak from 15 to 18 weeks of gestation
  - Ideal sampling time
- AFAFP, in contrast, decreases with fetal age
- Common reason for elevations
  - Incorrect dates
- AFP levels vary with gestational age
  - If the fetus is older or younger than expected
  - AFP levels will be reported as increased or decreased

- **Other reasons for elevations**
  - **Acrania**
  - **Encephalocele**
- **Concentration of AFP correlates with the size of the defect**
  - **AFP levels tend to be significantly higher in fetuses with anencephaly than with spina bifida, because more tissue is exposed**
- **Important to remember that approximately 20% of spina bifida lesions are covered by skin**
  - **AFP elevations will not be detected in serum or amniotic fluid**
- **Sacrococcygeal teratomas are also known to be associated with high AFP levels**

- **Two common abdominal wall defects produce elevations of AFP**
  - **Omphalocele**
    - **AFP leaks through the membrane encasing the herniated bowel or liver**
  - **Gastroschisis**
    - **AFP diffuses directly into the serum and amniotic fluid from the herniated bowel, which lacks a covering membrane**
    - **AFP levels are higher in gastroschisis**
- **Other abdominal wall defects cause ↑ AFP level**
  - **Bladder extrophy**
  - **Ectopia cordis**
  - **Limb–body wall complex**
  - **Amniotic band syndrome**

- **In multiple gestations**
  - **AFP level in a twin pregnancy will be twice that of a singleton pregnancy**
    - **Two fetuses make twice the AFP**
  - **Death of a co-twin (fetus papyraceous) or when one twin is an acardiac twin**
    - **AFP may be higher than normal**

- **Additional reasons for increased AFP**
  - Fetus with a kidney lesion
  - Polycystic kidneys and urinary tract obstruction
  - Placental lesions
  - Heart failure
  - Cystic hygroma
  - Liver disease in
    - **Mother**
    - **Fetus**

- **Additional reasons for increased AFP (cont)**
  - **Chromosomal abnormalities**
    - **Trisomy 13**
    - **Trisomy 18**
      - **Renal anomalies**
      - **Neural tube defects**
      - **Ventral wall defects**
      - **Skin lesions**
    - **Turner's syndrome**
      - **Cystic hygromas**
    - **Triploidy**
      - **Abnormal placental molar degeneration**

- **Low AFP levels**
  - Chromosomal abnormalities
    - **Trisomy 21**
    - **Trisomy 18**
    - **Trisomy 13**

    Choroid plexus cysts
    Hand anomalies
    Cardiac defects
  - Incorrect patient dates
    - **Fetus younger than expected**
  - Fetal death
  - Hydatidiform moles
  - Spontaneous abortion
  - Obstructions of the gastrointestinal tract

- Amniocentesis may be offered when MSAFP levels are elevated and ultrasound reveals no obvious explanation
- Amniotic fluid tests usually include
  - Karyotyping for chromosomal abnormalities
  - AFAFP levels
  - Acetylcholinesterase
    - Specific for detecting an open neural tube
- AFAFP is more specific for detecting levels of AFP
- Beyond 20 weeks of gestation
  - AFP analysis is no longer sensitive

Quadruple Screen

- **Biochemical screening test (blood test)**
- **Evaluates**
  - **AFP**
  - **Human chorionic gonadotropin (hCG)**
  - **Unconjugated estriol**
  - **Dimeric inhibin A (improves sensitivity in detecting Down fetuses)**
- **May suggest <u>trisomy 21 if:</u>**
  (Better than MSAFP testing alone)
  - **High hCG levels**
  - **Decreased AFP**
  - **Decreased estriol levels**

Quadruple Screen

- **May suggest trisomy 18 if:**
  - **hCG, AFP, and estriol levels are all decreased**
- **Risk for a neural tube defect or chromosomal problem is calculated for each mother**
- **Patient may elect to undergo ultrasound with or without amniocentesis**
  - **Based on the risk for chromosomal or neural tube defects**

First-Trimester Screening

- **Pregnancy-Associated Plasma Protein A (PAPP-A)**
  - Glycoprotein derived from trophoblastic tissue
  - Levels increase in maternal serum throughout pregnancy
  - Levels are decreased in pregnancies affected by aneuploidy
- **Free beta Human Chorionic Gonadotropin (β-hCG)**
  - Glycoprotein derived from placenta
  - Evaluates for increased risk of Down syndrome

First-Trimester Screening

- **When PAPP-A and hCG assessments combined with information regarding maternal age and nuchal translucency (NT), detection rates for Down syndrome reported to be greater than or equal to that of quadruple screen.**

Medical Genetics

- Normal karyotype consists of
  - 46 chromosomes
  - 22 pairs of autosomes
  - A pair of sex chromosomes
- Aneuploidy
  - An abnormality of the number of chromosomes
- One of the most common aneuploid conditions is Down's syndrome
  - Has an extra chromosome number 21

Chromosomal Abnormalities

- Found in 1 of every 180 live births
- High prevalence of chromosomal abnormalities in patients referred for
  - Second trimester amniocentesis
    - Advanced maternal age
    - Abnormal AFP
    - Abnormal triple screen (hCG, AFP, and estriol)
    - Ultrasound detection of multiple fetal anomalies

Nuchal Translucency

- Abnormal fluid collection behind the fetal neck
  - Strongly associated with aneuploidy
- Reported as a late first trimester finding
  - identified between 11 and 14 weeks of gestation
- 3 mm or greater has been associated with chromosomal abnormalities such as
  - Trisomies 13, 18, and 21
  - Triploidy
  - Turner's syndrome

Trisomy 21

- Also known as Down's syndrome
- Occurs in 1 in ~704 births
- One of the most common chromosomal disorders
  - Characterized by an extra chromosome number 21
- There is an association with advanced maternal age
  - May affect infants born to women of all ages
- Associated with an abnormal quadruple screen

Trisomy 21

- **Infants may present with a variety of physical features**
  - **Brachycephaly**
  - **Epicanthal folds**
  - **Flattened nasal bridge**
  - **Round, small ears**
  - **Broad neck with extra skin (nuchal fold)**
  - **Protruding tongue**

Trisomy 21

- **Other anomalies associated with Down's syndrome include**
  - **Heart defects**
    - **Septal defects**
    - **Endocardial cushion defect**
    - **Tetralogy of Fallot**
  - **Duodenal atresia**
  - **Esophageal atresia**
  - **Anorectal atresia**
  - **Omphalocele**

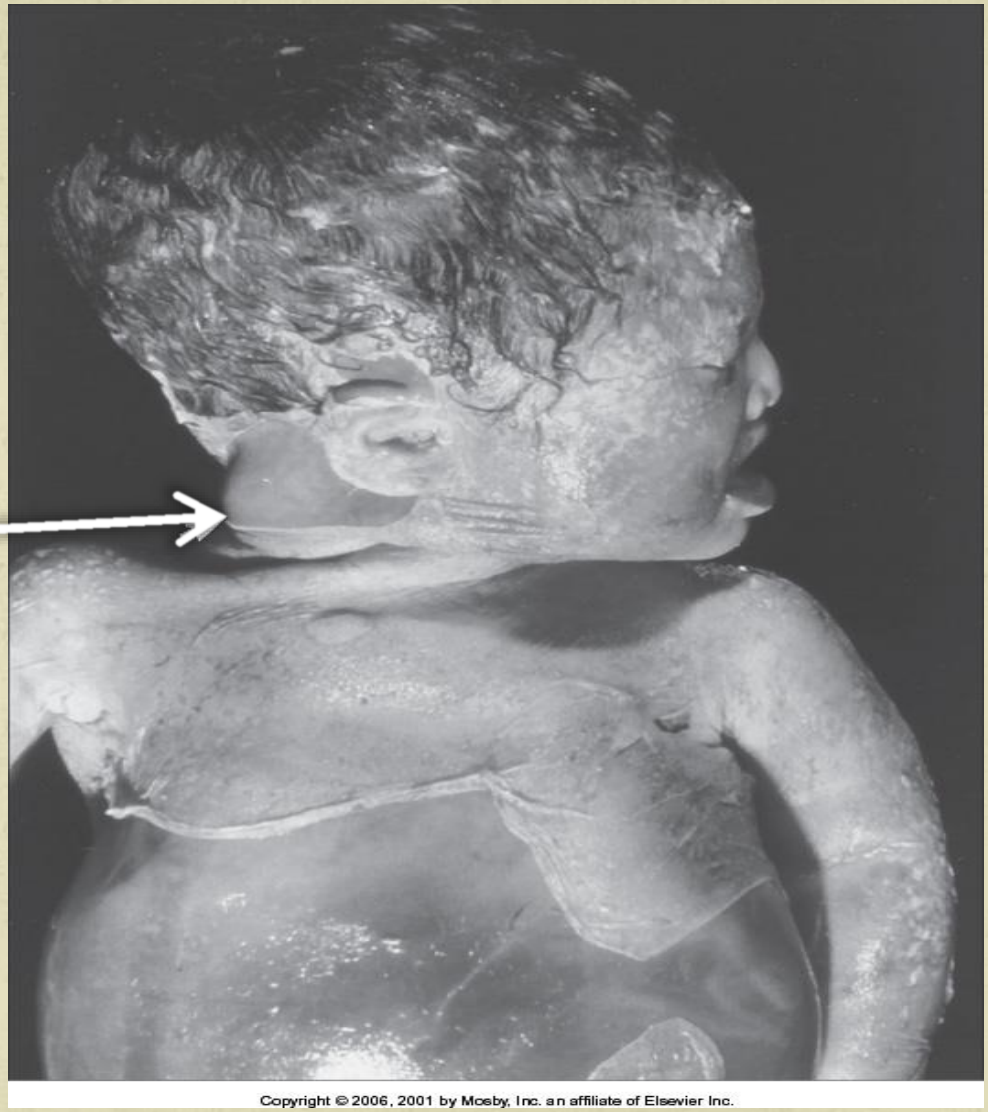
Trisomy 21

- **Other anomalies associated with Down's syndrome include (cont)**
  - **Cystic hygroma**
  - **Nonimmune hydrops**
  - **Hydrothorax**
  - **Skeletal anomalies**
    - **Shortened extremities**
    - **Space between the first and second toes**
    - **Hypoplasia of the middle fifth phalanx**
    - **Clinodactyly of the fifth finger (inward curving)**

Trisomy 21

- **Prognosis for survival depends on associated anomalies**
  - **Heart anomalies a major cause of mortality**
  - **Alimentary defects also can be life threatening**
- **Other common problems**
  - **Respiratory problems**
  - **Eye problems**
  - **Premature aging**
- **Mental retardation is always present**
  - **IQ ranges between 25 and 50 in childhood**

