22nd Obstetrical Ultrasound: Setting the Standard 2019

Fetal Musculoskeletal Dysplasia Emphasis on Lethal Disorders

The Role of Ultrasound

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Fetal Musculoskeletal Disorders

- Rare, incidence typically < than 1/10,000
  - Individually rare but overall compose 5% genetic disorders in neonates.
  - Over 400 subtypes….approach?

*Nosology Group of the International Skeletal Dysplasia Society charged with classification of distinct skeletal disorders

No Disclosures

Nosology Classification of Genetic Skeletal Disorders * 2015

- Recognizes 436 genetic bone disorders with a substantial skeletal component
  - 40 groups based on molecular, biochemical, radiographic criteria, clinical phenotype
  - Hybrid between clinically defined disorders awaiting molecular clarification & those with molecular confirmation

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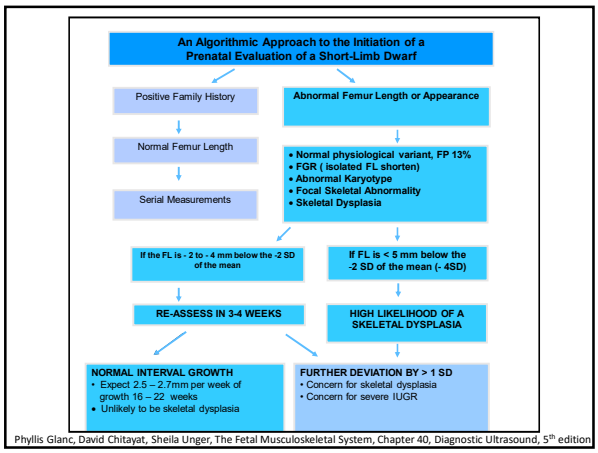
LEARNING OBJECTIVES

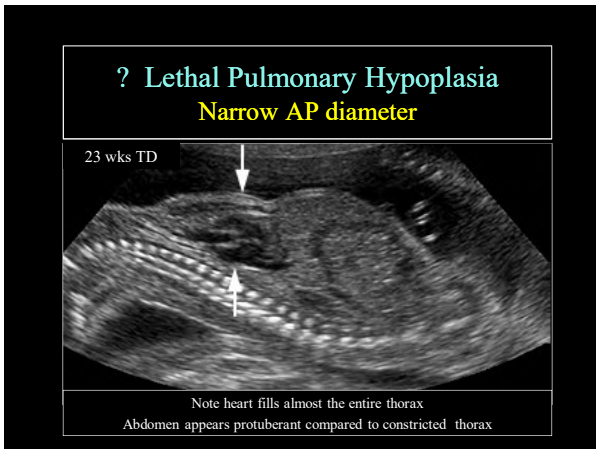
1. **Develop** a systematic key features algorithmic approach to the diagnosis of common lethal skeletal dysplasias on US
2. **Review** the US features of lethal pulmonary hypoplasia
3. **Correlate** US findings with pathology
4. **Utilize** the combination of pulmonary hypoplasia and key features to diagnose common lethal skeletal dysplasias (LSD)

Fetal Skeletal Dysplasias in a Tertiary Center: Radiology, pathology, and molecular analysis

- Incidence 112/2002 (5.6%) perinatal autopsies
  - 91 had both US and Pathology
  - 16/40 Nosology 2010 groups
  - Commonest specific diagnoses
    - Thanatophic Dysplasia 22%
    - Osteogenesis imperfecta 20%
      - Then……Limb hypoplasia reduction defects, Chondrodysplasia punctate, short-rib polydactly syndromes.

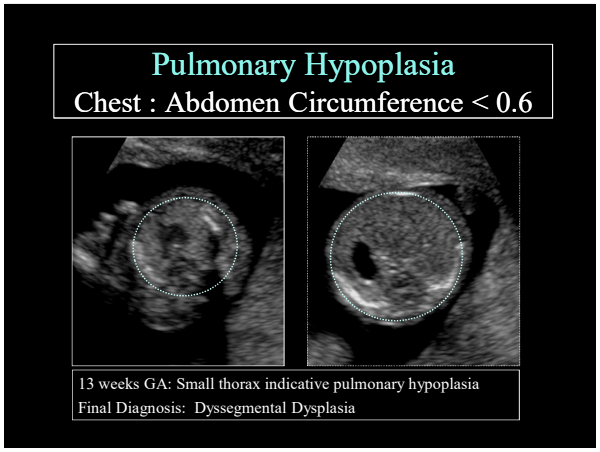
P. Glanc et al **Clin Genetics 2014**.





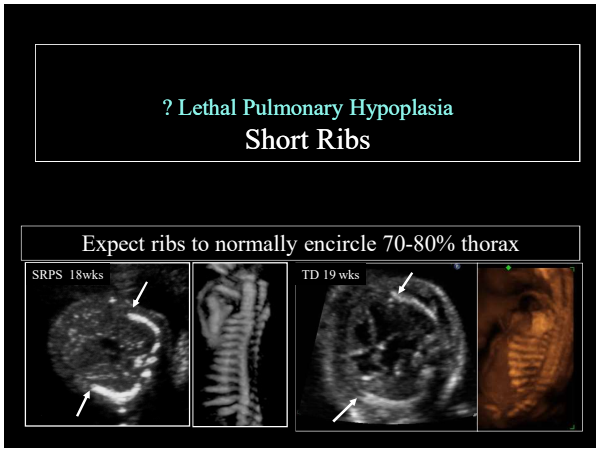
Key Questions : If have abnormal Femur Length

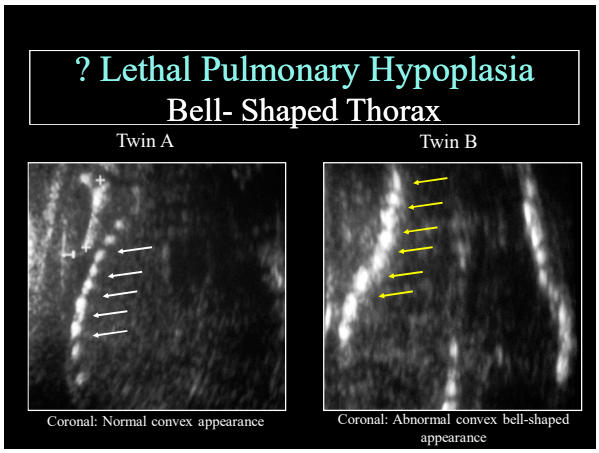
1. Is it a lethal malformation?
2. What is the appearance of the long bones?
3. What are the key features & associated findings?



