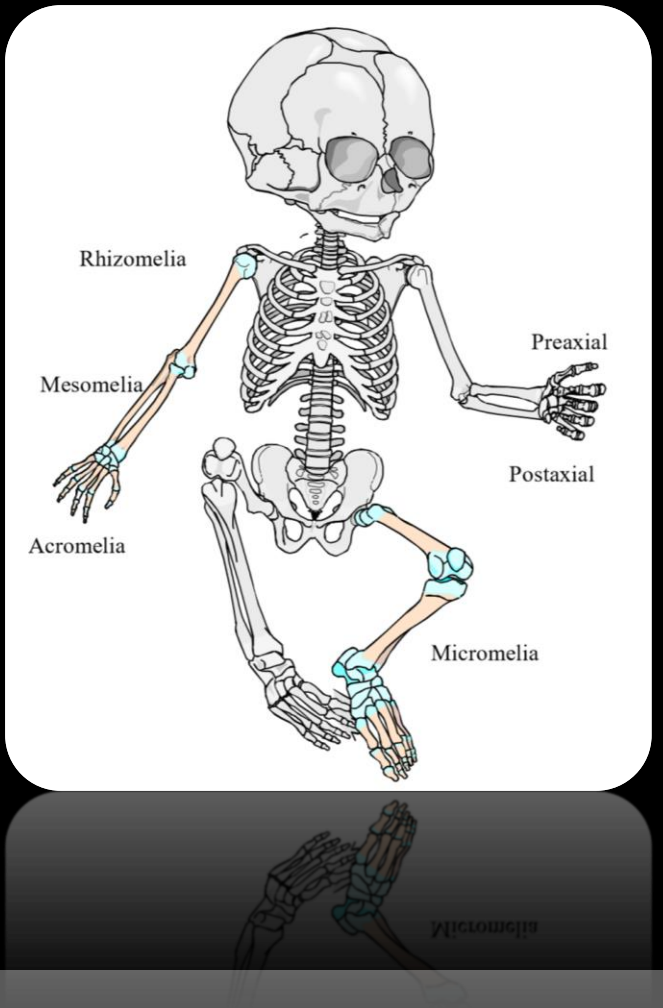
The Bare Bones

Prenatal Sonography of Skeletal Dysplasia



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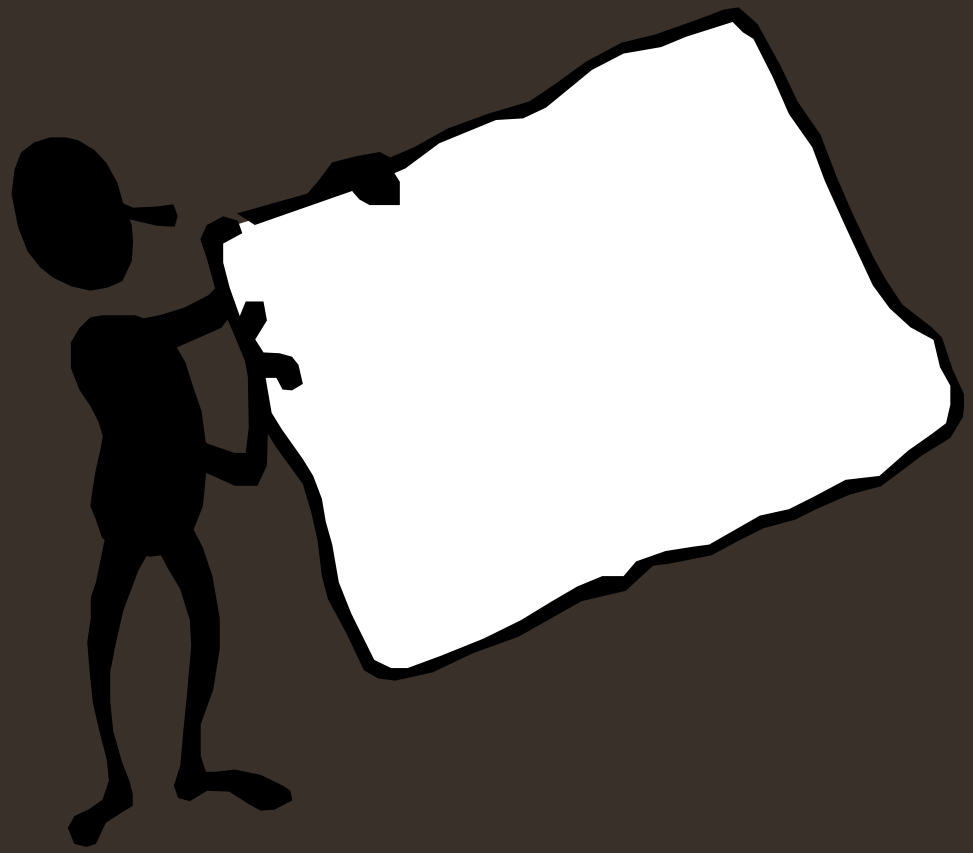
Disclosures

- Speakers bureau
  - March of Dimes
  - Hologic, Inc
- Trainer
  - Nexplanon

- I will not be discussing any of these organizations or products in this presentation.

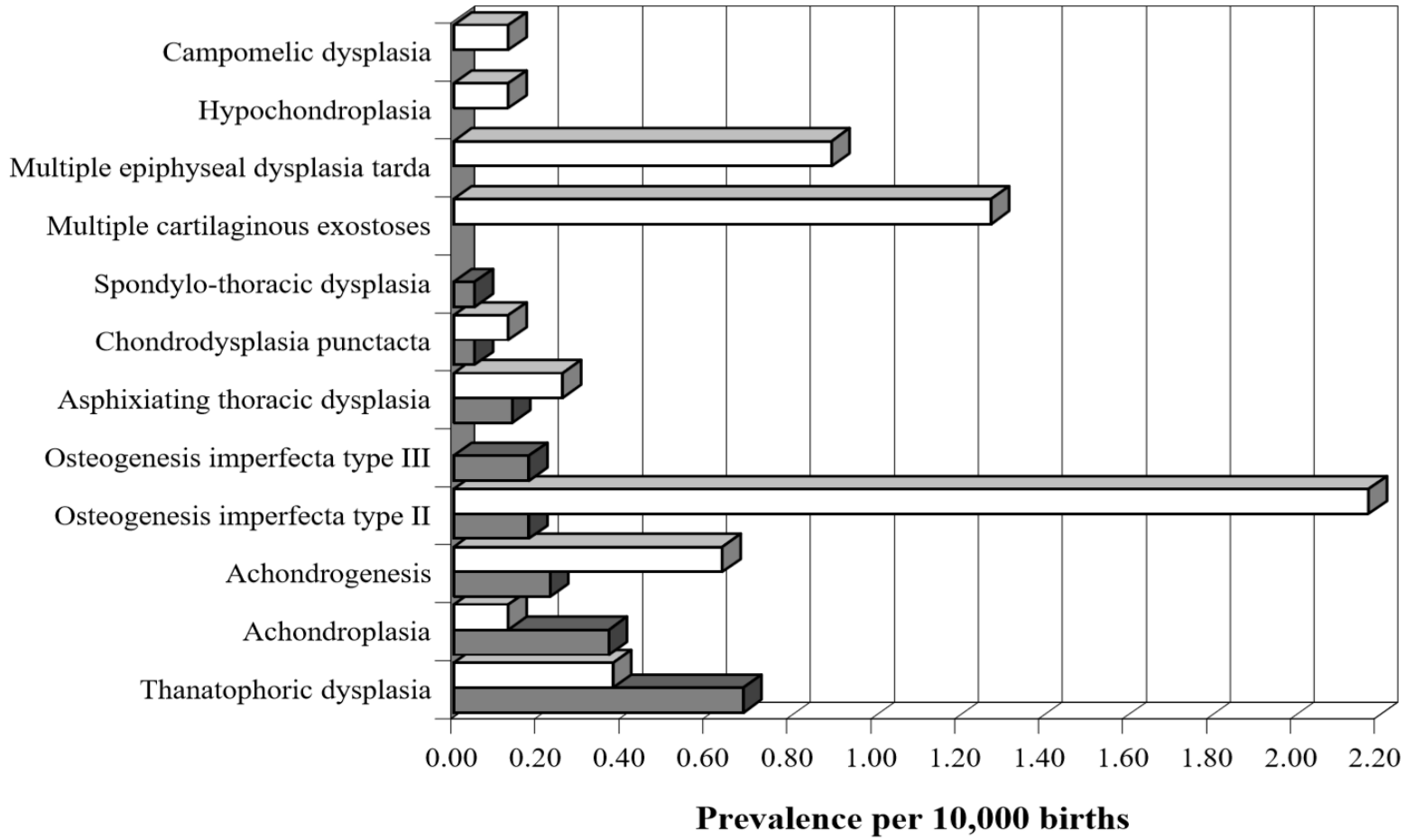


Objectives

- Define the various skeletal dysplasias
- Described the important clinical aspects of the more common skeletal dysplasias
- Outline sonographic algorithm for differentiating the various skeletal dysplasias
- Recognize features associated with potentially lethal skeletal dysplasias
- Tips for counseling patients with a fetus the may have a skeletal dysplasia

Introduction

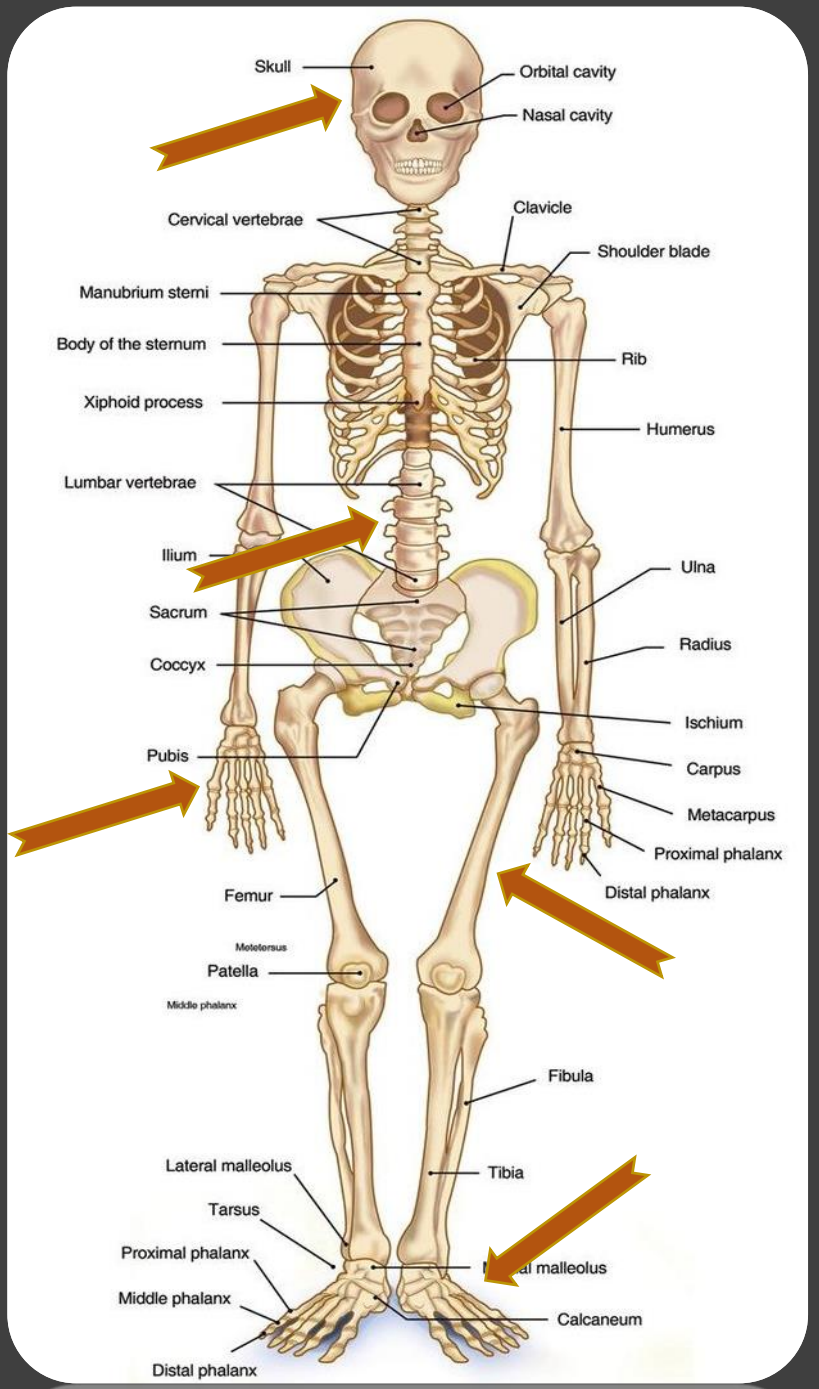
- Heterogeneous group of conditions associated with various abnormalities of the skeleton
- Etiologies
  - Disturbance of bone growth
- Difficult to diagnose in utero
  - Large number of skeletal dysplasias
  - Phenotypic variability with overlapping features
  - Lack of precise molecular diagnosis
  - Lack of a systematic approach
  - Variability in time findings identifiable in prenatal period
- Sonographic parameters able to predict lethality in 92% to 100% of cases
- Accurate prenatal diagnosis made only 48% to 65% of the time



Andersen P, Hauge M. Congenital generalised bone dysplasia: a clinical, radiological, and epidemiological survey. J Med Genet 1989;26:37-44.

Camera G, Mastroiacovo P. Birth prevalence of skeletal dysplasias in the Italian multicentric study. In: Papadatos C, Bartsocas C. Skeletal dysplasias, eds. Proceedings of the Third International Clinical Genetics Seminar. New York: Liss, 1982, 441-9.

Considerations



The Sonographic Approach

1. Long bones affected in a skeletal dysplasia

2. Measurement of the femur length provides first clue that bone formation or growth is abnormal

3. FL < 2 SD of the mean not diagnostic for a skeletal dysplasia

4. Differential diagnosis of a short femur includes: normal physiologic variation, intrauterine growth restriction, a focal shortening; abnormal karyotype

5. Femur length 5 mm below 2 SD of the mean is consistent with a significant skeletal dysplasia

6. If femur length between 2 SD of the mean and 5 mm below 2 SD, interval growth of the FL can be evaluated

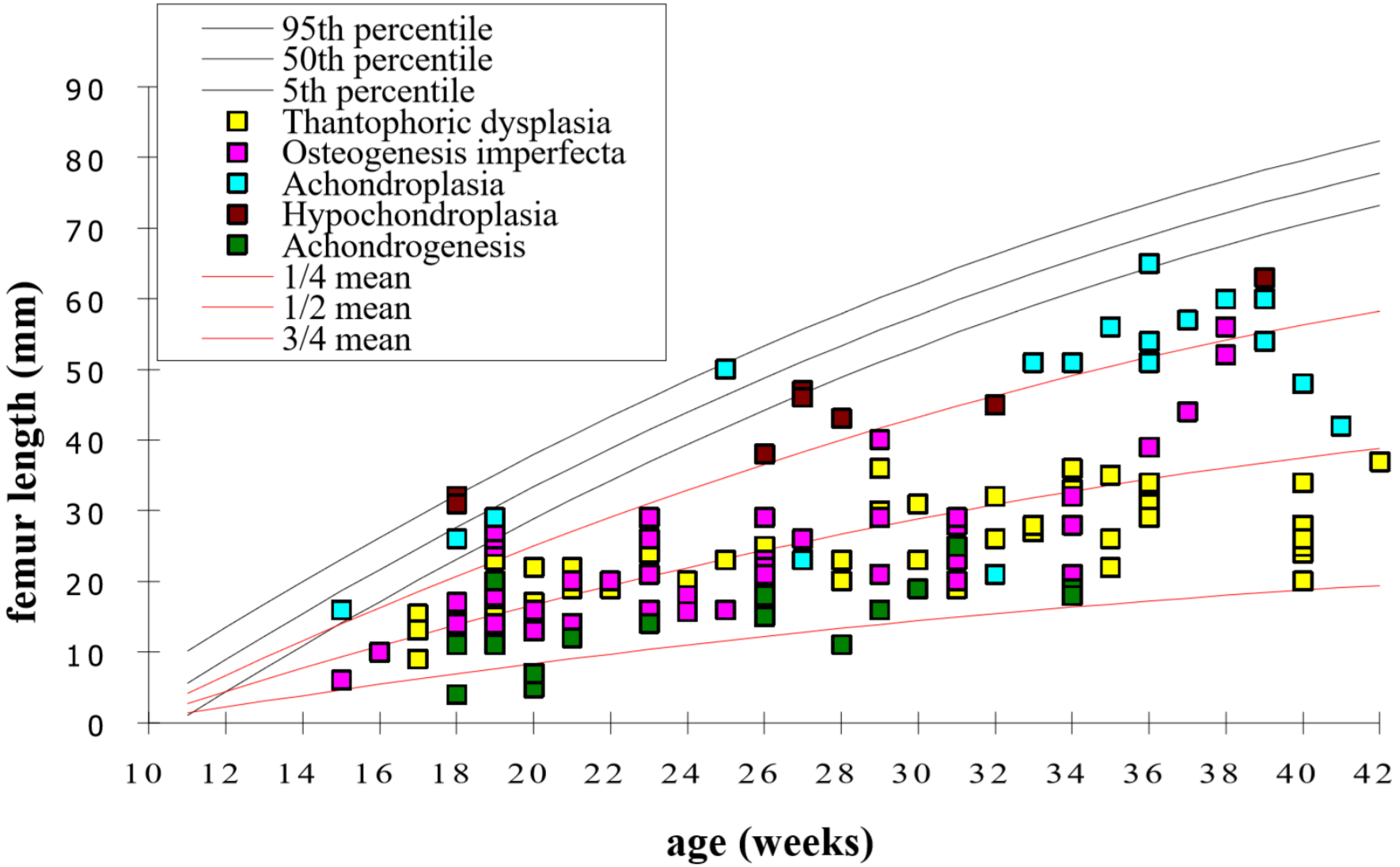
7. In 2nd trimester femur length increases 2.5 mm/week

8. Time of onset and degree of shortening of the FL specific for each skeletal dysplasia

9. Fetus with heterozygous achondroplasia may have a normal FL between 21 and 27 weeks' menstrual age

10. Femur length of fetuses with osteogenesis imperfecta type II is abnormal at 15 weeks' gestation

Femur length in skeletal dysplasias



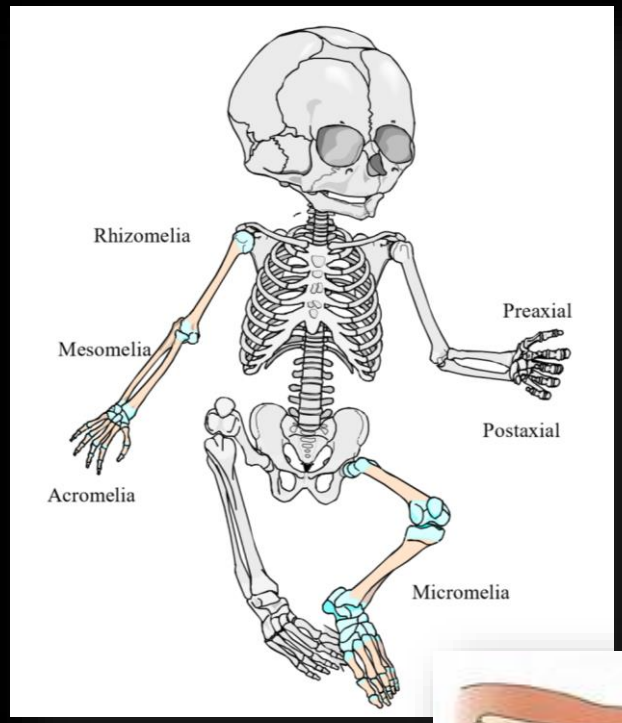
Considerations

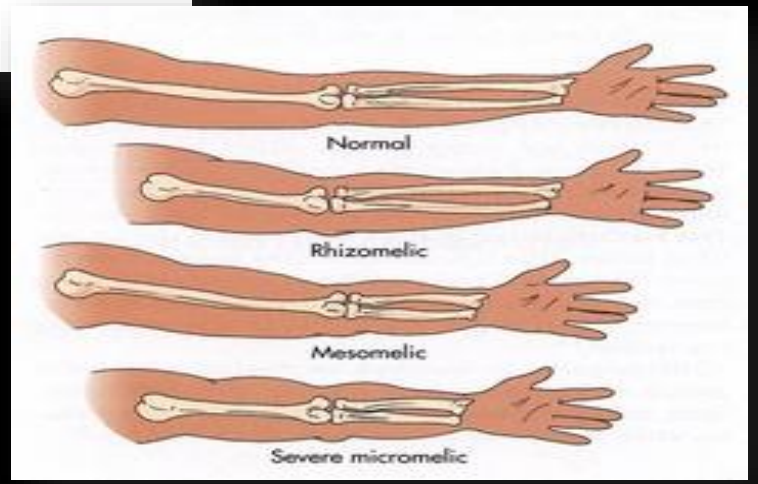
- Long Bones Short
  - Skeletal dysplasia
  - Dysostosis
  - Malformation
  - Deformation
    - Amniotic band syndrome
    - Oligohydramnios/anhydramnios

Considerations

- IS THE BONE NORMAL OR DEMINERALIZED?
- ARE THE BONES SHORT BUT NORMAL?
- ARE THE BONES SHORT WITH FRACTURES?
- ARE THE BONES SHORT AND ALSO ANORMALLY SHAPED?
- ARE ALL LONG BONES EQUALLY AFFECTED OR ARE SOME LONG BONES SHORTER THAN OTHERS?

