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Skeletal Dysplasia- Determining Lethality

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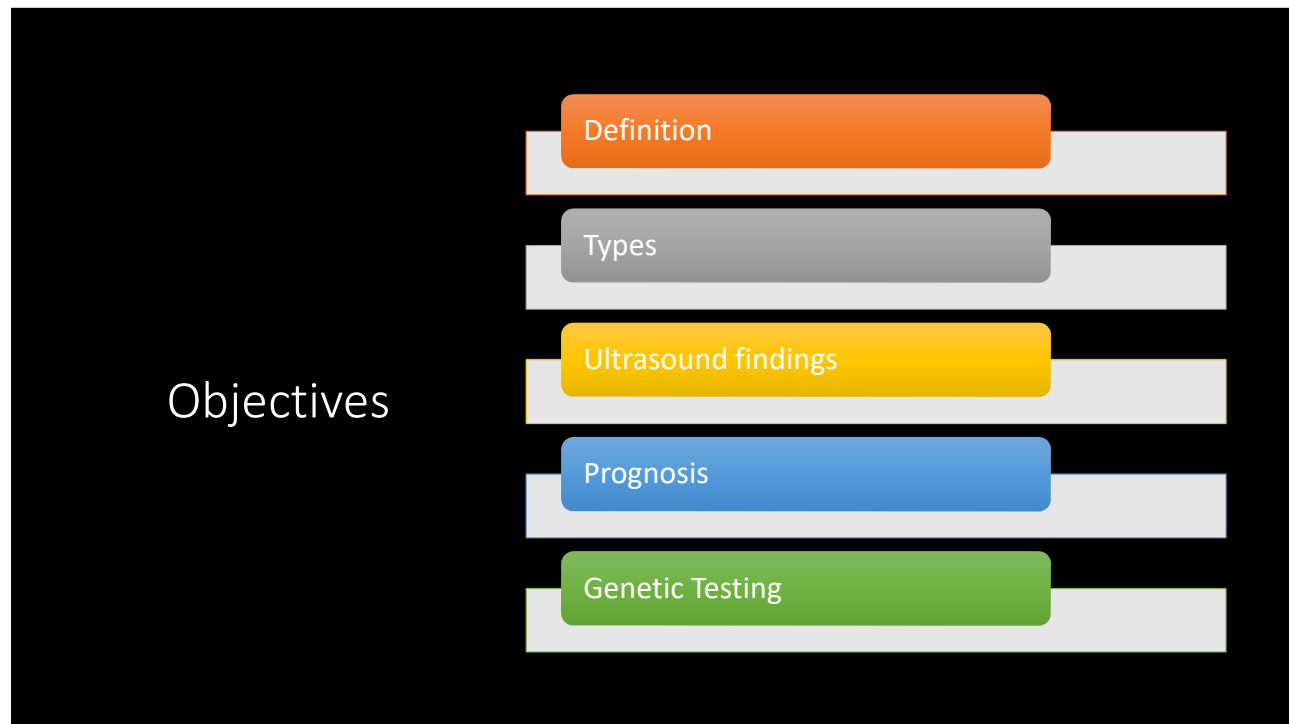
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Definition

"Skeletal dysplasias are a complex group of bone and cartilage disorders that may affect the fetal skeleton as it develops in utero."

Children's' Hospital of Philadelphia

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Incidence

- Estimated 15.7 in 100,000 births
- Classification and understanding of pathophysiology has improved
 - Molecular studies
 - Gene discoveries
- Over 771 disorders
 - 42 groups

Unger S, Ferreira CR, Mortier GR, Ali H, Bertola DR, Calder A, Cohn DH, Cormier-Daire V, Girisha KM, Hall C, Krakow D, Makitie O, Mundlos S, Nishimura G, Robertson SP, Savarirayan R, Silience D, Simon M, Sutton VR, Warman ML, Superti-Furga A. Nosology of genetic skeletal disorders: 2023 revision. Am J Med Genet A. 2023 May;191(5):1164-1209. doi: 10.1002/ajmg.a.63132. Epub 2023 Feb 13. PMID: 36779427; PMCID: 1000000000000000

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Etiology and Background

- Genetic variants
- Extrinsic causes
 - Exposure to drugs
 - Diabetes- poor glycemic control
 - Autoimmune disease
- 5% of genetic disorders
- 456 known conditions
 - 50% lethal



Offiah AC. Skeletal Dysplasias: An Overview. Endocr Dev. 2015;28:259-276. doi: 10.1159/000381051. Epub 2015 Jun 12. PMID: 26138847.

Mortier GR, Cohn DH, Cormier-Daire V, Hall C, Krakow D, Mundlos S, Nishimura G, Robertson S, Sangiorgi L, Savarirayan R, Silience D, Superti-Furga A, Unger S, Warman ML. Nosology and classification of genetic skeletal disorders: 2019 revision. Am J Med Genet A. 2019 Dec;179(12):2393-2419. doi: 10.1002/ajmg.a.61366. Epub 2019 Oct 21. PMID: 31633310.

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Ultrasound

- *Difficult to diagnose specific disorders*
- Over 200 skeletal elements throughout the human body
- Each skeletal dysplasia is rare
- Overlap and similar findings in disorders
- Variable timing of when US features appear
 - Some findings not apparent until the 3rd trimester

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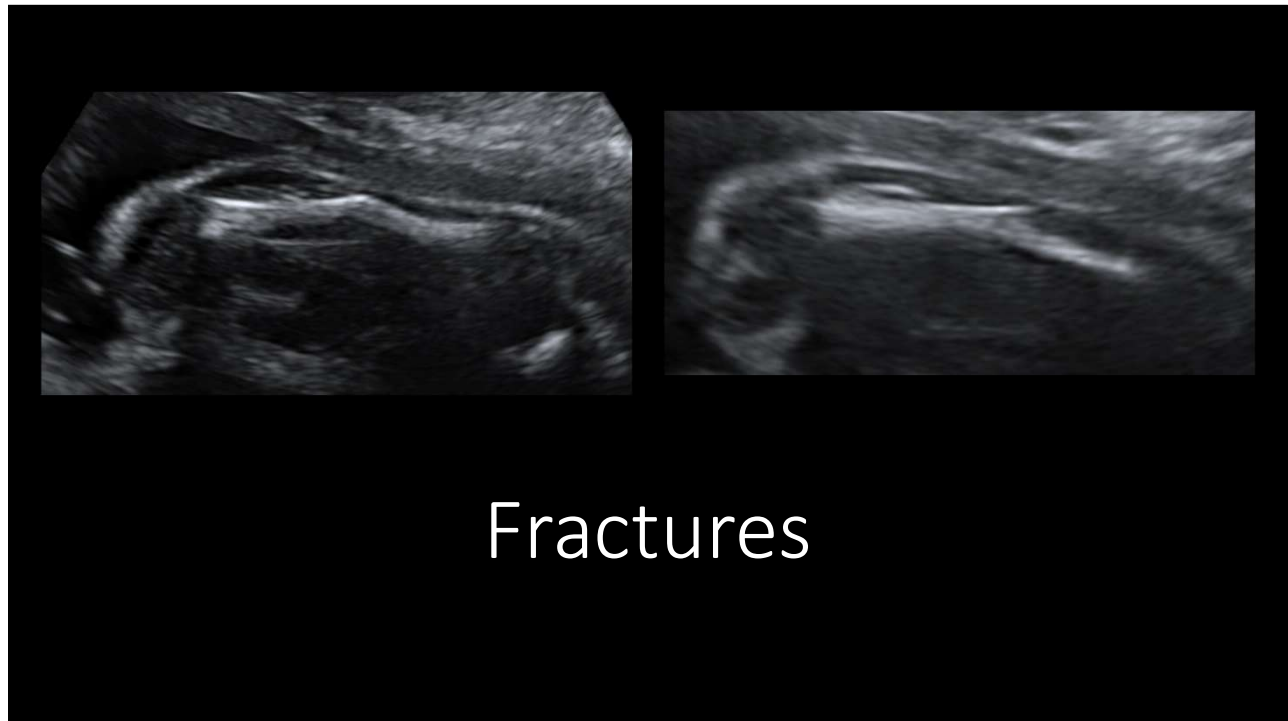
Components of Ultrasound Evaluation

- Pattern of limb shortening
- Shape
- Mineralization/ presence of fractures
- Absence of long bones
- Joint deformities



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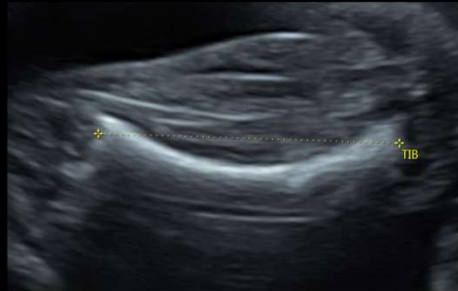
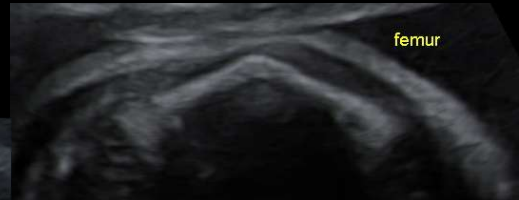
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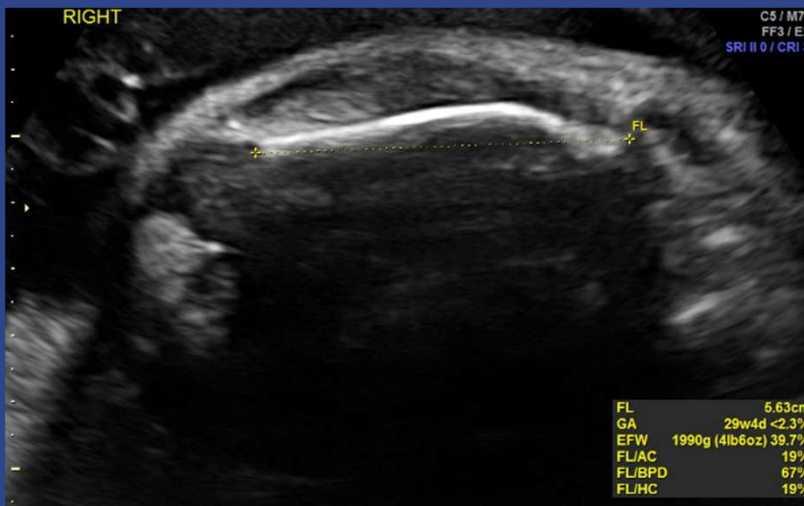
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Shape of bone

- Bent, bowed, or straight
- Unilateral or bilateral



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33 + 3 weeks.