Key Questions : If have abnormal Femur Length

1. Is it a lethal malformation?
   - Key factor is degree pulmonary hypoplasia
   - US diagnosis is accurate in ~ 85-100%



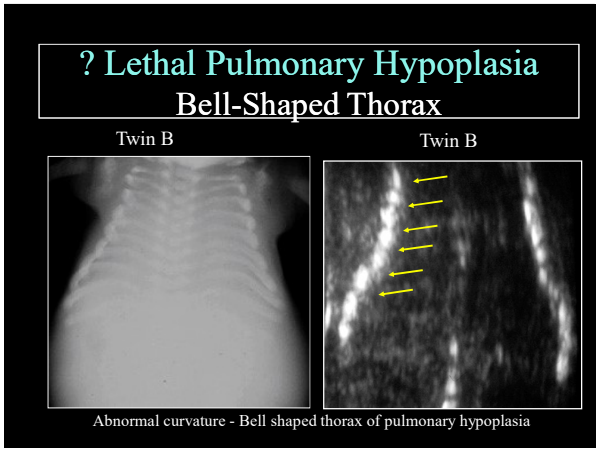


Prediction Lethality : Multiple sonographic parameters on basis pulmonary hypoplasia

- Short thoracic length (from neck to diaphragm)
- Markedly narrowed anteroposterior diameter (sagittal view)
- Concave or bell-shaped contour of the thorax (coronal view)

- At level 4- chamber heart view:
  - Thoracic circumference <5th %ile
  - Ribs encircle < 70% thoracic circumference
  - Heart : Chest circumference ratio > 50%

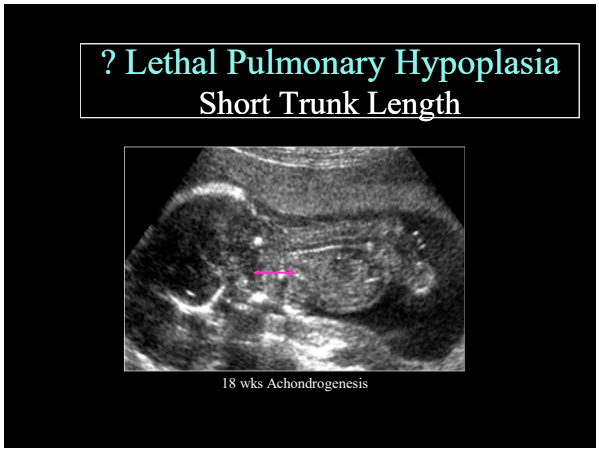
- Thoracic to abdominal circumference ratio <0.6



Evaluation Fetus with mildly shortened femur

< 5th percentile for GA or below 2SD from mean for GA consider following

1. Majority normal variation or constitutional short stature.
2. Up to 13% isolated mildly short femurs at 18-24 weeks are re-classified as normal on follow-up suggesting measurement errors
3. Family and maternal ethnicity should be considered.
4. Aneuploidy, in particular Trisomy 21, should be considered.
5. FGR – isolated FL in biometry can be indication, look other evidence
6. Assess serial growth over 3-4 weeks, if normal then skeletal dysplasia unlikely.
7. Findings predictive of skeletal dysplasia include:
   - Femur length > 5 mm below the -2 SD value for GA (> 4SD below mean 18-22 wk)
   - Femur : Foot length < 0.9 is concerning
   - Femur : Abdominal circumference < 0.16 (especially if polyhydramnios)
   - Chest: Abdomen circumference < 0.6



Predictive Numbers SD

< 5th percentile for GA or below 2SD from mean for GA consider following

- FL > 5 mm below the -2 SD value for GA (> 4SD below mean 18-22 wk)

- FL : Foot length < 0.9

- FL: abdominal circumference < 0.16 (Increased if poly)

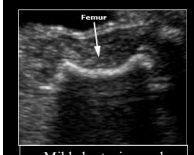
- Chest: Abdominal circumference < 0.6

Key Questions : Abnormal Femur Length

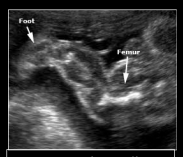
1. Is it a lethal malformation?
   - Is there pulmonary hypoplasia?

2. What is the appearance of the long bones?
   - Pattern of limb shortening
   - Degree of limb shortening
   - Interval growth of the extremities
   - Onset of limb shortening

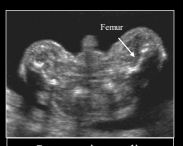
Degree Limb Shortening
Abnormal Short Femurs



Mild shortening and bowing
20.2 wk
Asphyxiating Thoracic Dystrophy



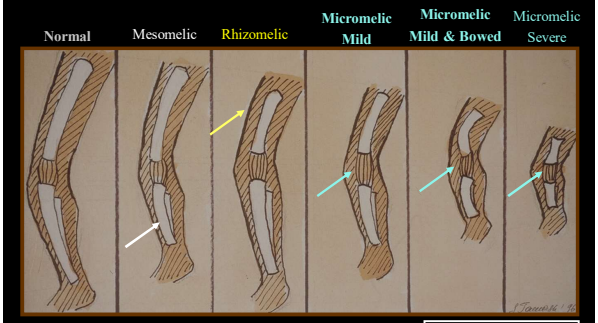
Severe micromelia
24 weeks
Thanatophoric dysplasia type 2
Thickened redundant soft tissues which grow relatively faster than the short long bones



Severe micromelia
22 weeks
Achondrogenesis
Note the poor bone visualization due to limited mineralization

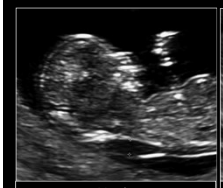
"Tripod appearance"

PATTERNS OF LIMB SHORTENING

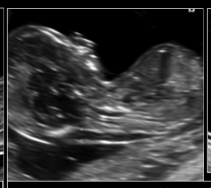


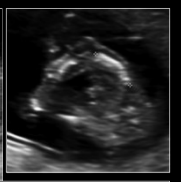
Courtesy Dr. J. Tomash

Timing: Earlier Onset Worse Prognosis



11 wks
Large NT



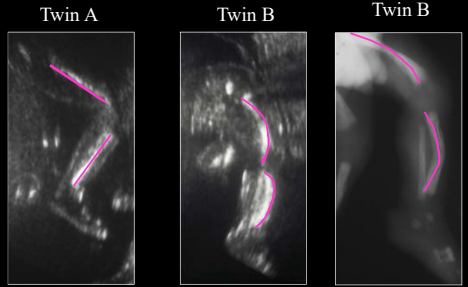


13.7 weeks
Severe micrognathia
Small Chest
Curved short long bones
Femur & Tibia

Final Diagnosis:Campomelic dysplasia

Courtesy Anne Kennedy

Mild & Bowed Micromelia



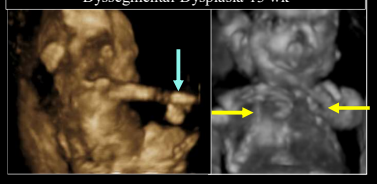
Normal
20 wks

Campomelic Dysplasia

Timing Onset Limb Shortening

- T1 diagnosis generally lethal - Earlier diagnosis the worse the prognosis

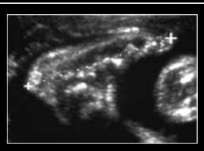
Dyssegmental Dysplasia 13 wk

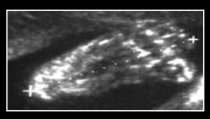


- T3 onset want to consider
  - Familial, constitutional, normal variation, FGR, nonlethal (Htz achondroplasia)

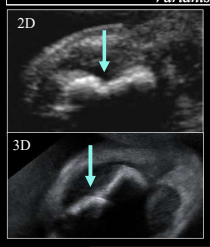
FEMUR: FOOT LENGTH
Normal ~ 1.0

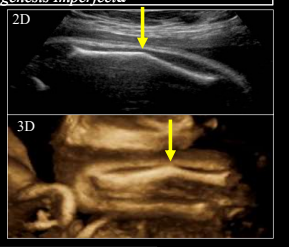
- Not affected by GA
  - After 14 wks
- < 0.9 abnormal
- > 0.9 in severe IUGR