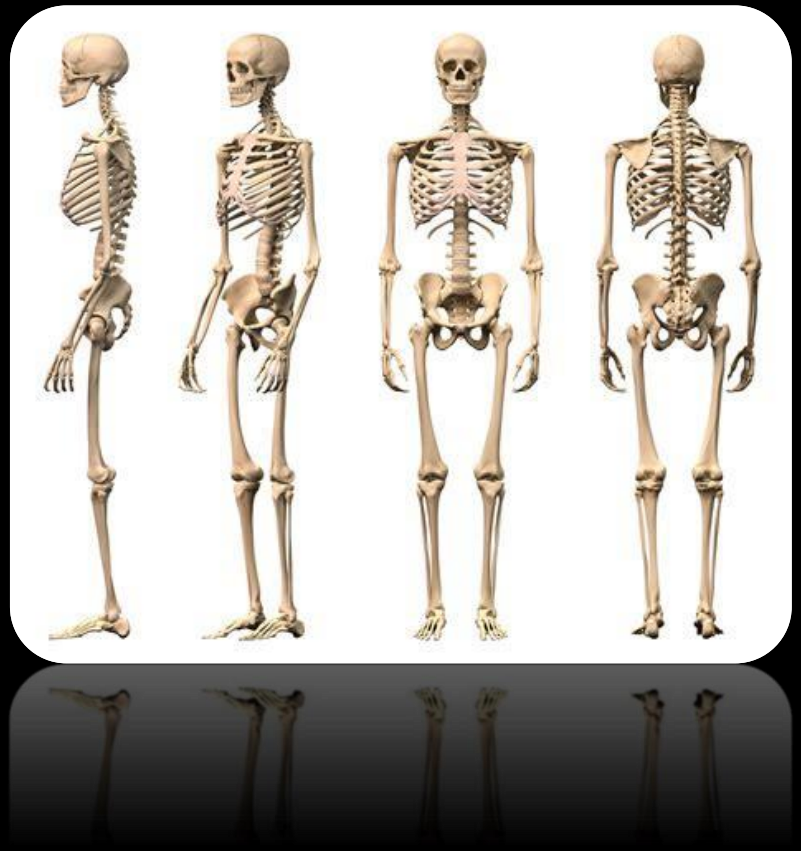
Considerations Definitions





- Rhizomelia
  - Disproportion of the length of the proximal limb
  - Achondroplasia
- Mesomelia
  - Disproportion of the length of the middle parts of the limb
- Acromelia
  - Shortening of the most distal portion of the limb
- Micromelia
  - Shortening of the proximal and distal limb
  - Osteogenesis Imperfecta Type II
  - Achondrogenesis

Considerations



- Long Bone Appearance
  - Multiple long bone fractures
    - Osteogenesis imperfecta type II
  - Bowed extremities
    - Camptomelic dysplasia
    - Thanatophoric dysplasia
    - Osteogenesis imperfecta type II
- Fetal Spine
  - Widening of the intervertebral spaces and flattening of the spine (platyspondyly)
    - Achondroplasia
    - Thanatophoric dyplasia

Considerations

- Bone Mineralization – Hypomineralization
  - Lack or decreased acoustic shadowing
  - Compressible calvarium
  - *Osteogenesis imperfecta type II*
  - Hypomineralization of the spine is characteristic of *achondrogenesis type II*
- Hands and Feet
  - Pre-axial (thumb side) or post-axial (5th finger side) polydactyly
  - Abnormalities of the feet non-diagnositic

The Sonographic Approach

Body Proportionality

As the fetus grows there is an inherent proportionality between the body parts

Comparison of femur length with another independently growing body part can help to confirm a diagnosis of a skeletal dysplasia

FL/Head Circumference

FL/HC ratio < 3 SD below the mean suggests a skeletal dysplasia

FL/Abdominal Circumference

FL/AC ratio normally between 0.20 and 0.247

Ratio < 0.16 diagnostic in a patient with suspected skeletal dysplasia

FL/Foot

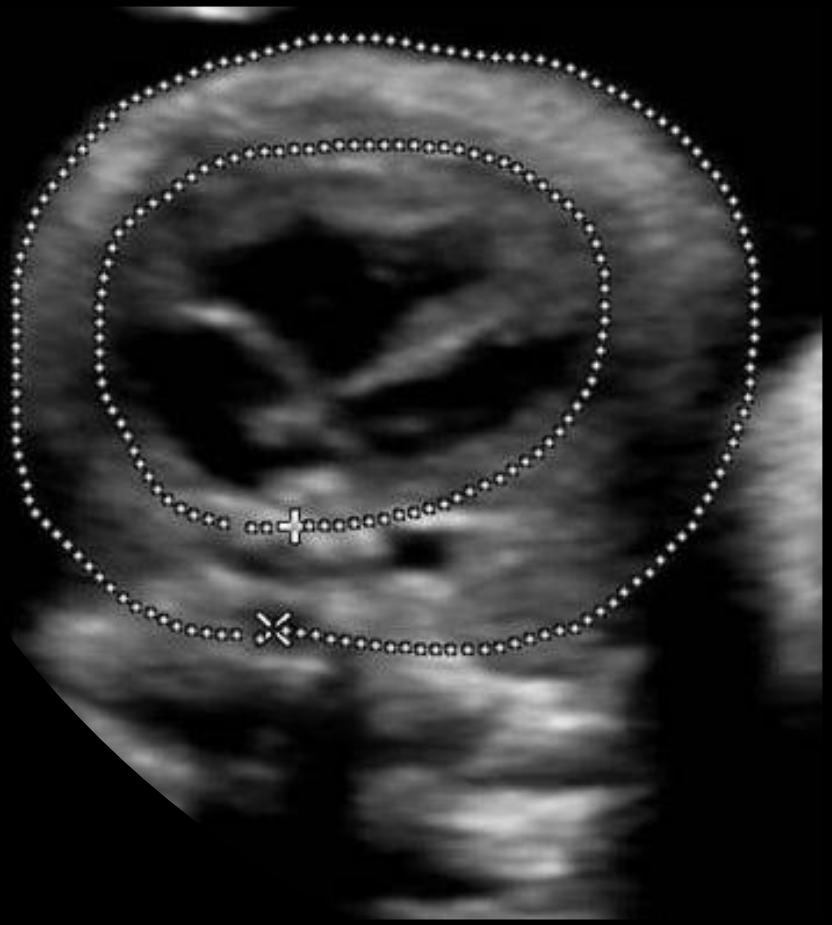
FL and foot generally equivalent in length

Growth of the foot not affected by skeletal dysplasia

FL/foot ratio is < 0.8711 in a severe skeletal dysplasia

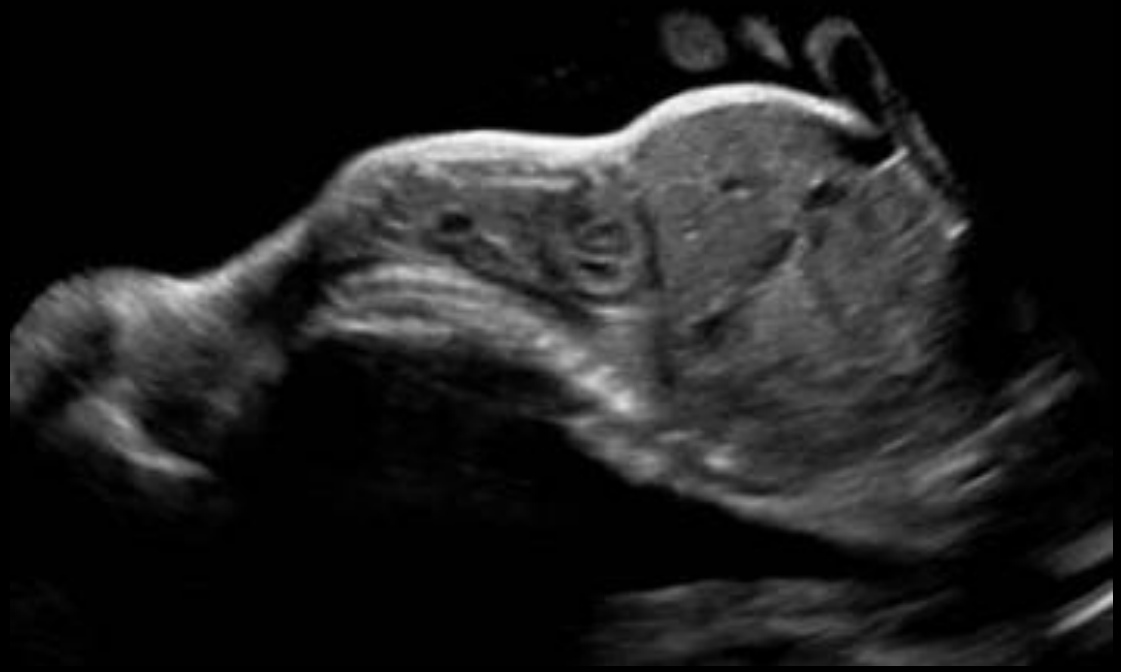
The Sonographic Approach

- **Chest Circumference/AC**
  - Chest circumference measured perpendicular to the fetal spine at level of the 4-chamber view
  - Normal thoracic/AC ratio
    - **0.89 + 0.06**
    - **Ratio does not vary with gestational age**
- **Chest Circumference/HC**
  - Normal chest circumference/HC ratio
    - **0.80 + 0.12**
    - **Ratio does not vary with gestational age**



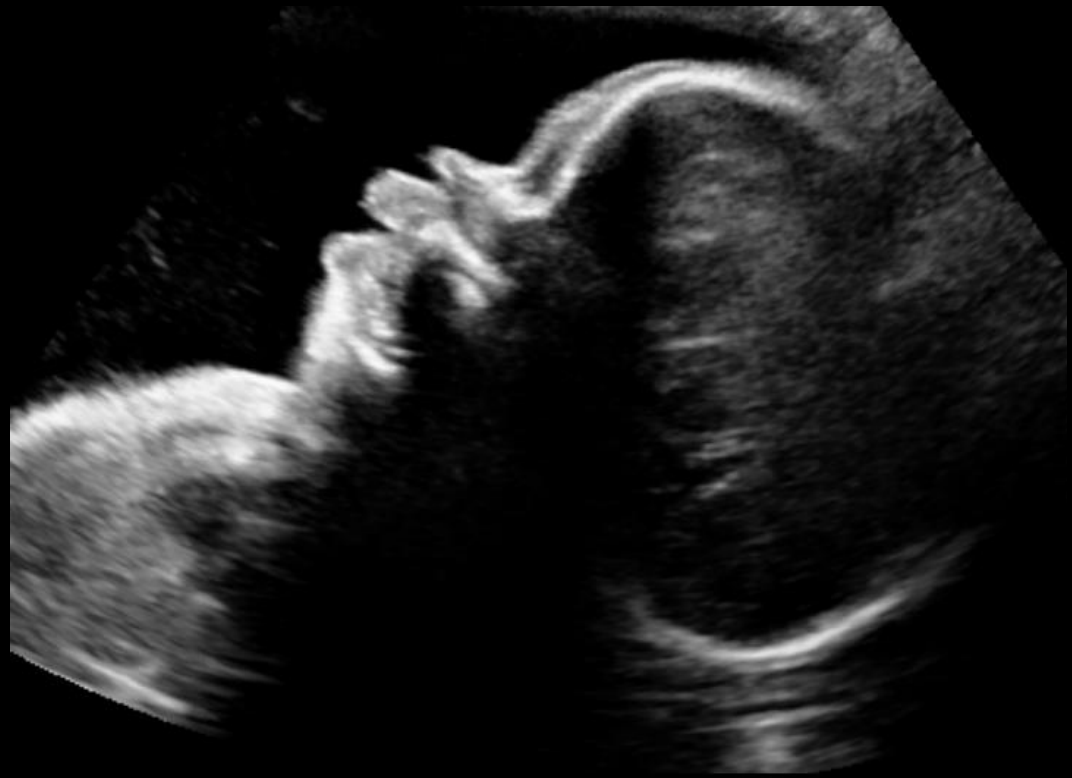
The Sonographic Approach

- CHEST APPEARANCE
  - In lethal skeletal dysplasias chest cavity is narrowed
    - The heart fills the chest cavity
  - On sagittal view, marked narrowing of the chest results in the abdomen appearing protuberant



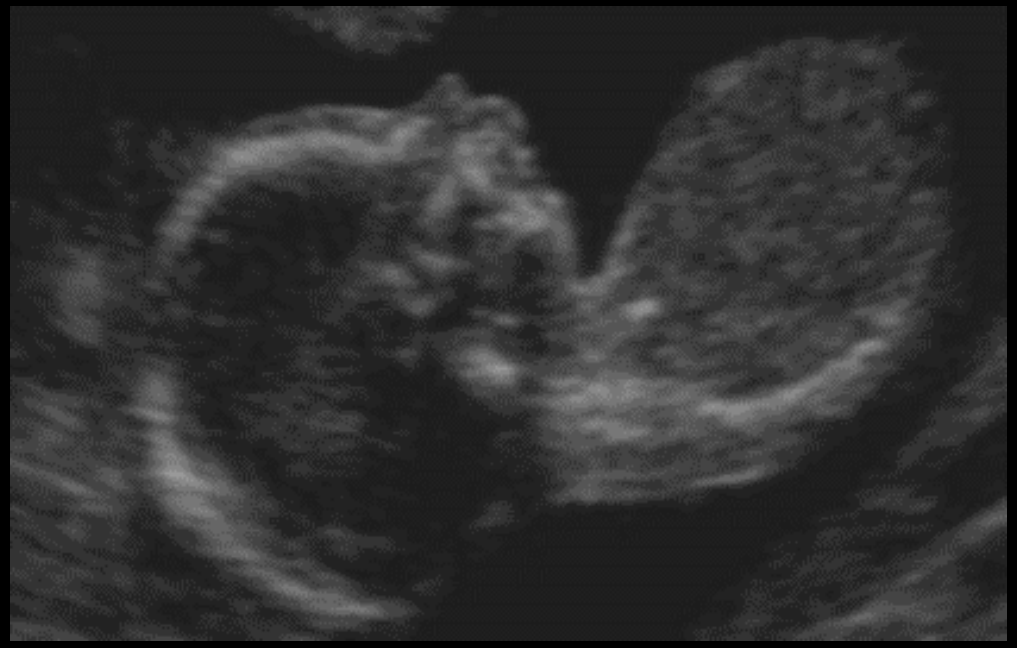
The Sonographic Approach

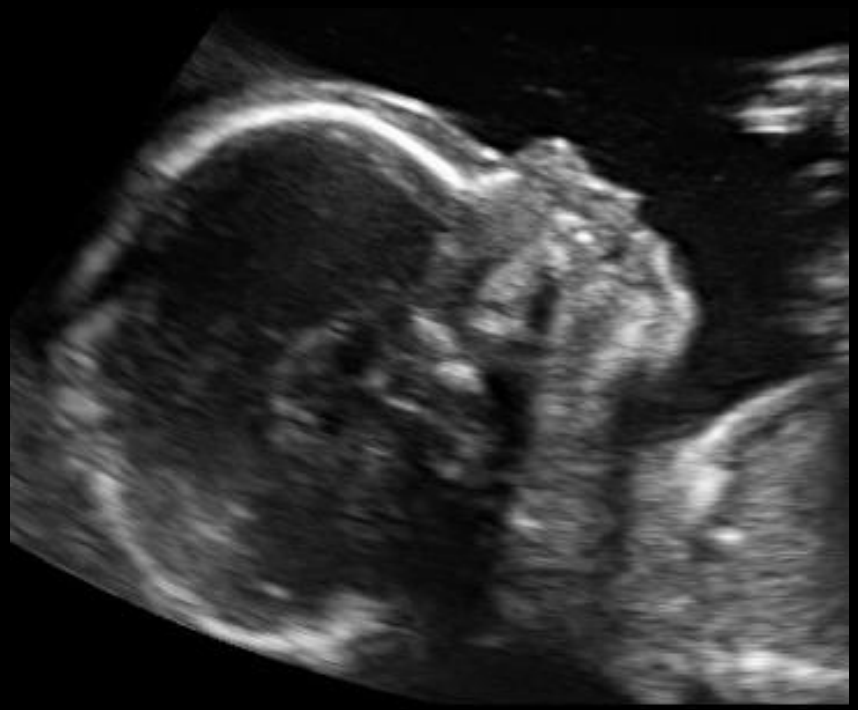
- FETAL PROFILE
  - Frontal bossing, a depressed nasal bridge, and/or micrognathia
  - Cloverleaf skull
    - 14% of fetuses with thanatophoric dysplasia
    - Fetuses with homozygous achondroplasia



The Sonographic Approach

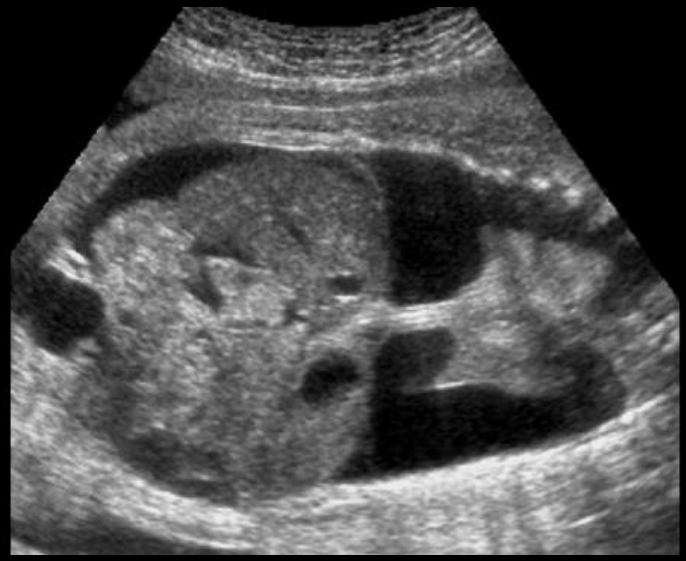
- FETAL PROFILE
  - Sagittal view of the face – micrognathia (small mandible)





The Sonographic Approach

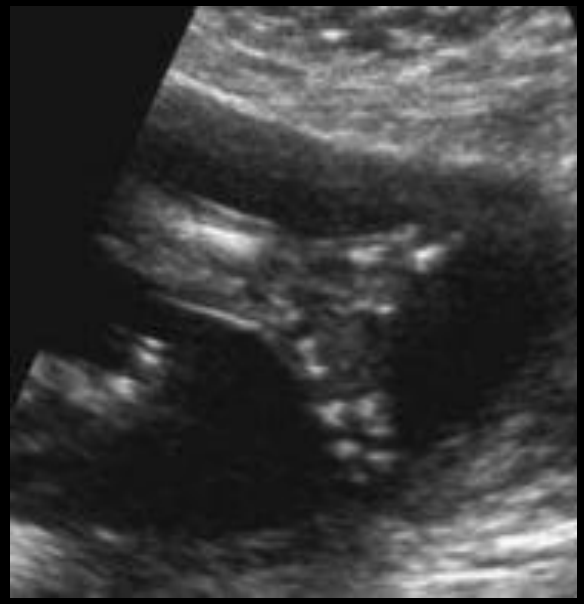
- POLYHYDRAMNIOS
  - Thanatophoric dysplasia
    - Approximately 50%
    - Achondroplasia
      - Approximately 25 %
    - Others
      - Rare
- NON-IMMUNE HYDROPS
  - Short-rib polydactyly
  - Achondrogenesis
  - Etiology unclear