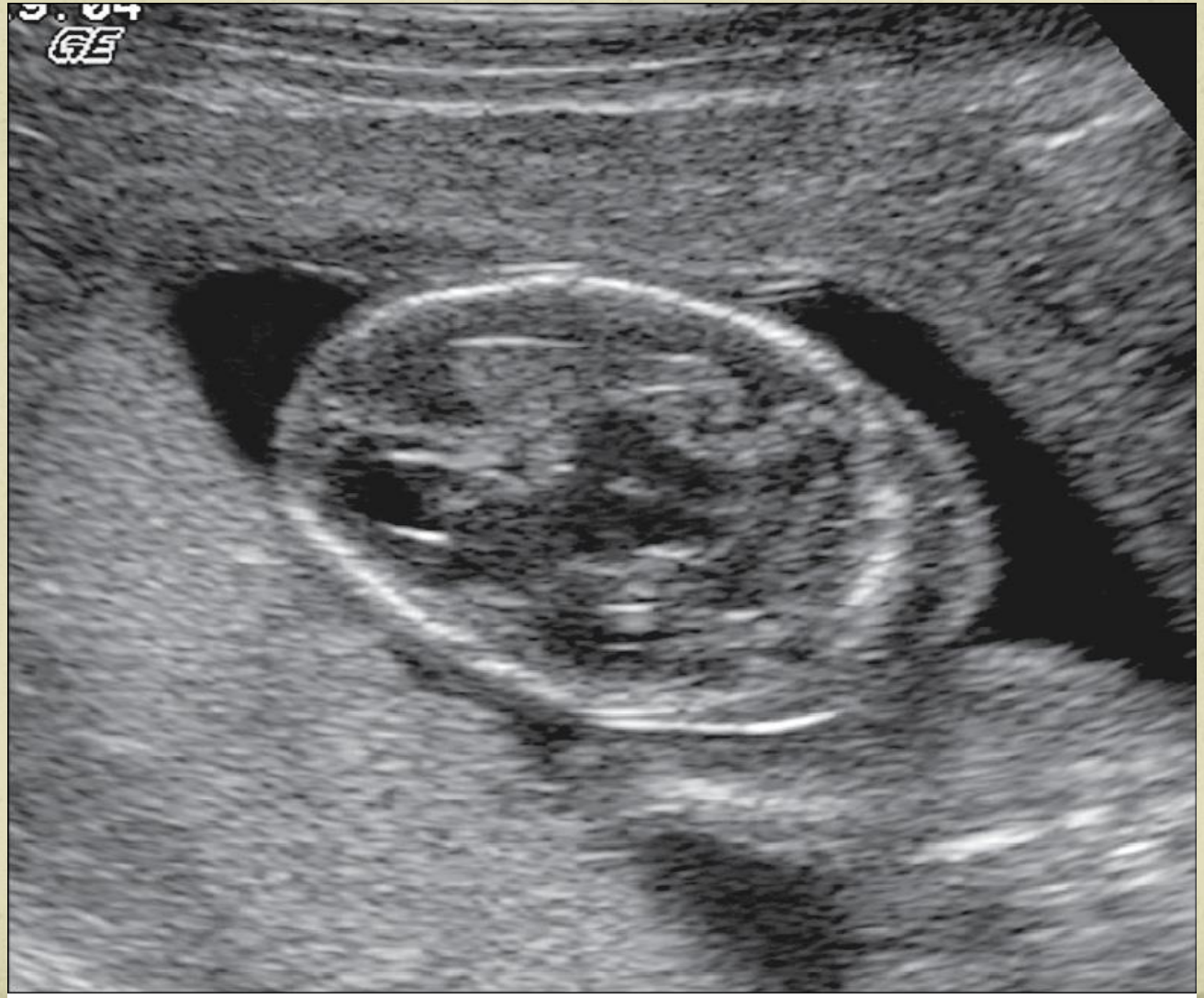
Nuchal Thickening



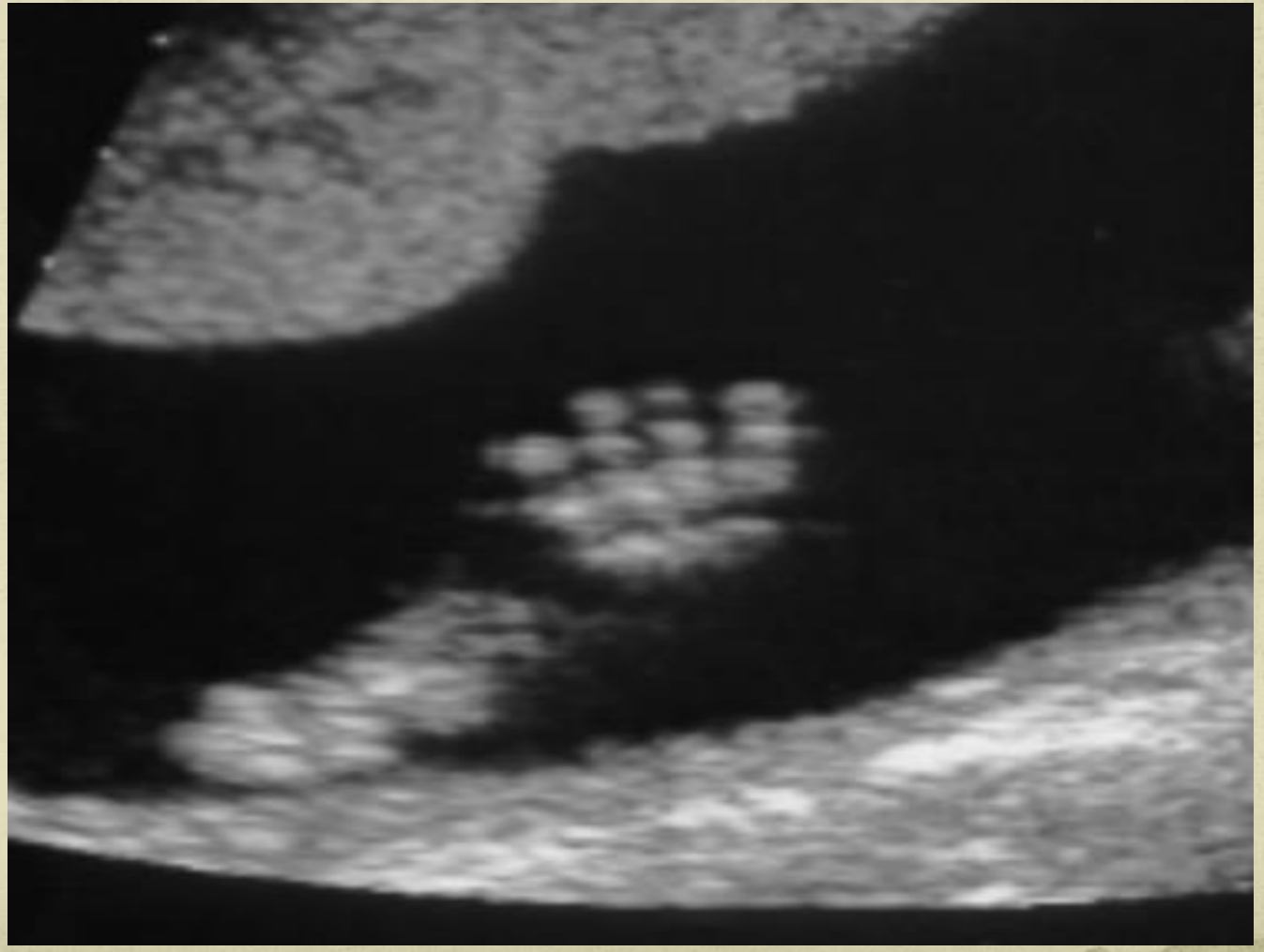
Trisomy 21 Sonographic findings:

- Ultrasound diagnosis is limited because of the subtleties
- Anomalies that may be identified include
  - Nuchal fold of 5 mm or greater
  - Extremity anomalies
  - Shortened femurs
  - Duodenal atresia Shortened ear length
  - Heart defects Intrauterine growth restriction (IUGR)
  - Mild pyelectasis (≥ 4 mm in anteroposterior diameter)
  - Echogenic bowel
  - Mild ventriculomegaly