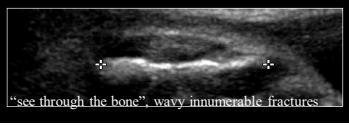




Key Features – Abnormal Mineralization – Fractures
Variants of Osteogenesis Imperfecta

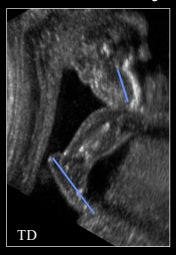


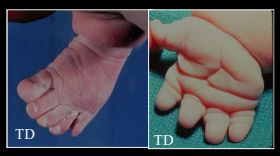




"see through the bone", wavy innumerable fractures

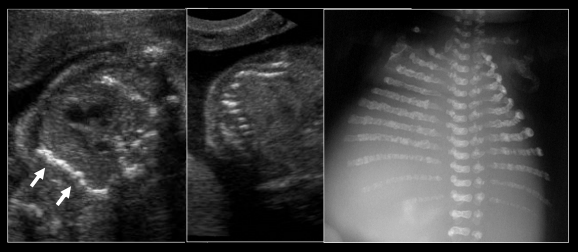
Lethal Skeletal Dysplasias
Tendency to sparing of foot length





Key Feature: Abnormal Mineralization
Fractures - Ribs

Multiple fractures within single bones
-Most diagnostic feature in OI type 2



Key Questions : Abnormal Femur Length

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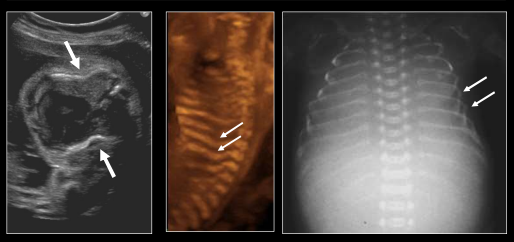
3. ? Key Features: Mineralization, Fractures, Macrocranium, Trunk length
4. ? Associated Features: Hands, Feet, Spine, Face

Key Feature: Abnormal Mineralization
Fractures - Ribs

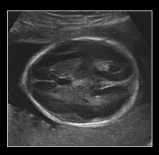
Typical lateral concavity chest wall "bashed in"



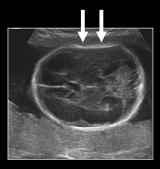
OI type 2-3: Ribs longer, occasional fractures

Abnormal mineralization:
Cranial Vault Compressibility

Most reliable feature for skull demineralization



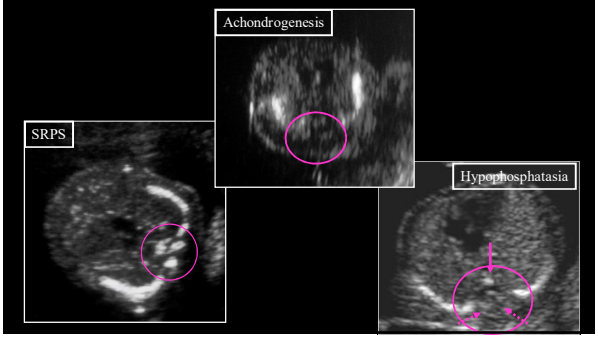
Appears normally mineralized



Mild transducer pressure flattens cranial vault

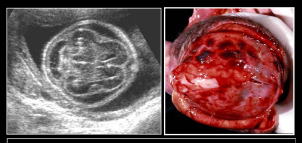
Consider diagnosis of osteogenesis imperfecta Type 2 or Hypophosphatasaia congenita

THE FETAL SPINE
All lethal basis short ribs/small CC = pulmonary hypoplasia

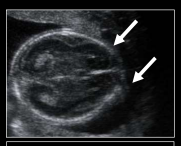


Abnormal Mineralization
Cranial Vault

- Other Features
  - Excellent visualization in near field due demineralized vault and/or widen fontanelles

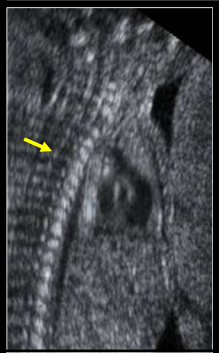


Caput membranacae
(Falx brighter than "vault")

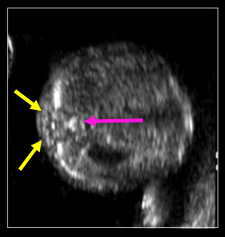


Wide anterior fontanelles

The Fetal Spine
Absent Posterior Ossification & Patchy Demineralization



18 wks Hypophosphatasia



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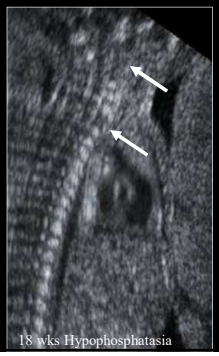
The Fetal Spine
Patchy demineralization



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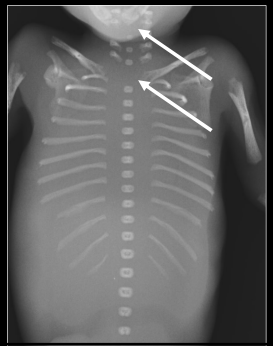
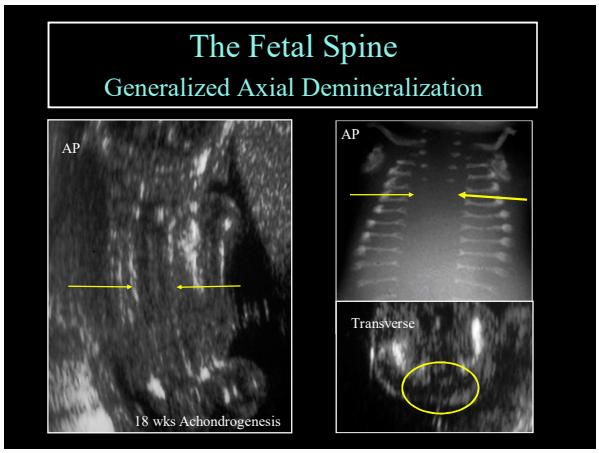
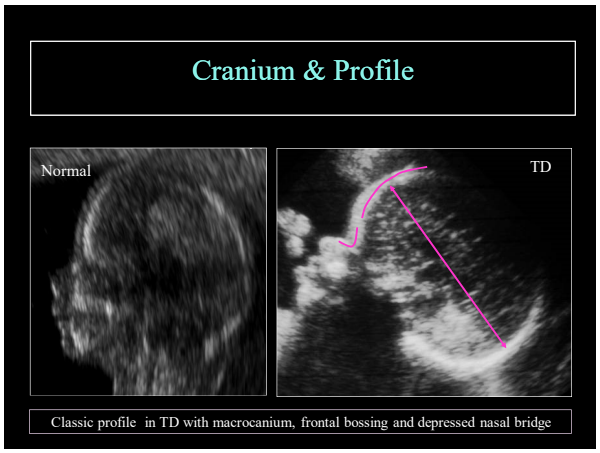
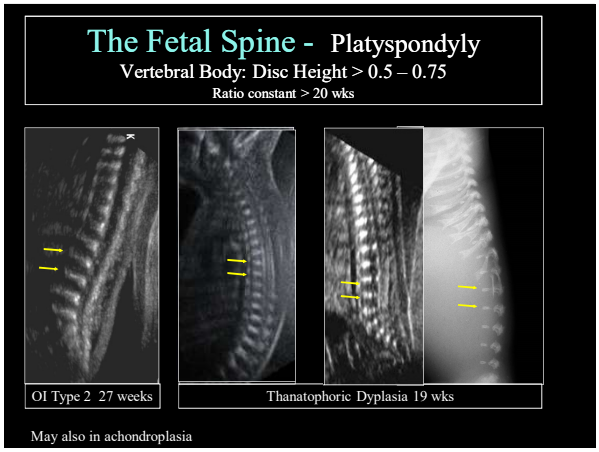
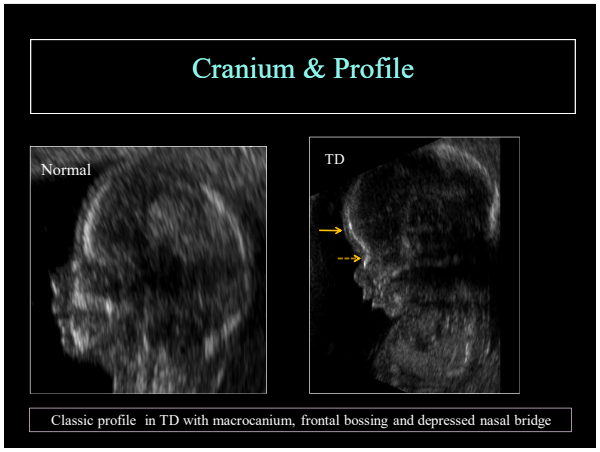