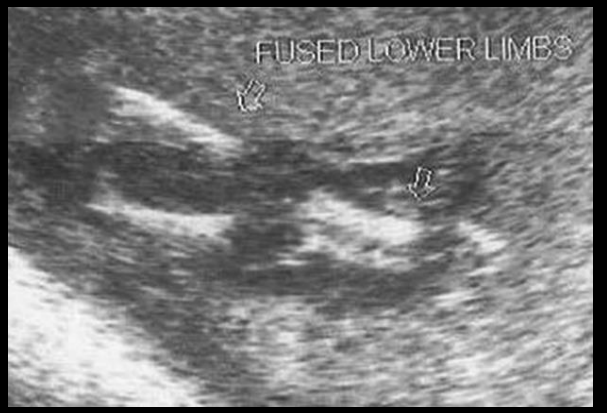


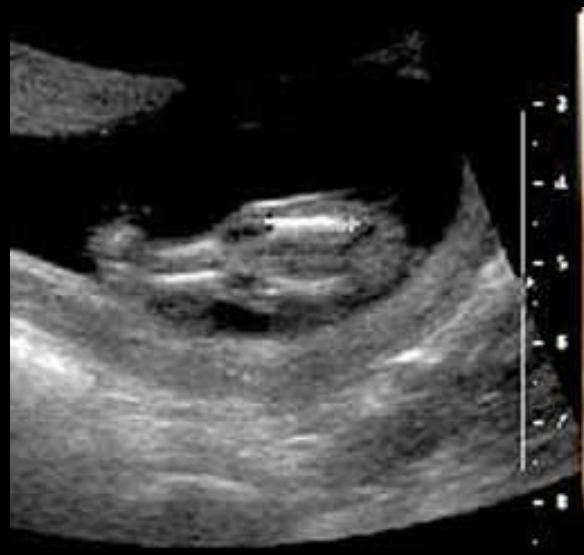
Examples

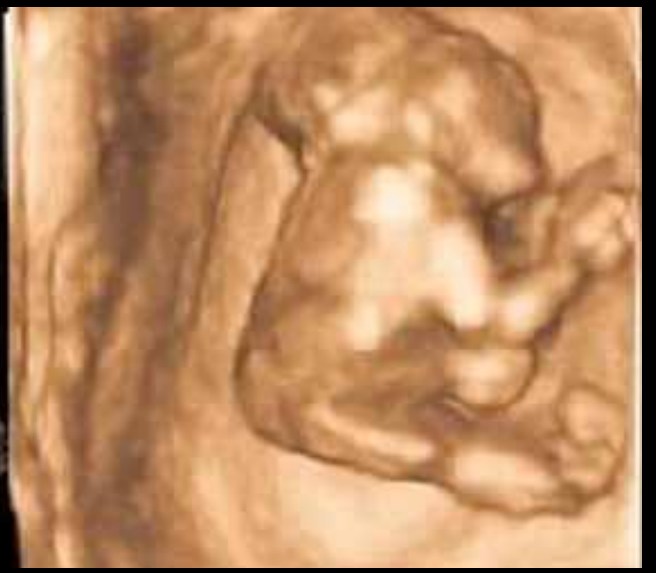
Sirenomelia

- 1 in 60,000 livebirths
- Injury to caudal end of developing embryo days 13 to 22
- Associated with monozygotic twinning
- First trimester sonographic findings
  - Fused lower limb
  - Increased nuchal translucency
- Second trimester sonographic findings
  - Single umbilical artery
  - Bilateral renal agenesis
  - Oligohydramnios
  - Growth restriction
- Differential diagnosis
  - Bilateral renal agenesis and caudal regression syndrome
- Karyotype usually normal
- Prognosis extremely poor for extrauterine survival



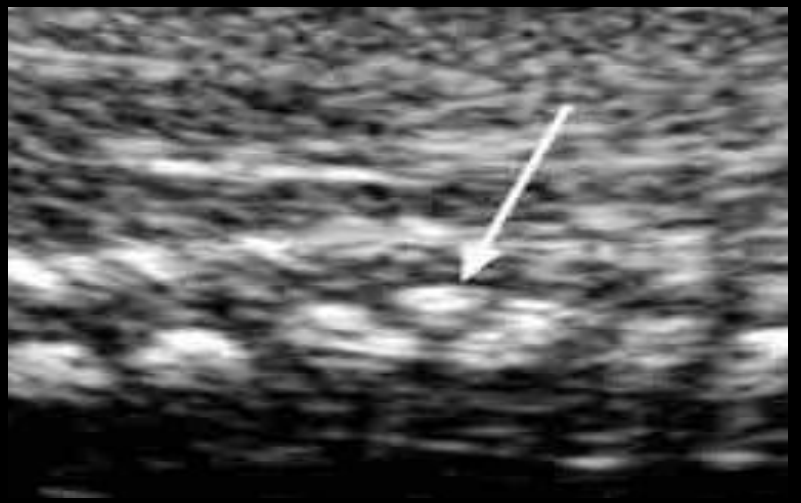


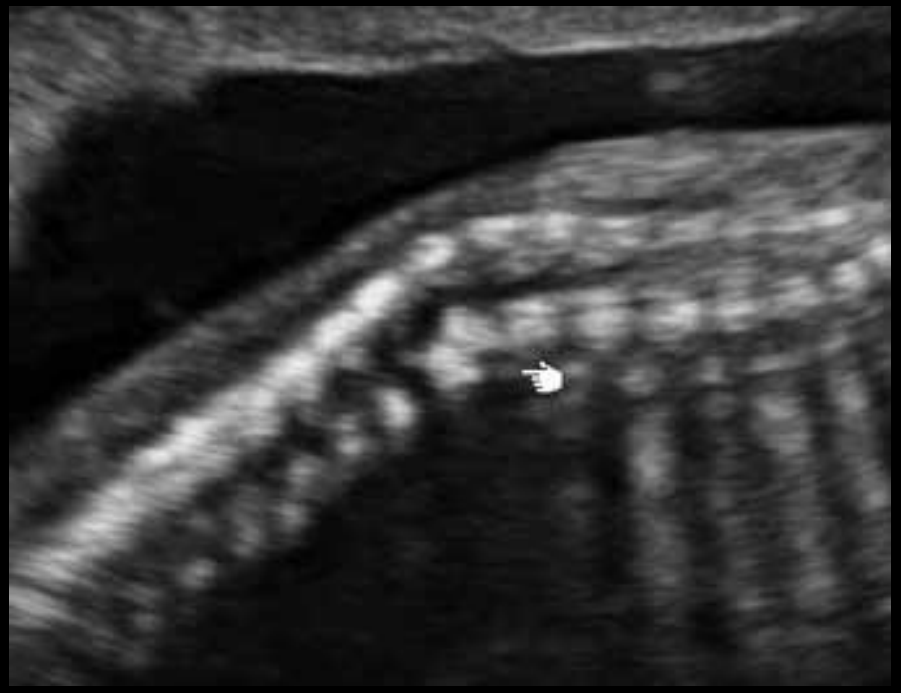


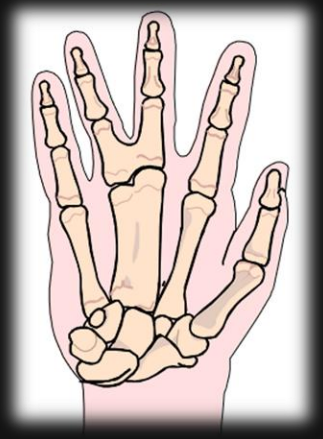


Hemivertebrae

- Cause of congenital scoliosis and kyphoscoliosis
- 0.3 to 1 per 1000 livebirths
- More common in females
- Vertebral anomalies develop in first 6 weeks of gestation
- Wedge within vertebral column results in curvature away from side of defect
- Prognosis for isolated hemivertebrae is good
- Associated with neural-tube defects, occult intraspinal defects, renal anomalies, tracheoesophageal atresia/fistula
- Associated with syndromes: Goldenhar, Jarcho–Levin, Poland, Robinow, chondrodysplasia punctate, Pallister–Hall

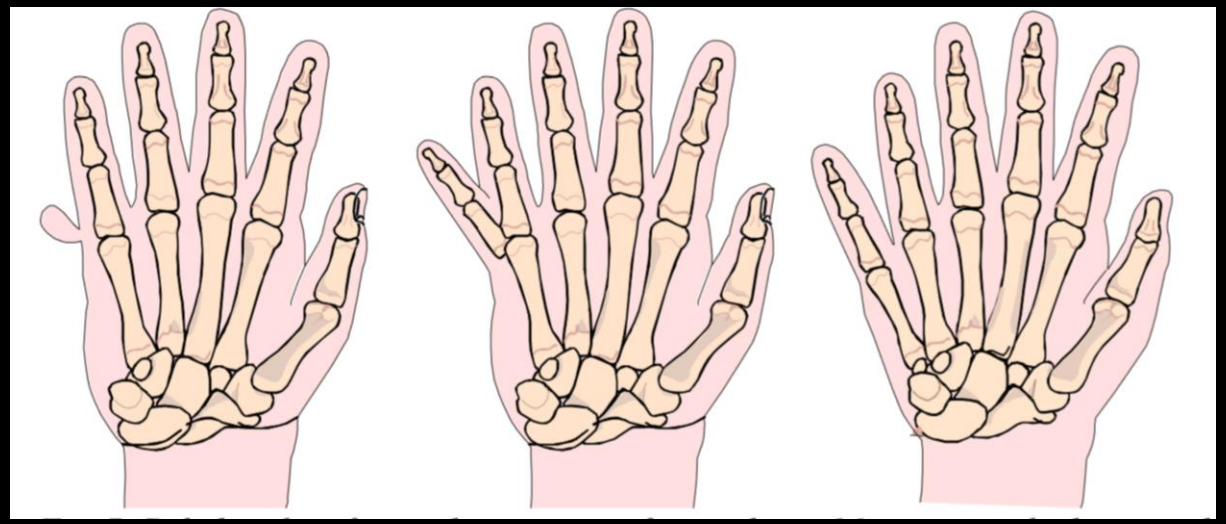


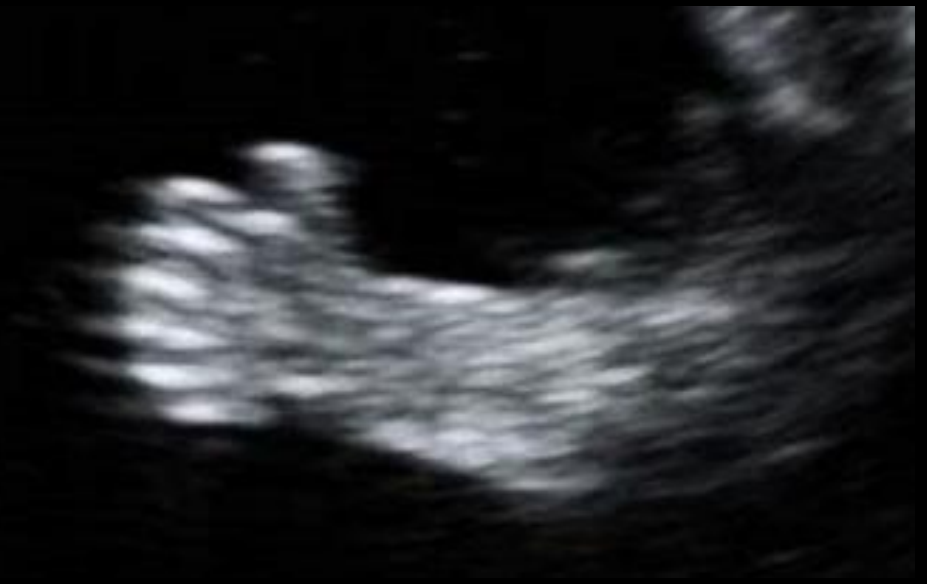


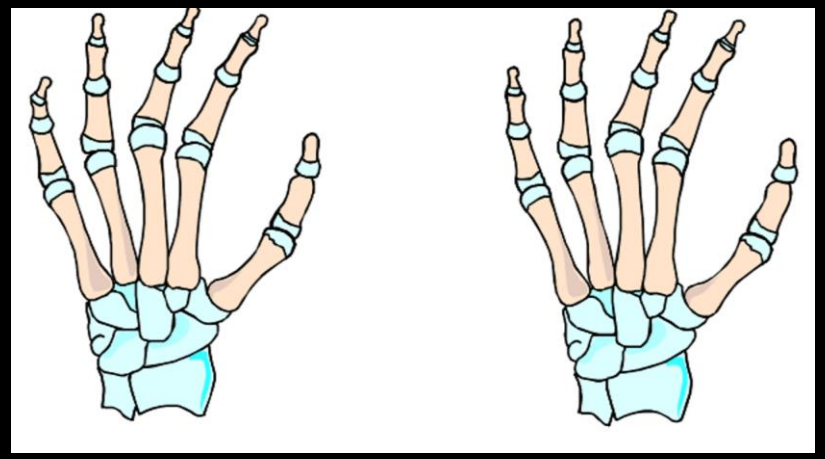


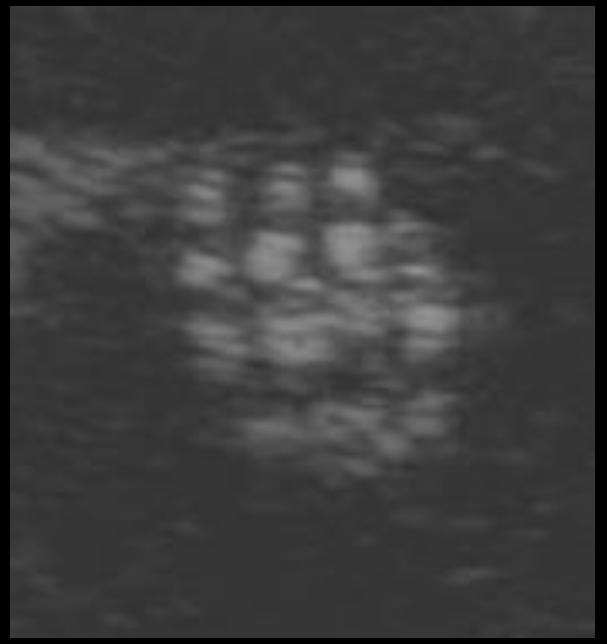
Acromelia

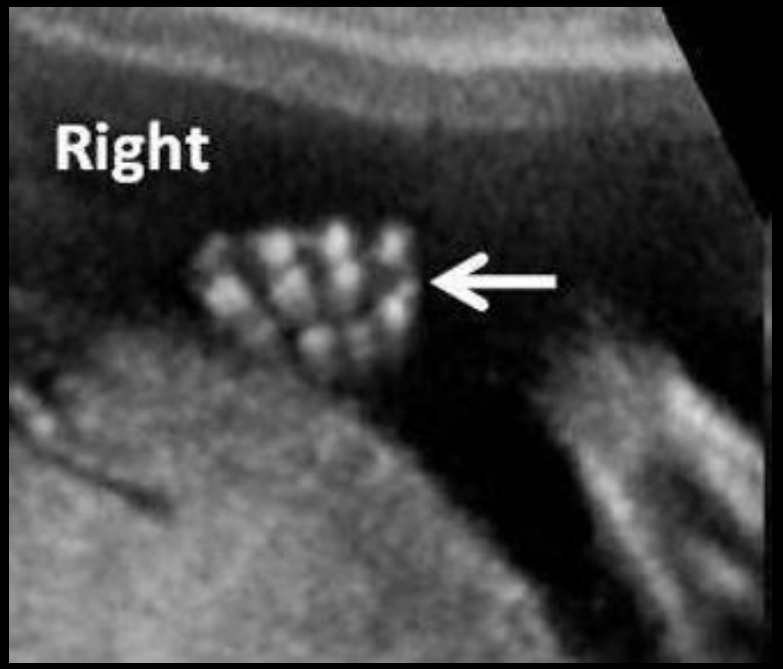
- Anomalies of the hands and feet
- Polydactyly
  - Presence of more than five digits
    - Post-axial - extra digits on the ulnar or fibular side
    - Preaxial – extra digits on the radial or tibial side
    - Most commonly the extra digit is a simple skin tag
- Syndactyly
  - Soft tissue or bony fusion of adjacent digits
  - Difficult to recognize
- Clinodactyly
  - Deviation of a finger







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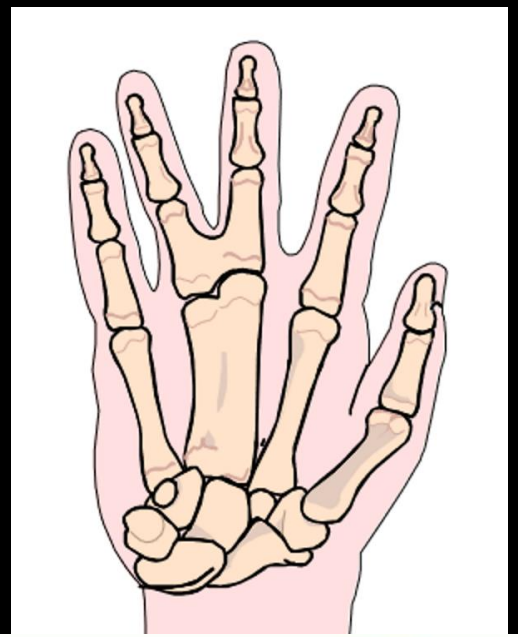
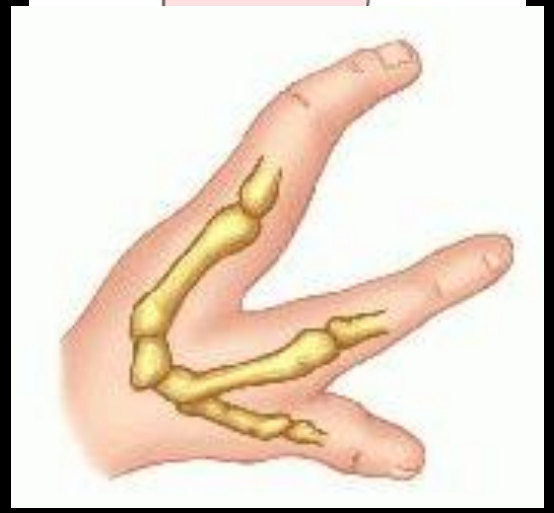
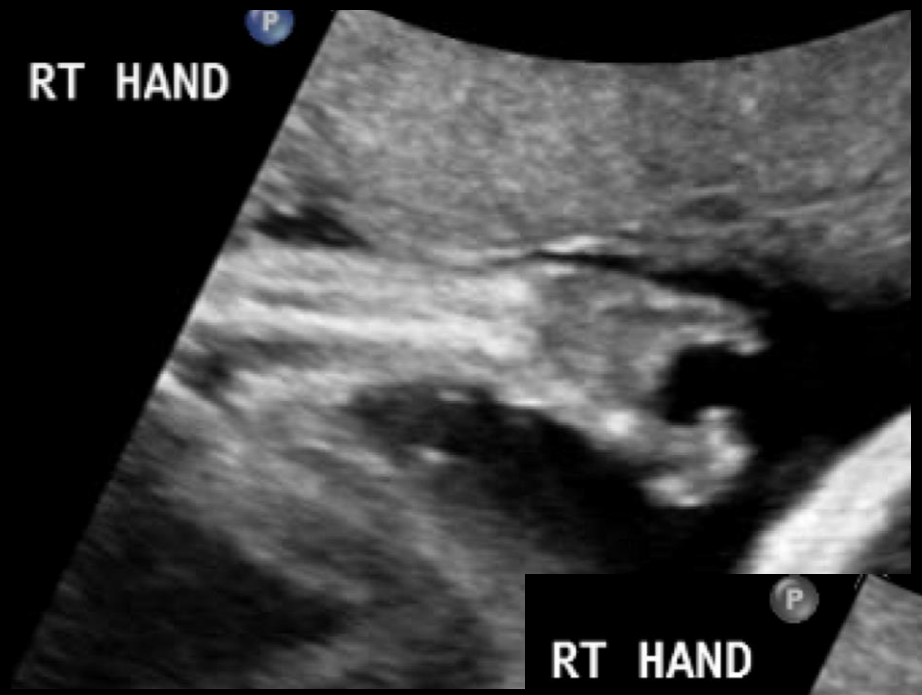
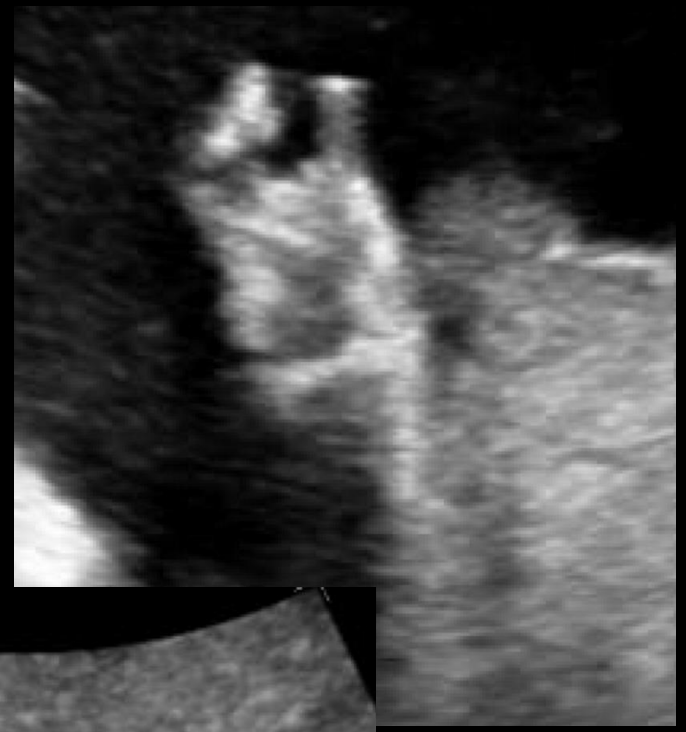
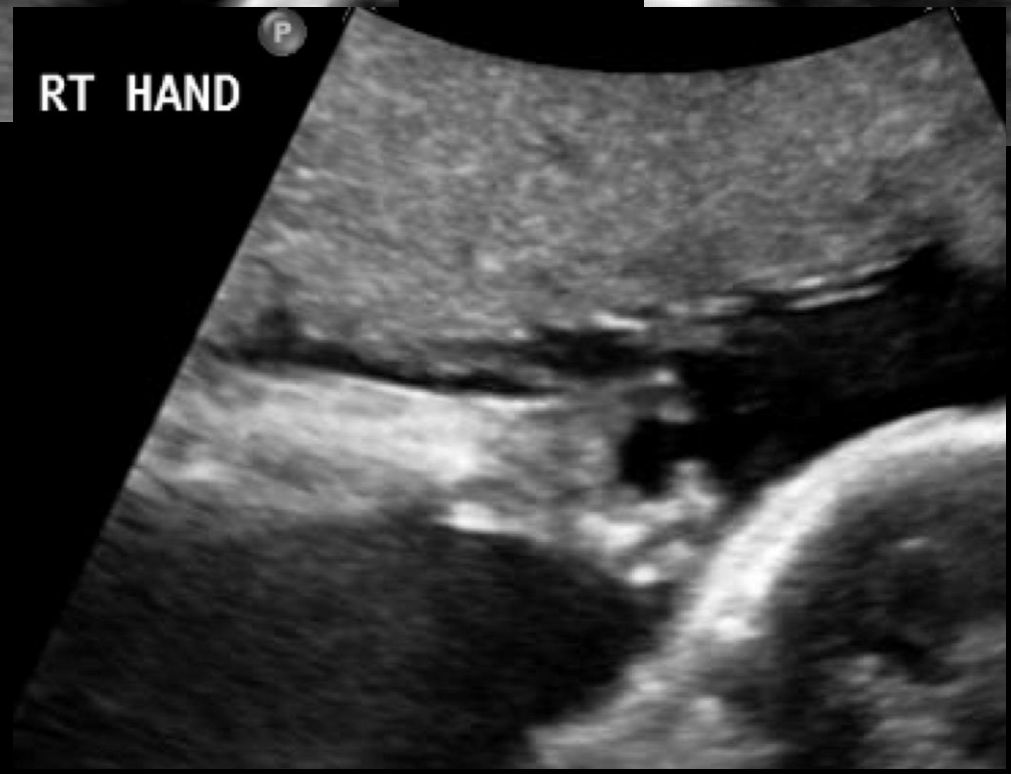