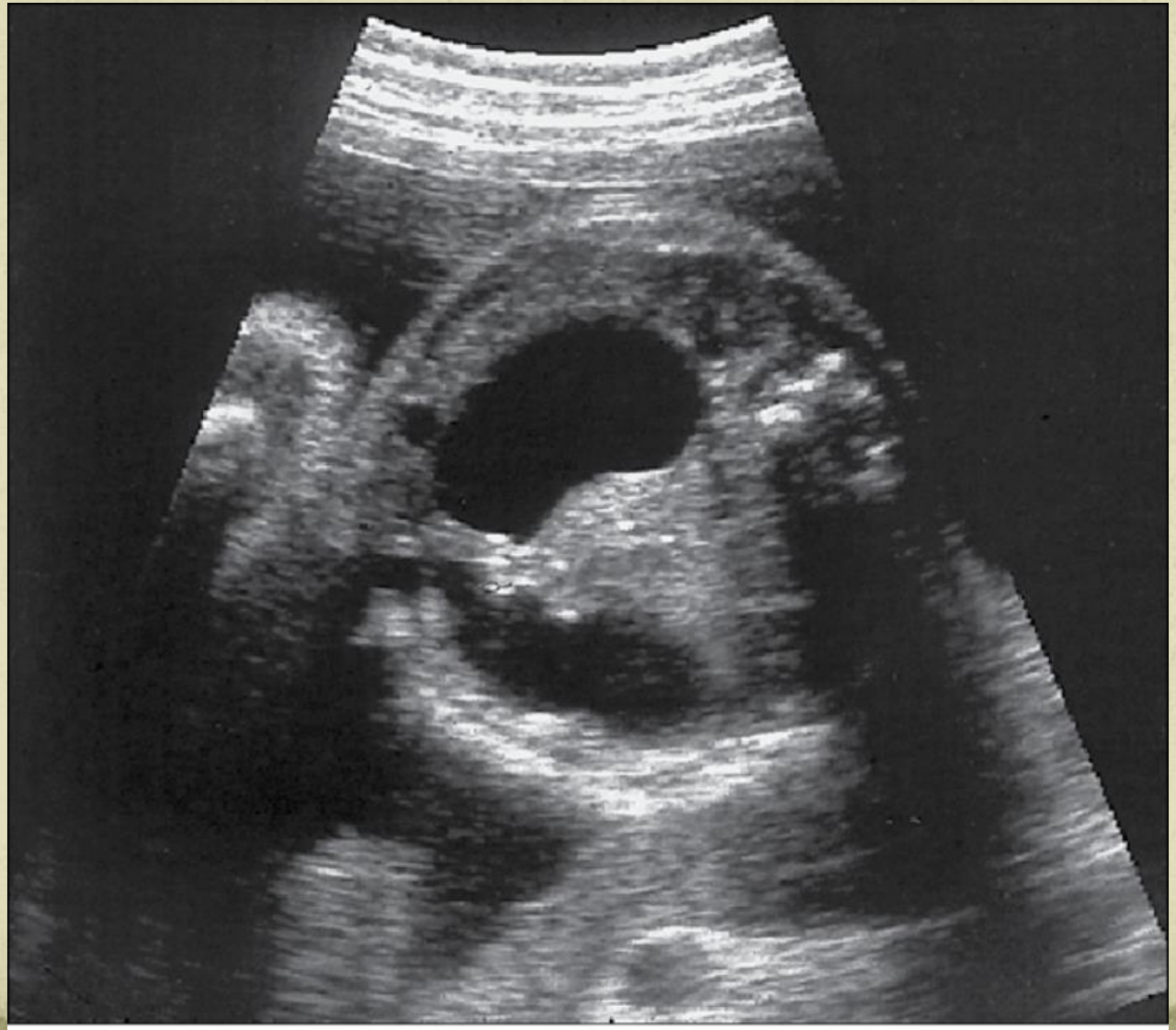
Thickened Nuchal Fold



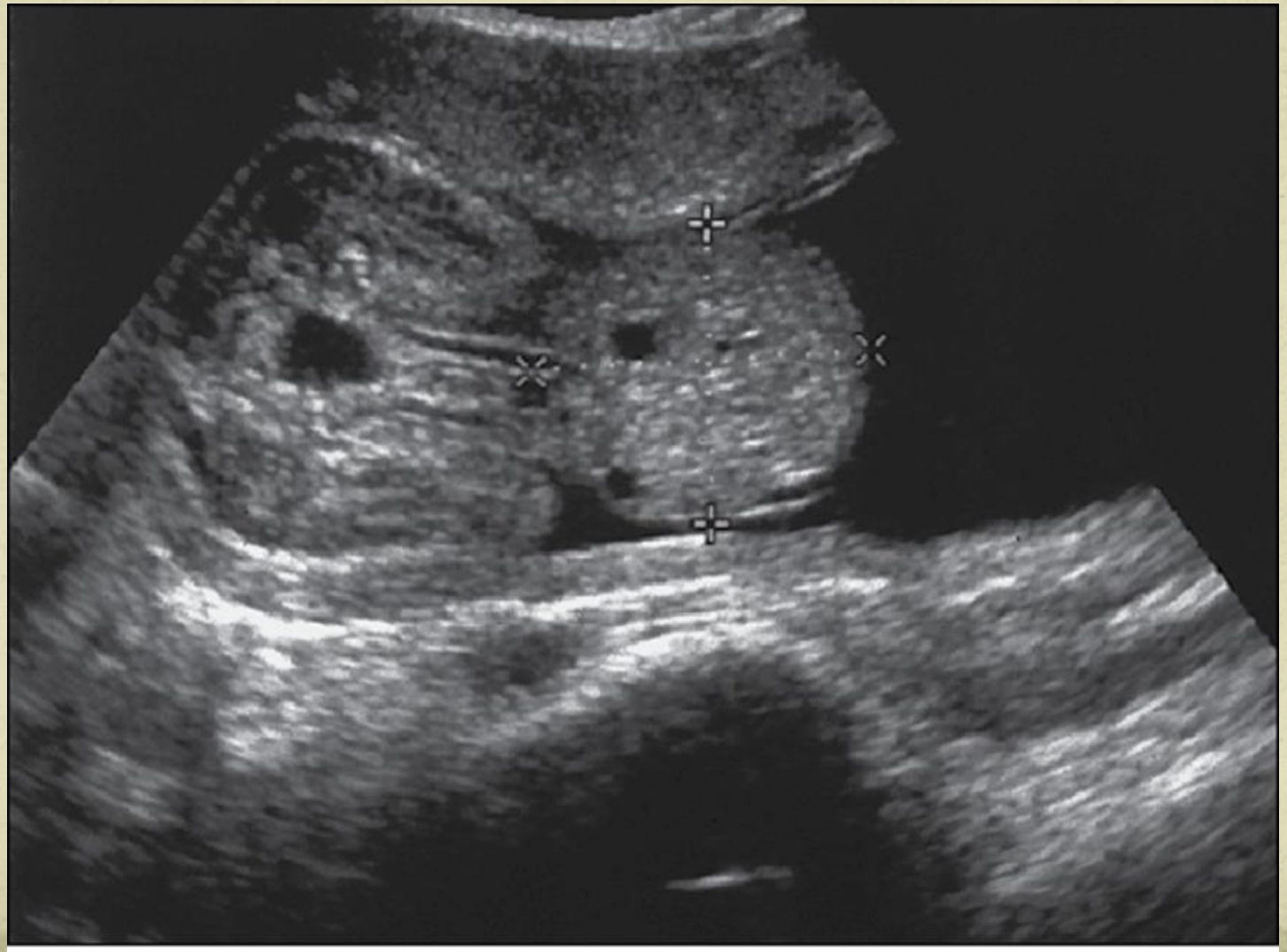
Absent fifth middle phalanx



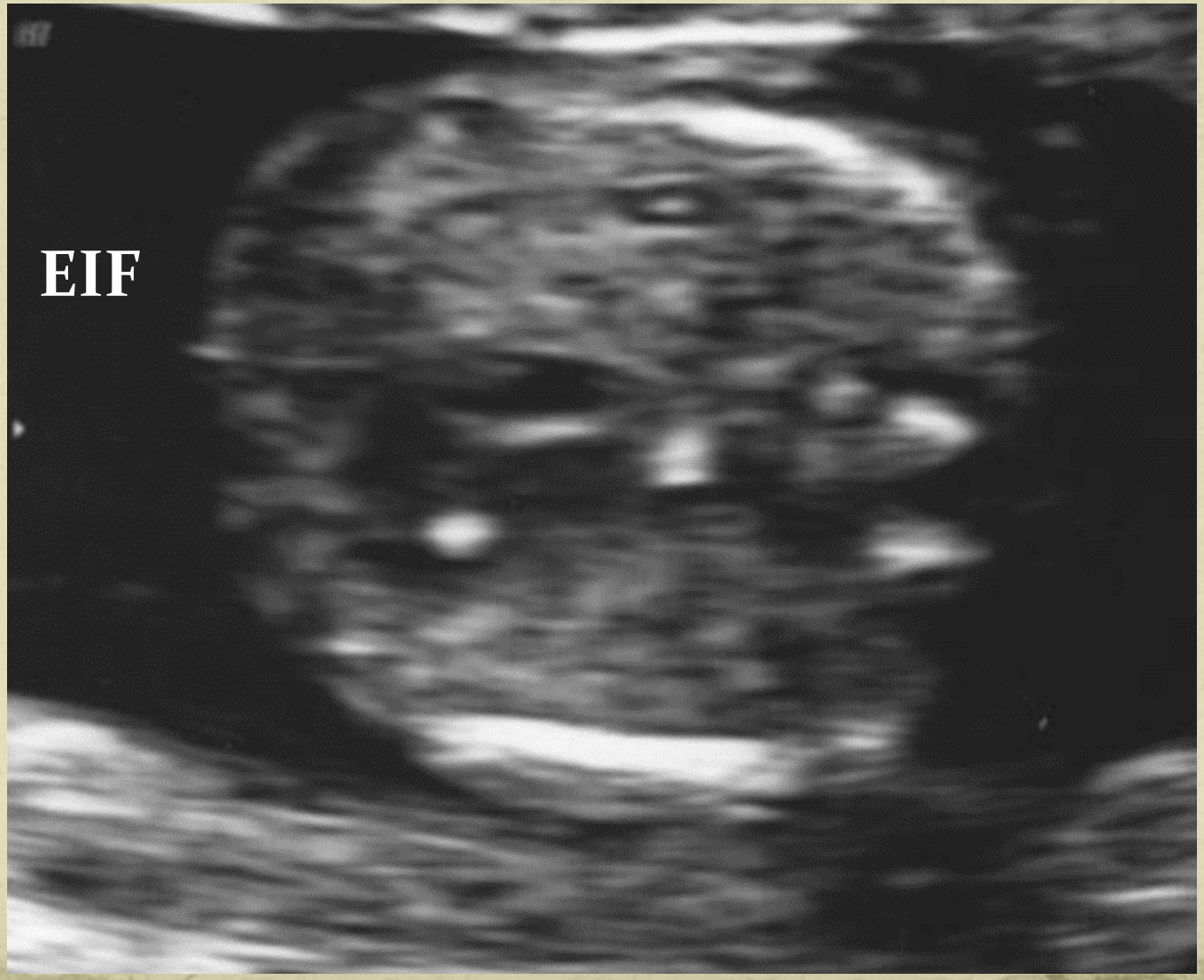
Duodenal Atresia



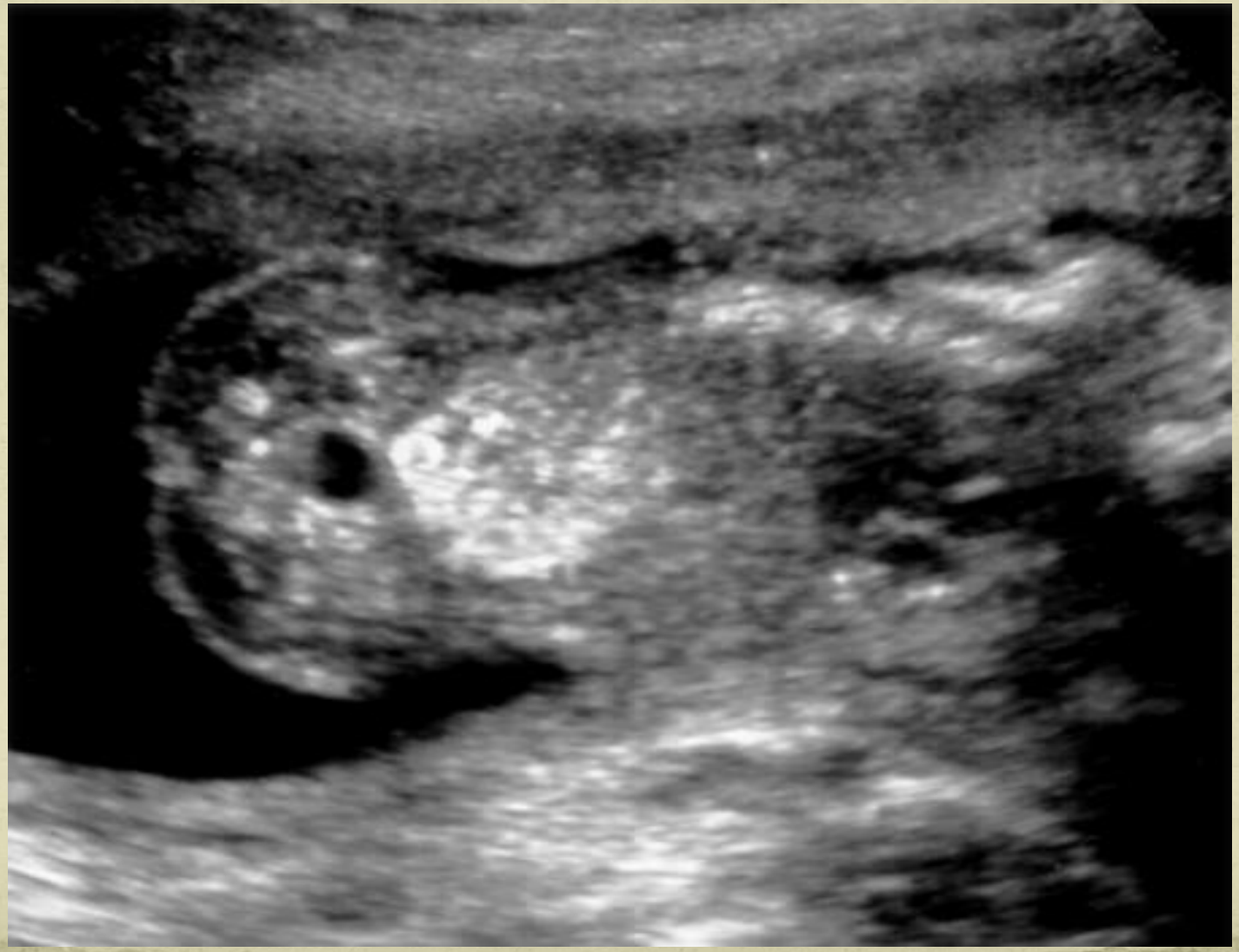
Omphalocele



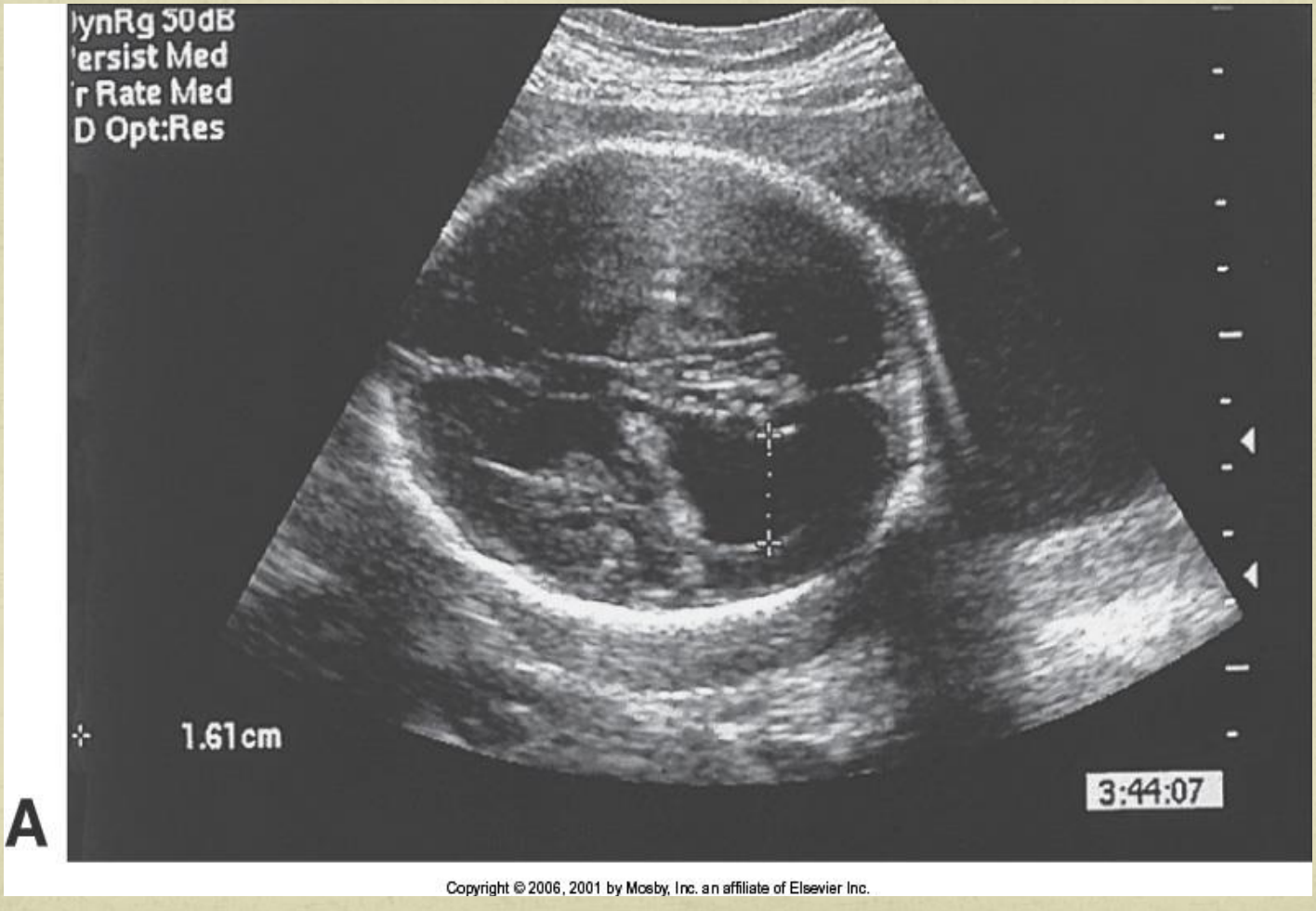
Heart Defects



Echogenic Bowel



Mild Ventriculomegaly

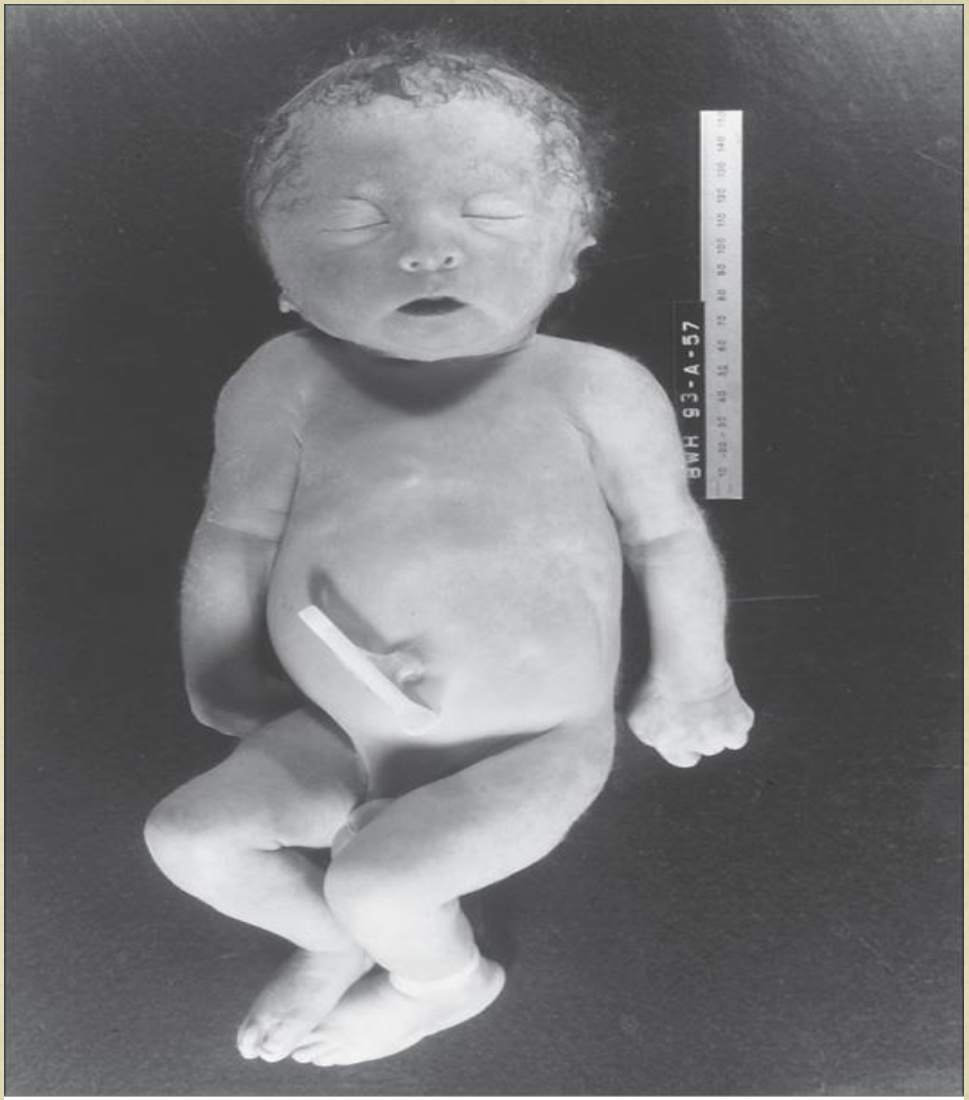


Trisomy 18

- Also known as Edward's syndrome
  - Second most common chromosomal trisomy
  - Occurs 1 of 8,000 live births
- Characterized by an extra chromosome number 18
- Associated with an abnormal quad screen