The Fetal Spine
Generalized Axial Demineralization
AP
AP
Transverse
18 wks Achondrogenesis


Cranium & Profile
Normal
TD
Classic profile in TD with macrocanium, frontal bossing and depressed nasal bridge


The Fetal Spine - Platyspondyly
Vertebral Body: Disc Height > 0.5 – 0.75
Ratio constant > 20 wks
OI Type 2 27 weeks
Thanatophoric Dyplasia 19 wks
May also in achondroplasia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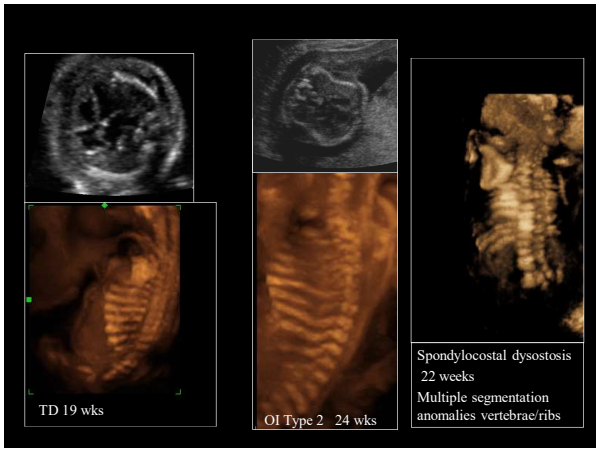
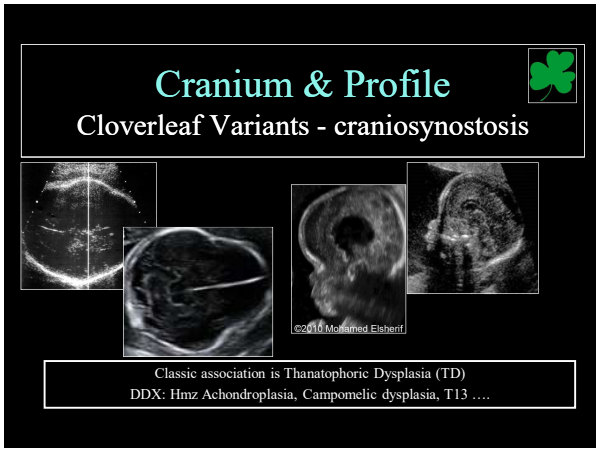
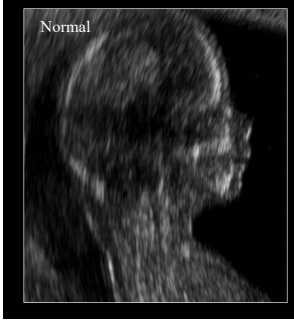
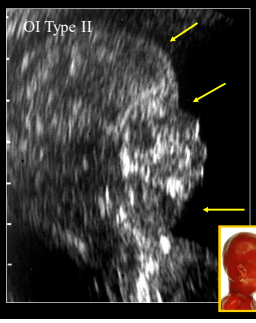

TD 19 wks
OI Type 2 24 wks
Spondylocostal dysostosis
22 weeks
Multiple segmentation
anomalies vertebrae/ribs

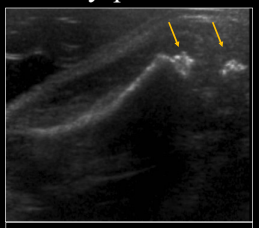

Cranium & Profile
Cloverleaf Variants - craniosynostosis
©2010 Mohamed Elsherif
Classic association is Thanatophoric Dysplasia (TD)
DDX: Hmz Achondroplasia, Campomelic dysplasia, T13 ….

Cranium & Profile
14 weeks GA



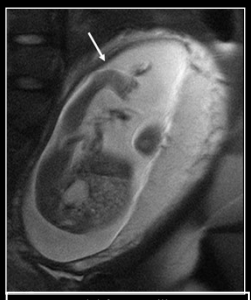


Basic Good Technique
G2P1 @ 24 weeks
Chondrodysplasia Punctata

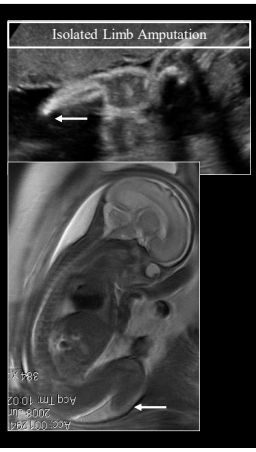


Premature & stippled epiphyseal ossification femoral epiphysis

Role of MRI



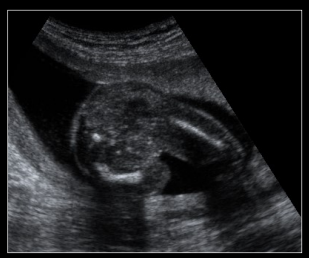
Clubfoot ? Utility



LEARNING OBJECTIVES

1. **Develop** a systematic key features algorithmic approach to the diagnosis of common lethal skeletal dysplasias on US
2. **Review** the US features of lethal pulmonary hypoplasia
3. **Correlate** US findings with pathology
4. **Utilize** the combination of pulmonary hypoplasia and key features to diagnose common lethal skeletal dysplasias (LSD)

Basic Good Technique
Isolated Femoral Hypoplasia 20 weeks



Lethal Skeletal Dysplasias **characterized** by severe micromelia and pulmonary hypoplasia