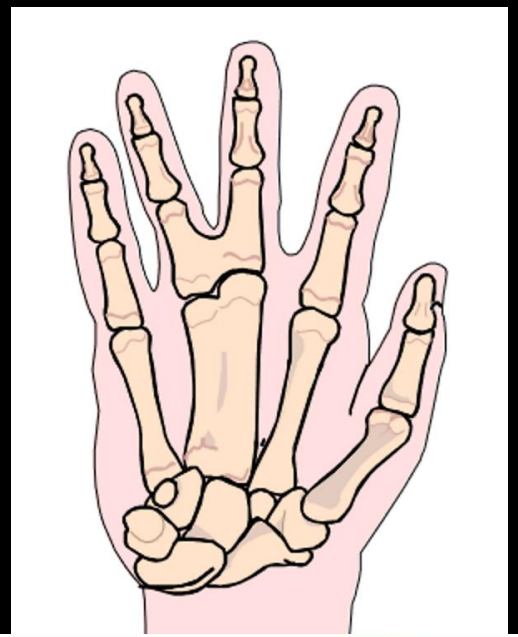


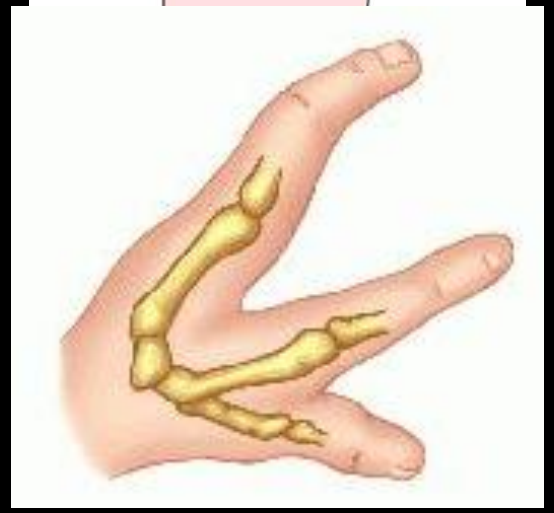


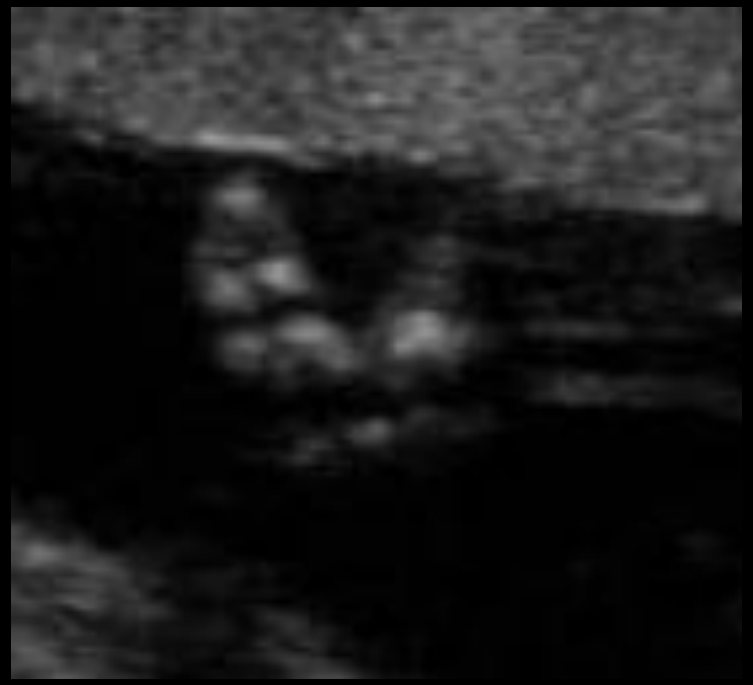


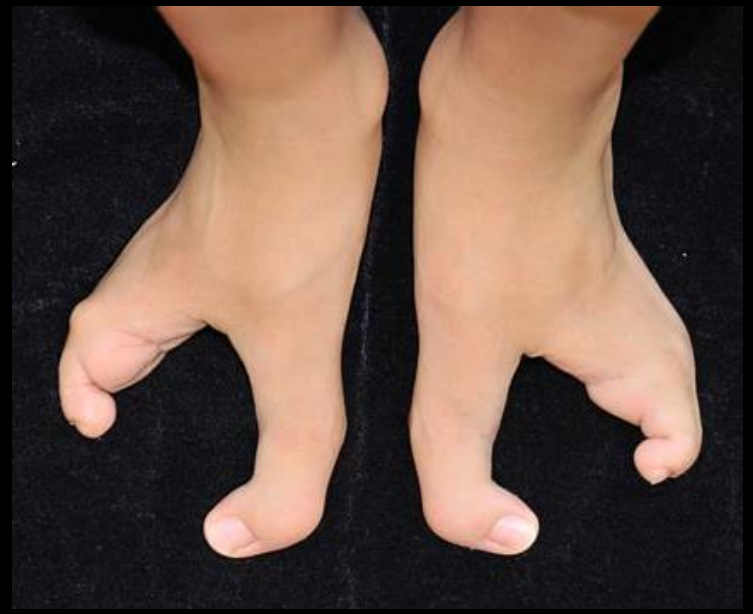


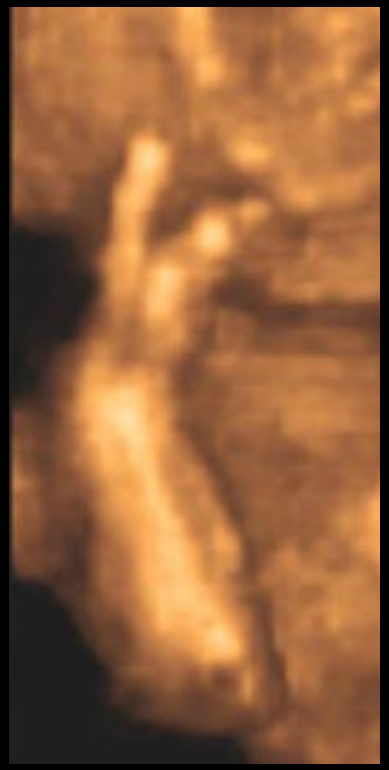
Ectrodactyly

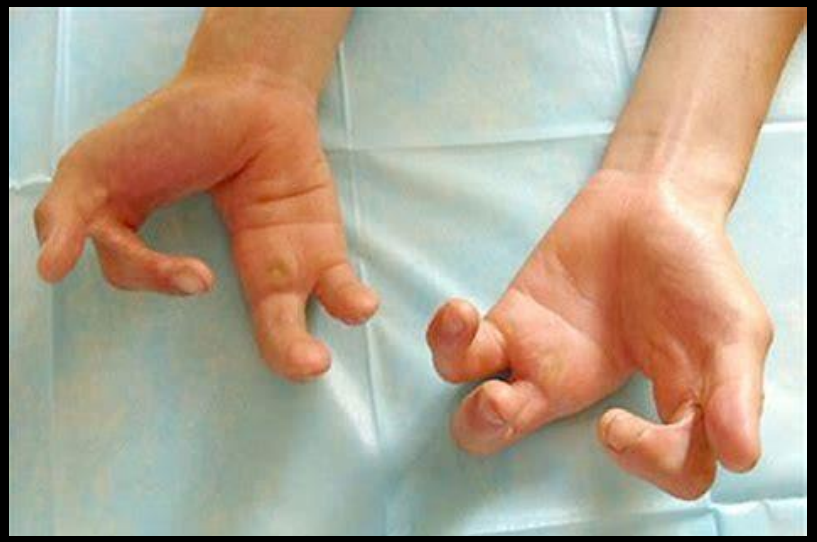








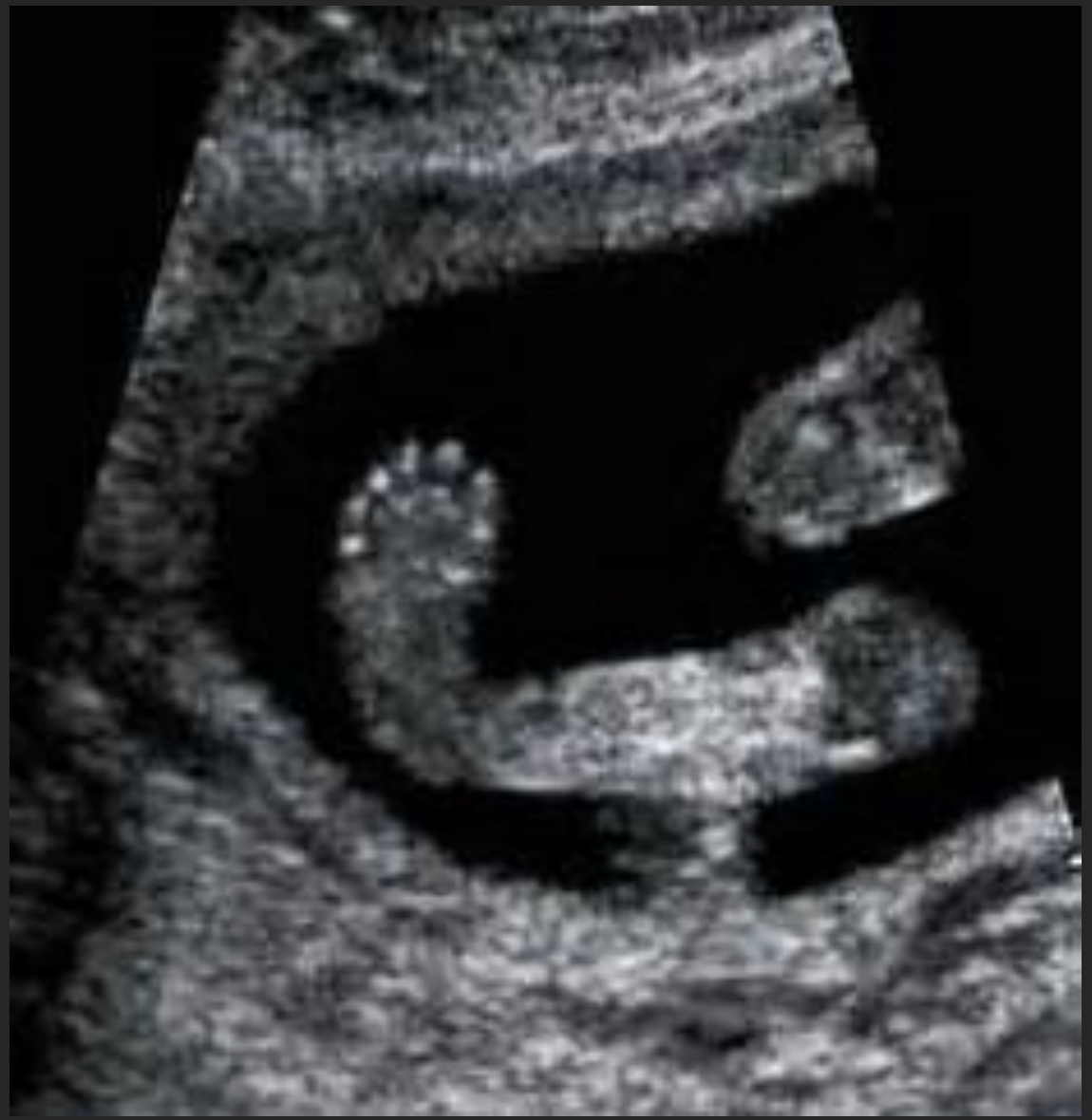


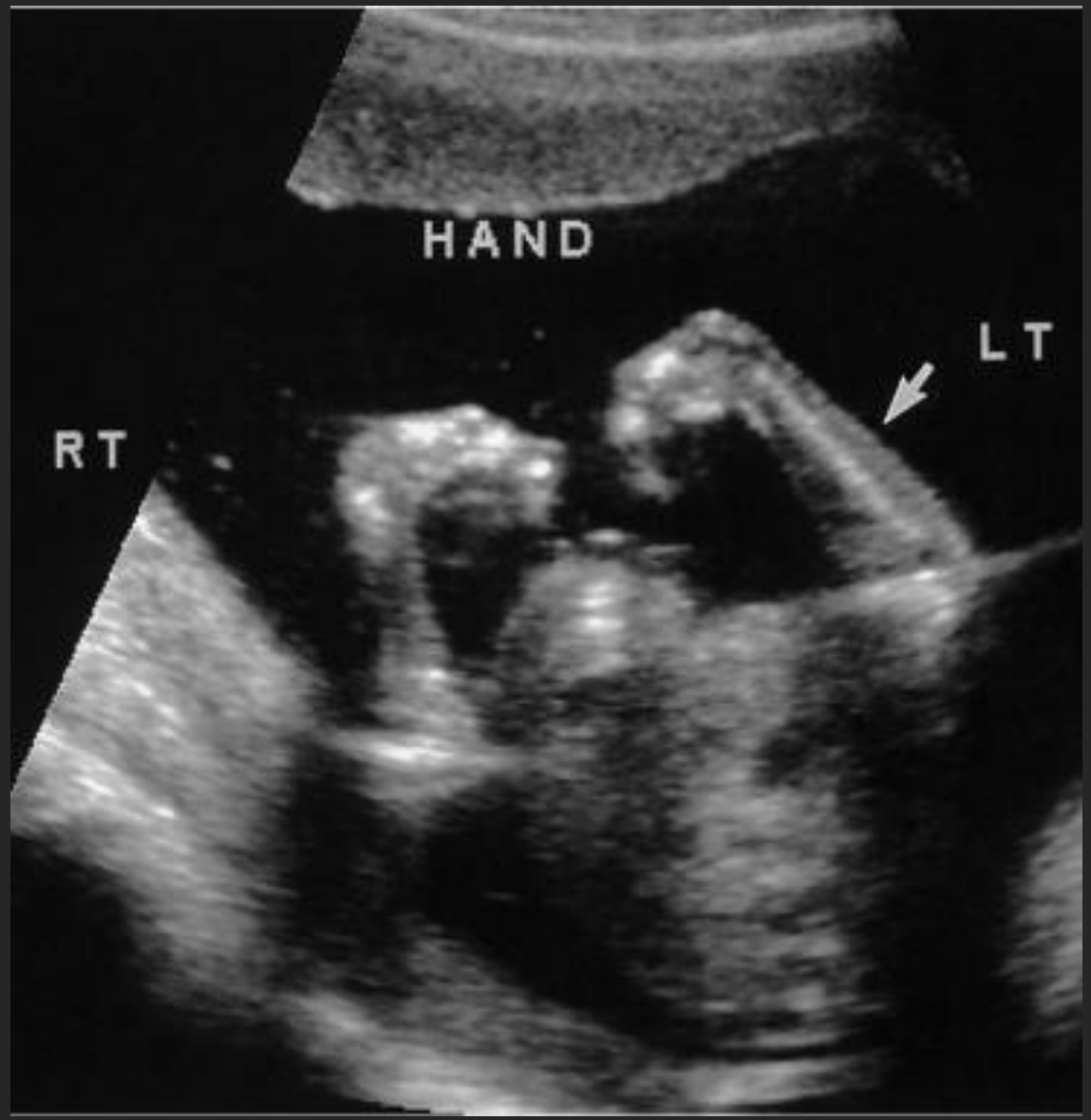


Ectrodactyly

Acromelia

- Clubbing of the hand
  - Suggestive of “radial-ray” anomalies
    - Holt-Oram syndrome
    - Thrombocytopenia-absent radius (TAR) syndrome
    - Trisomy 18
- Clubbing of the foot
  - Talipes equinovarus
    - Adduction of forefoot, inversion of heel and plantar flexion of the forefoot and ankle
  - Talipes calcaneovalgus
    - Dorsal flexion of forefoot with plantar surface facing laterally
  - Metatarsus varus
    - Inversion and adduction of the forefoot alone




HAND
LT
RT

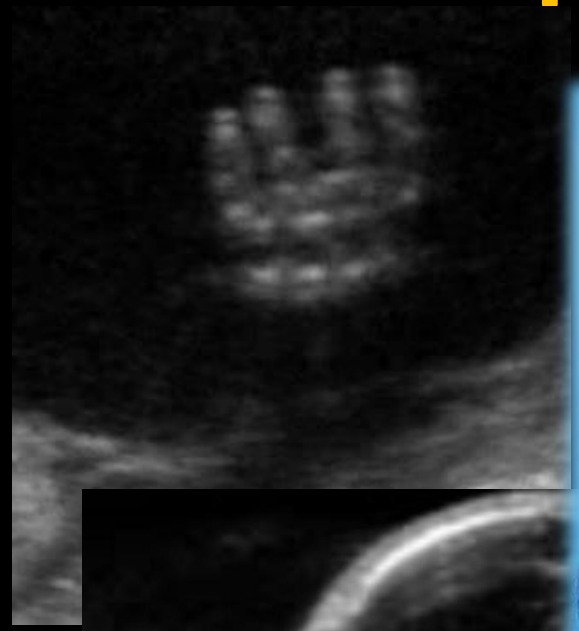
Achondroplasia

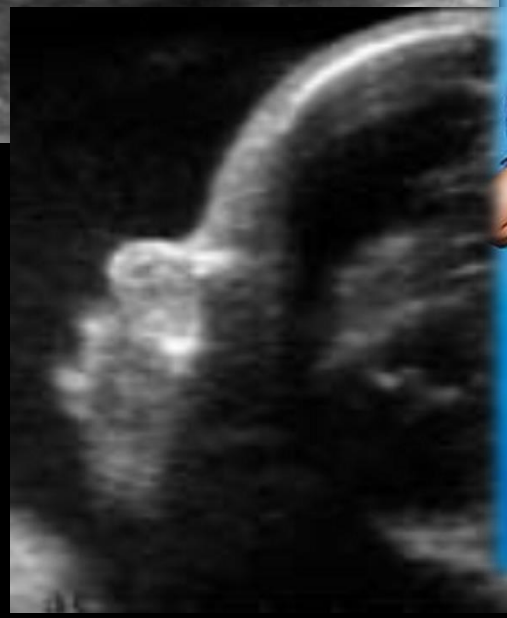
- “Absence of cartilage”
- Most common form of short-limbed dwarfism
- Recognized since ancient times
- Incidence is 1 in 26,000 livebirths
- Shortening of long bones between 21 and 27 weeks’ gestation
- Additional findings
  - Acrocrania
  - Frontal bossing
  - Trident-shaped hand