Clenched hands

Rocker-bottom feet



Trisomy 18

- Physical features identified include
  - Cardiac anomalies
    - Which are present in approximately 90% of fetuses
    - Fetuses most commonly have associated ventricular septal defects

Trisomy 18

- **Cranial anomalies that have been identified**
  - Dolichocephaly
  - Microcephaly
  - Hydrocephalus
  - Agenesis of the corpus callosum
  - Cerebellar hypoplasia
  - Strawberry-shaped head
  - Choroid plexus cysts
- **Facial abnormalities include**
  - Low-set ears
  - Micrognathia
  - Cleft lip and palate

Trisomy 18

- **Abnormal extremities identified include**
  - **Persistently clenched hands**
  - **Talipes**
  - **Rocker-bottom feet**
  - **Radial aplasia**
- **Other anomalies associated include**
  - **Omphalocele**
  - **Congenital diaphragmatic hernia**
  - **Neural tube defects**
  - **Cystic hygroma**
  - **Renal anomalies**

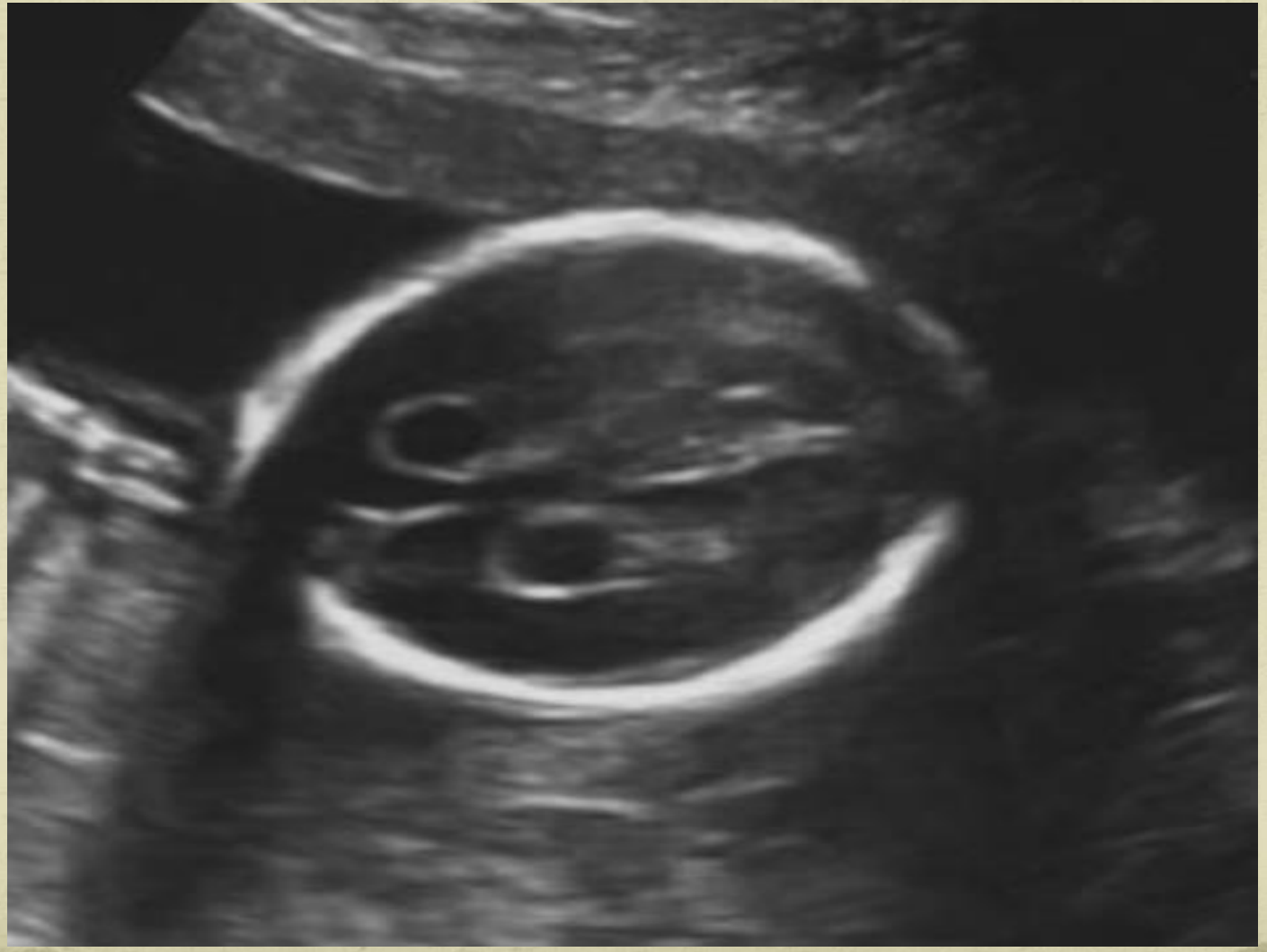
Trisomy 18

- Fetus often spontaneously aborts
- Infants are profoundly retarded
- Considered a "lethal anomaly"
  - 90% of infants die within the first year of life

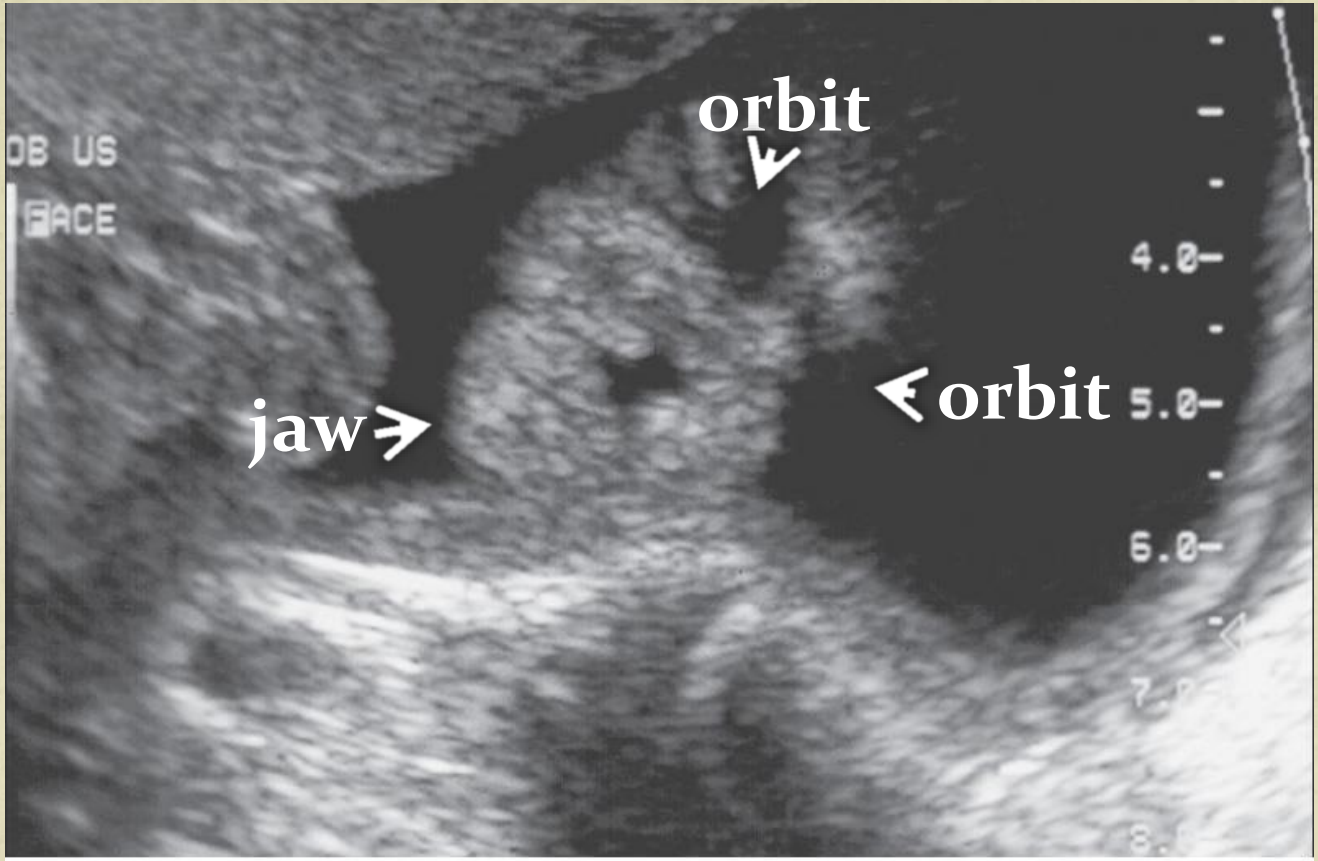
Trisomy 18 Sonographic findings:

- Sonographic features are evident in 80% of affected fetuses
- Additional features may include
  - Polyhydramnios
  - IUGR
  - Single umbilical artery
  - Nonimmune hydrops