2 Previous babies
with bowed femurs.

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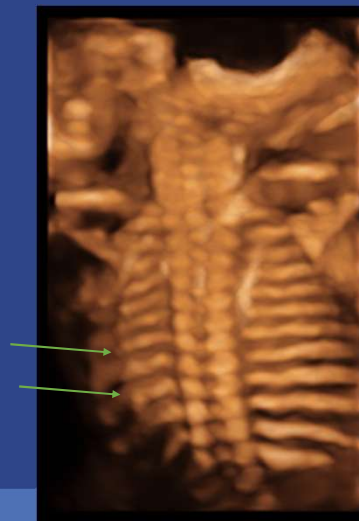
Other Bone Evaluation

- Spine
- Hands and Feet
- Calvarium
- Face
- Ribs
- Scapula



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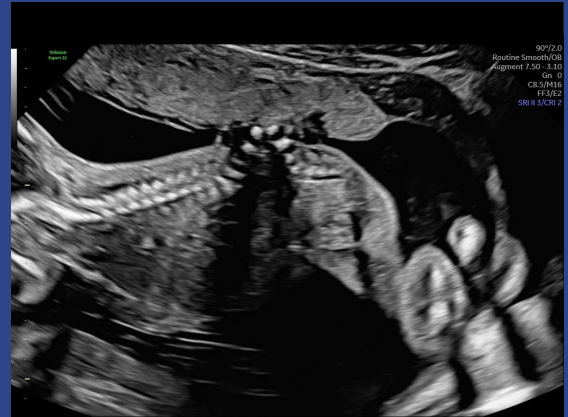
Fractured ribs



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Kyphosis



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Kyphosis Case



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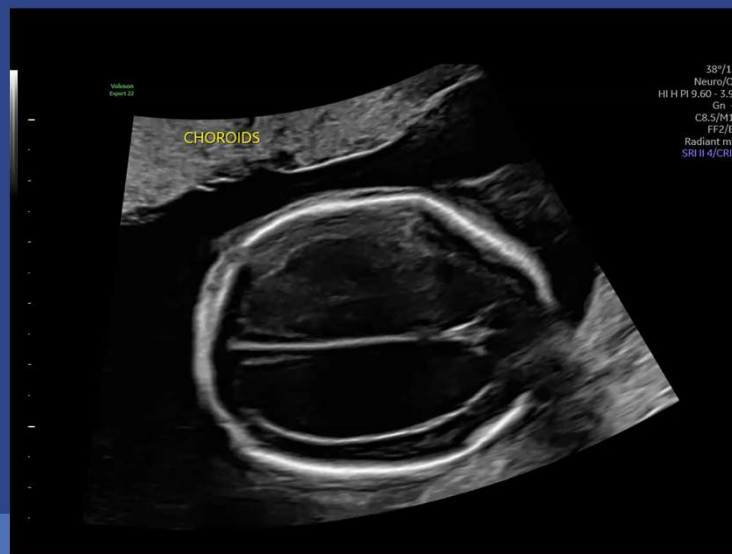
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Kyphosis Case



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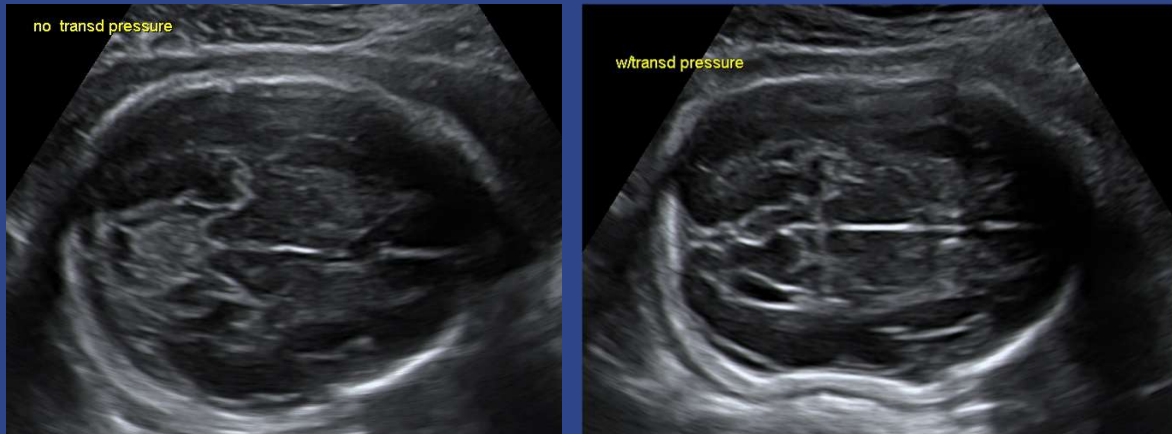
Kyphosis Case



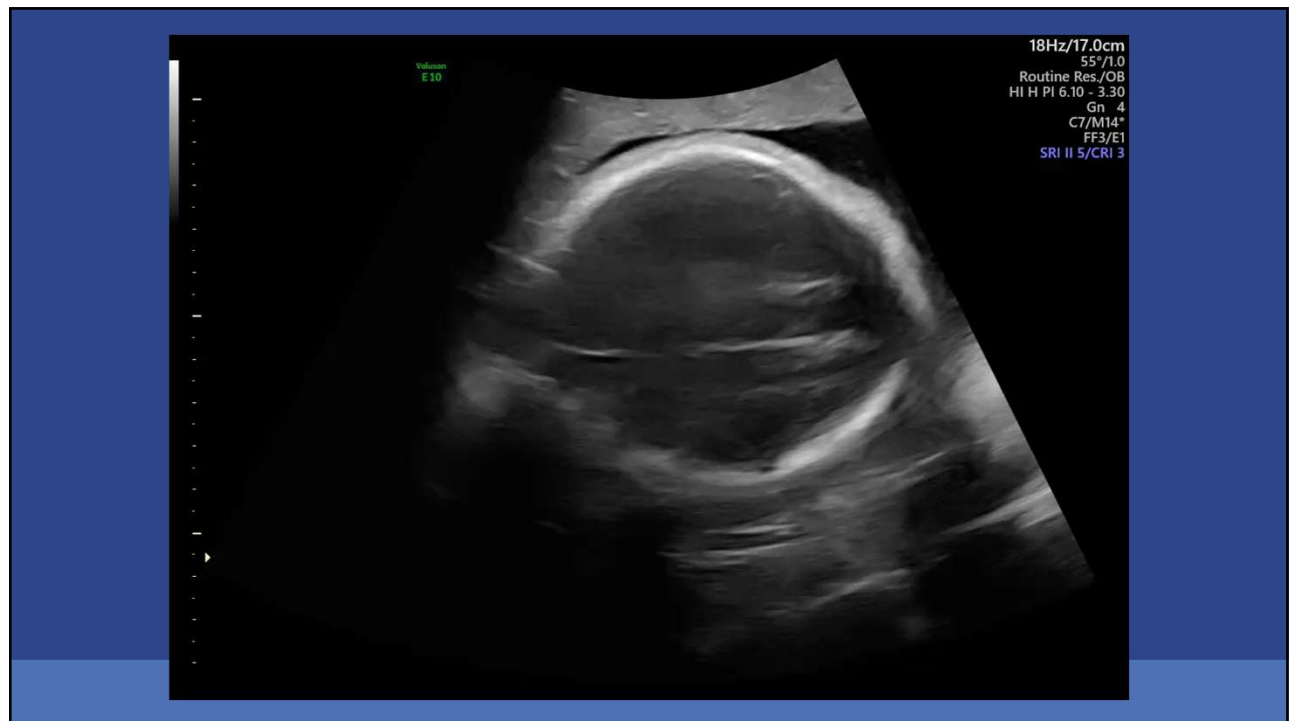
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Easy to deform/demineralization



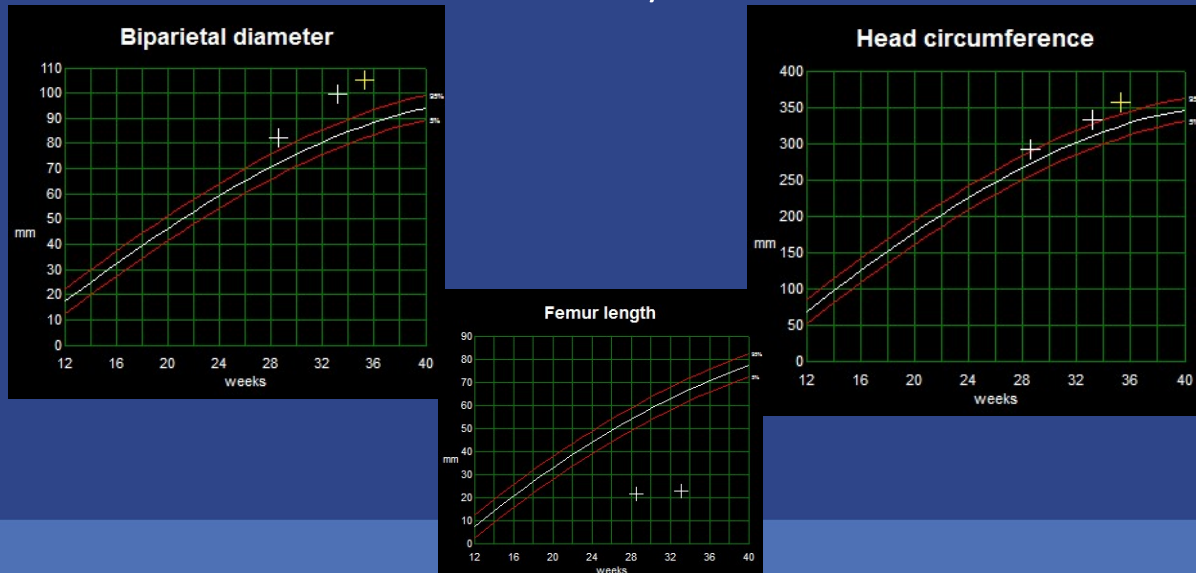
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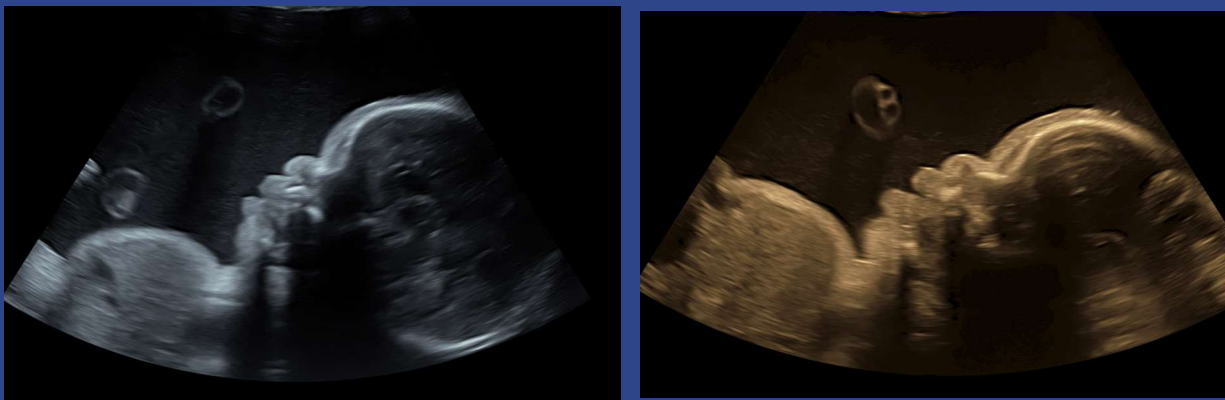
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Abnormal head biometry