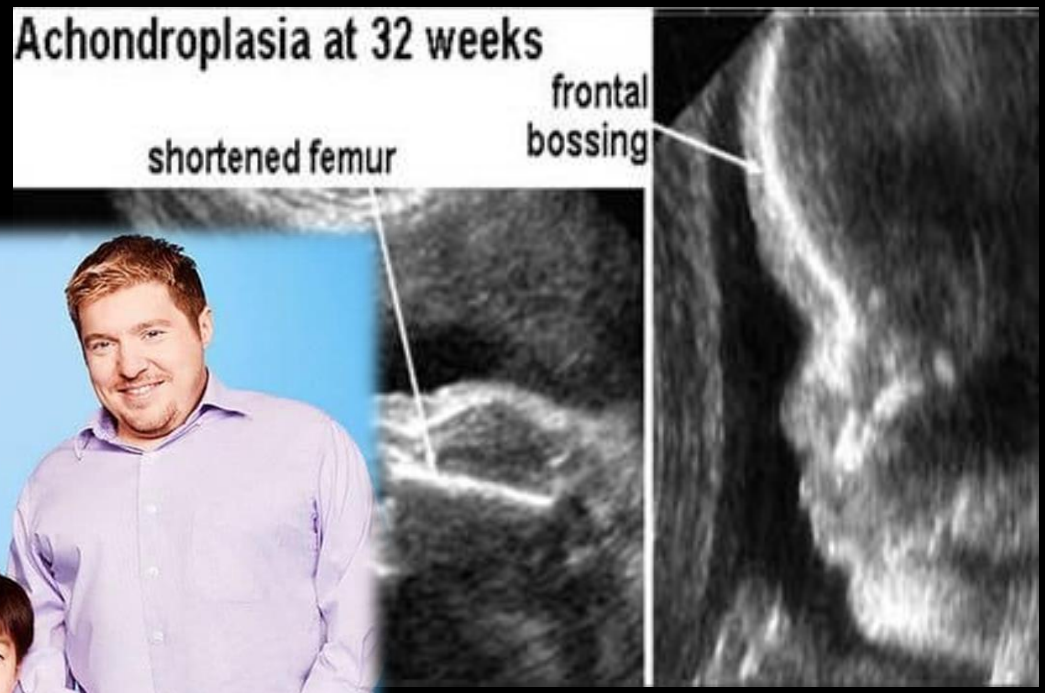
Achondroplasia

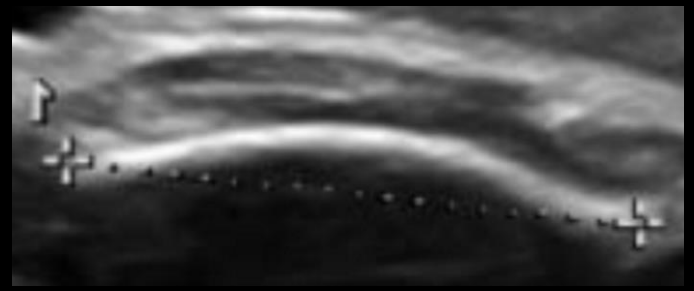
- Differential diagnosis
  - Diastrophic dysplasia, achondrogenesis, Ellis–van Creveld syndrome, hypochondroplasia
- Mutations in fibroblast growth factor receptor 3 (FGFR3) gene
  - Negative regulator of chondrocyte proliferation
  - Mutations activate the receptor and cause gain of function
- Prenatal diagnosis sonography or by DNA analysis
- Postnatal complications
  - Short stature, spinal stenosis, restrictive pulmonary disease, hypotonia
  - IQ is normal
- Inherited as an autosomal dominant condition
  - 80% of cases new mutations associated with advanced paternal age

Achondroplasia









Thanatophoric Dysplasia

- “Death bearing”
- Most common lethal skeletal dysplasia
- Presents in the second trimester
- Two subtypes
  - TD I
    - Short curved femurs with or without a cloverleaf skull
  - TD II
    - Straight, longer femurs and generally a more severe cloverleaf skull
- Sporadic inheritance associated with advanced paternal age (>35 years)
- Mutations in fibroblast growth factor receptor 3 (FGFR3)
  - DNA diagnosis highly accurate
  - FGFR3 pressed in the brain
    - Rare survivors are uniformly severely developmentally delayed

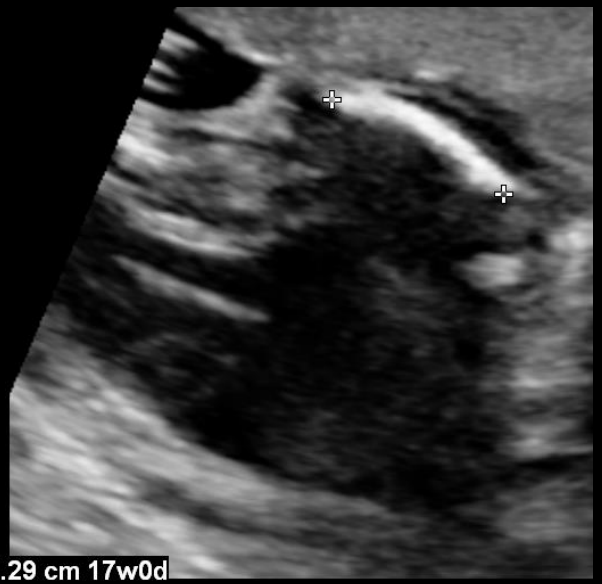
Thanatophoric Dysplasia

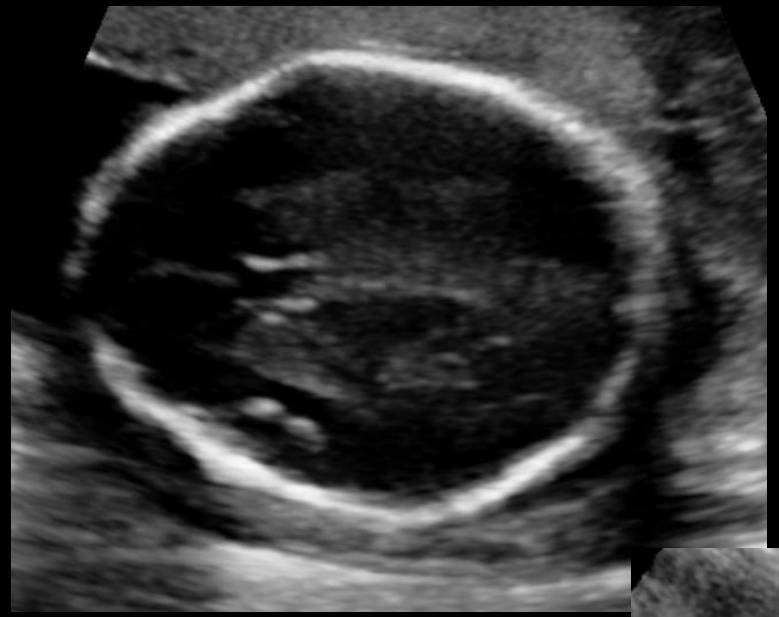
- Limbs markedly shortened and the femurs have a "telephone receiver" appearance
- Macrocephaly
- Chest significantly narrowed due to extremely short ribs
- Abdomen is protuberant
- Generalized redundancy in subcutaneous tissue
- Polyhydramnios is common
- Neonatal death from respiratory failure

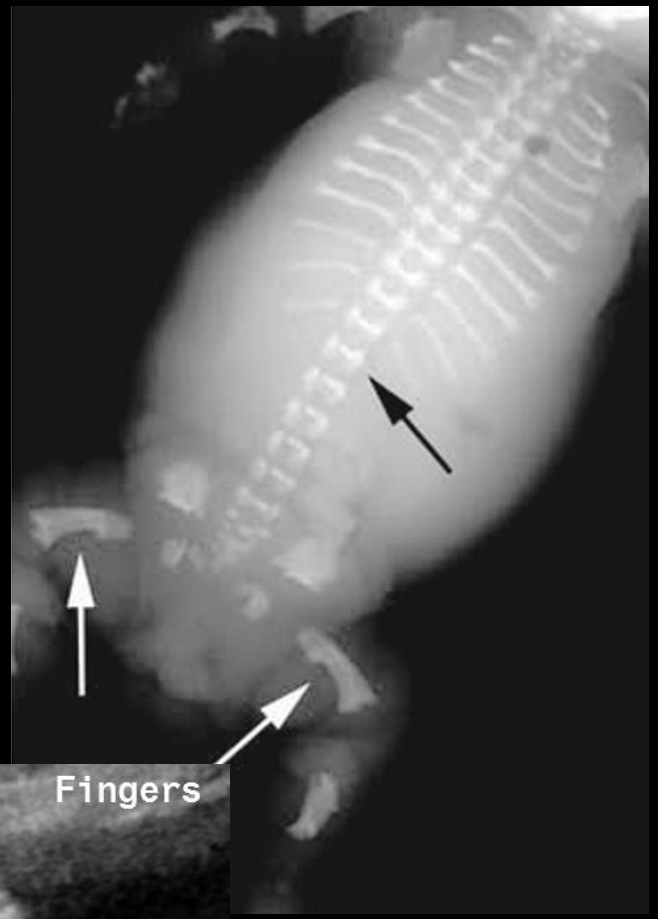
- Camptomelic dysplasia very similar and must be excluded
  - Characterized by shortened bowed lower extremities, hypoplastic fibulas and hypoplastic scapulas
  - Hypertelorism, cleft palate, ventriculomegaly and clubbed feet
  - Phenotypic female fetuses may have a male karyotype

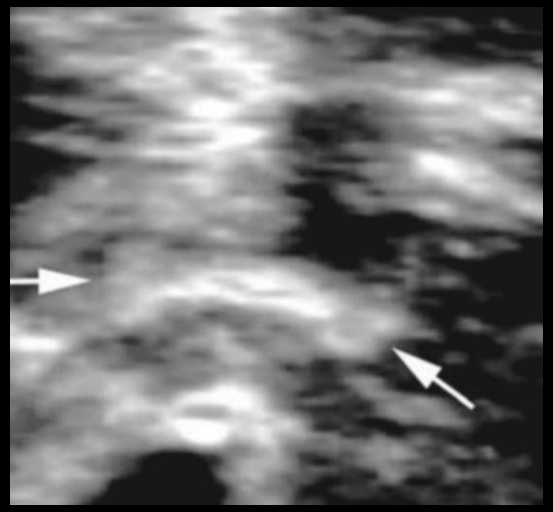
- Fetal karyotyping helpful

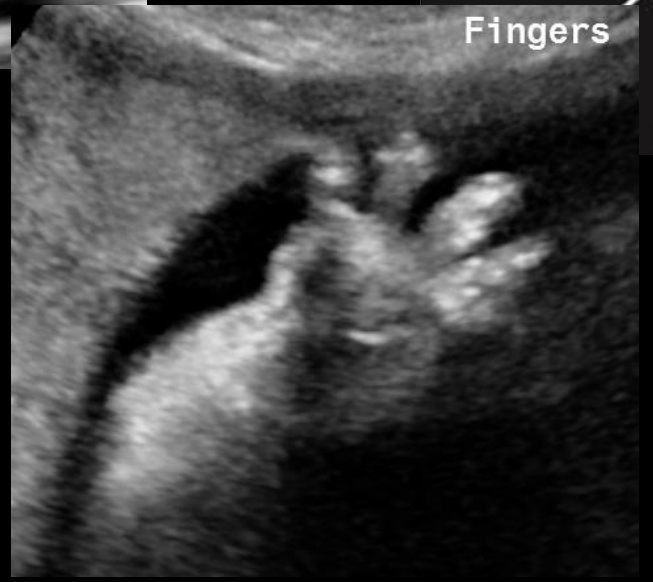
Thanatophoric Dysplasia

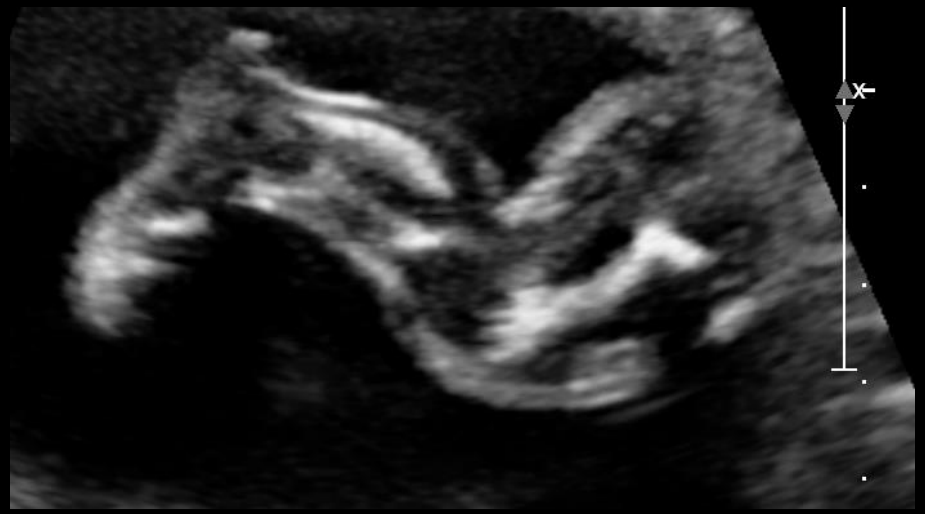


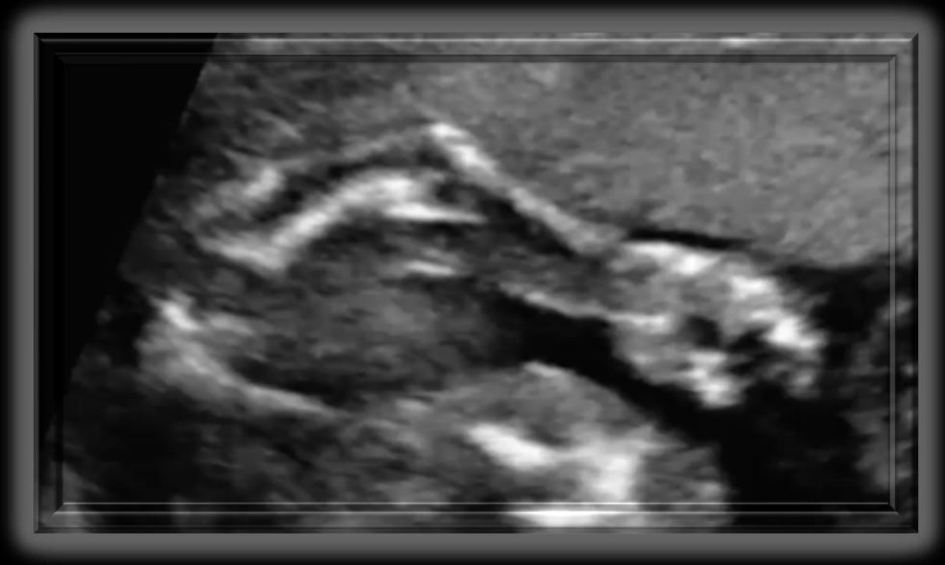


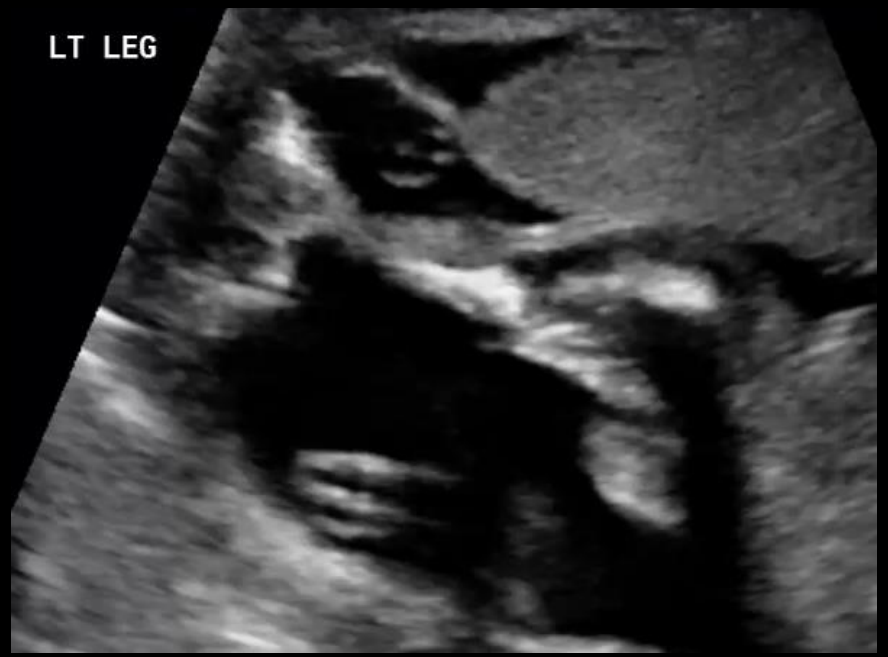








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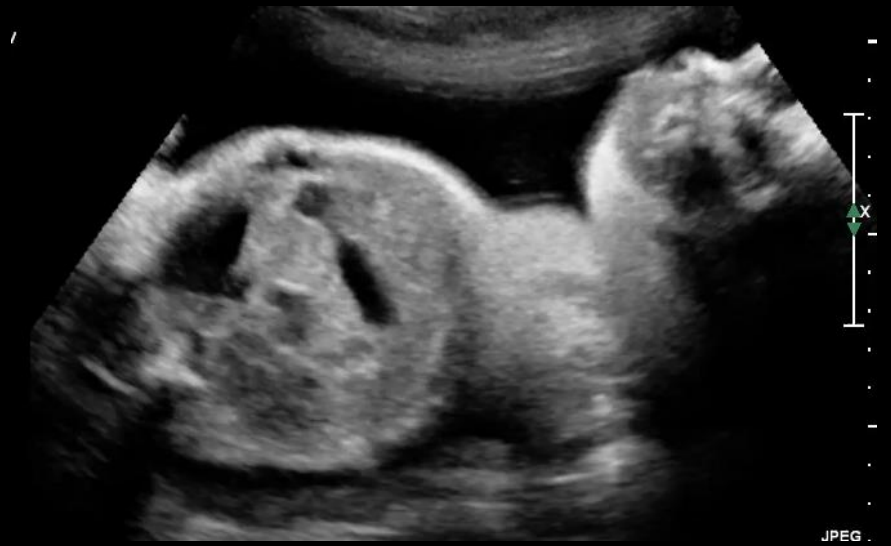
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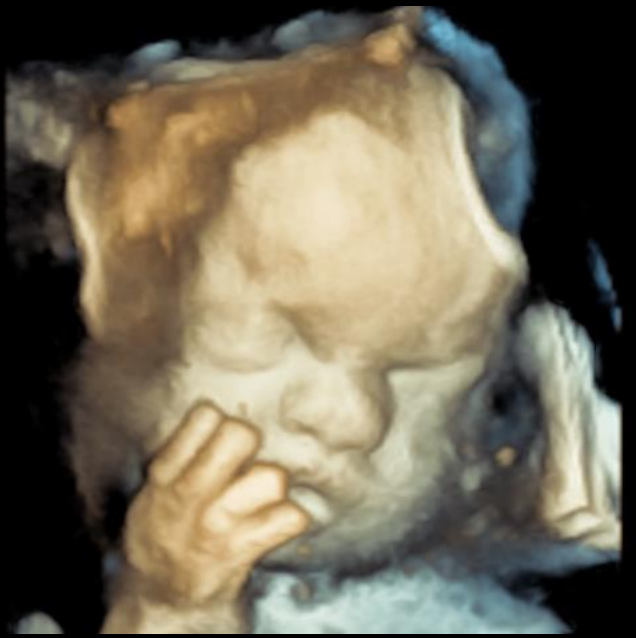