Choroid Plexus Cysts

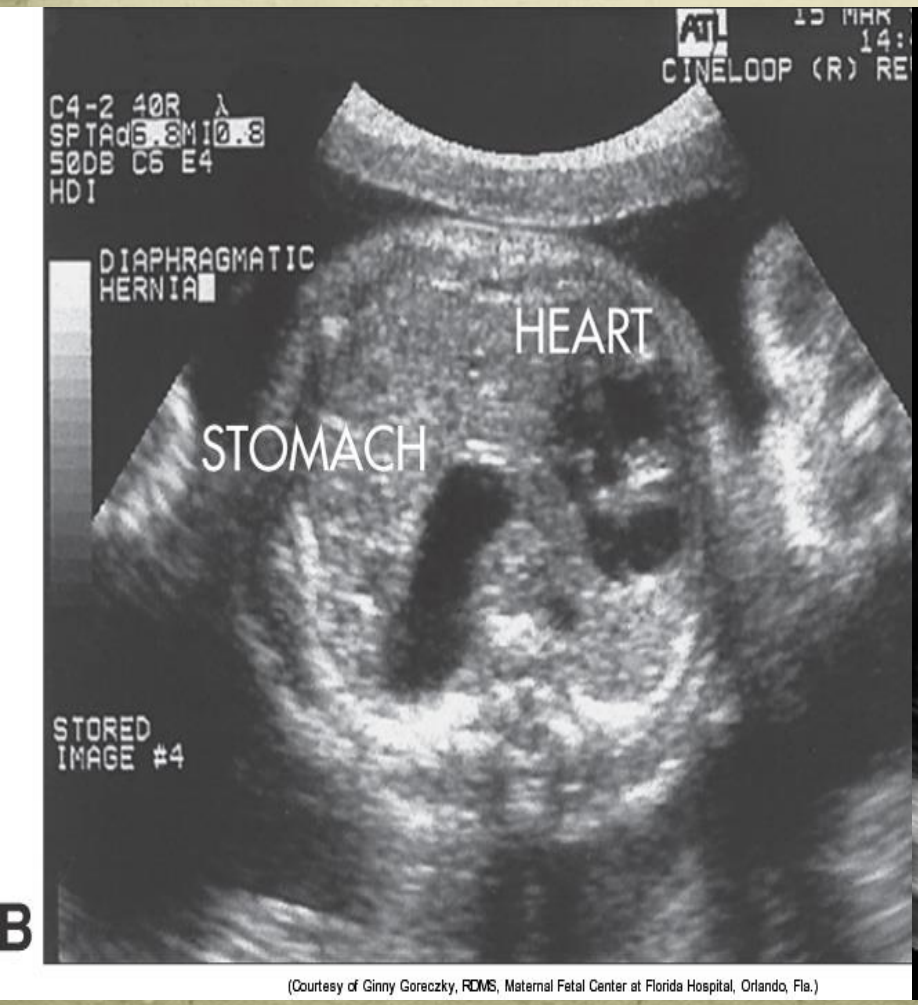


Cleft Lip and Palate

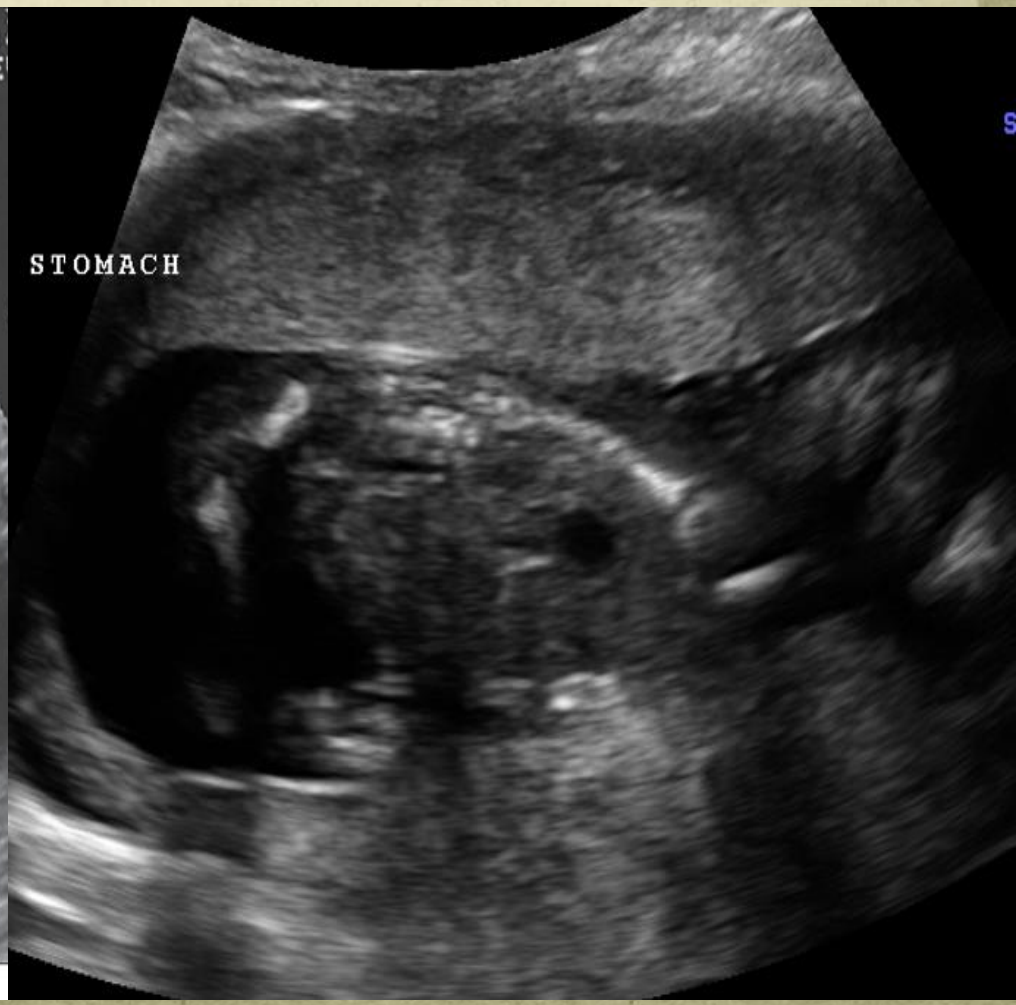


(From Henningsen C: *Clinical guide to ultrasonography*, St Louis, 2004, Mosby.)

Congenital Diaphragmatic Hernia



(Courtesy of Ginny Goreczky, RDMS, Maternal Fetal Center at Florida Hospital, Orlando, Fla.)

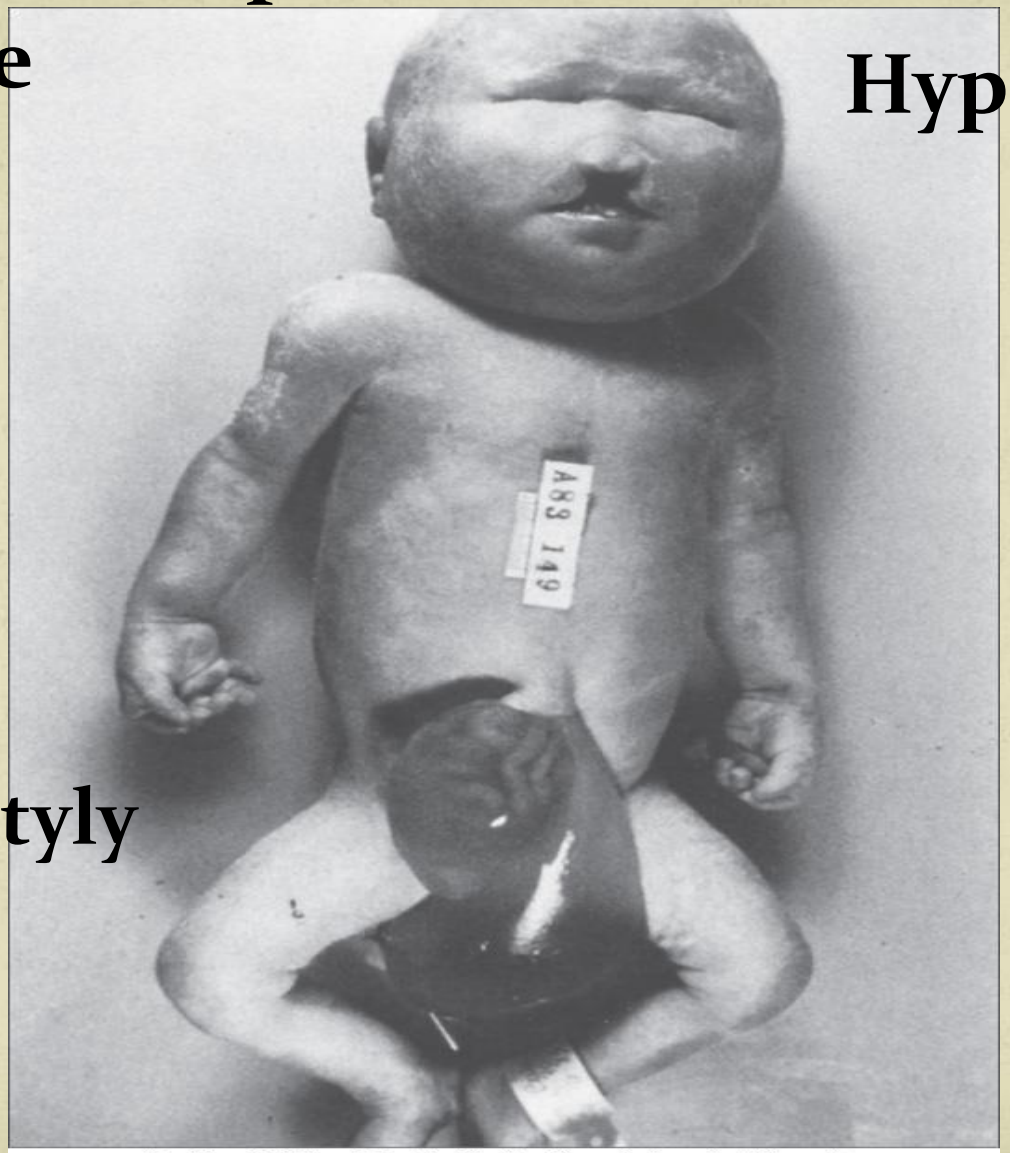


Trisomy 13

- Also known as Patau syndrome
- Occurs in 1 in 6,500 births
- Characterized by an extra chromosome number 13
- Extremely severe anomaly consists of multiple anomalies
  - Many involve the brain
    - Holoprosencephaly
    - Agenesis of the corpus callosum
    - Microcephaly

Bilateral Cleft lip and palate

Hypotelorism



(From Nyberg DA, Mahony BS, Pretorius DH, editors: *Diagnostic ultrasound of fetal anomalies: text and atlas*, St Louis, 1990, Mosby.)

Polydactyly

Trisomy 13

- **Facial anomalies may include**
  - **Hypotelorism**
  - **Proboscis**
  - **Cyclopia**
  - **Nose with a single nostril**
  - **Cleft lip and palate**
  - **Microphthalmia**
  - **Micrognathia**

Trisomy 13

- **Heart defects are present in 90% of fetuses**
  - Ventricular septal defect
  - Atrial septal defect
  - Hypoplastic left heart
- **Other anomalies associated include**
  - Omphalocele
  - Renal anomalies
  - Meningomyelocele
- **Associated limb anomalies include**
  - Polydactyly
  - Talipes
  - Rocker-bottom feet
  - Overlapping fingers

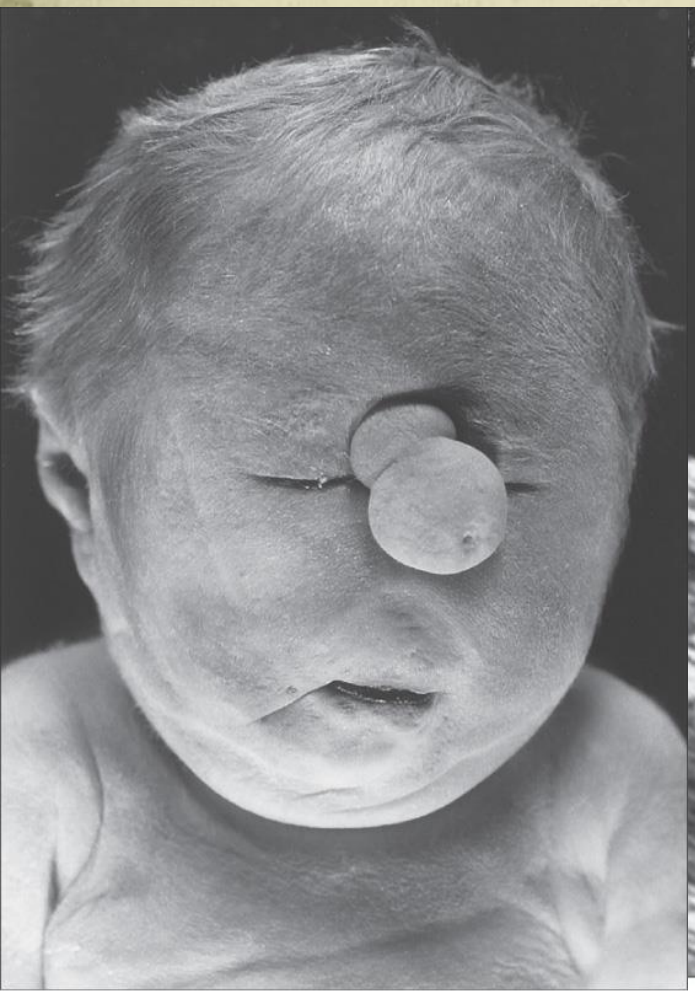
Trisomy 13

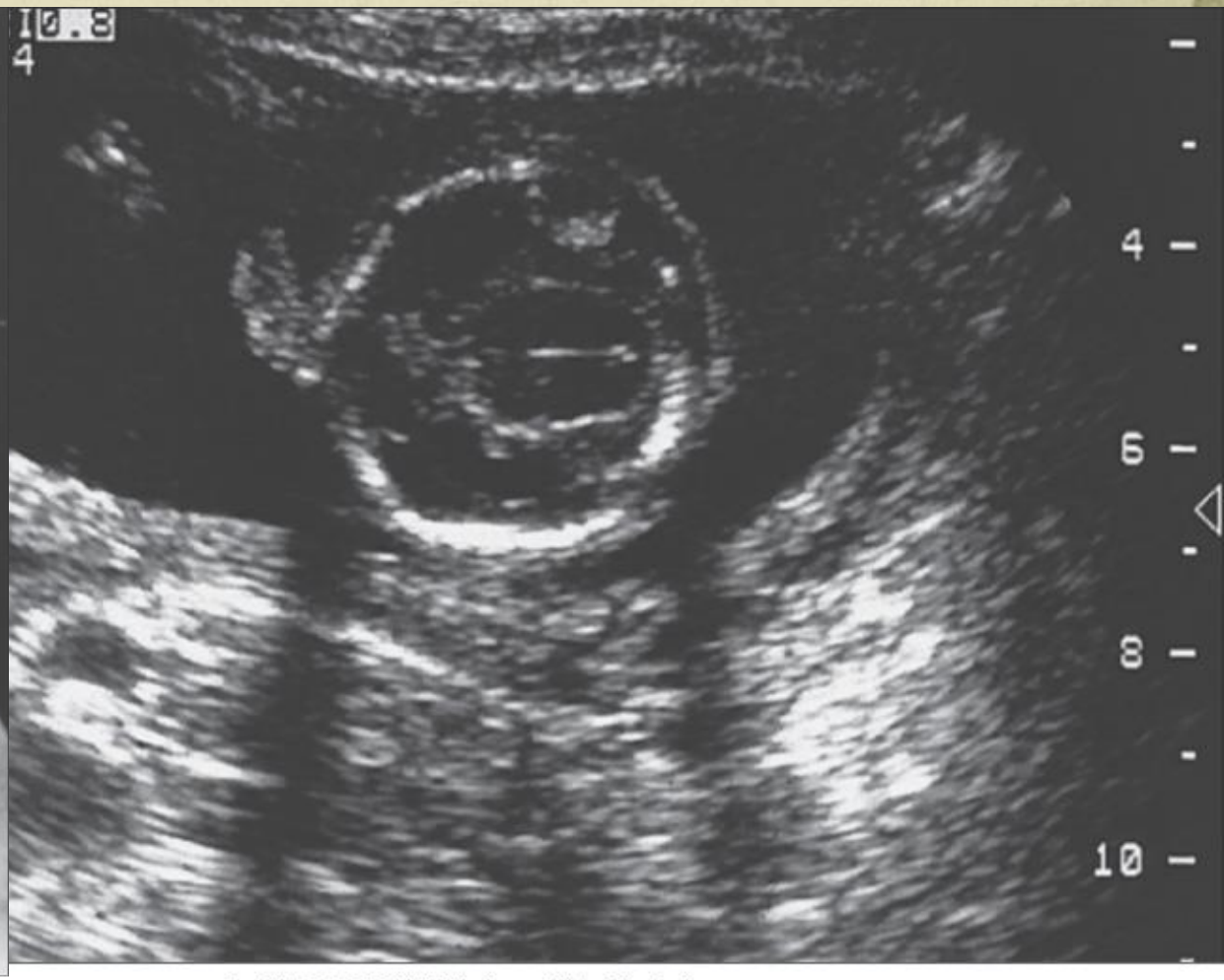
- Other anomalies that may be identified
  - Cystic hygroma
  - Echogenic chordae tendineae
- Prognosis for trisomy 13 is extremely poor
  - 80% die within the first month
- Considered a “lethal anomaly”
- Survivors are profoundly retarded