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Profile



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Micrognathia



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Polydactyly



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Clubbing



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Clubbing



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Clubbing, polydactyly and syndactyly



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Arthrogryposis



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One hand missing (Acromelia)



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Evaluate Amniotic Fluid

- Polyhydramnios
 - Severity directly proportional to severity of dysplasia



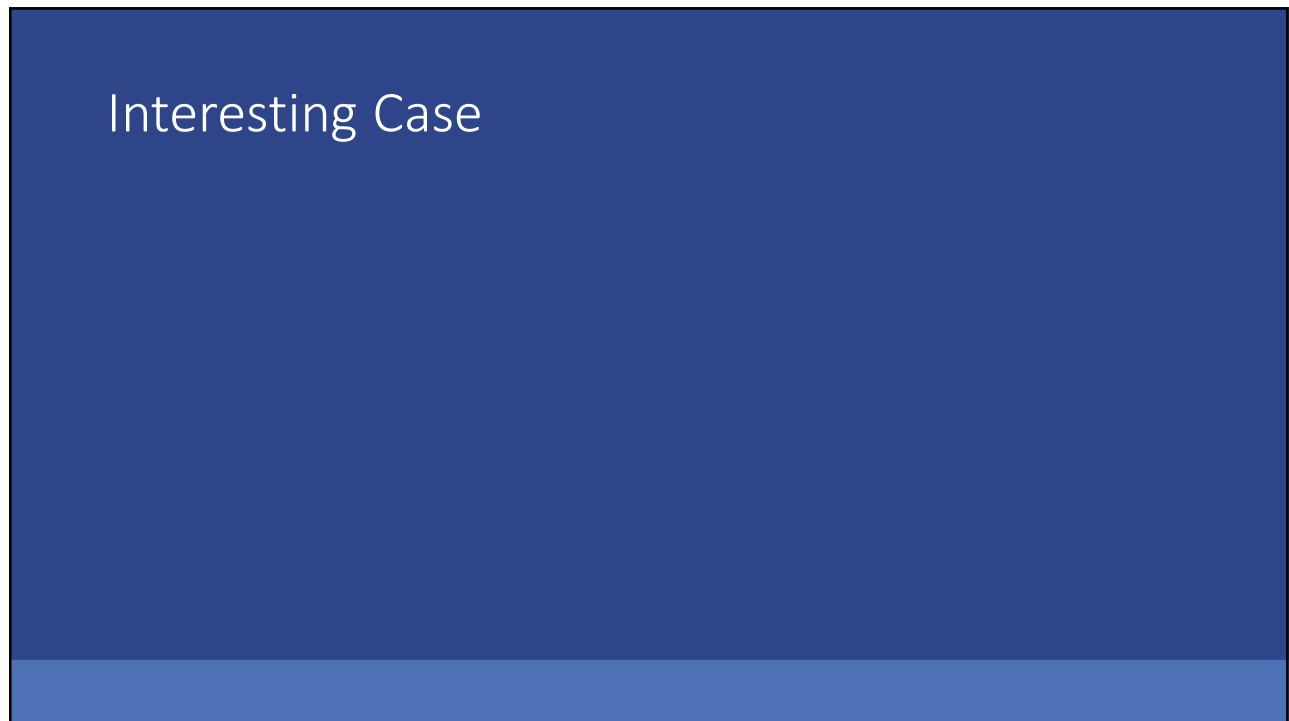
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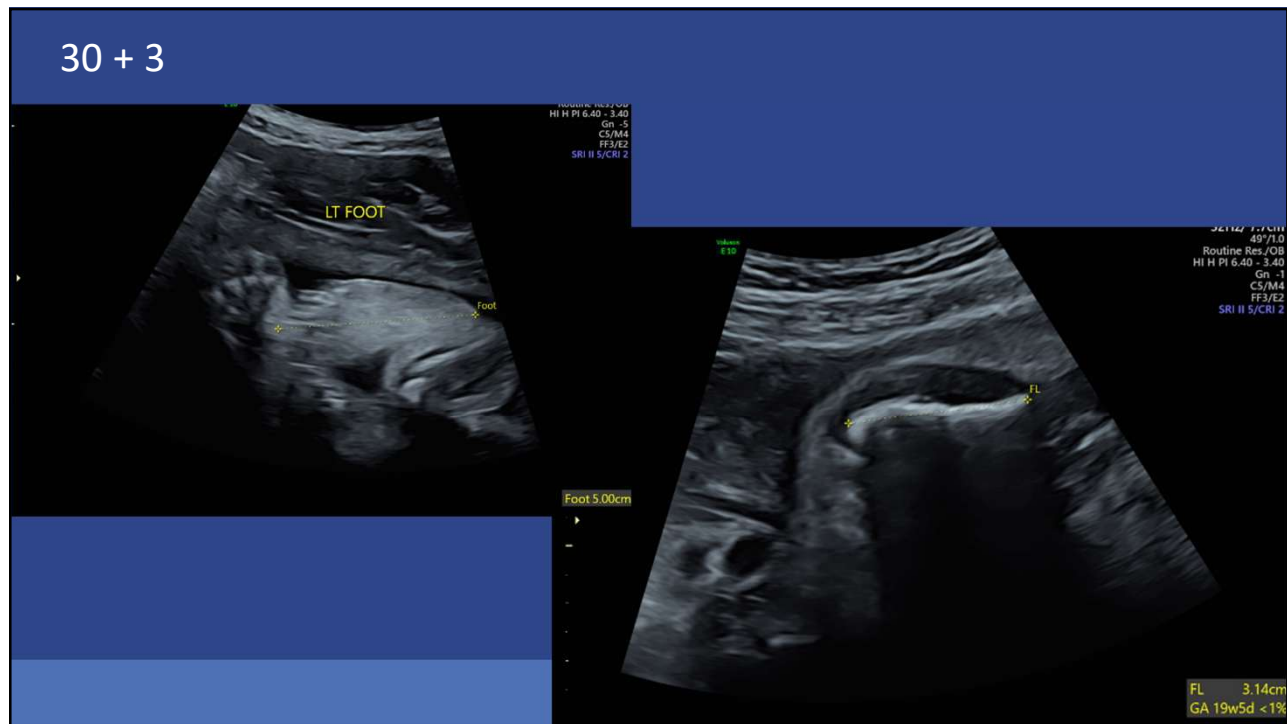


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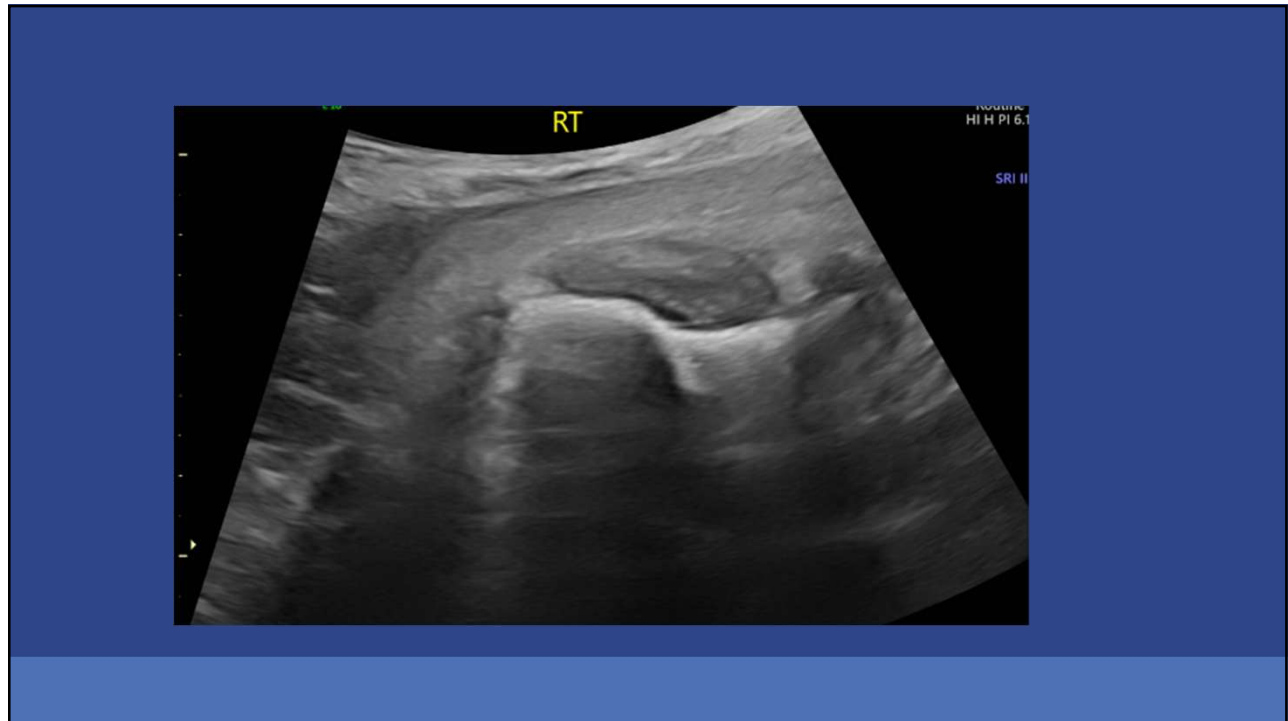