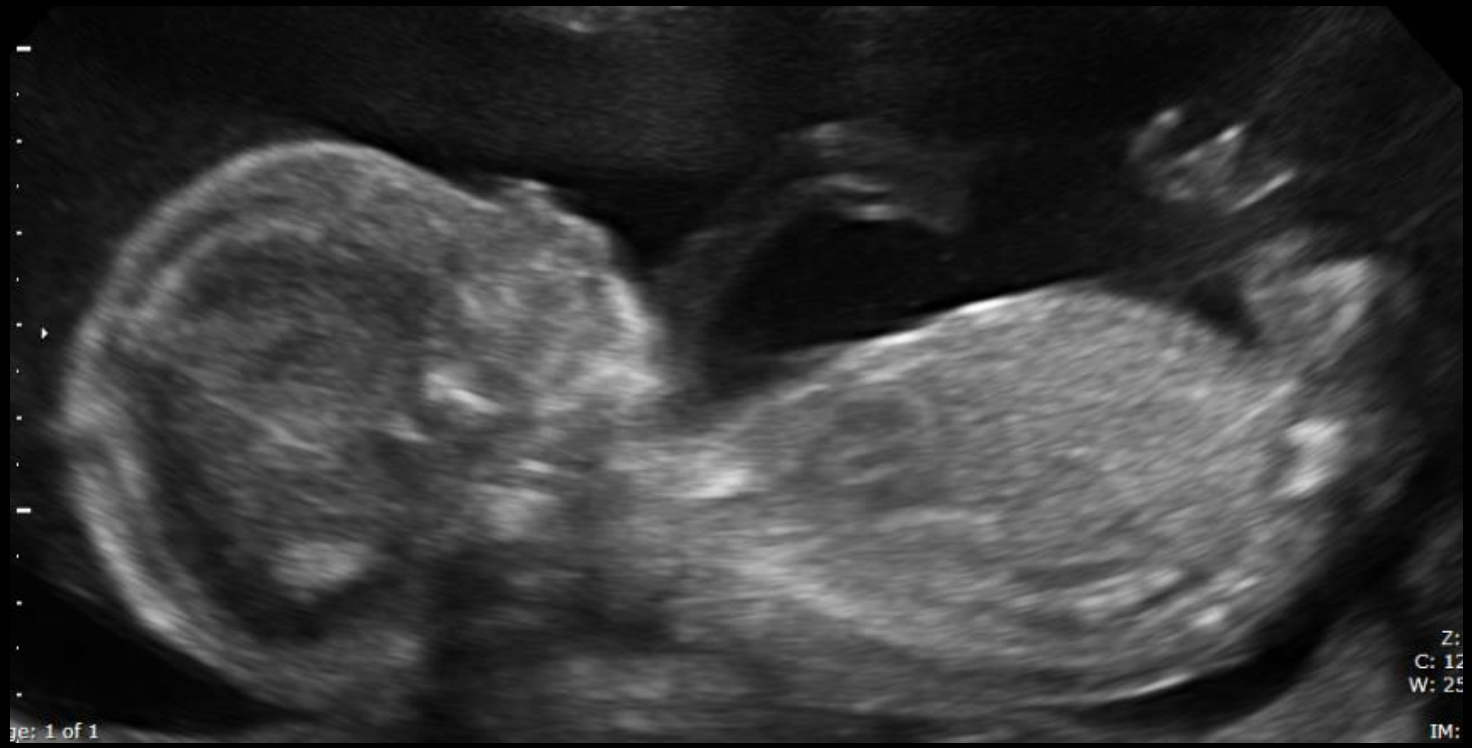
Osteogenesis Imperfecta

- Clinically and genetically heterogeneous disorder
  - Bone fragility and low bone mass
- Seven subtypes
- Severity is as follows
  - Type II >type III >types IV = V = VI = VII >type I
  - Most common prenatal diagnoses - type II or III
  - Only 10% of fetuses with type I have fractures in utero
  - Blue sclerae, abnormal teeth, joint hyperlaxity, adult-onset hearing loss, and normal intelligence
- Prenatal sonographic findings: long bone fractures with callus formation, limb shortening, poor mineralization of the skull, and bent femurs
- Differential diagnosis: campomelic dysplasia, hypophosphatasia, and achondrogenesis
- 90% of cases have mutation in one of the genes that codes for type I procollagen

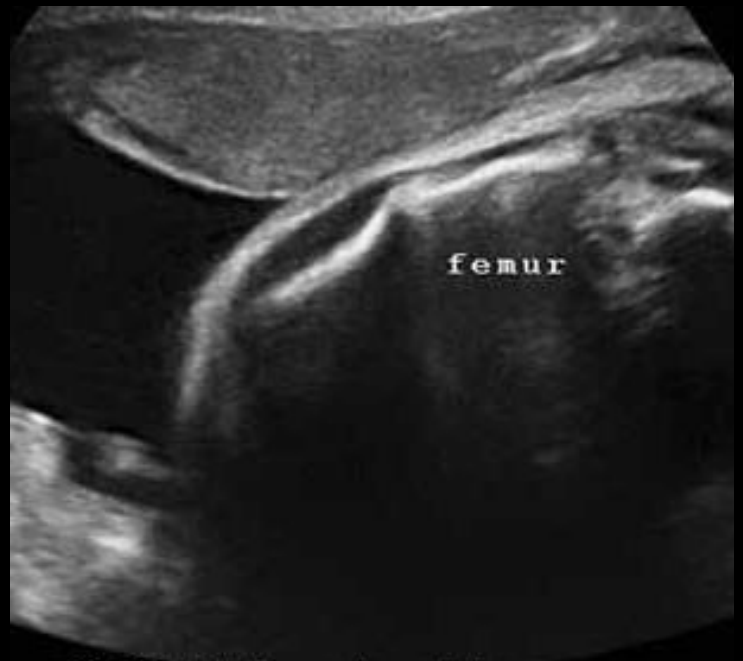
Osteogenesis Imperfecta

- Type II is lethal in utero or in the early neonatal period
  - Can be diagnosed in the 1st trimester
- Types I and IV have fractures, but survive
- Type III
  - May have long bone bowing but normal bone mineralization and normal chest circumference
  - Variable expression; may become apparent after 24 weeks' gestation
- Third trimester polyhydramnios can be present
- In some cases can mimic camptomelic dysplasia
- Most cases dominantly inherited
  - 2006 two additional forms of osteogenesis imperfecta described with AR inheritance

Osteogenesis Imperfecta



Osteogenesis Imperfecta



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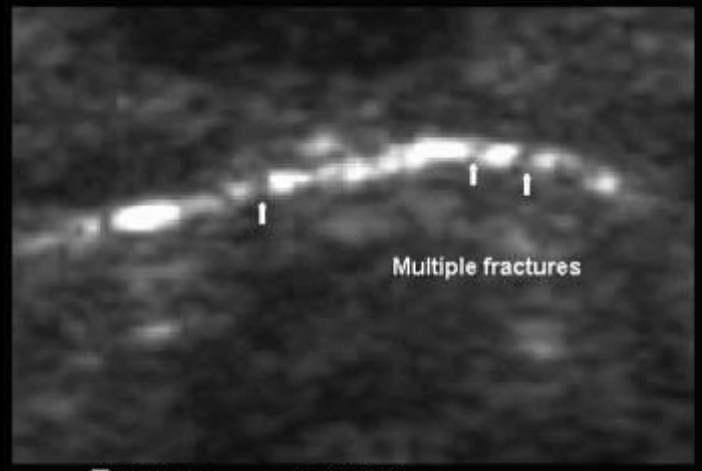
Osteogenesis imperfecta Type III



Femur img007.gif

Bowed femur;
Multiple fracture represented by discontinuities in the femur;
Decreased ossification - no posterior shadowing.

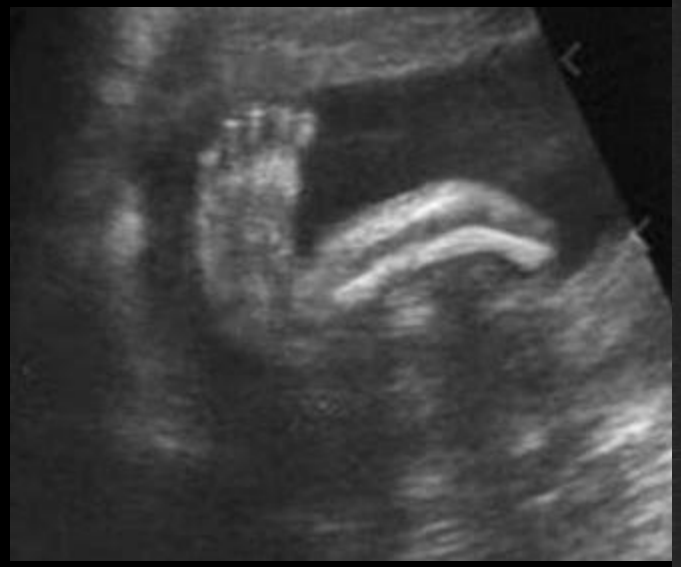
Campomelic Dysplasia

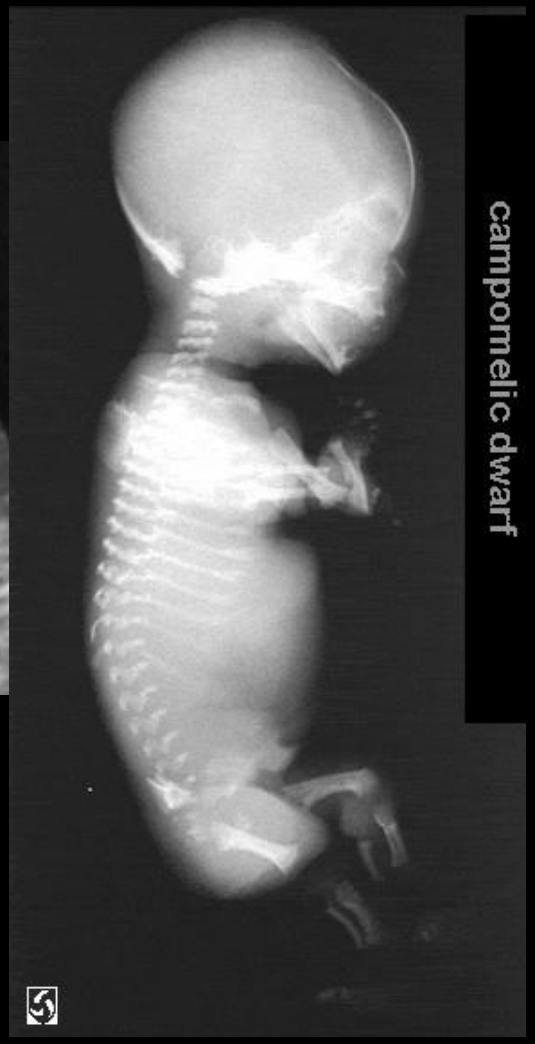
- Bowing of long bones of the lower extremity, phenotypic sex reversal, flat face, micrognathia, cleft palate, renal and cardiac abnormalities
- Incidence is 0.05 to 1.6 per 10,000 livebirths
- Sonographic findings
  - Acute femoral angulation
  - Small bell-shaped chest
  - Marked micrognathia
- Differential diagnosis: osteogenesis imperfecta type II, diastrophic dysplasia, campomelic dysplasia

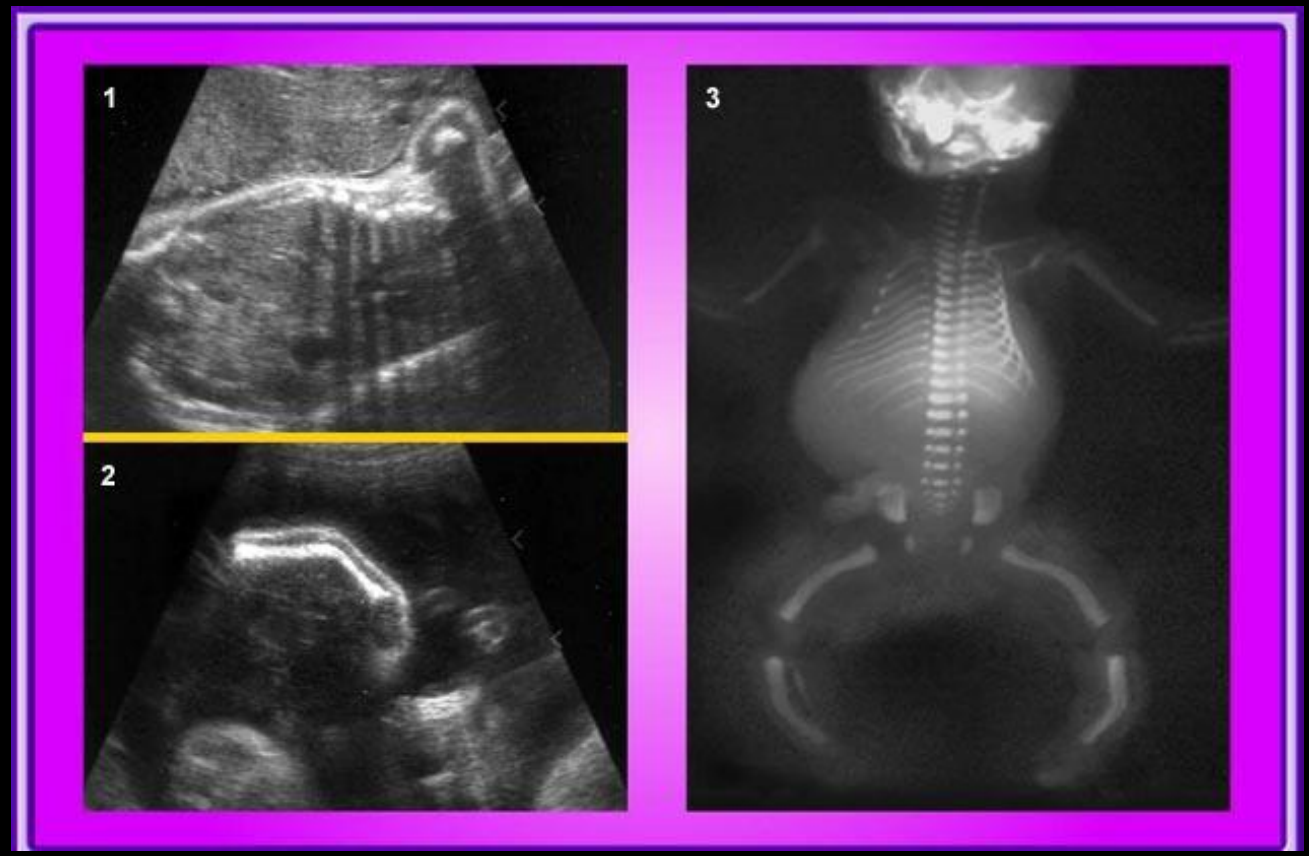
Campomelic Dysplasia

- Fetal karyotype indicated to screen for chromosome 17 rearrangements
  - Better prognosis and to determine chromosomal gender
  - 72% of 46, XY fetuses have female genitalia
- 95% of affected neonates die in perinatal period or during 1st year of life
- Long-term survivors have short stature, recurrent apnea and respiratory infections, progressive kyphoscoliosis, and developmental delay
- Caused by mutations in SOX9, transcription factor in chondrogenesis
- Autosomal dominant disorder

Campomelic Dysplasia



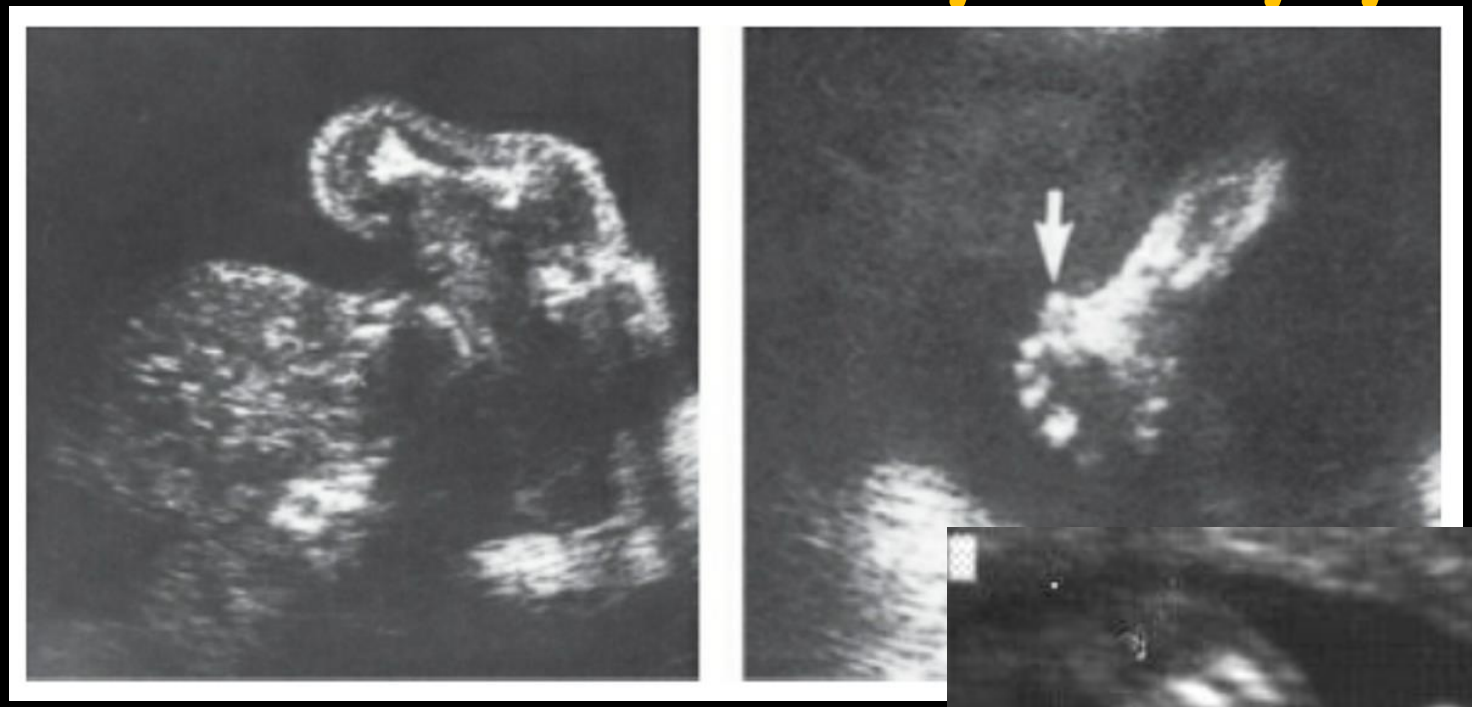


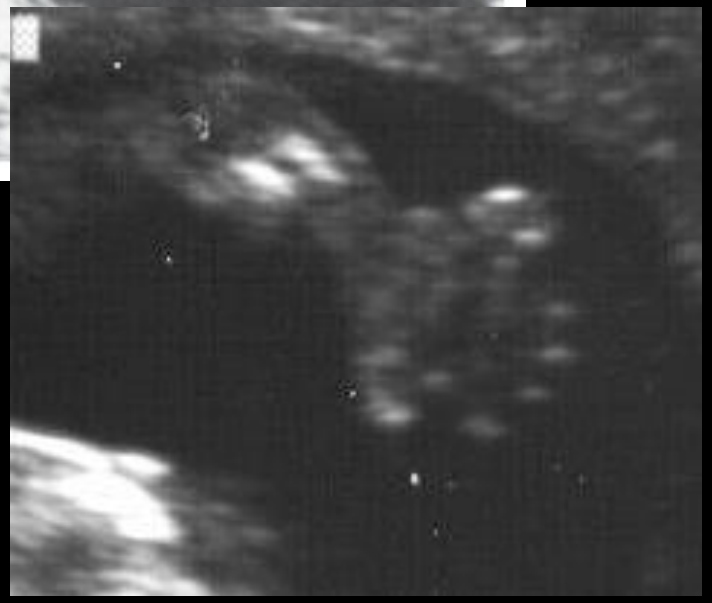


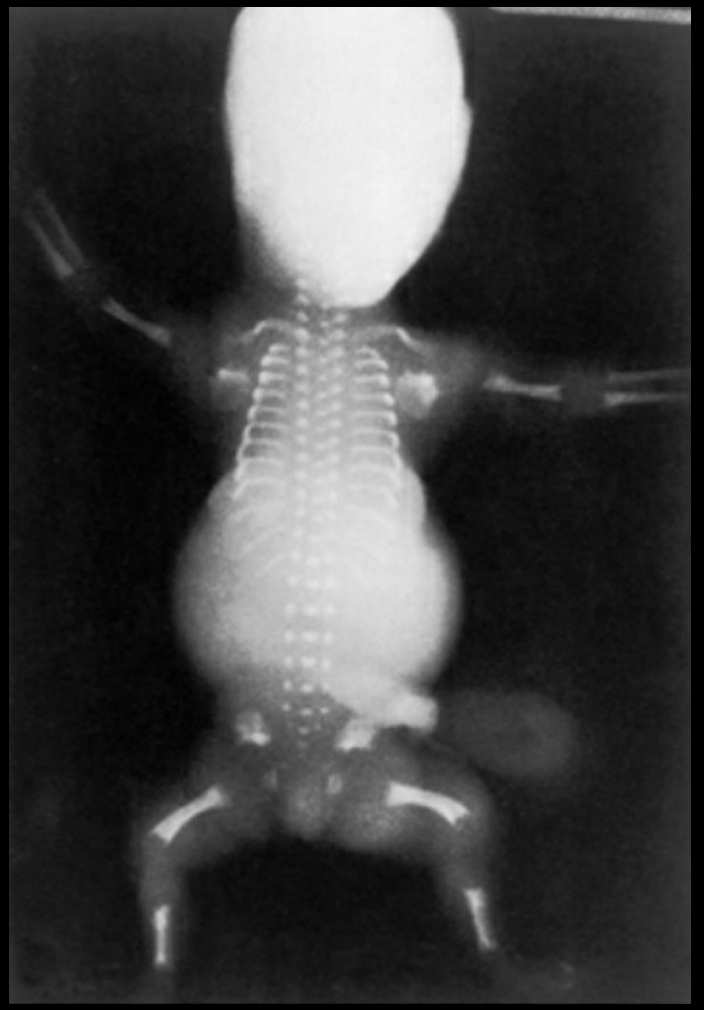
Short-Rib Polydactyly Syndrome

- Group of rare, generally lethal skeletal dysplasias
  - Short limbs
  - Short ribs
  - Polydactyly
- Clinical overlap exists between the four subtypes
- Extremely rare in general population
- Differential diagnosis: Ellis–van Creveld syndrome, asphyxiating thoracic dystrophy (Jeune syndrome), Meckel–Gruber syndrome, and trisomy 13
- All affected infants have severe pulmonary hypoplasia that is lethal
- Chromosomes usually normal
- Genes responsible for these conditions have not yet been identified