Trisomy 13 Sonographic findings:

- Sonographic features are evident in 90% of fetuses
- Additional features may include
  - IUGR
- Trisomy 13 and Meckel-Gruber syndrome have similar sonographic appearance of
  - Encephalocele
  - Cystic kidneys
  - Polydactyly

Proboscis





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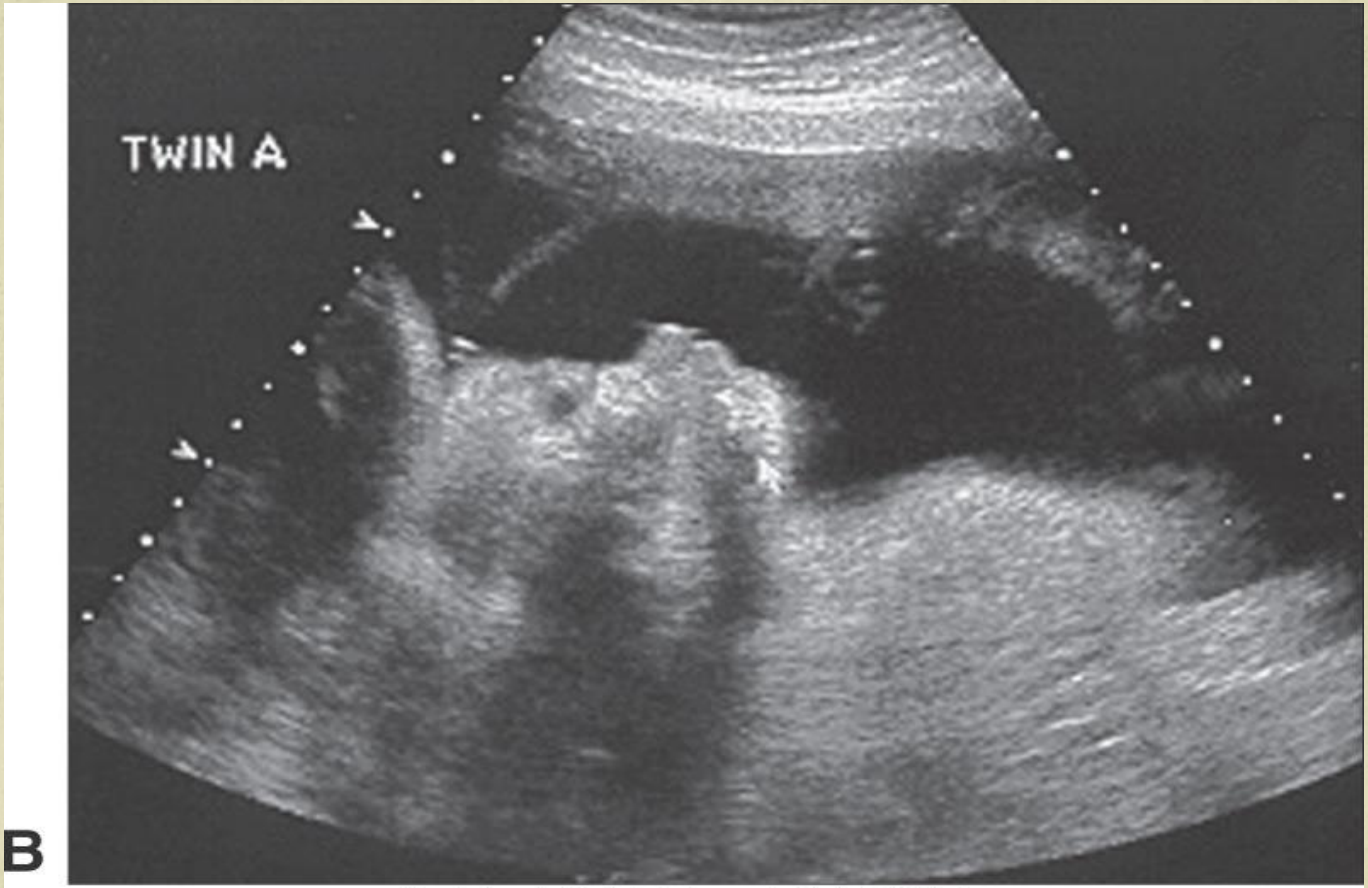
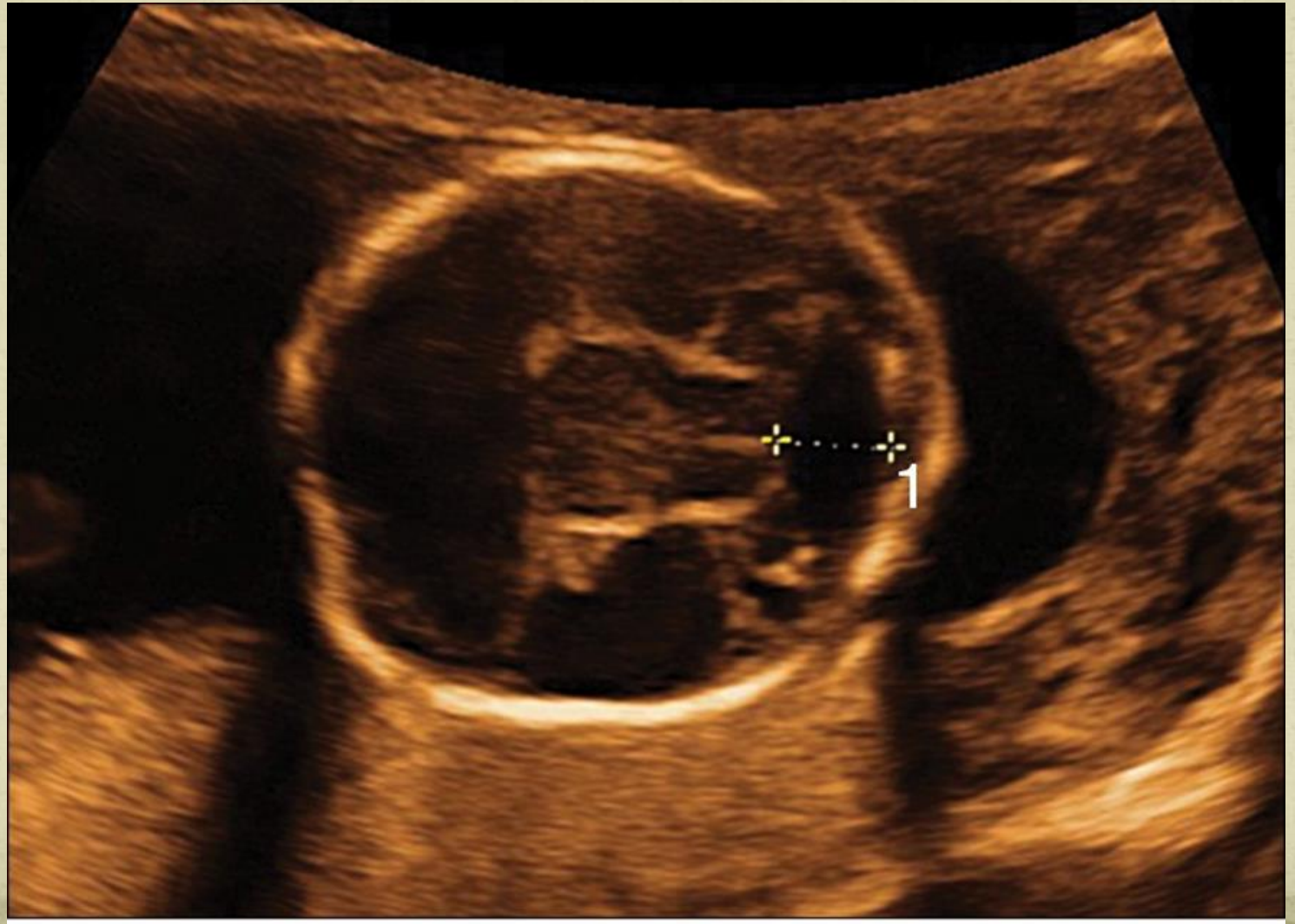
Absent Nose

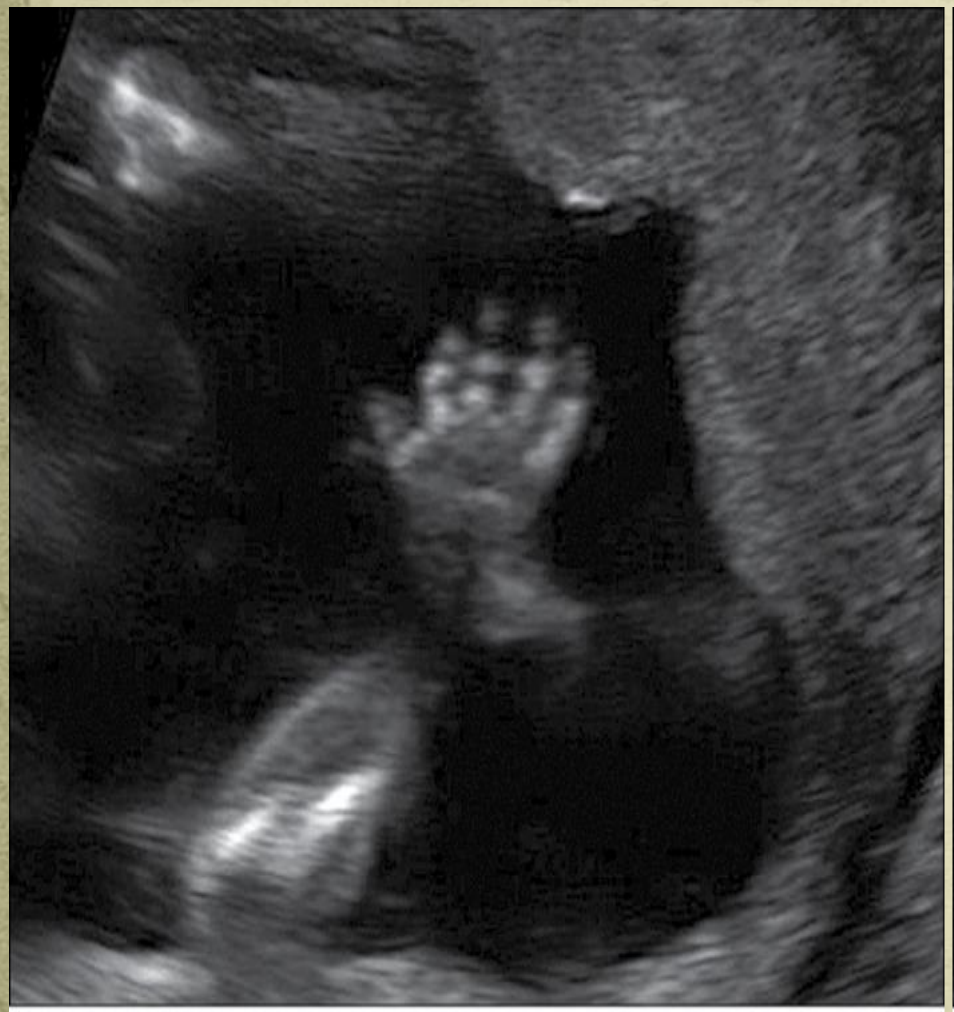


(From Henningsen C: *Clinical guide to ultrasonography*, St Louis, 2004, Mosby.)