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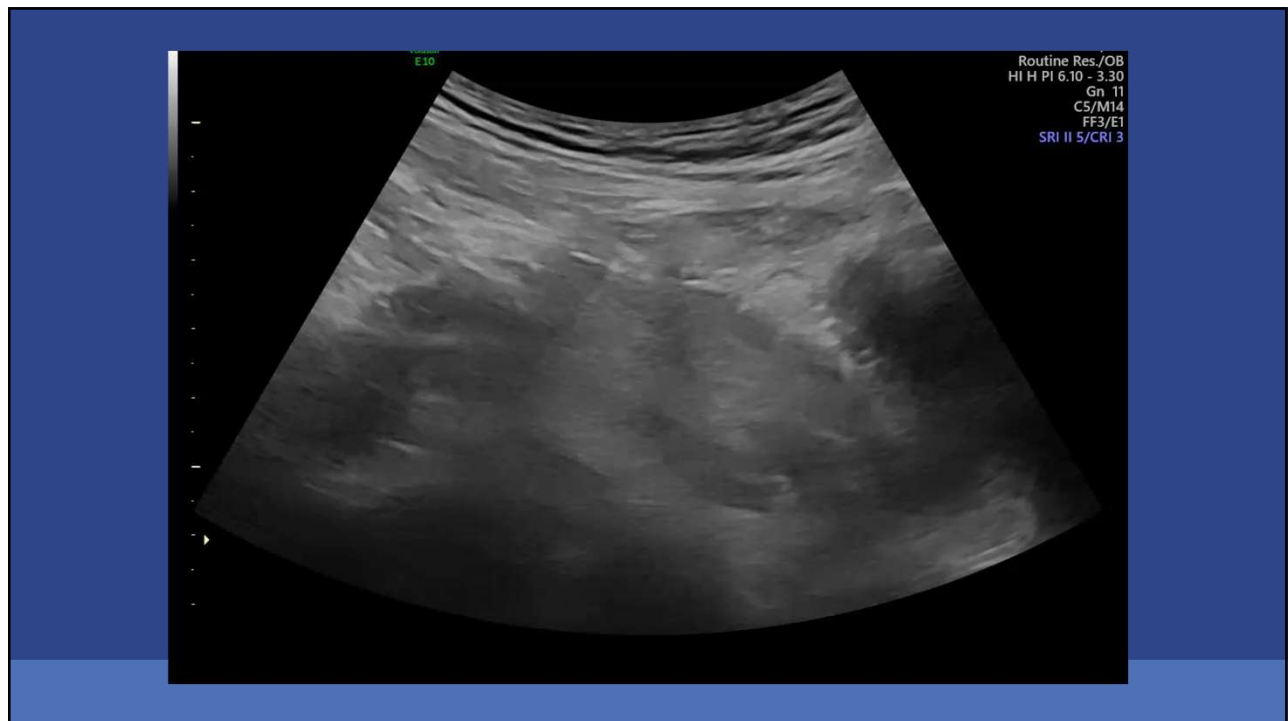


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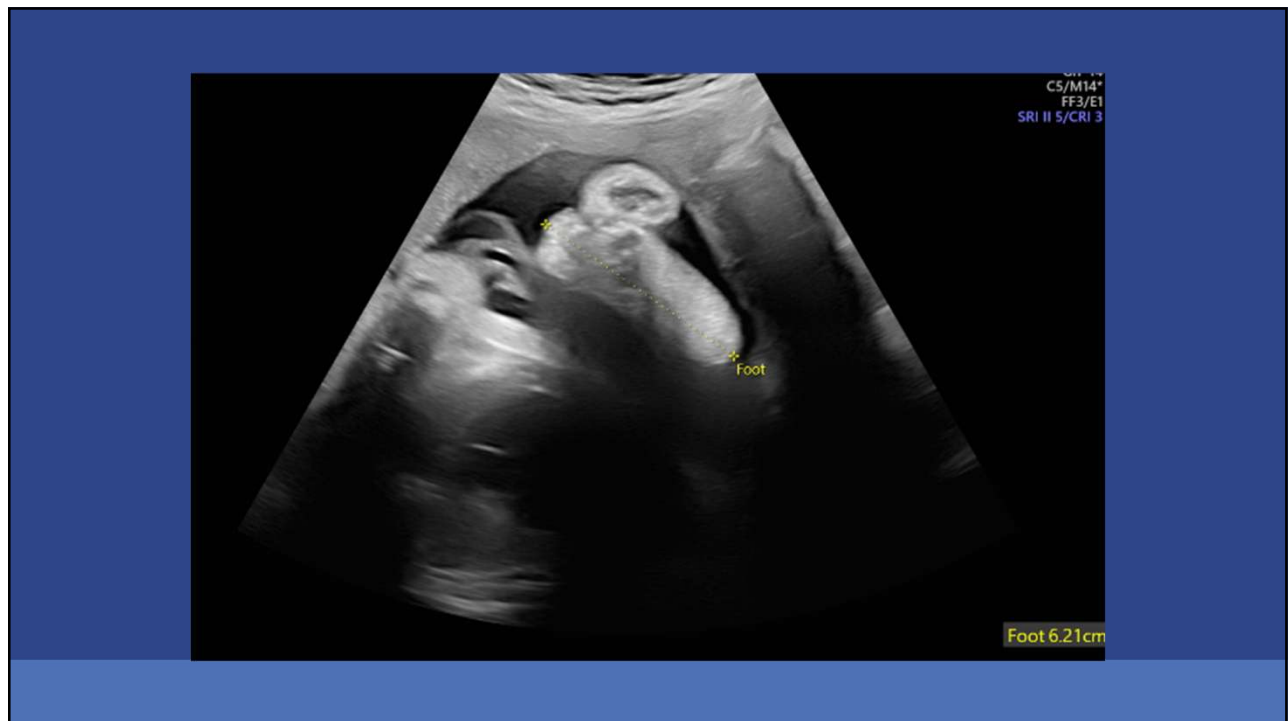


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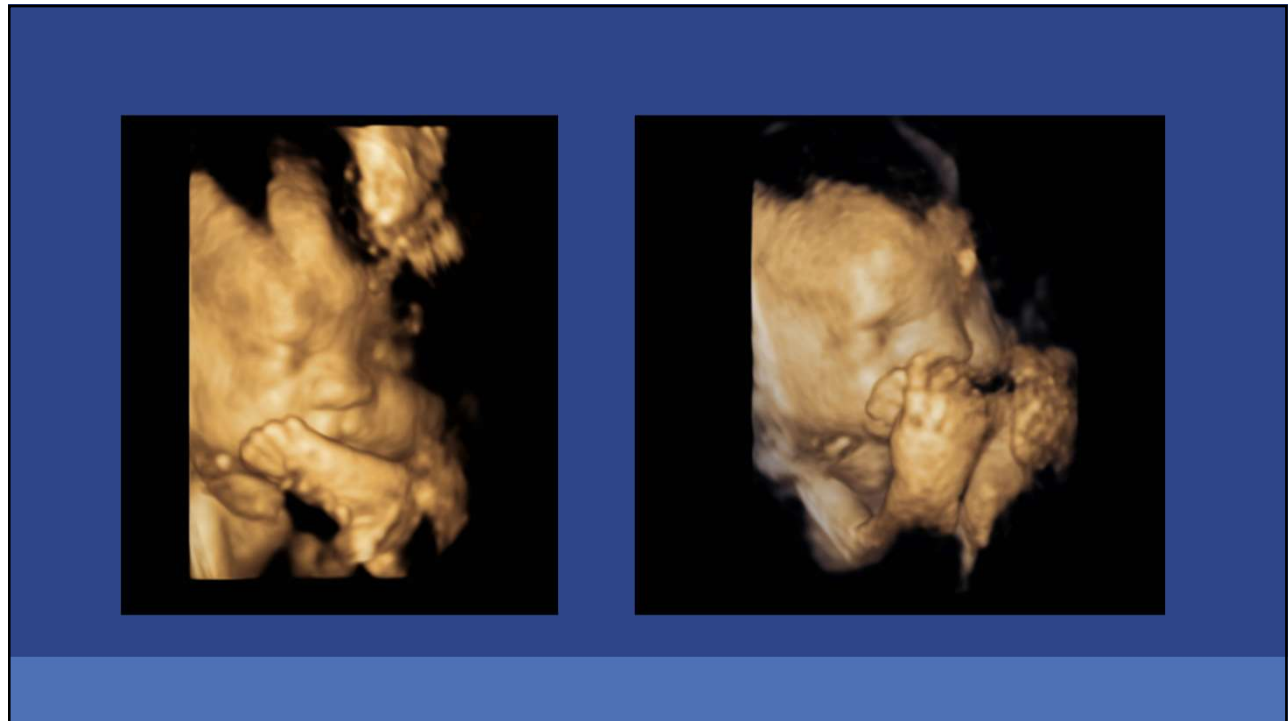


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Diagnostic Testing

- CVS
- Amniocentesis

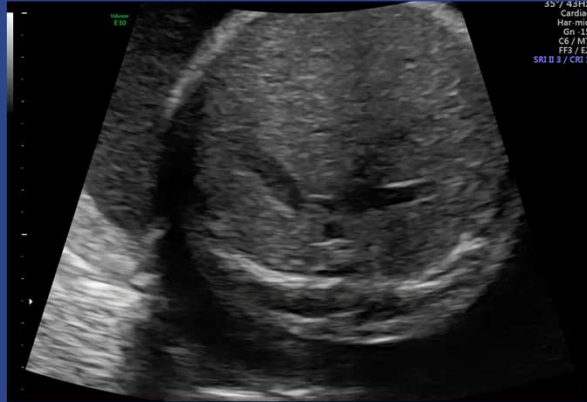


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Determining Lethality



- 81-99% accurate with ultrasound
- International Skeletal Dysplasia Registry
 - 96.8% accurate on prediction
- Respiratory failure
- Earlier in gestation detected, worse prognosis

Tretter AE, Saunders RC, Meyers CM, Dungan JS, Grumbach K, Sun CC, Campbell AB, Wulfsberg EA. Antenatal diagnosis of lethal skeletal dysplasias. Am J Med Genet. 1998 Feb 17;75(5):518-22. PMID: 9489797.

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Determining Lethality

Thoracic circumference <5th percentile, measured at the level of the four-chamber heart view

Thoracic to abdominal circumference ratio <0.6

Short thoracic length (from the neck to the diaphragm compared with nomograms)

Ribs that encircle less than 70 percent of the thoracic circumference at the level of the four-chamber cardiac view

Markedly narrowed anteroposterior diameter (sagittal view)

Concave or bell-shaped contour of the thorax (coronal view)

Heart to chest circumference ratio >50 percent

Femur length (FL) to abdominal circumference ratio <0.16; this ratio is even more predictive when associated with polyhydramnios

Hersh JH, Angle B, Pietrantoni M, Cook VD, Spinnato JA, Clark AL, Kurtzman JT, Bendon RW, Gerasimides A. Predictive value of fetal ultrasonography in the diagnosis of a lethal skeletal dysplasia. South Med J. 1998 Dec;91(12):1137-42. doi: 10.1097/00007611-199812000-00008. PMID: 9853726.