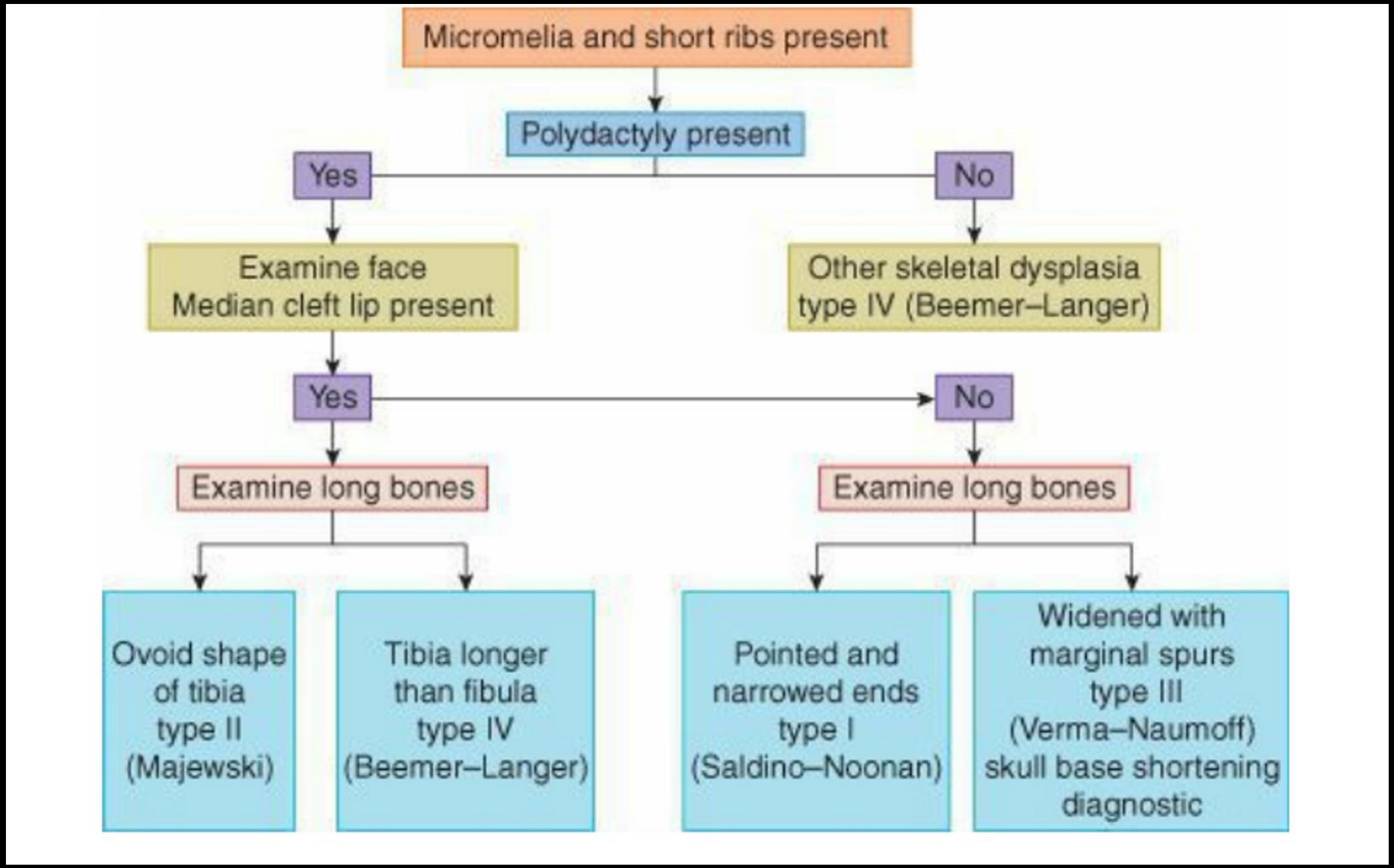
Short-Rib Polydactyly Syndrome







Short long bones
Widened metaphyses with spurs
Polydactyly


Micromelia and short ribs present
Polydactyly present
Yes
No
Examine face
Median cleft lip present
Other skeletal dysplasia
type IV (Beemer–Langer)
Yes
No
Examine long bones
Examine long bones
Ovoid shape
of tibia
type II
(Majewski)
Tibia longer
than fibula
type IV
(Beemer–Langer)
Pointed and
narrowed ends
type I
(Saldino–Noonan)
Widened with
marginal spurs
type III
(Verma–Naumoff)
skull base shortening
diagnostic

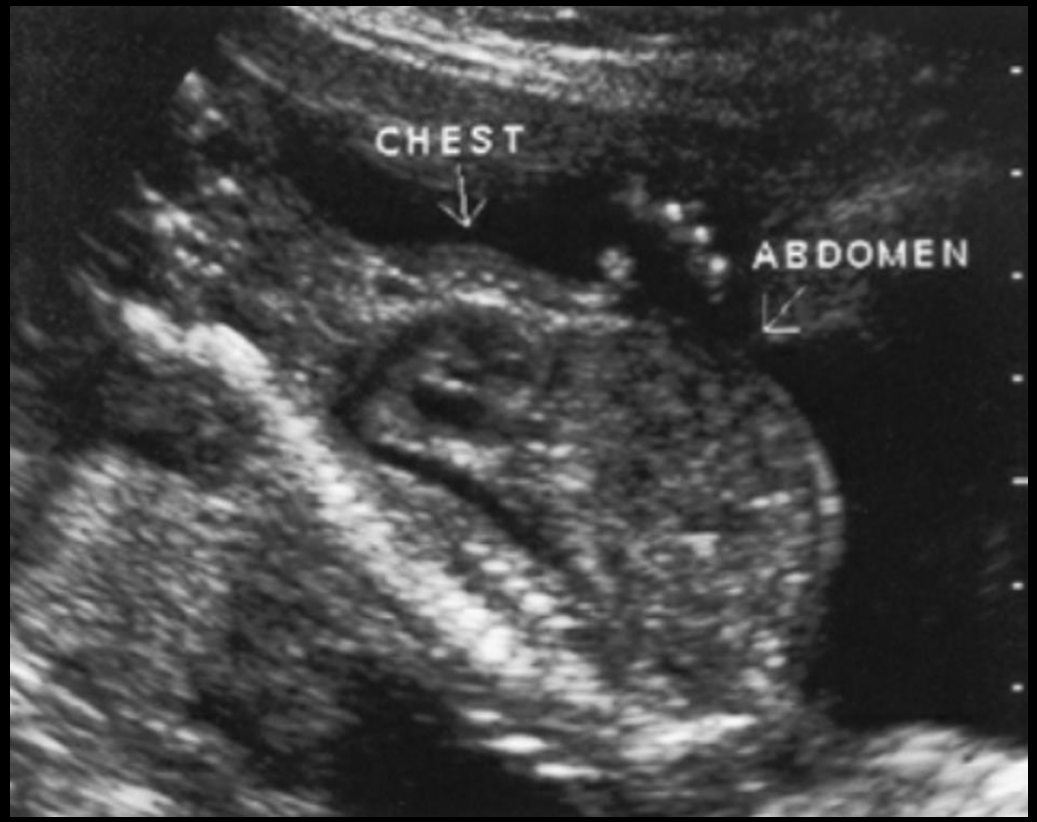
Achondrogenesis

- Second most common lethal short-limb dysplasia
- Incidence is 1/40,000 to 1/50,000 livebirths
- Characteristics
  - Severe micromelia
  - Lack of vertebral ossification
  - Large head with relatively normal ossification of the calvarium
  - Cystic hygroma
  - Polyhydramnios and hydrops fetalis
- Increased incidence of prematurity and stillbirth
- Lethal in perinatal period

Achondrogenesis

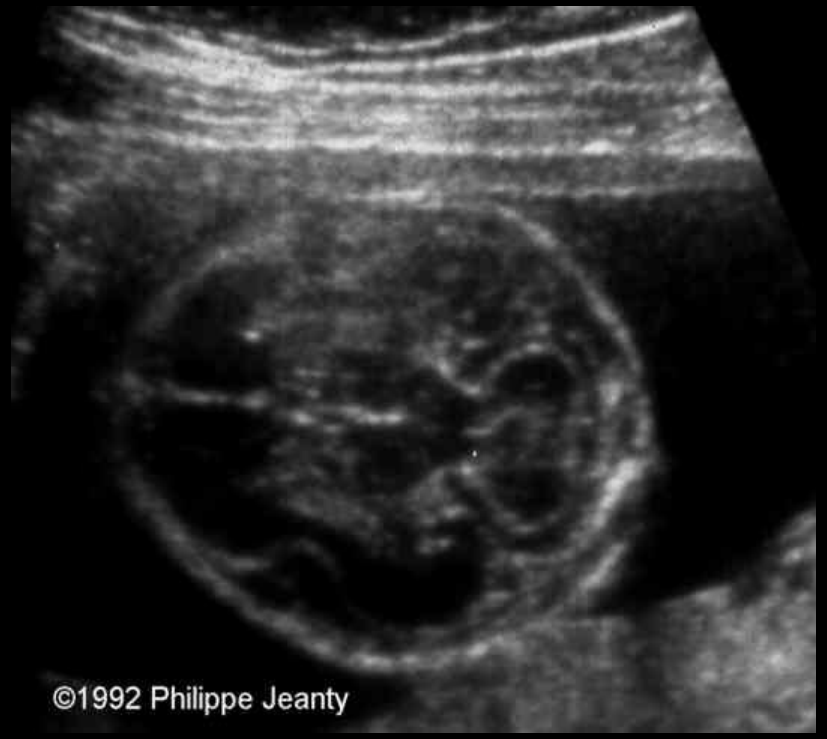
- Defective cartilage formation results in poor ossification
- Type I
  - 20 percent of cases
  - Almost a complete lack of skull ossification
  - Short neck and trunk
  - Type IA
    - Rib fractures
  - Type IB
    - No rib fractures
    - Inheritance pattern is autosomal recessive
- Type II
  - 80% of cases
  - Usually de novo mutation – results in decrease of Type II collagen
  - Greater degree of calcification of the spine and pelvis
  - Normal skull ossification
  - Polyhydramnios and hydrops common

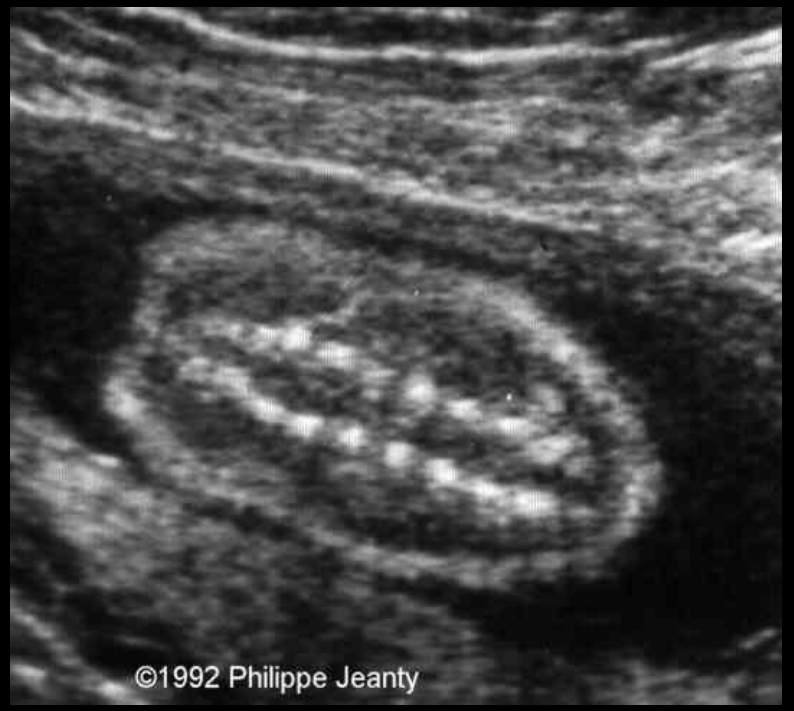
Achondrogenesis

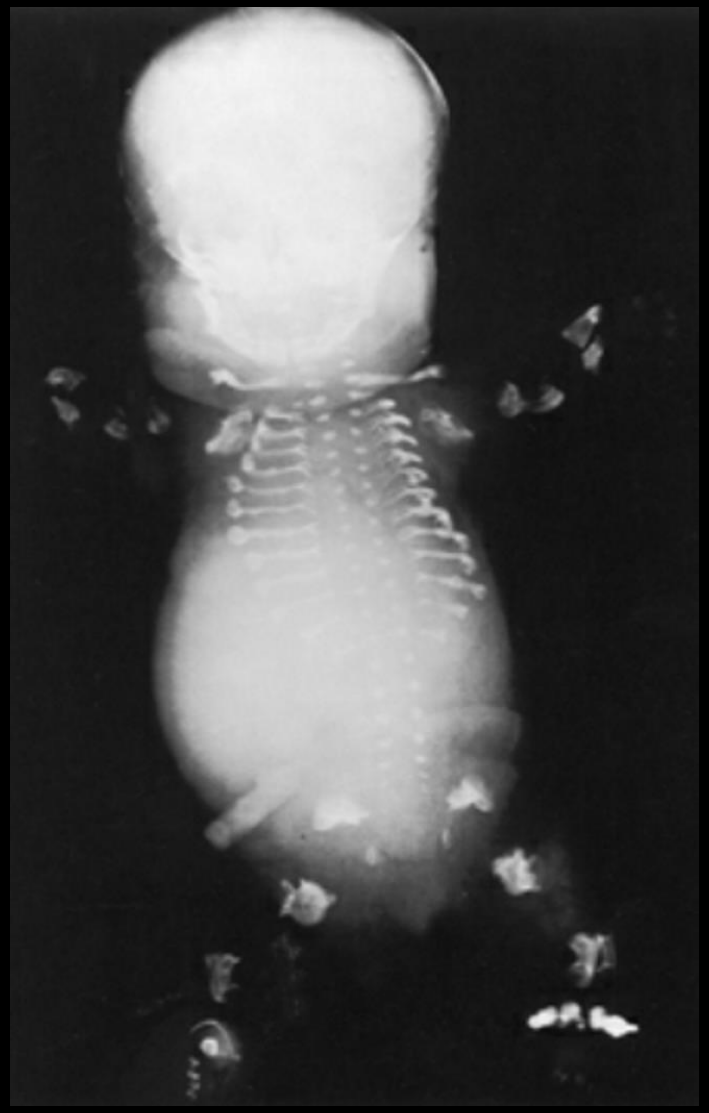


- Narrow chest
- Protuberant abdomen
- Absent rib calcification

Achondrogenesis





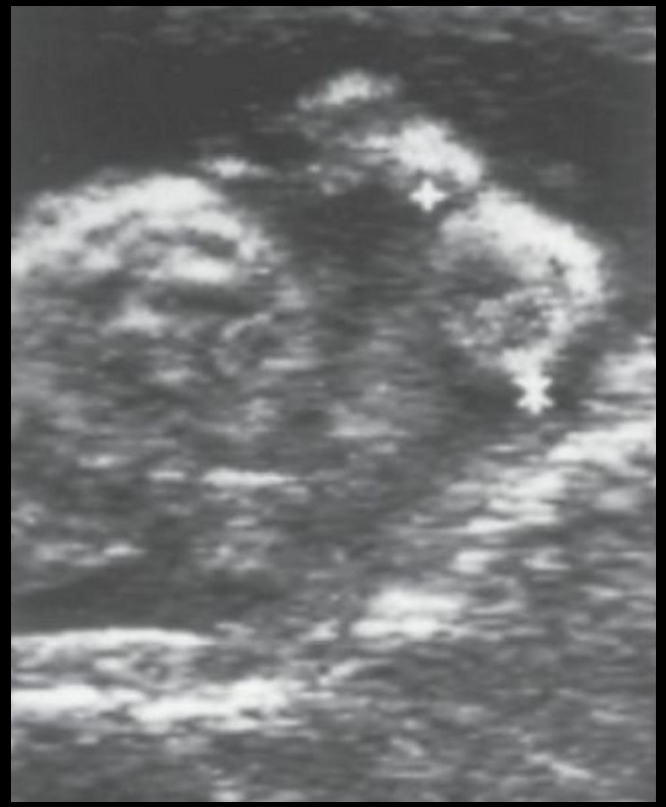


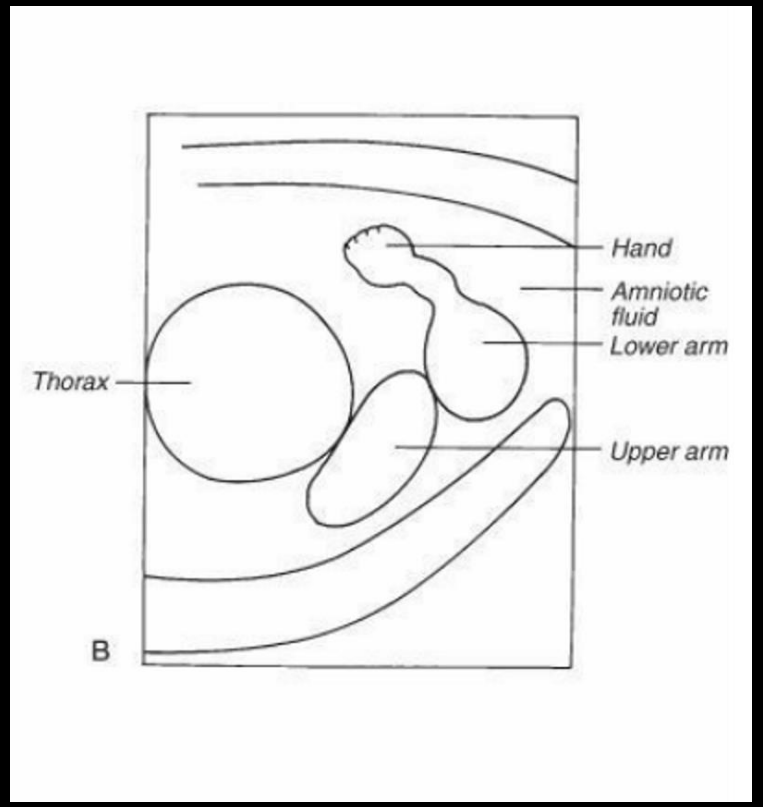
- Poor mineralization of the skull
- Normal mineralization of the spine
- Short ribs with small chest