Lethal Skeletal Dysplasias **distinguished** by several key features

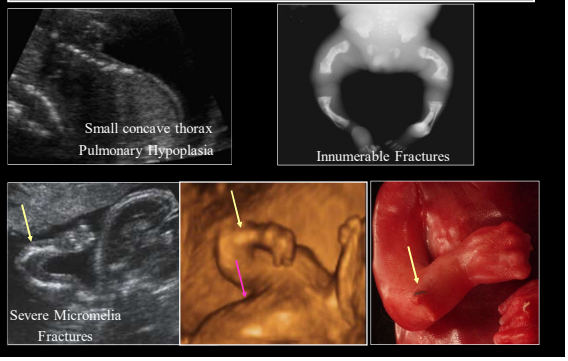
Common lethal skeletal dysplasias with severe micromelia and small thorax

Diagnosis	Bone Mineralization	Fractures	Macrocranium	Short Trunk
Thanatophoric Dysplasia*	Normal	No	Yes	No
Achondrogenesis	Patchy	Occasional	Yes	Yes
Osteogenesis imperfecta type 2	Generalized	Innumerable	No	Yes
Hypophosphatasia	Patchy or generalized	Occasional	No	No

*Distinguish from homozygous achondroplasia because both parents are heterozygotes
*Distinguish form short-rib polytdactyly syndrome because normal cranial size & polydactyly

Osteogenesis Imperfecta

Severe micromelia and small thorax
Multiple fractures & normal size cranium



Osteogenesis Imperfecta Type II

- Characterize by: Severe micromelia & pulmonary hypoplasia
- Distinguished by:
  - Generalized demineralization with multiple #'s within individual bones
  - No macrocranium
- Prenatal diagnosis : COL1A1 gene, generally new dominant mutation but germ line mosacism so recurrence risk 6-7%

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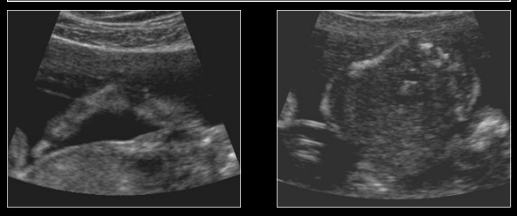
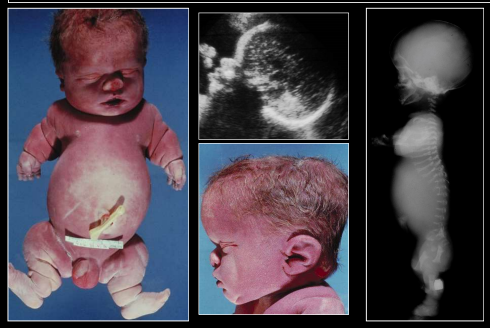
Severe micromelia & pulmonary hypoplasia
Normal mineralization, No fractures
Macrocranium



Thanatophoric Dysplasia

Characterized :Severe Micromelia & Pulmonary hypoplasia

Distinguish by normal mineralization with no fractures, macrocranium, normal trunk length



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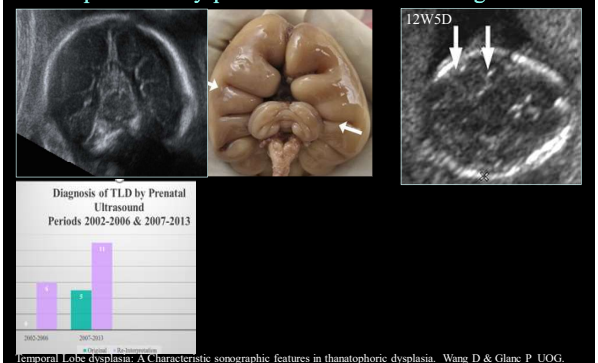
Temporal lobe dysplasia: Characteristic findings in TD



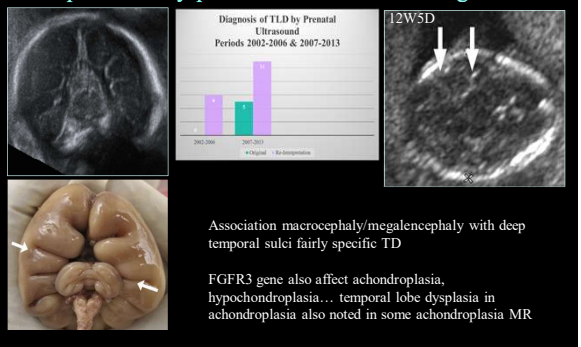
Temporal Lobe dysplasia: A Characteristic sonographic features in thanatophoric dysplasia. Wang D & Glanc P UOG. 2014 Nov;44(5):588-94. Manikkam, S. A., et al. "Temporal lobe malformations in achondroplasia: expanding the

Thanatophoric Dysplasia

- Characterize by severe micromelia and pulmonary hypoplasia
- Distinguish by normal mineralization & macrocranium
- TD type 1
  - Femora are curved or "telephone reciever
  - Cloverleaf deformity uncommon

- TD type II
  - Less severe micromelia
  - Femora are straight
  - Cloverleaf deformity common

Temporal lobe dysplasia: Characteristic findings in TD



Association macrocephaly/megalencephaly with deep temporal sulci fairly specific TD

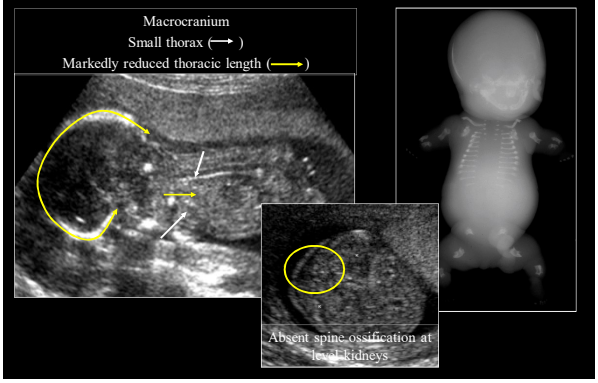
FGFR3 gene also affect achondroplasia, hypochondroplasia… temporal lobe dysplasia in achondroplasia also noted in some achondroplasia MR

Temporal Lobe dysplasia: A Characteristic sonographic features in thanatophoric dysplasia. Wang D & Glanc P UOG. 2014 Nov;44(5):588-94. Manikkam, S. A., et al. "Temporal lobe malformations in achondroplasia: expanding the

FGFR3 Disorders

- Thanatophoric dysplasia – one of most common lethal SK, AD
- Achondroplasia – commonest non-lethal SK characterized by relative macrocephaly, characteristic facies, short long bones, brachydactyly with trident configuration
  - AD
- Hypochodroplasia - < severe features

Characterize: Severe micromelia & pulmonary hypoplasia



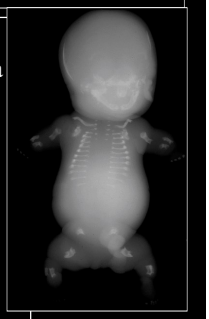
Skeletal Dysplasias: Role NIPT Screen Single Gene Disorders