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Bell shaped/narrowed



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Achondroplasia

Achondrogenesis

Camptomelic
Dysplasia

Thanatophoric
Dysplasia

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Achondroplasia

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Achondroplasia

- Most common nonlethal
- 1/20,000 births
- Autosomal dominant



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Ultrasound Findings

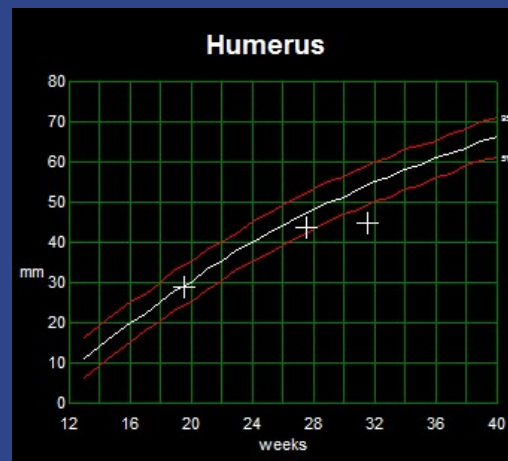
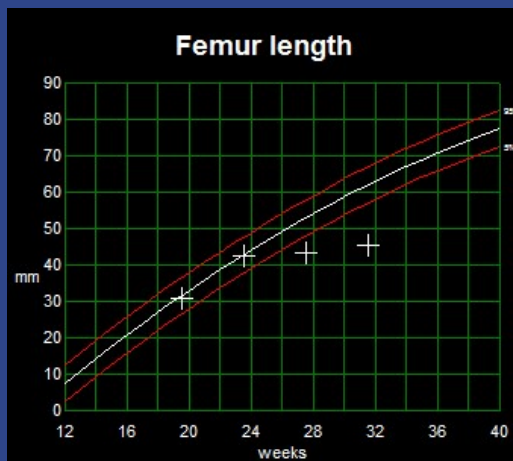
- Rhizomelic shortening
- Macrocephaly
- Trident hands



<https://www.orthobullets.com/pediatrics/4094/achondroplasia>

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3rd trimester lag in bone growth



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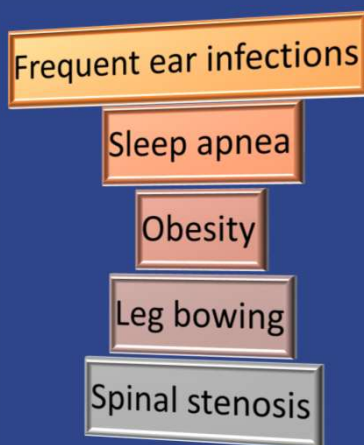
Diagnosis

- Clinical manifestations
- Radiographic findings
- Molecular tests



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Complications in later life



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Achondrogenesis

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Achondrogenesis

- Second most common lethal skeletal dysplasia
- Type 1
 - 20%
 - Autosomal recessive
 - Calvarial demineralization
- Type 2
 - 80%
 - Autosomal dominant
 - Low recurrence risk



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Ultrasound Findings

- Severe micromelia
- Small thoracic circumference
- Macrocrania
- Short trunk length
- Decreased mineralization
- Occasional fractures
- Polyhydramnios in 25% of affected fetuses



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Achondrogenesis

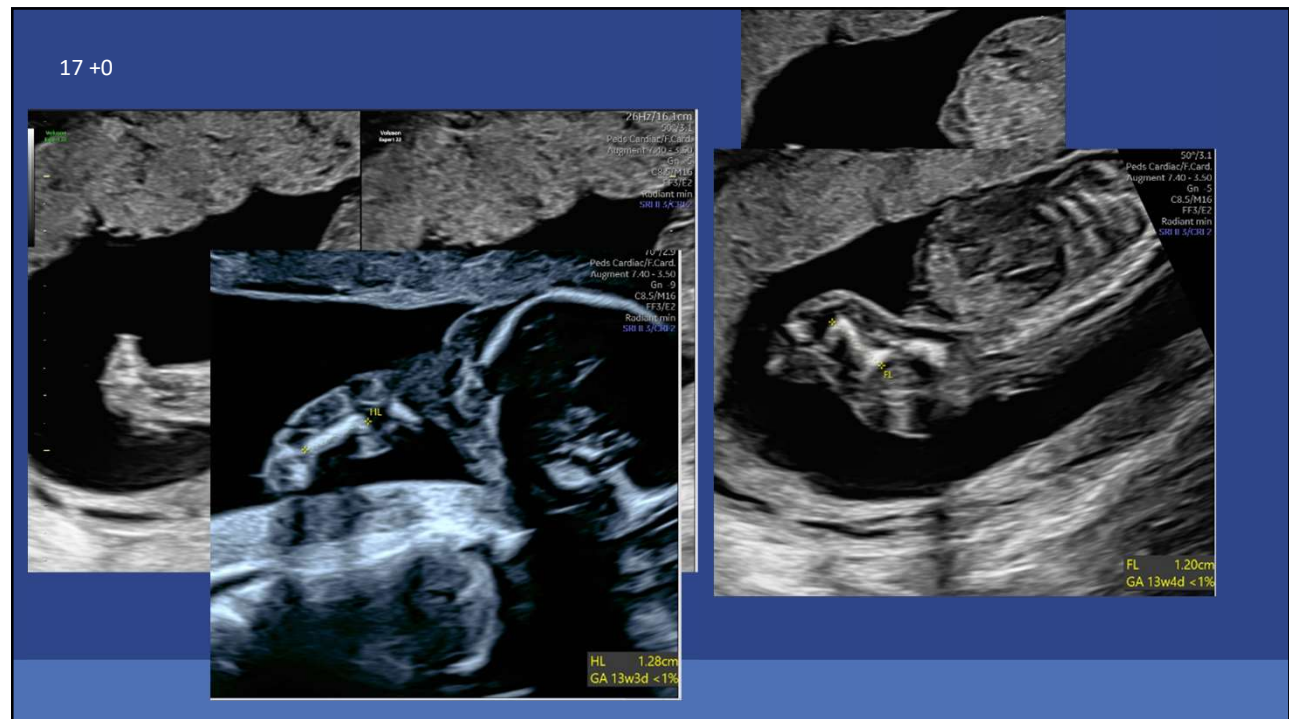


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Interesting Case

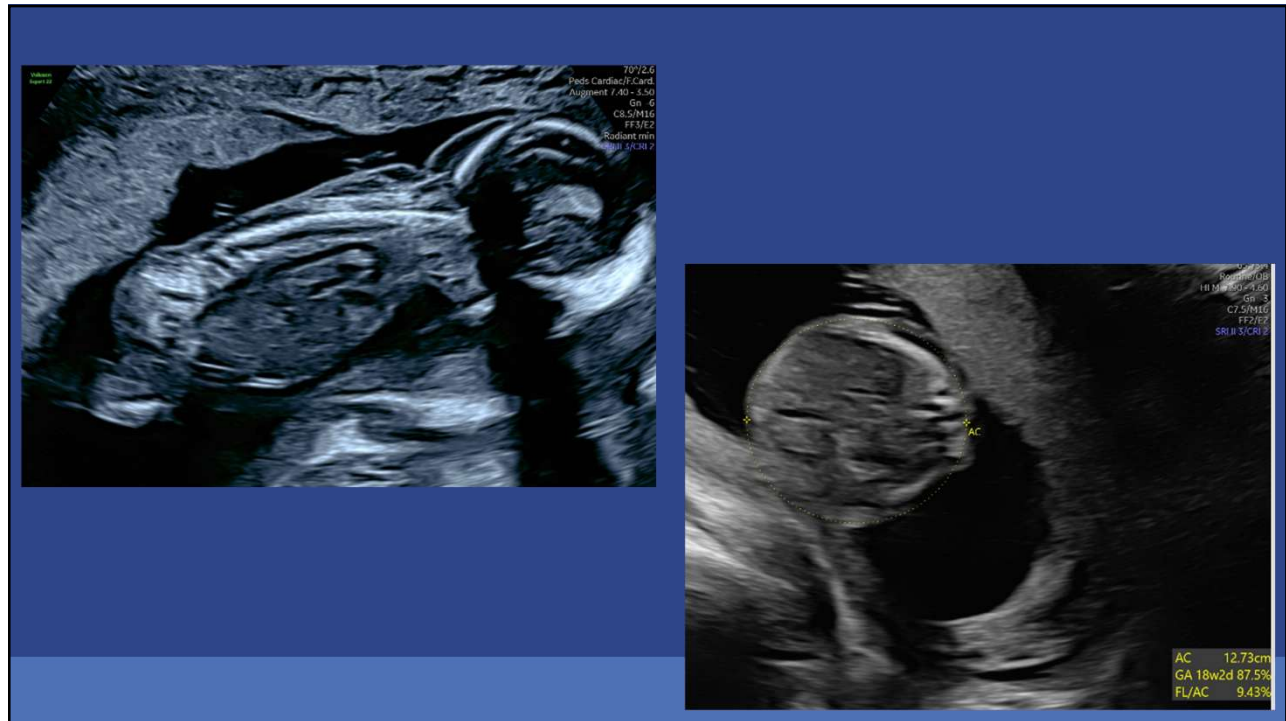
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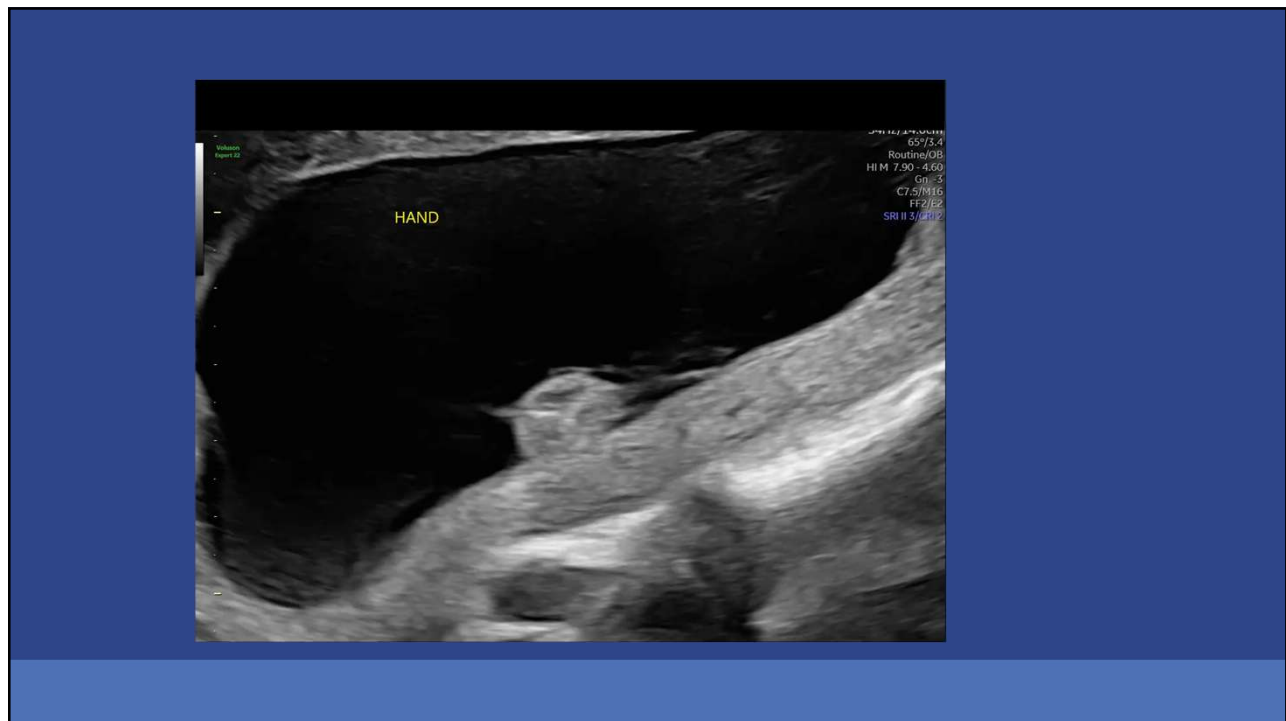
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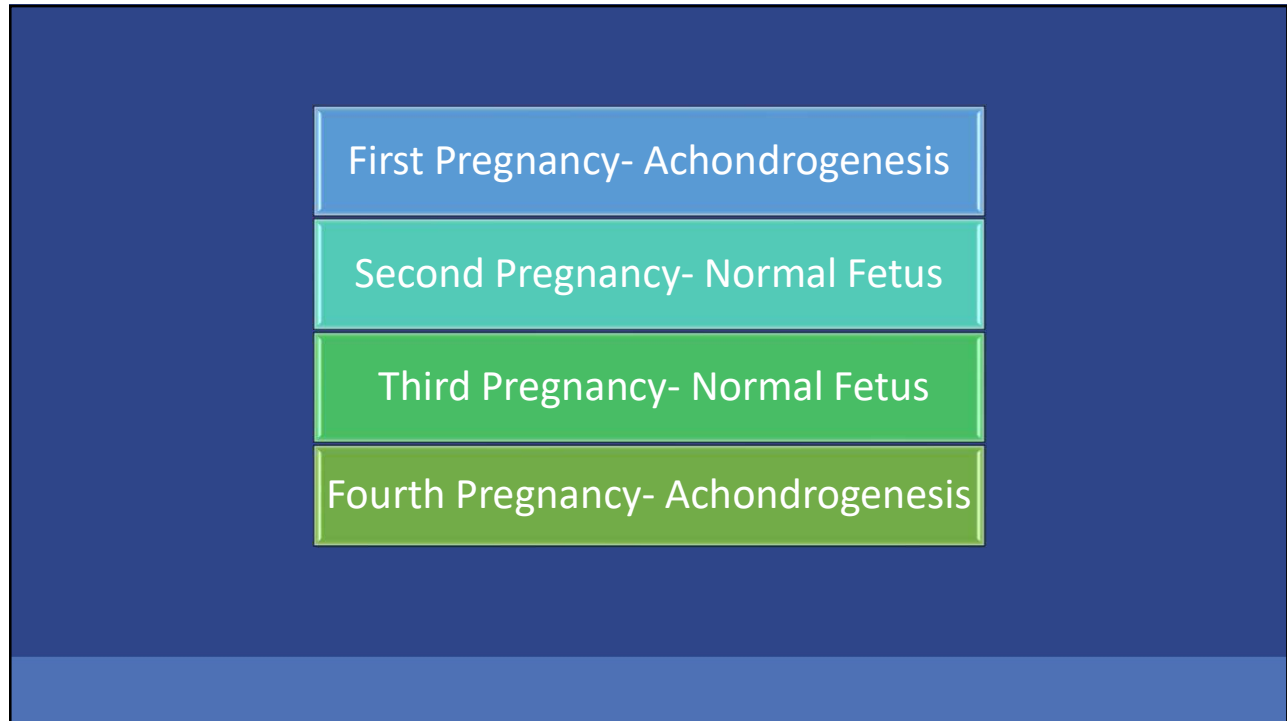
Interesting case- Patient history