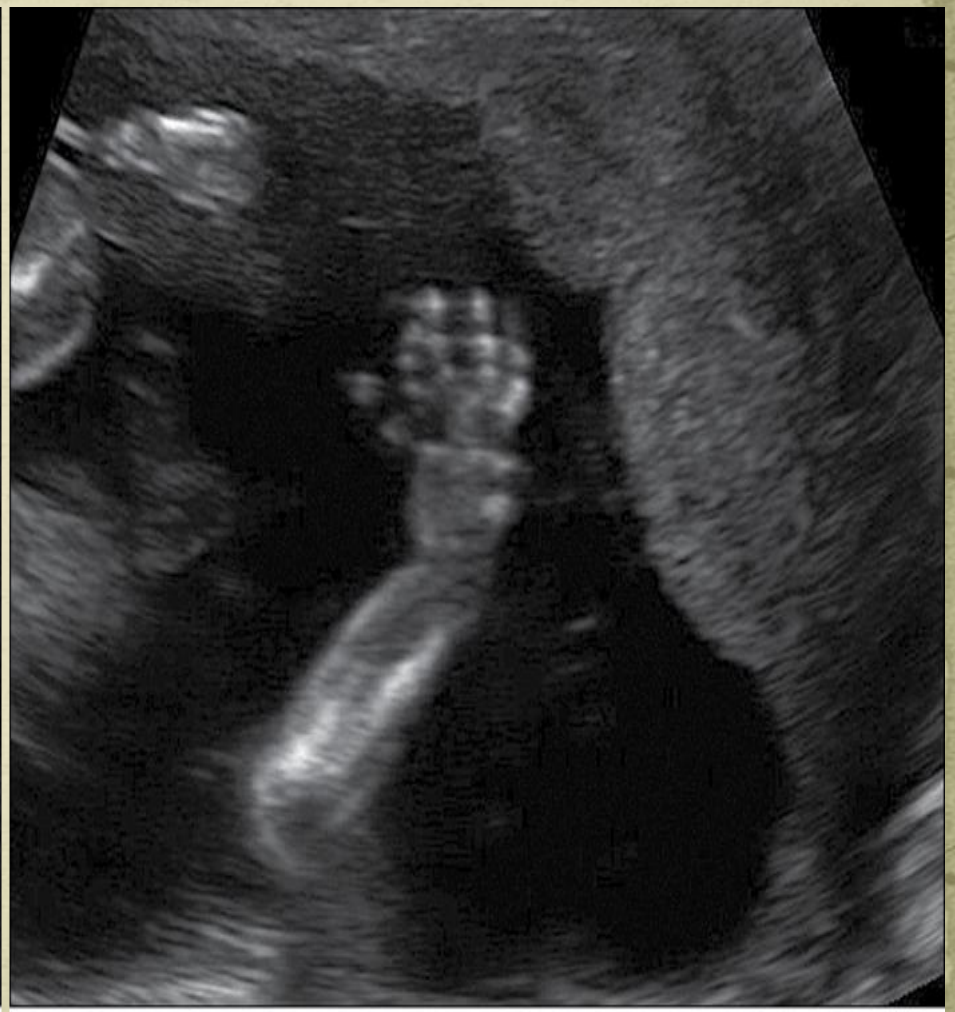
Holoprosencephaly



Polydactyly

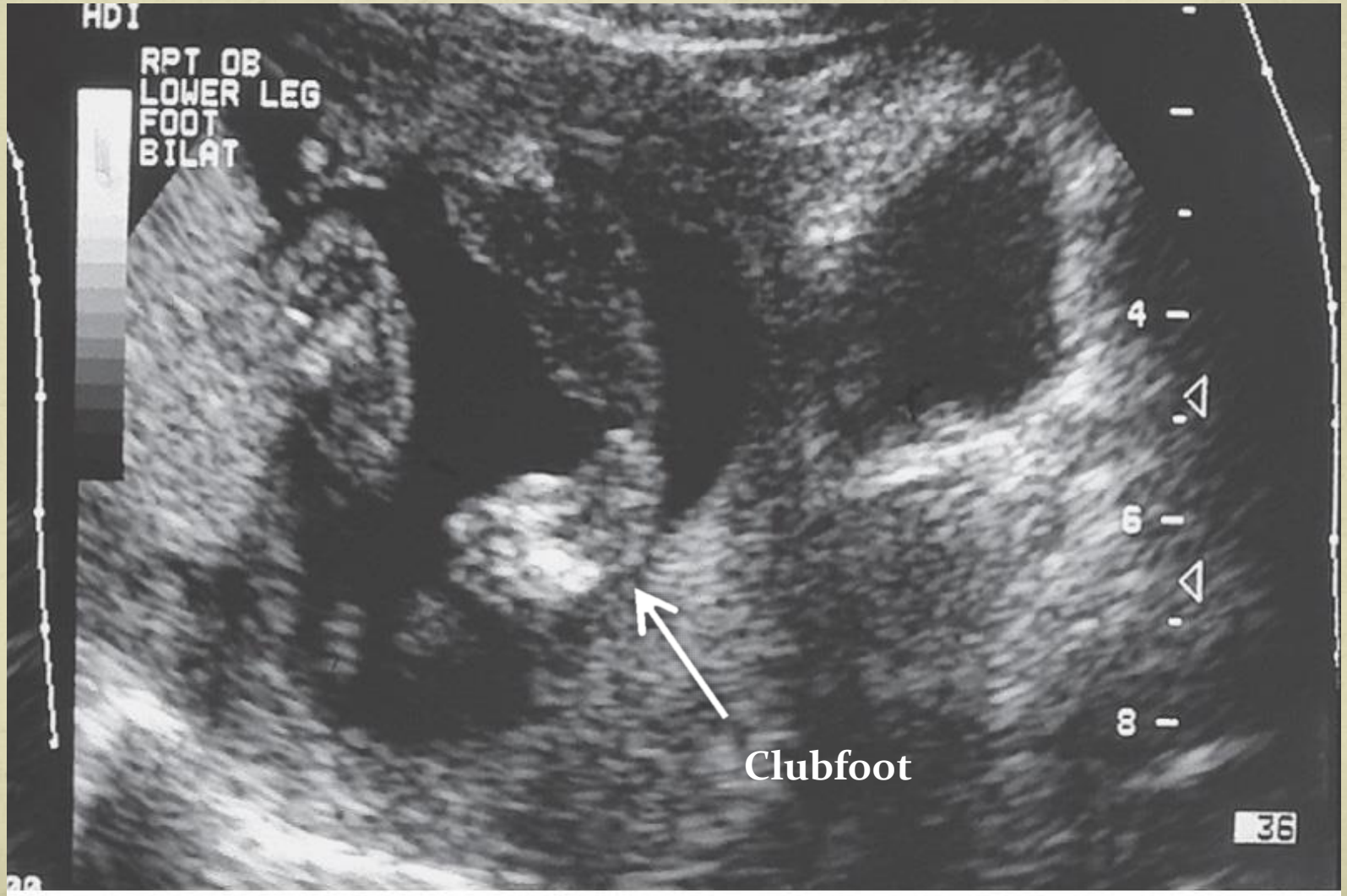


B

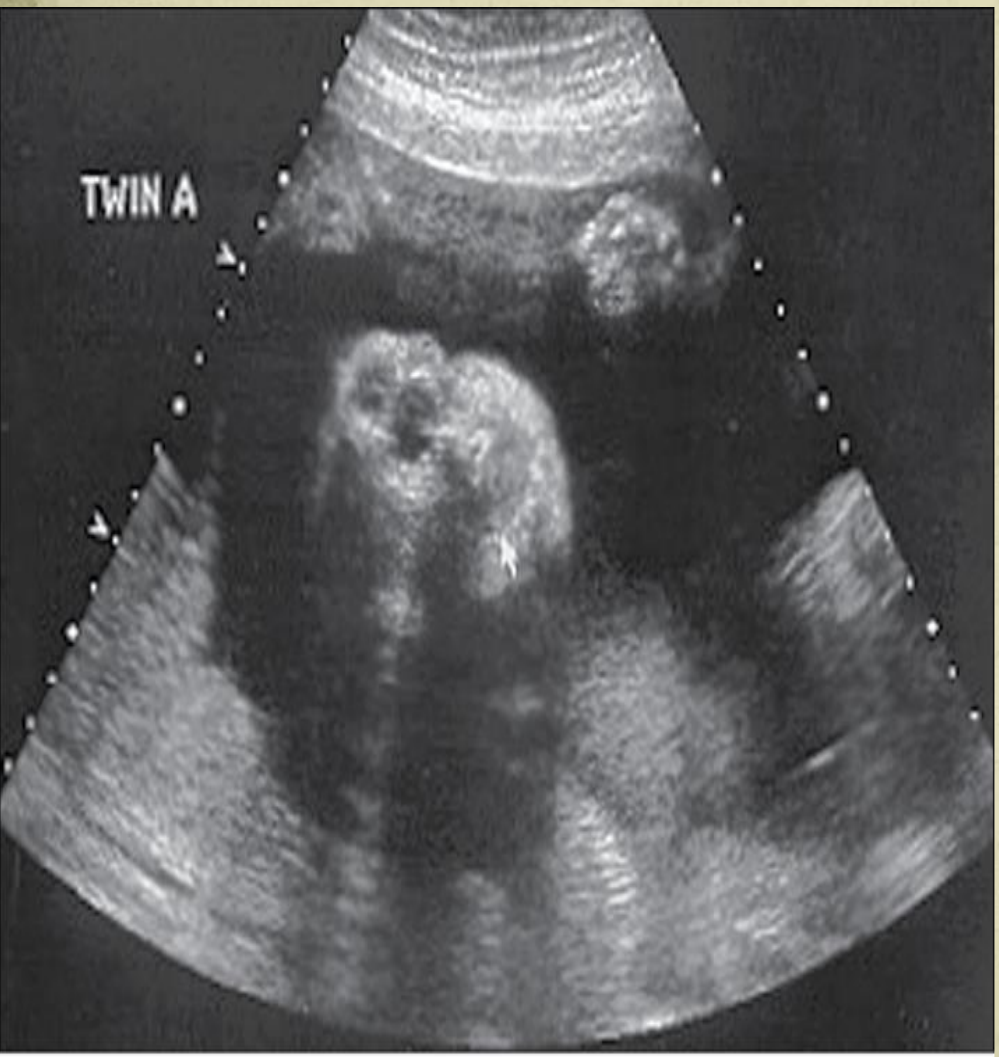


C

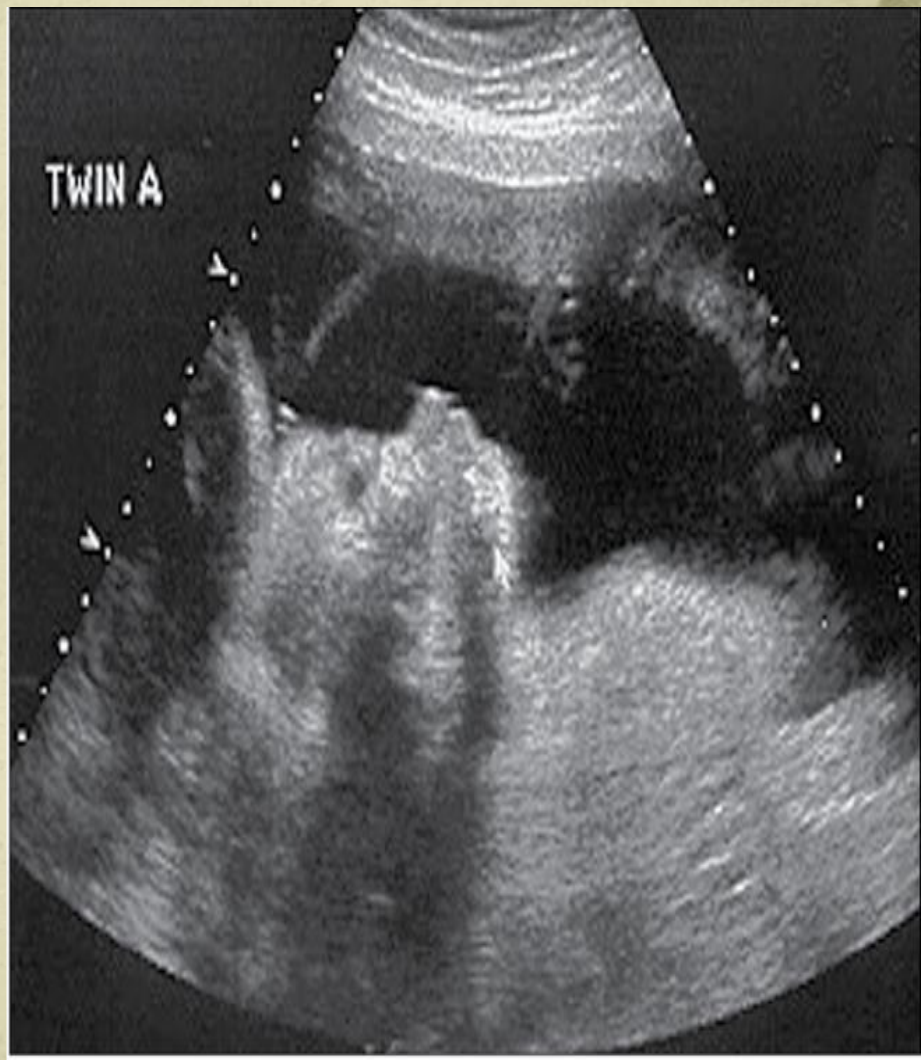
Talipes



Cyclopia, Absent Nose



A



B

Triploidy

- Result of a complete extra set of chromosomes
- Often occurs as the result of an ova being fertilized by two sperm
- Estimated to occur in approximately 1% of conceptions
- Most fetuses spontaneously abort in the first trimester
- Only 1 in 5000 continue to 16 to 20 weeks of gestation
- Considered a lethal condition
  - Die shortly after birth