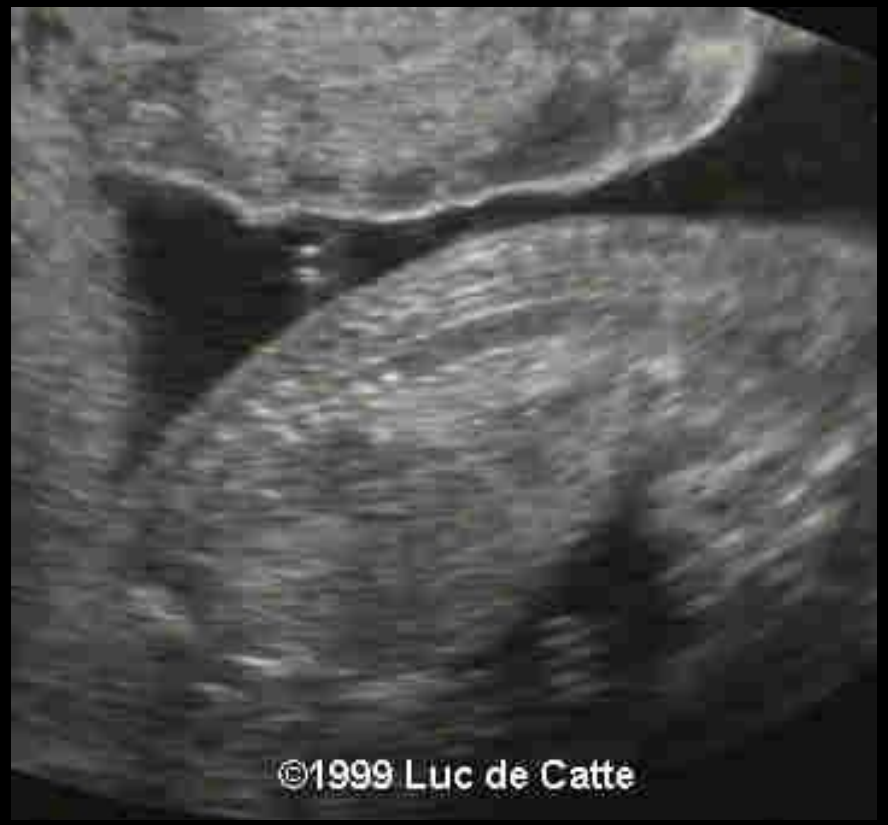
Hypophosphatasia

- Rare hereditary metabolic bone disorder
- Deficient activity of tissue-nonspecific isoenzyme of alkaline phosphatase
- Incidence is 1 in 100,000 births
  - 1 in 2500 in Canadian Mennonites
- Two forms present perinatally
  - Severe (lethal)
    - Increased nuchal translucency
    - Under mineralized calvarium
    - Shortened, bent , fixed limbs with decreased echogenicity
    - Lack of ossification of vertebral bodies and hands
    - Recessive inheritance
  - Benign - resolves spontaneously
    - Symmetric bowing of long bones
    - Dominantly inheritance

Hypophosphatasia





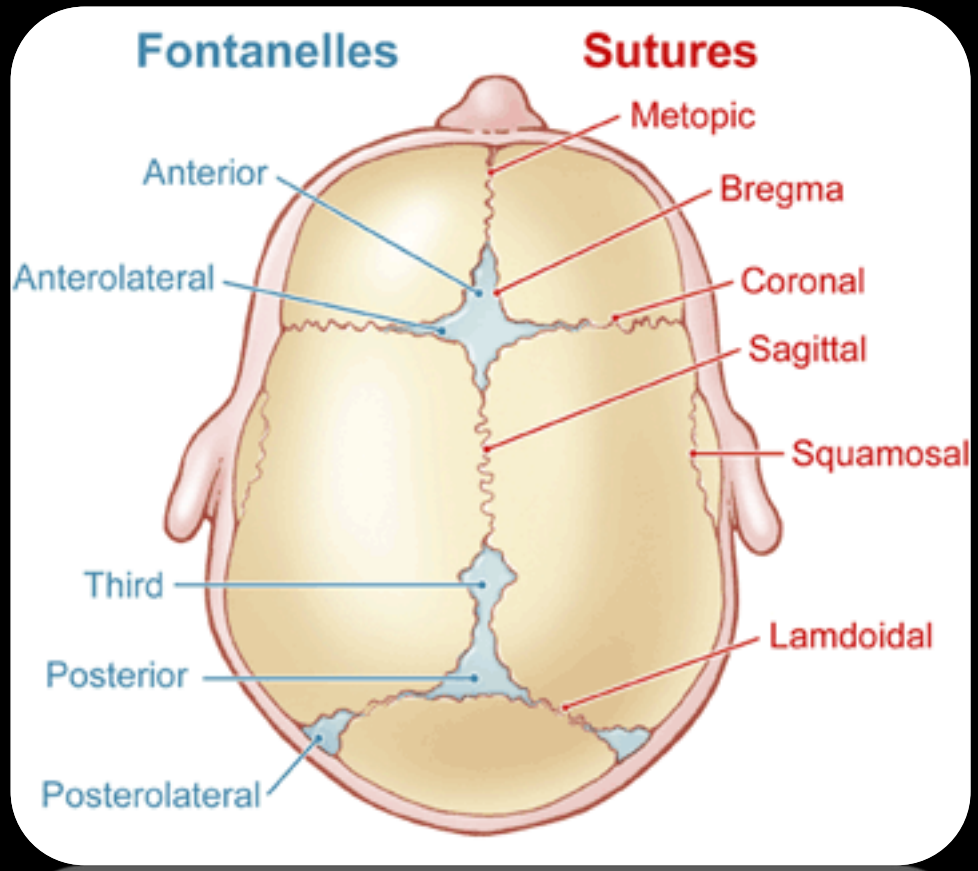


Hypophosphatasia

- Inborn error of metabolism
- Perinatal HPP
  - Features noted at birth or before based on a prenatal ultrasound
  - Skeletal abnormalities and hypomineralized bones
  - Almost universally fatal in the neonatal period
- Infantile HPP
  - Diagnosed by 6 months of age
  - Characteristic changes of rickets on X-ray, fractures often present
  - Infants fail to grow appropriately, can experience vitamin B-6 responsive seizures.; hypercalcemia, nephrocalcinosis
  - Mortality is high
- Childhood HPP
  - Diagnosed when disease manifests after 6 months of age
  - Delay in gross motor milestones and a static myopathy; premature loss of deciduous teeth (before 5 years of age) with the root intact
  - Radiographs reveal changes of rickets and a radiolucent band extending from growth plate into the metaphysis
- Adult HPP
  - Recurrent or slow-to-heal metatarsal fractures or subtrochanteric femoral pseudofractures
- Odontohypophosphatasia
  - Least severe form
  - Diagnosed when dental abnormalities

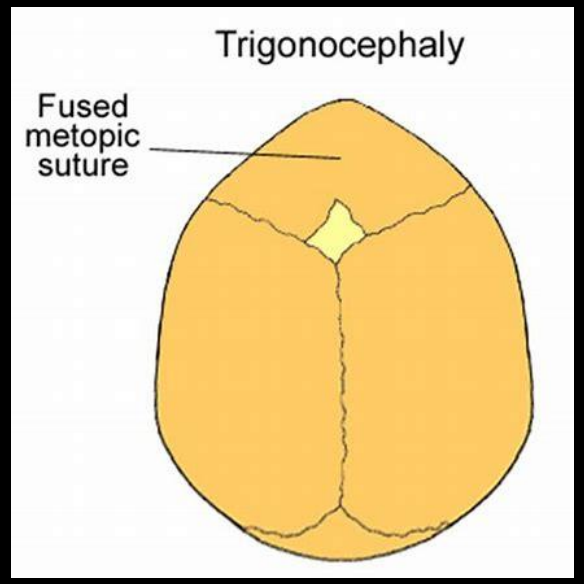
Abnormalities of the Calvarium

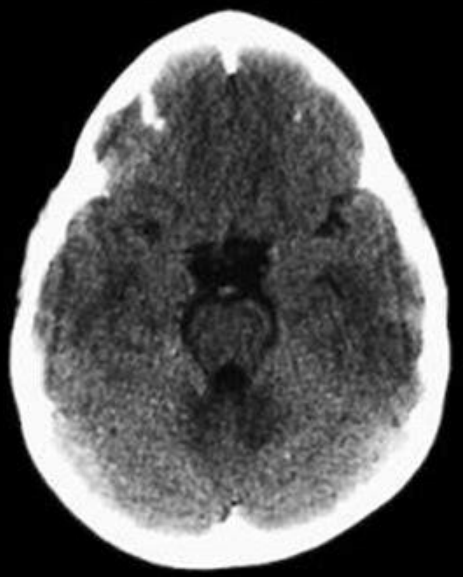
- Craniosynostosis
  - Trigonocephaly
    - Trisomy 13
  - Cloverleaf skull
    - Thanatophoric dysplasia
- Lemon sign
  - Neural tube defect
    - Chiari II malformation
- Strawberry Skull
  - Trisomy 18

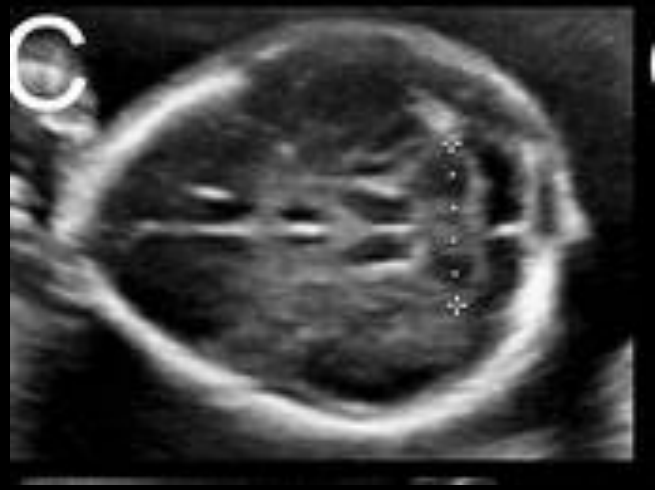


Trigonocephaly

- Associated with Trisomy 13
  - Premature closure of the metopic sutures

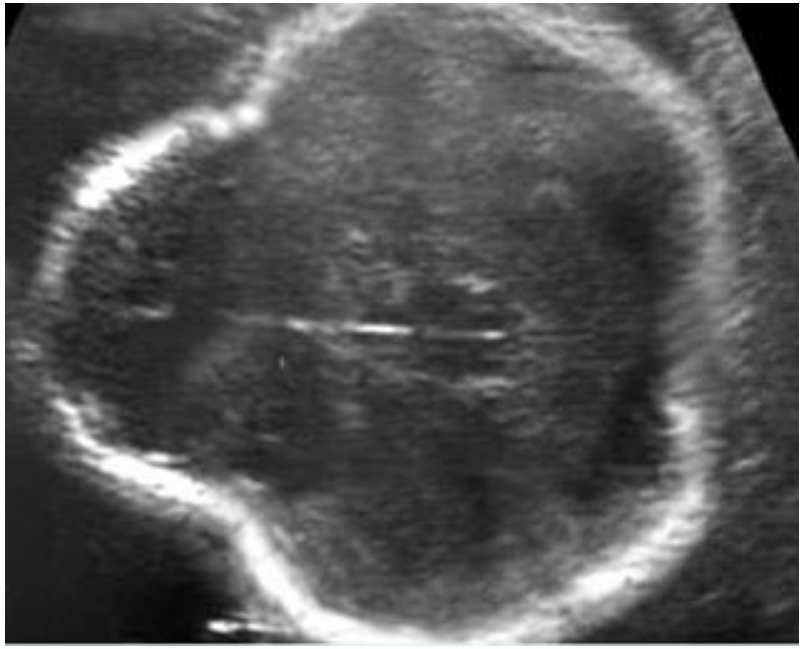


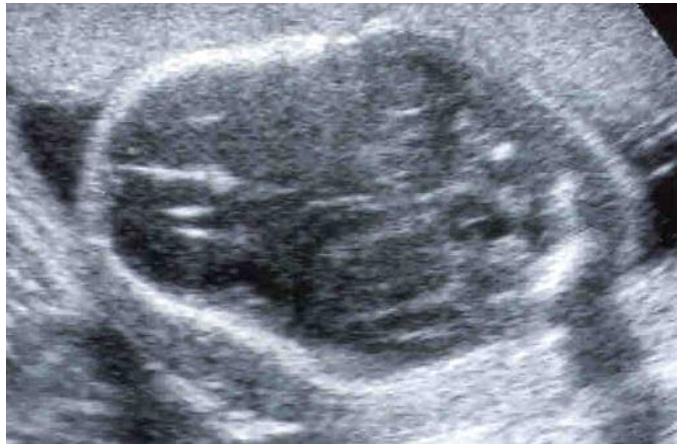


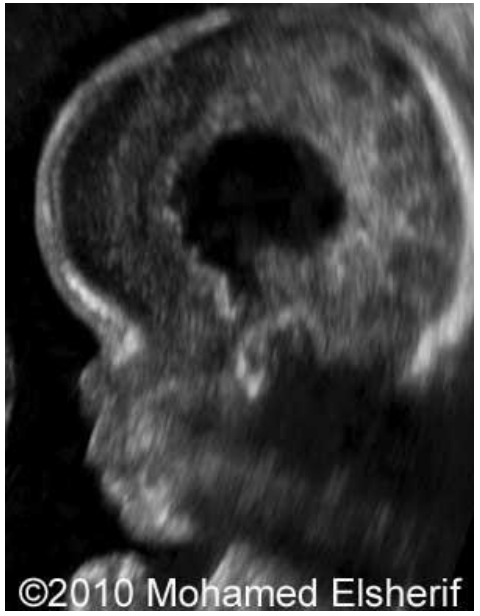


Cloverleaf Skull

- Skeletal Dysplasia
  - Thanatophoric dwarfism
- Craniosynostosis

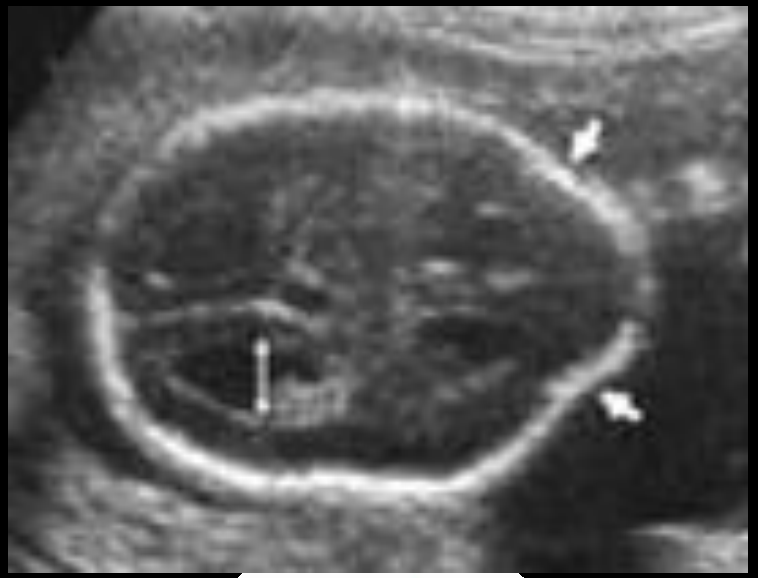


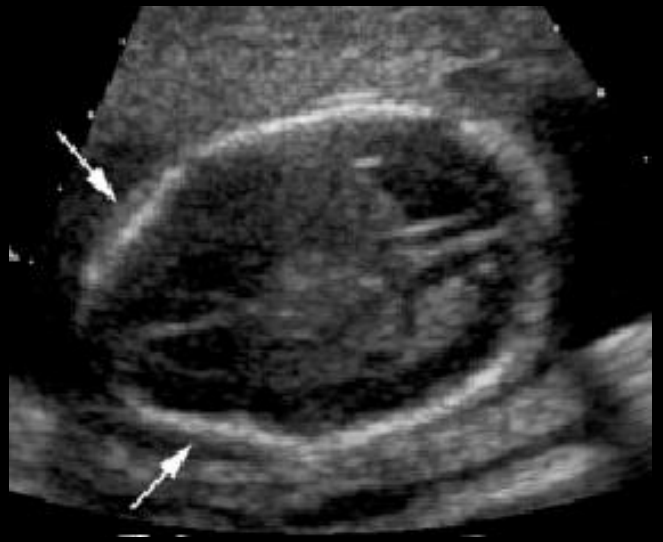


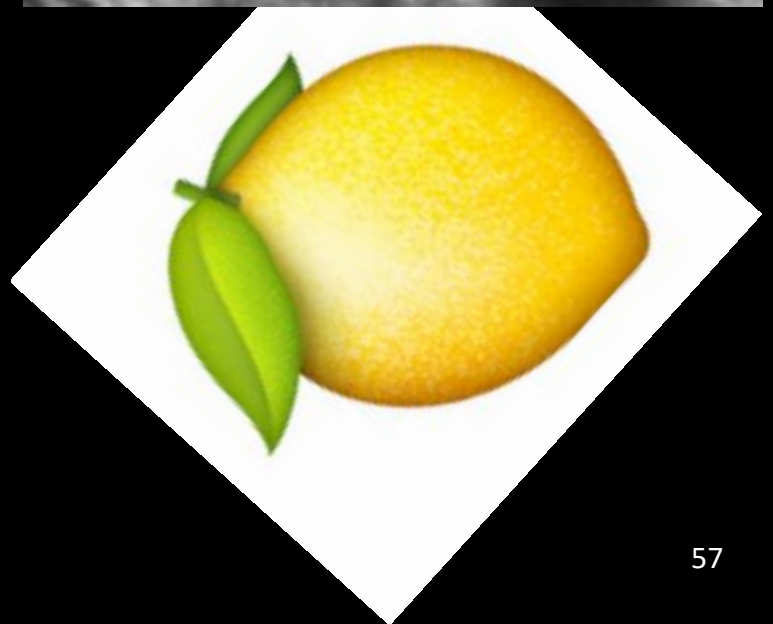


The Lemon Sign

- Neural tube defect
- Skull defect
- Normal variant
  - Rarely

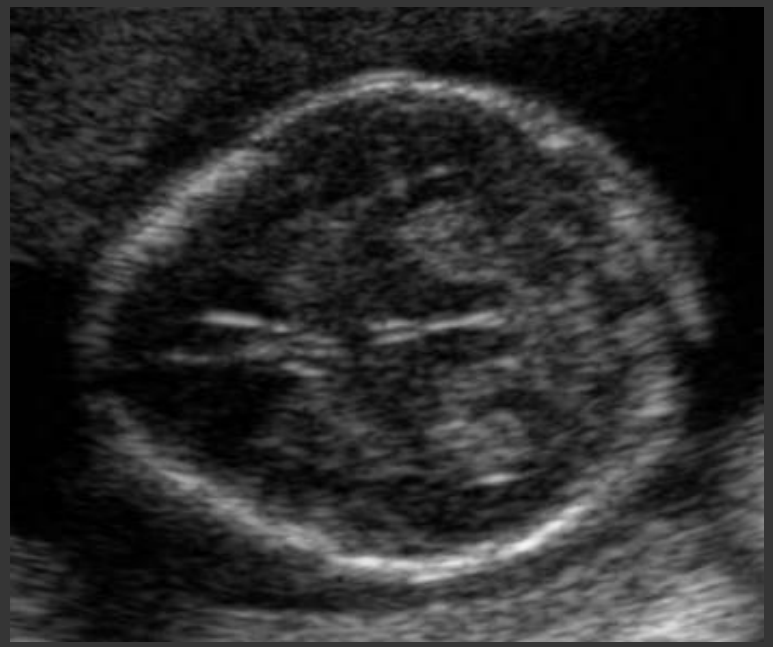






Strawberry Skull

- Associated with Trisomy 18 (Edwards Syndrome)



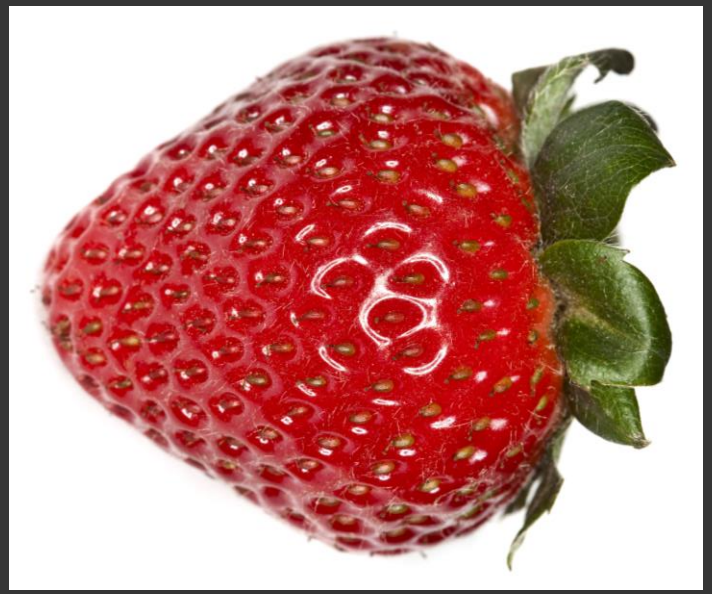


TABLE I. INHERITANCE OF SKELETAL DYSPLASIAS.

Usually Lethal Dysplasia	**Mode of Inheritance**
Achondrogenesis	AR
Short-rib polydactyly	AR
Osteogenesis imperfecta	AD*, AR
Congenital hypophasphatasia	AR
Usually Non-lethal Dysplasia	
Camptomelic dysplasia	AR
Achondroplasia	AD
Diastrophic dysplasia	AR
Asphyxiating thoracic dysplasia	AR

Derived from: Wigglesworth JS, Singer DB. Textbook of Fetal and Perinatal Pathology. Oxford:Blackwell Scientific, 1991;1176.

*Majority of cases are new mutations.


POSITIS SIGNIS ET ANA
MENTIS XIII PONT MAX OPVS CVM