- Previous pregnancy- two pathogenic variants in the SLC26A2 gene.
- Pt then had genetic testing- showed she is a carrier for one of these variants. Presumed that partner carries one as well.
- 25% chance for recurrence with each pregnancy.

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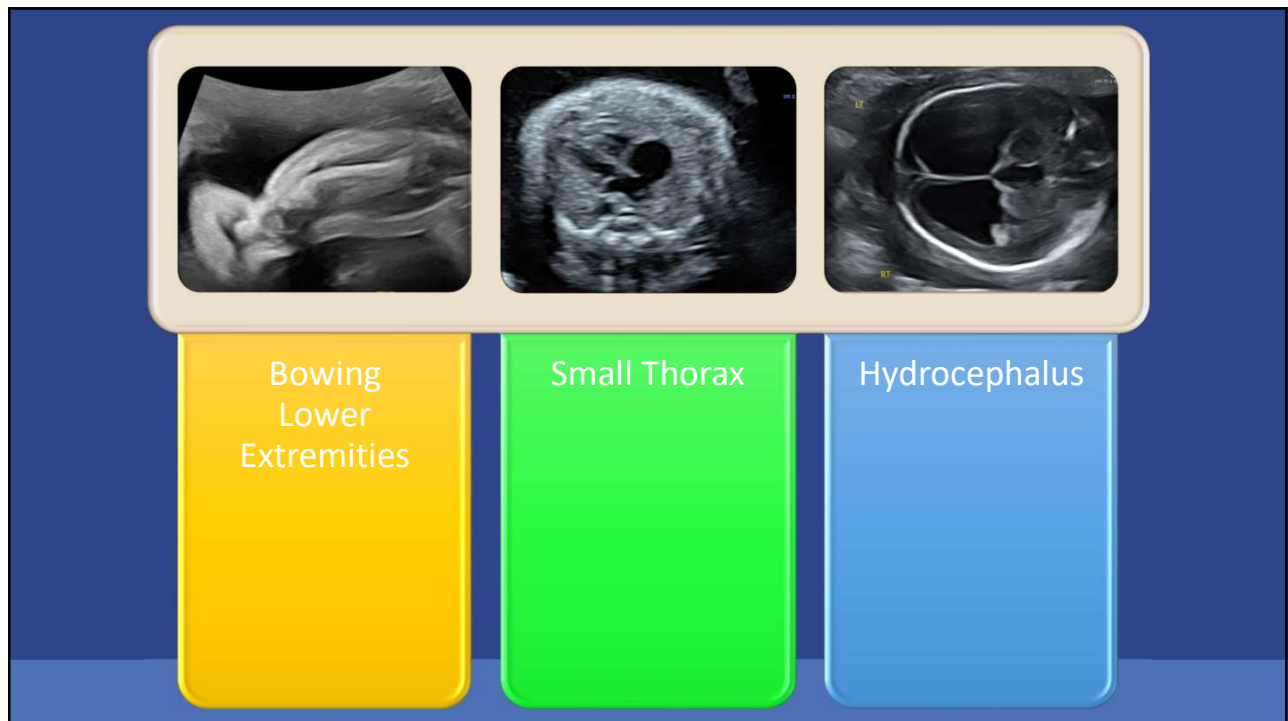


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- Group of lethal skeletal dysplasias
- AKA- Bent-limb dysplasia
- Bowing of long bones
- Rare
- Most spontaneous, but also inherited autosomal recessive
- Pulmonary hypoplasia

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Thanatophoric Dysplasia

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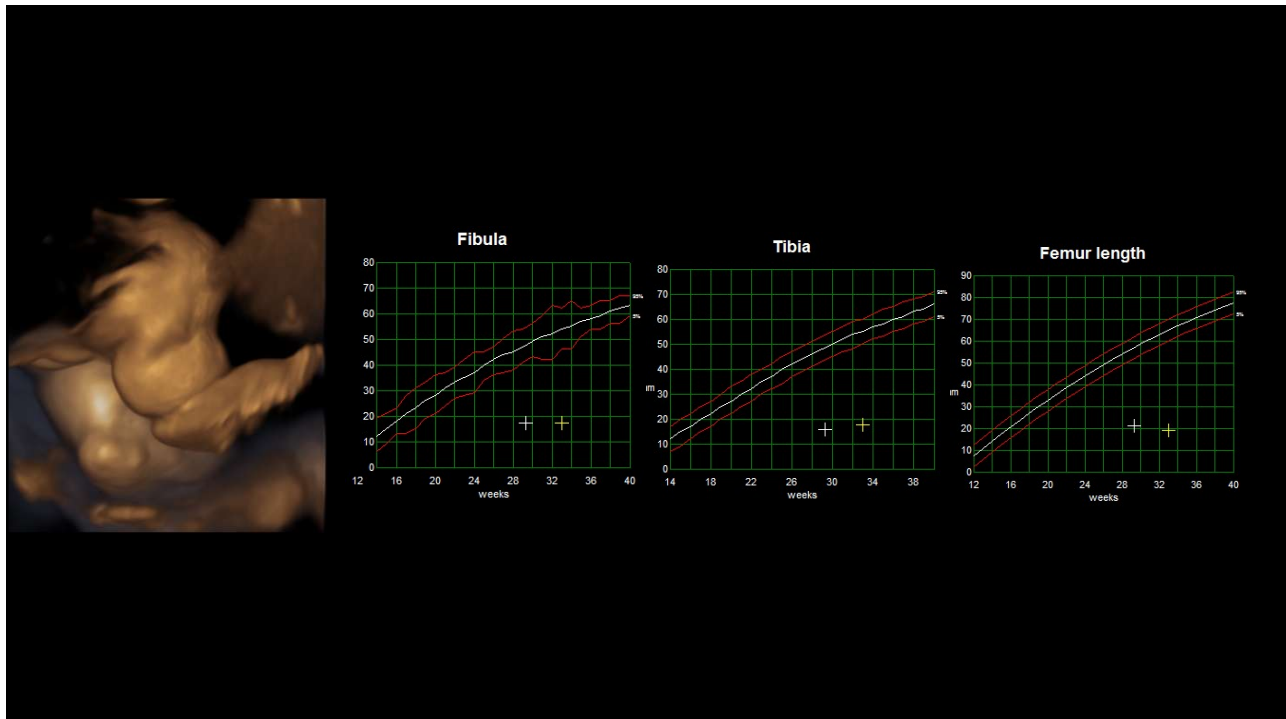
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Thanatophoric Dysplasia

- 0.24 to 0.69 per 10,000 births
- Most common lethal
- Severe micromelic shortening
- Narrow thorax
- Thickened skin folds
- Polyhydramnios
- 2 types



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Type I Thanatophoric Dysplasia

- Most common lethal
- Autosomal dominant disorder
- Most mutations are sporadic
- Stillborn or respiratory failure
 - Narrow thorax with underdeveloped lungs

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Type 1



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Type I Thanatophoric Dysplasia