- **TD commonest lethal SD – confirm diagnosis**
  - Prevalence TD remains low 2-3/100,000 births
  - BPD/FL ratio decreases rapidly to less than 3 prior to 13 wk, less than 2 prior 18 weeks
  - BPD/FL ratio > 3 after 13 weeks; > 2 after 18 weeks concerning
    - Follow NIPT reliable if fetal DNA concentration > 3% 100% sensitivity/specificity for FGFR3 gene mutation (Ren et al)
    - See anomalies by **12-14 weeks** such that macrocephaly or severe limb shortening cause abnormal BPD/FL ratio
- **Screening for single gene disorders NIPT may aid narrow differential diagnosis**
  - Achondrogenesis: <1% recurrence risk when associated with de novo mutations in COL2A1, or 25% if associated with AR TRIP11 or SLC26A2 homozygous mutations
  - Case: FL below 5th percentile. Father carrier hypophosphatasia (AR), Mother negative carrier
    - NIPT SGD panel identified COLA1A2 mutation consistent with osteogenesis imperfecta
  - Case: FL below 3rd percentiles at 29 weeks. Diagnosis suggested was achondroplasia heterozygous form.
    - NIPT SGD panel identified COL1A2 mutation consistent with osteogenesis imperfecta

Mohan, Pooja, et al. "Skeletal dysplasias screening by NIPT for single-gene disorders: Clinical value of narrowing the differential diagnosis." AJOG 220.1 (2019). Wang, Liangcheng, Isao Horiuchi, and Kenjiro Takagi. "Comment on "noninvasive prenatal test for FGFR3-related skeletal dysplasia based on next-generation sequencing and plasma cell-free DNA." *Prenatal diagnosis* 39.2 (2019).

Achondrogenesis

- Characterize pulmonary hypoplasia & severe micromelia
- Distinguish by:
  - Macrocranium
  - Decreased Mineralization
    - patchy
    - axial spine, pelvis, calvarium
  - +/- rib fractures
  - Short trunk length



Future : Preliminary Work

- **Main factor in lethality is small rib cage**
  - SRPS due short ribs
  - Spondylothoracic or spondylocostal dystostosis have rib crowding
  - Cerebrocostomandibular dysplasia abnormal ineffective or incomplete ribs
  - VEPTR- Vertical expandible prosthetic titanium ribs device scaphold used expand thoracic cavity volume via lengthen & widen
    - Utilize in asphyxiating thoracic dystrophy converting 70-80% mortality to 70% survival
- **Stem cell therapy**: Differentiate into osteoblasts & chondrocyts, have low immunogenic profile
  - 2 patients with OI treated with prenatal transplant improved linear growth, mobility and decrease fracture incidence

Victoria T, Zhu X, Lachman R, Epelman M, Oliver ER, Adzick NS, Biko DM. What Is New in Prenatal Skeletal Dysplasias?.AJR. 2018 May;210(5):1022-33.

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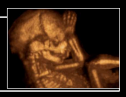
Conclusions – Common LSD

- Characterized by pulmonary hypoplasia and severe micromelia.
- Distinguished by key features
  - Macrocranium
  - Mineralization & fractures (occasional vs innumerable)
  - Trunk Length
- Systematic approach in combination with key features, may allow specific diagnosis of lethal skeletal dysplasias

Conclusion



Prenatal diagnosis provides an opportunity

Genetic counseling (current & future)

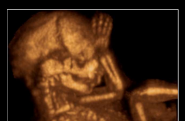
Pregnancy termination vs tertiary level care as appropriate

Best practice guidelines regarding prenatal evaluation and delivery of patients with skeletal dysplasia

https://doi.org/10.1016/j.ajog.2018.07.017

- Preconception genetic counseling recommended if individual/partner has SD or at increased risk (first degree family member SD
  - Consider safety pregnancy, mode delivery, anesthetic implications
- Women with SD
  - Standard weight gain recommendations do not apply
  - May need delivery prior term
  - Extra attention fluid management peripartum
- Antenatal diagnosis suspected SD important for pregnancy management and counseling
- If suspect SD should reefer to appropriate centers
- US main imaging modality
- Best indicator of lethality is micromelia
- Should postmortem Xray
- Incidence fractures newborn with OI not decreased by CS
- Low dose CT, 3D US (facial)and prenatal MRI (spine)can be helpful refine diagnosis
- Key predictors lethality at 18-20wks:
  - Chest : Abdomen ratio < 0.6
  - FL:AC ratio < 0.16
  - FL:BPD ratio
  - Micromelia > 3SD below mean
  - Severely decreased mineralization
- Postmortem / natal evaluation recommended, bank fetal DNA

Thank you



Suggested references

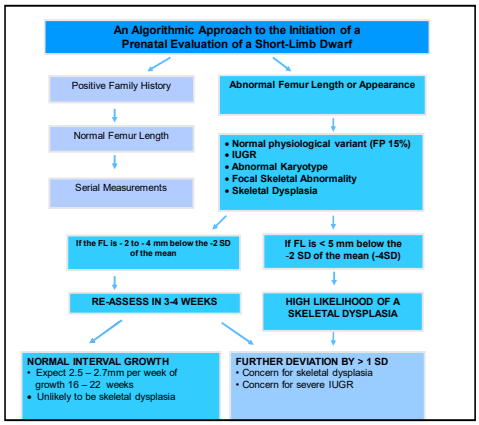
1. Bonafe, Luisa, Valerie Cormier-Daire, Christine Hall, Ralph Lachman, Geert Mortier, Stefan Mundlos, Gen Nishimura et al. "Nosology and classification of genetic skeletal disorders: 2015 revision." *American journal of medical genetics Part A* 167, no. 12 (2015): 2869-2892.
2. Glanc, P. and Chitayat, D. 2018. Prenatal diagnosis of lethal skeletal dysplasias. UpToDate. Available at http://www.uptodate.com.
3. Diagnostic Ultrasound 5th Ed. Chap 40 Fetal MSK by Glanc et al

Suggested Resources: Phyllis.Glanc@Sunnybrook.ca

Online Mendelian Inheritance in Man (OMIN)

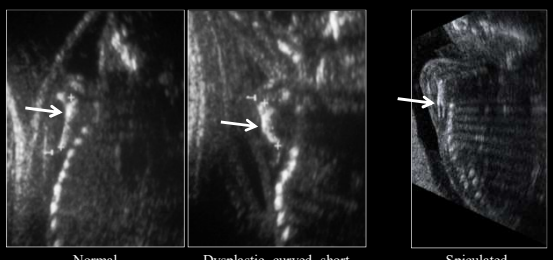
Registry: European Dysplasia Network; International Skeletal Dysplasia Registry

phyllis.glanc@sunnybrook.ca



Phyllis Glanc, David Chitayat, Sheila Unger, The Fetal Musculoskeletal System, Chapter 40, Diagnostic Ultrasound, 5th edition

Tips and Hints - Scapulae



Normal | Dysplastic, curved, short Campomelic Dysplasia | Spiculated (TD)

Comprehensive Evaluation includes:

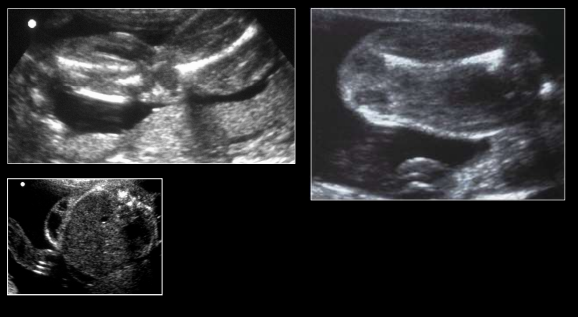
1. Determine if it is a lethal malformation on basis potential pulmonary hypoplasia.
2. Determine pattern and degree of limb shortening.
3. Evaluate interval growth of extremities.
4. Perform a qualitative assessment of long bones:
   - Shape, contour, mineralization, bowing, angulation, fractures, hypoplasia or aplasia, number and symmetry
   - Assess joints for alignment, contracture or extension deformities
5. Perform a qualitative assessment of other bone
   - Emphasis spine, hands & feet, calvarium, face, ribs, scapulae, pelvic bones
6. Perform a detailed anatomic survey
7. Couple should be counseled and given options by a team which includes perinatal imaging specialists, medical geneticists, maternal-fetal medicine specialists, and neonatologists. If both parents have skeletal dysplasia, their diagnoses should be determined and the implications of these diagnoses on their pregnancy should be discussed, including the mode of delivery and the postnatal management.
8. After delivery or pregnancy termination diagnosis should be determined using clinical, radiographic, photographic, histomorphic and DNA analysis. Cell cuture and DNA should be banked and used for microarray and molecular diagnosis.