Triploidy

- **Physical features of include**
  - **Heart defects**
  - **Renal anomalies**
  - **Omphalocele**
  - **Meningomyelocele**
- **Cranial defects associated include**
  - **Holoprosencephaly**
  - **Agenesis of the corpus callosum**
  - **Hydrocephalus**
  - **Dandy-Walker malformation**

Triploidy

- **Facial anomalies may include**
  - **Low-set ears**
  - **Hypertelorism**
  - **Cleft lip and palate**
  - **Micrognathia**
- **Additional features may include**
  - **Cryptorchidism**
  - **Ambiguous genitalia**
  - **Syndactyly**
  - **Talipes**

Triploidy Sonographic findings:

- Additional features may include
  - Severe IUGR
  - Placental changes
    - Hydatidiform degeneration
- Oligohydramnios is often present
  - may hamper adequate visualization of the fetus

Turner's Syndrome

- Turner's syndrome (45 X) is a genetic abnormality marked by the absence of the X or Y chromosome
- Not associated with advanced maternal age
- Occurs in every 1 of 2,500 births
- Patients may present with an elevated MSAFP when a cystic hygroma is present

Turner's Syndrome

- Cystic hygroma is most common
- Other physical features include
  - Cardiac anomalies
    - Coarctation of the aorta - most common
- Generalized lymphedema and hydrops also may be present
- Renal anomalies may coexist such as
  - Horseshoe kidney
  - Renal agenesis
  - Hydronephrosis
  - Hypoplastic kidney

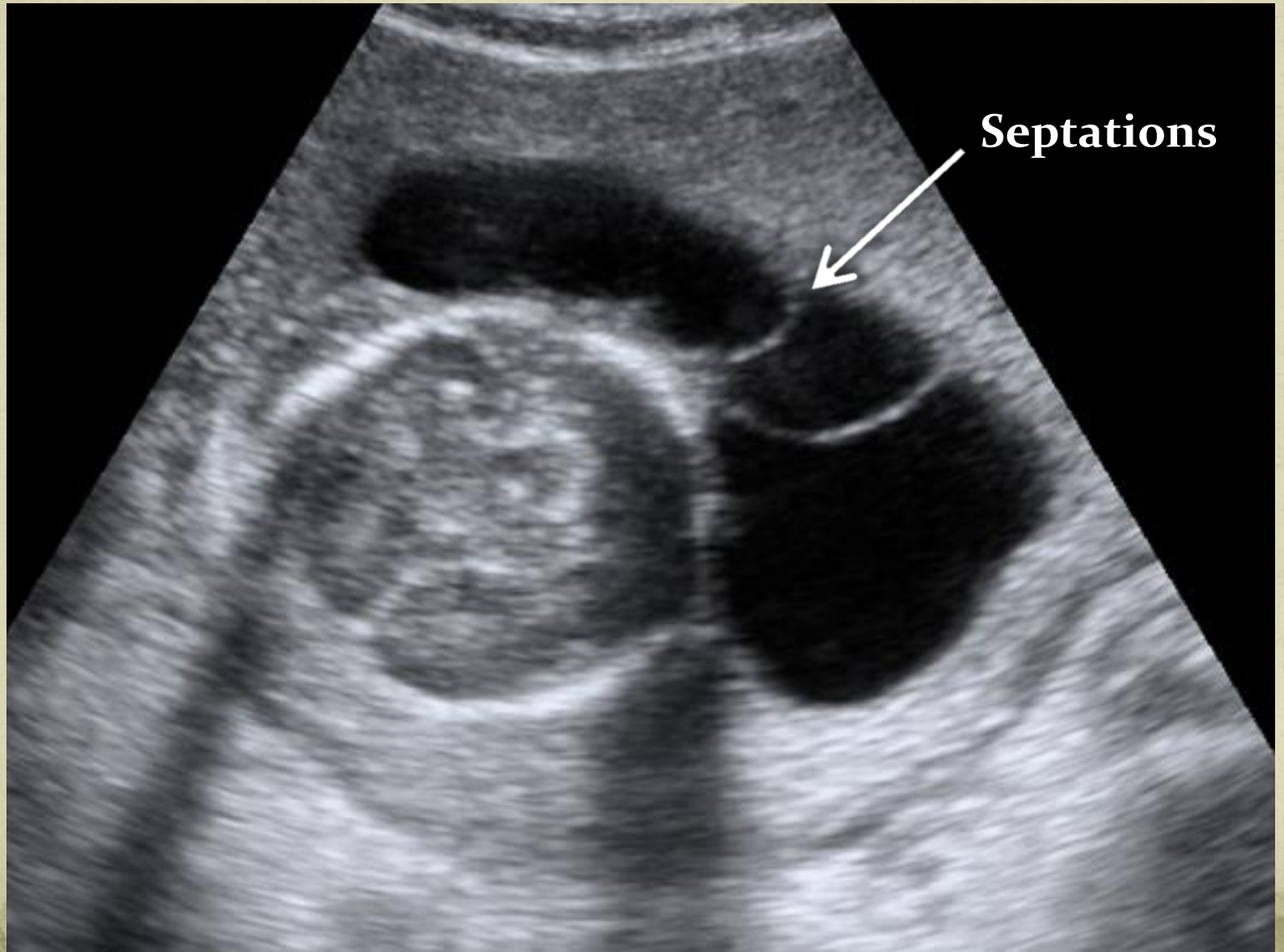
Turner's Syndrome

- Short femurs are also associated
- Most fetuses spontaneously abort
- Prognosis is especially grave when fetus presents with
  - Large cystic hygroma and edema
  - Hydrops

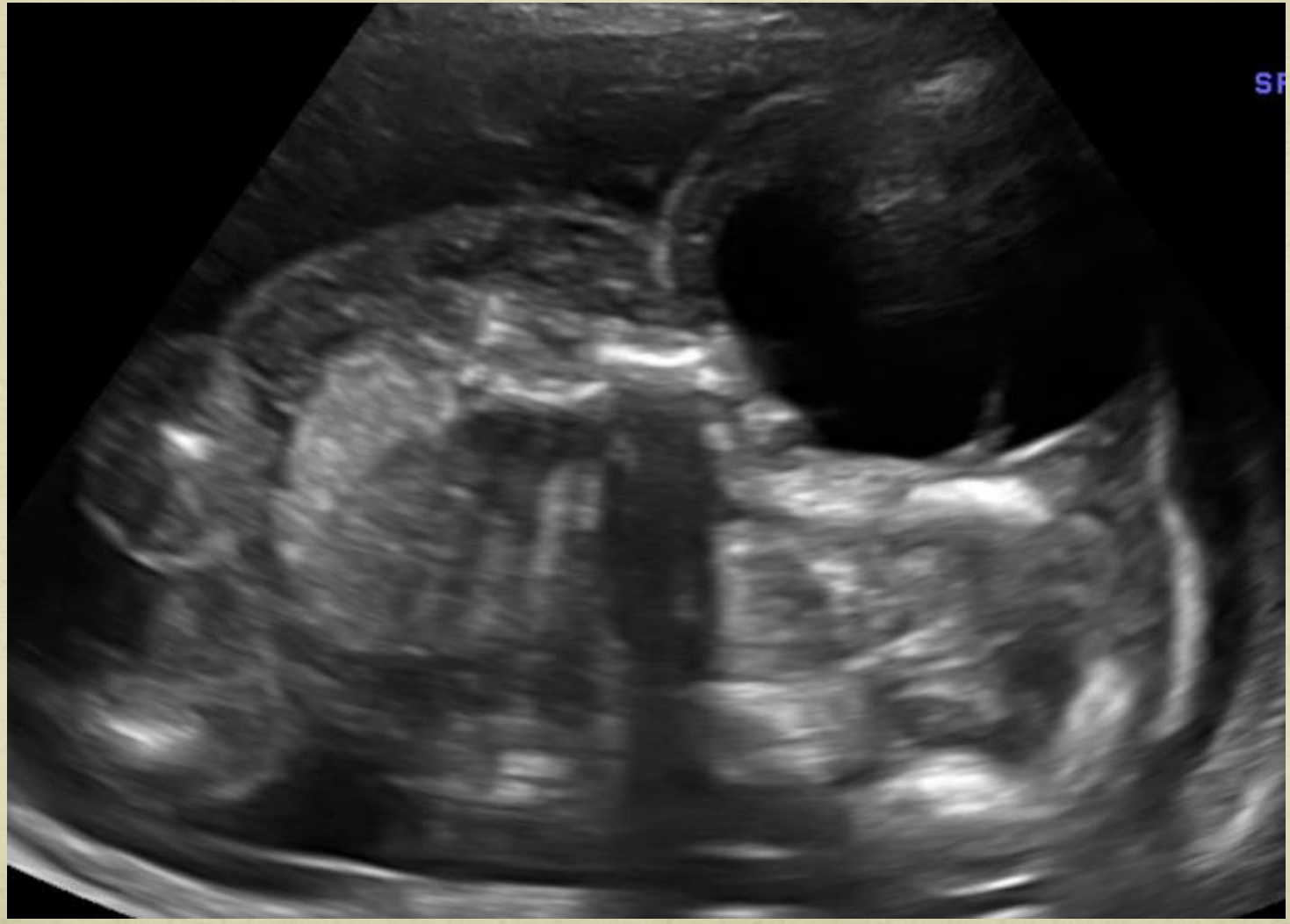
Turner's Syndrome

- **Female infants who survive have immature sexual development, amenorrhea, short stature, webbed neck, and shield chest**
- **Hormone replacement necessary for sexual development**
- **Usually have normal intelligence**

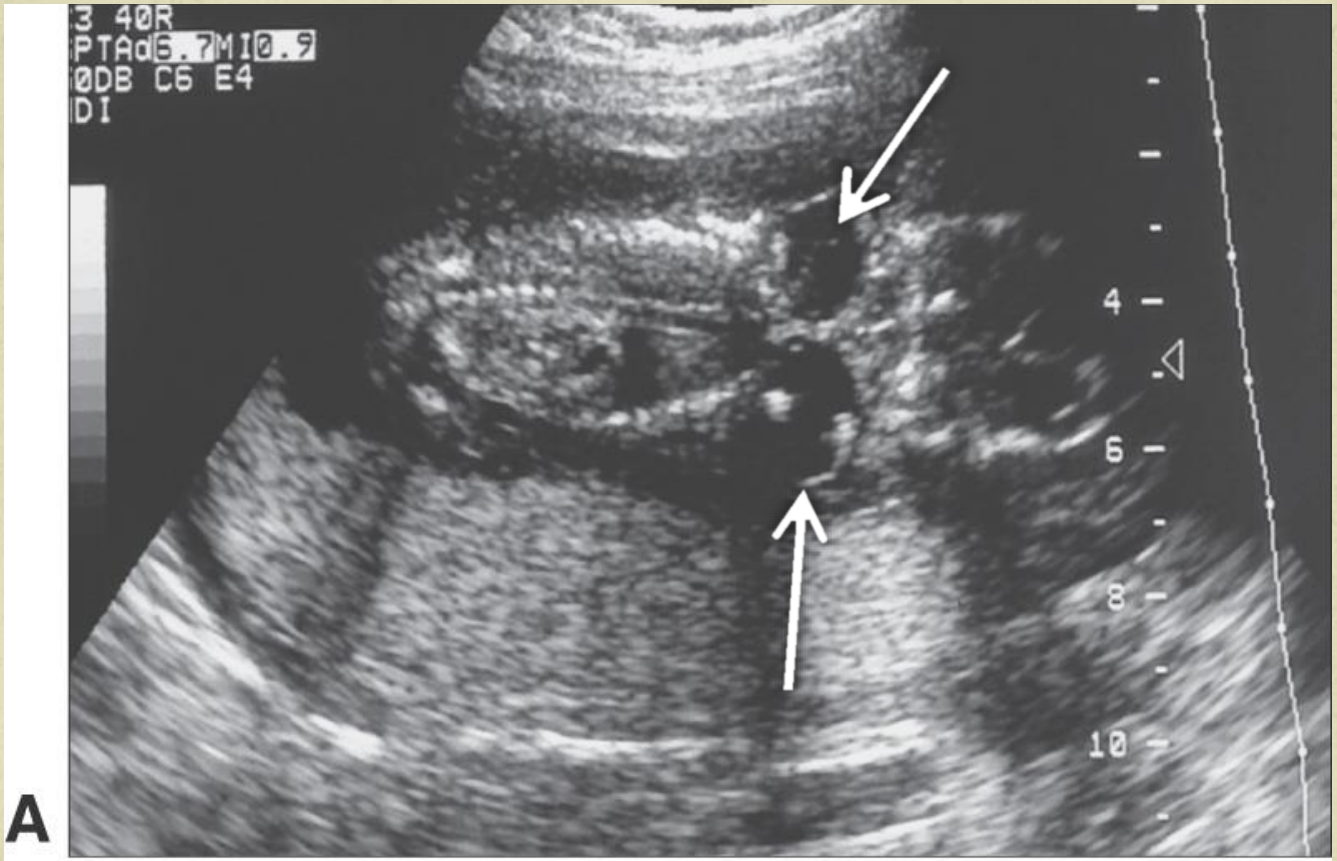
Cystic Hygroma



Cystic Hygroma



Cystic Hygroma



Edema Around Head