- Curved long bones
- Macrocephaly
- Redundant skin folds
- Flat nasal bridge



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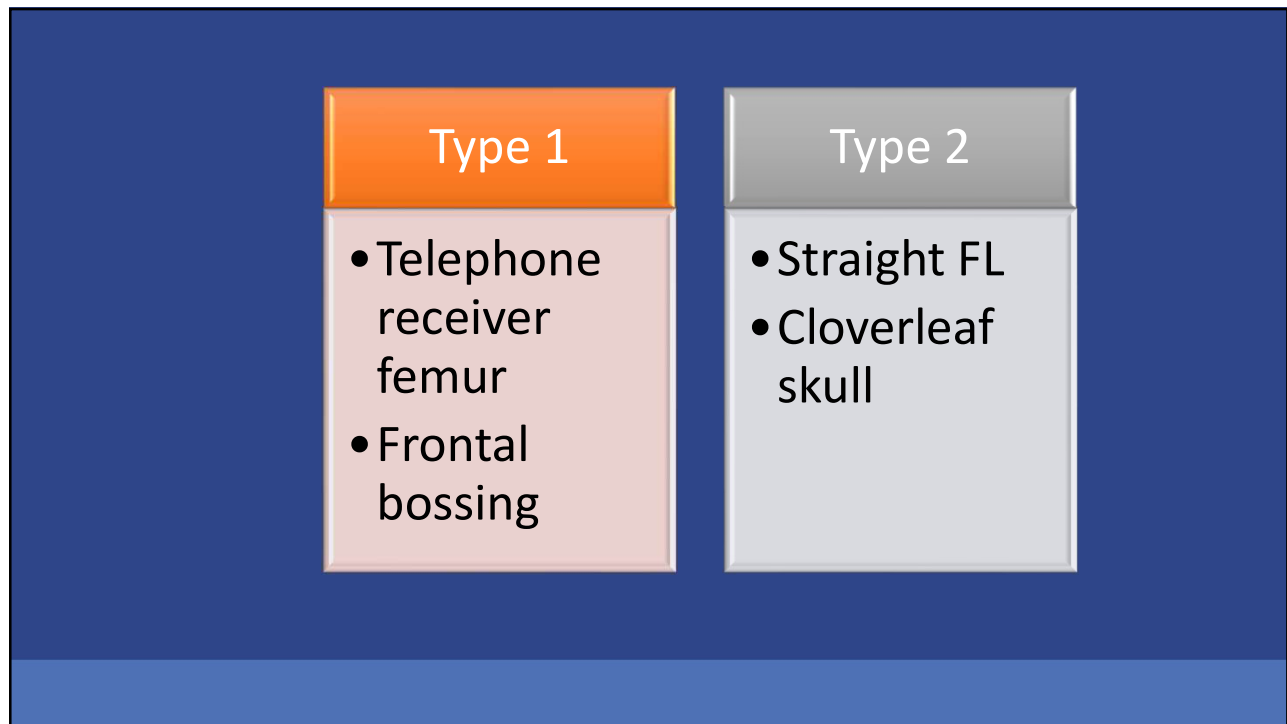
Type II Thanatophoric Dysplasia

- Autosomal recessive disorder
- “Cloverleaf” skull
- Straight long bones



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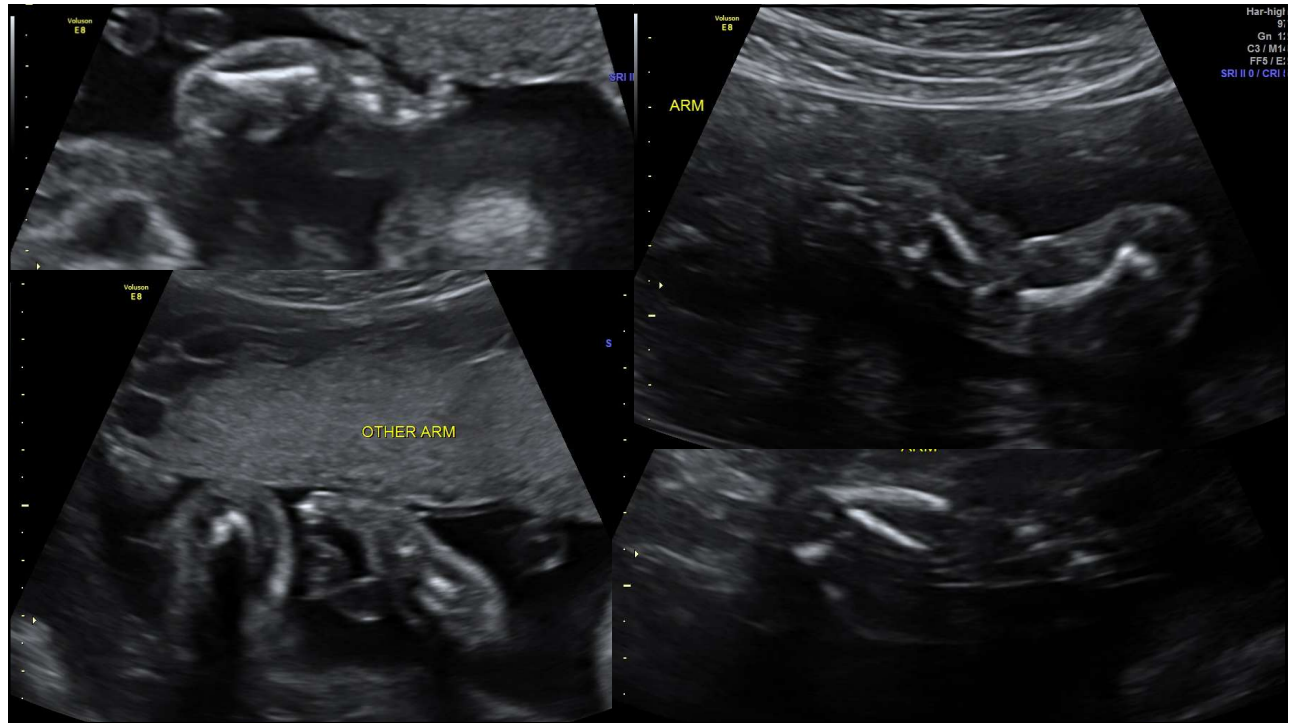


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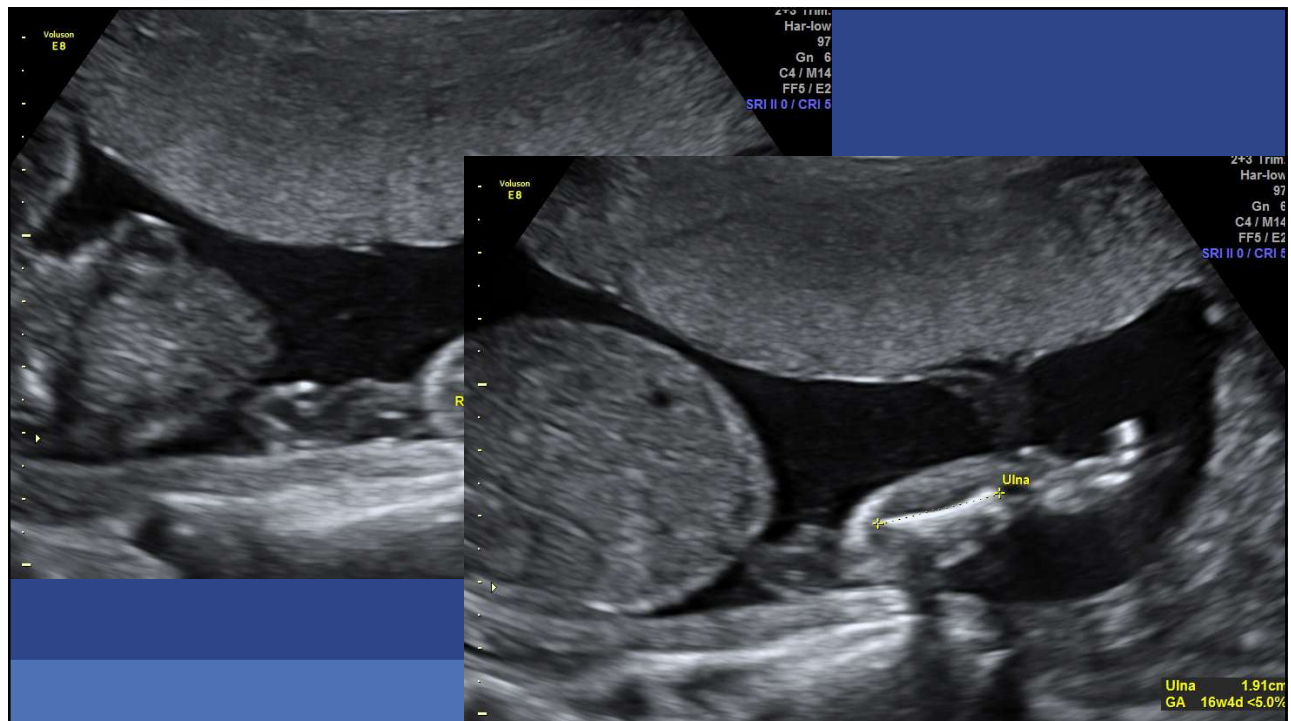
Case Study-
8/30/13
GA 20+3
G1 P0
Anatomy scan

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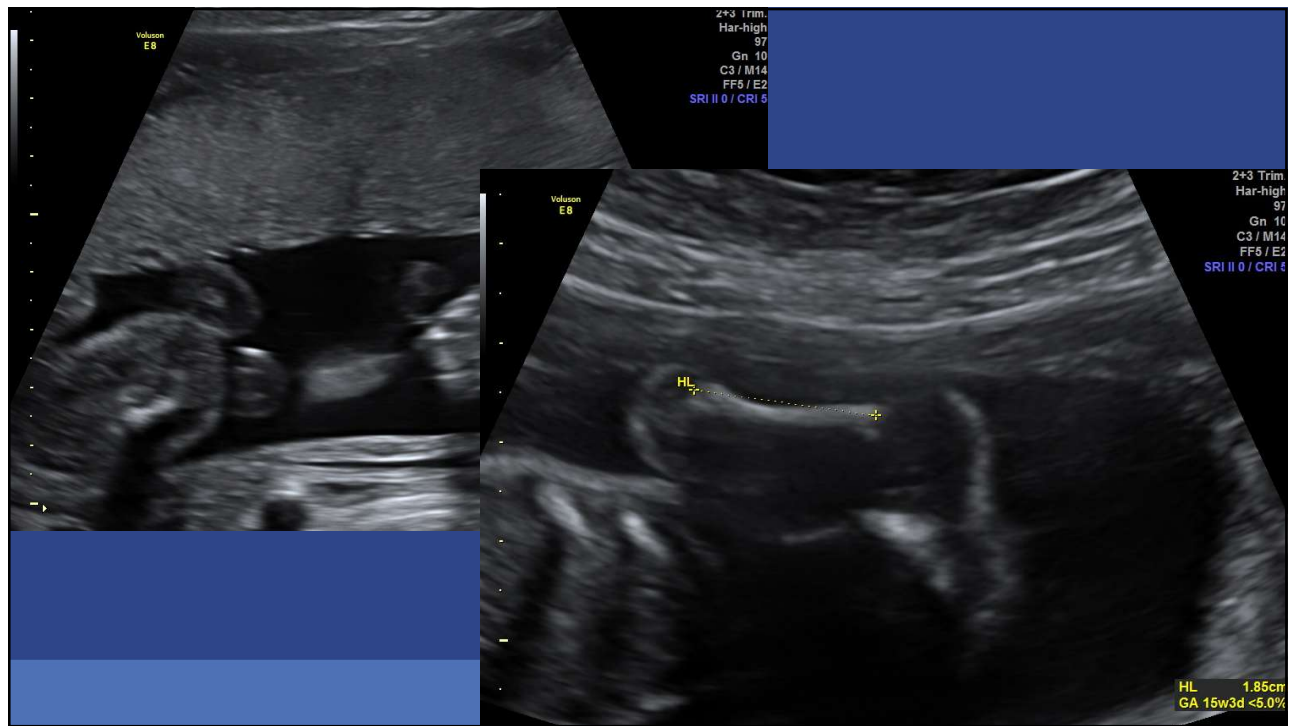