For additional detail please review: "Approach to prenatal diagnosis of the lethal skeletal dysplasias" in uptodate.com; last update August 8, 2018. Authors Phyllis Glanc, David Chitayat.

Prediction Lethality : Multiple sonographic parameters

- 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 to 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 to abdominal circumference ratio <0.16; this ratio is even more predictive when associated with polyhydramnios]

Hereditary Lymphedema



Evaluation Fetus with mildly shortened femur

Evaluation of fetus with mildly shortened femur: < 5th percentile for GA or below 2SD from mean for GA suggest must consider following:

1. Majority normal variation or constitutional short stature.
2. Up to 13% isolated mildly short femurs at 18-24 weeks are re-classified as normal on follow-up suggesting measurement errors
3. Family and maternal ethnicity should be considered.
4. Aneuploidy, in particular Trisomy 21, should be considered.
5. Fetal growth retardation is considered when supported by other sonographic evidence of growth restriction.
6. Assess serial growth over 3-4 weeks, if normal then skeletal dysplasia unlikely.
7. Findings predictive of skeletal dysplasia include:
   - Femur length > 5 mm below the -2 SD value for GA
     - ~ > 4 SD below the mean at 18 and 22 weeks)
   - Femur : Foot length < 0.9 is concerning
   - Femur : Abdominal circumference < 0.16

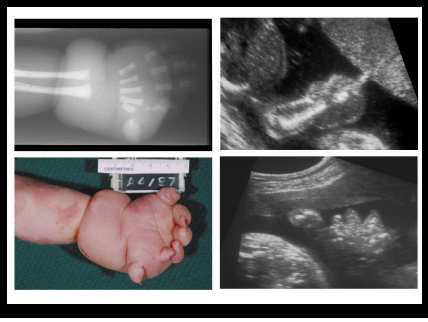
Best Practice

- Discussion with families re lethality
  - Based on ultrasound +/- molecular diagnosis
- Osteogenesis imperfecta broad phenotype thus molecular diagnosis helpful in predicting severity and recurrence risk
- Approximately 5% newborns with congenital defects have SD

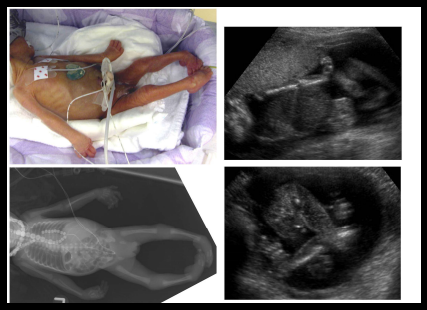
Hypophosphatasia

- Hypophosphatasia (HPP) is a rare inherited skeletal dysplasia due to loss of function mutation in ALPL gene located at chromosome 1p36.1-p34
- low prevalence of 1 in 300,000 in Europe with more than 359 mutations reported to date
- ALPL gene encodes for an enzyme, TNSALP (or bone ALP), which is essential for the proper mineralization of bones and teeth
- 6 subtypes: perinatal lethal, prenatal benign, infantile, childhood, adulthood, odontohypophosphatasia each with different age of presentation, symptoms and severity
- Lethal perinatal form lethal arelated small thorax and hypoplastic lung

Amniotic Band Syndrome



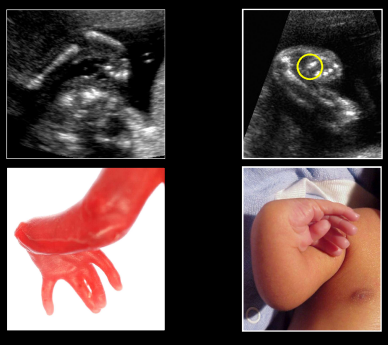
AMC



RADIAL RAY DEFECTS

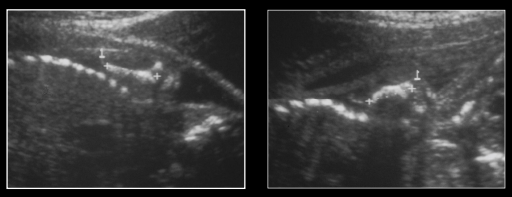
Fanconi's anemia
Hypoplastic/absent Thumb