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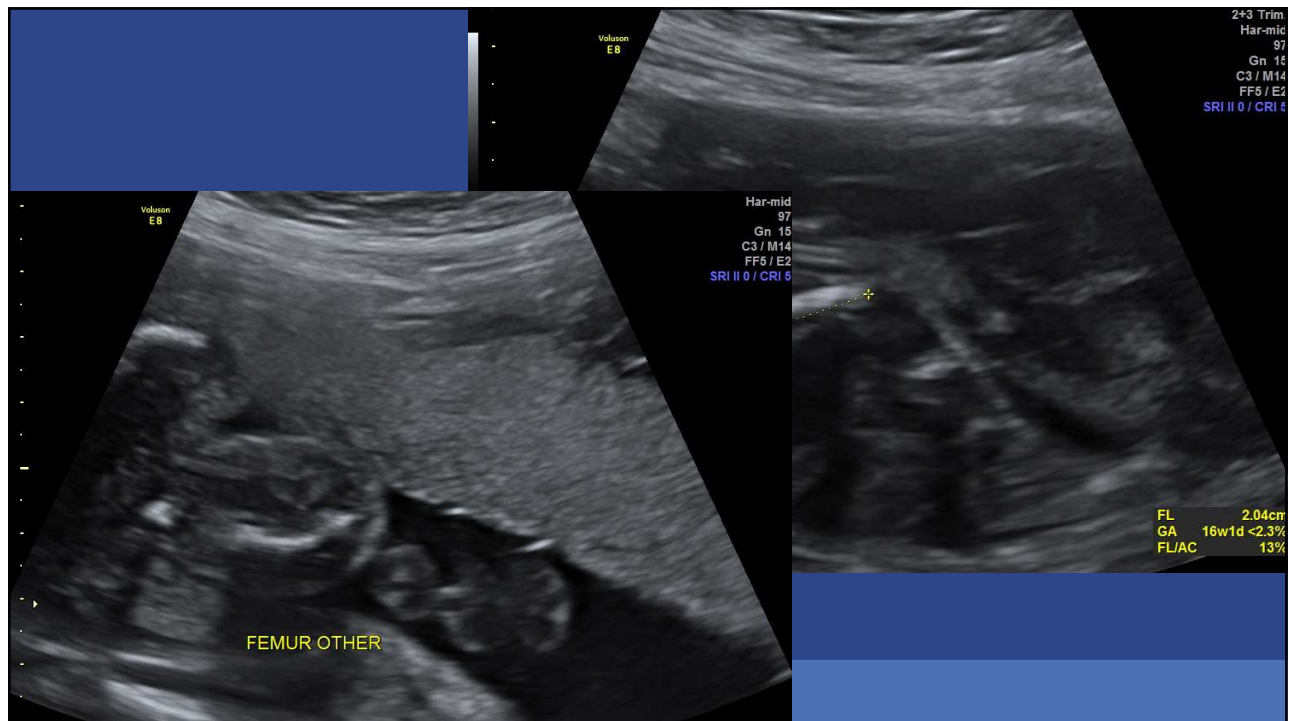


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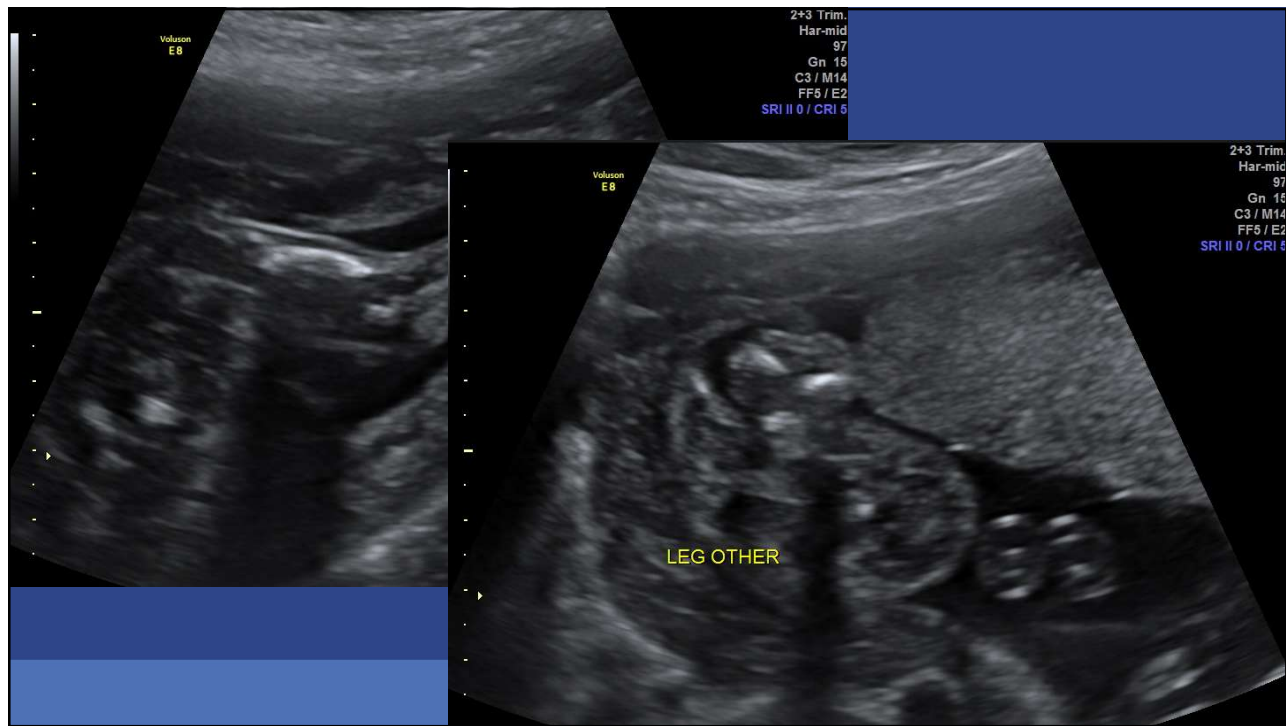


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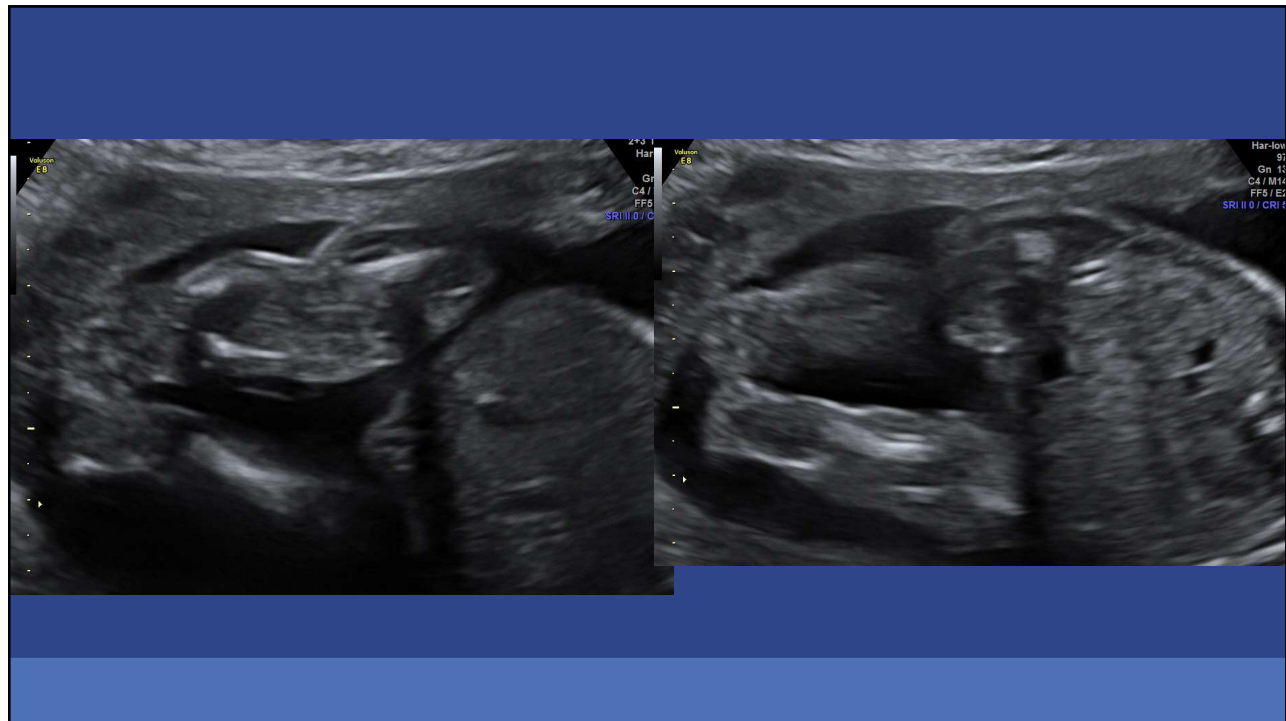


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Autopsy- 9/9/13

- Diffuse moderate micromelia
 - Bilat femoral bones 1.8cm
 - 2.5cm below lower limit of normal
- Prox long bones telephone receiver shape
- Hypertelorism- inner canthal 1.7cm (1.2-1.5cm)
- 11 ribs on each side
 - Not class type I TD
- Brachydactyly
- ✕ Chest circumference/lung size WNL

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Autopsy interpretation

- Osteochondrodysplasia
- Phenotypically represent thanatophoric dysplasia

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Recap

- Ultrasounds Findings
- Genetic Testing
- Pregnancy Management
- Postnatal evaluation



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Questions

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Thank you!



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References

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- All ultrasound images from personal files of Doyle K. (on file with author).

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