Thrombocytopenia Absent Radius (TAR)
Thumb Always Present, Csx

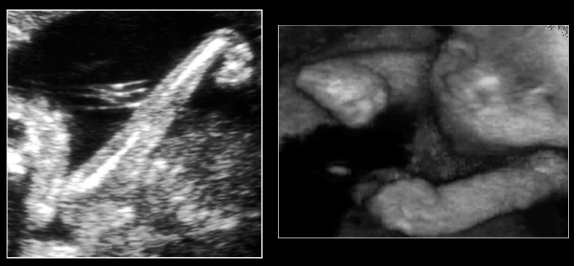


Scapulae

Campomelic Twins



CLUBHAND



ARTHROGRYPHOSIS MULTIPLEX CONGENITA

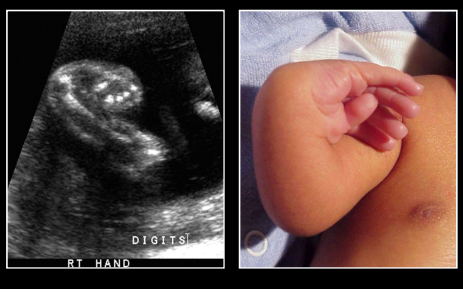
RADIAL RAY HYPOPLASIA

THROMBOCYTOPENIA –ABSENT RADIUS SYNDROME

Bilateral absent radii

Thumb is Always Present

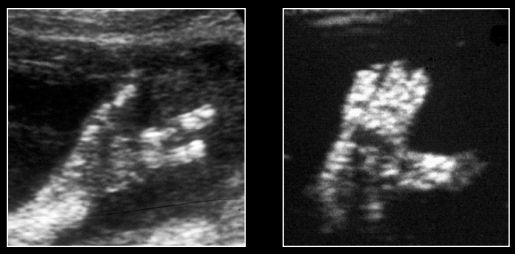
THROMBOCYTOPENIA - C-section indicated



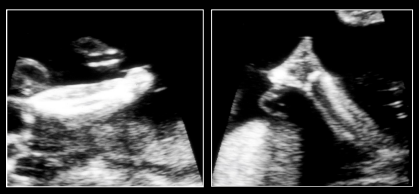
HANDS

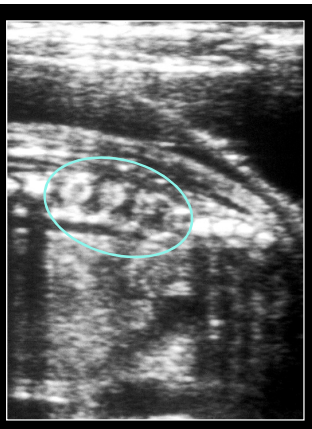
Ectrodactyly

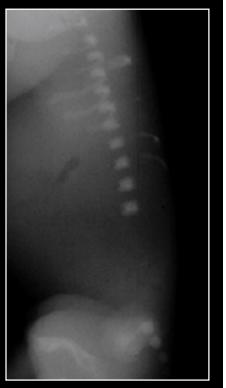
Syndactyly



ISOLATED HAND AMPUTATION







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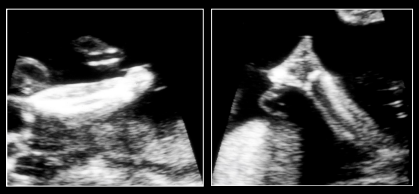
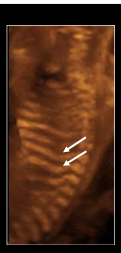
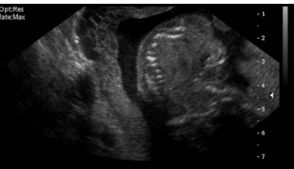
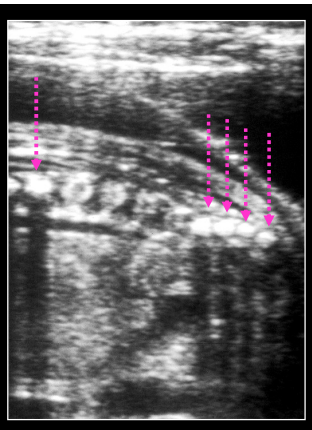
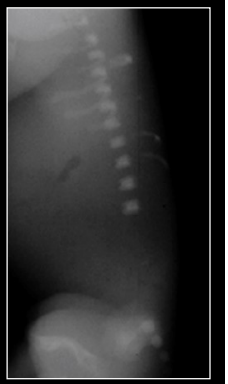






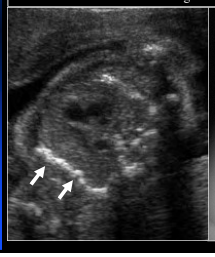
Key Feature: Abnormal Mineralization
Fractures - Ribs

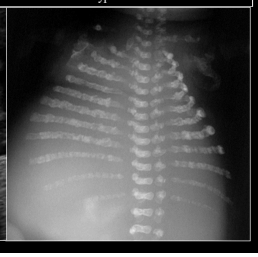




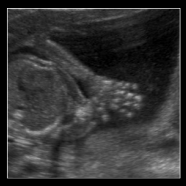
Key Feature: Abnormal Mineralization
Fractures - Ribs

Multiple fractures within single bones
-Most diagnostic feature in OI type 2



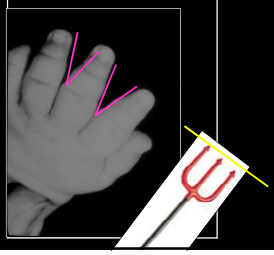


Hands & Feet
Important Clues

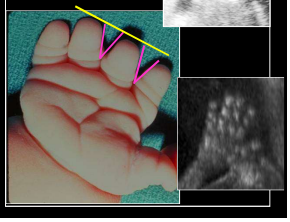


Achondroplasia
Brachydactyly & Trident Configuration

HETEROZYGOUS
(non-lethal)

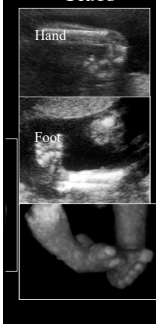


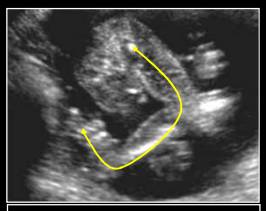
HOMOZYGOUS



Postural Deformities

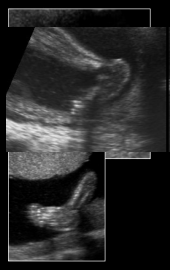
Clubs



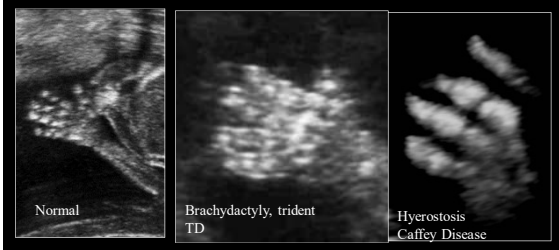


AMC – multiple joint contractions

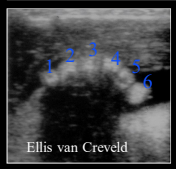
Rockers

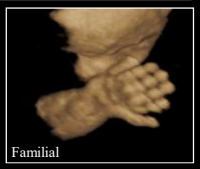


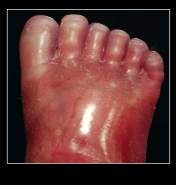
Recognizing Normal

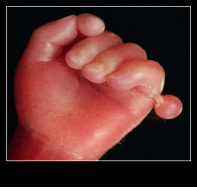


POLYDACTYLY

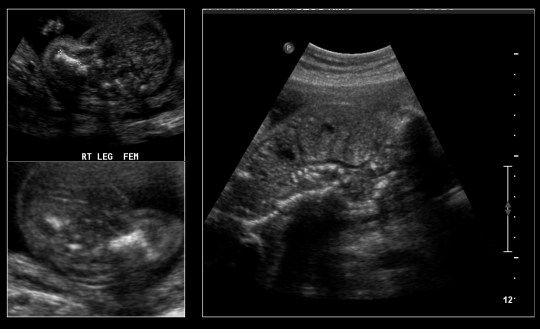






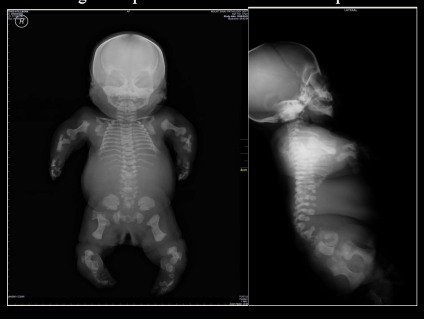


History: 25 year old G1P0, consanguineous, MSS unremarkable
Routine US 19 weeks severe micromelia (FL measuring ~ 13 weeks)
Counselled lethal form of MSKD - Delivered stillborn term infant



Dyssegmental Dysplasia

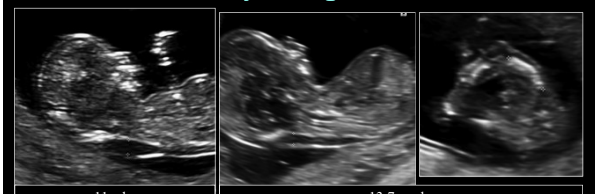
- Characterized by gross disorganization vertebral bodies or anisospondyly
  Variable degrees hypoplasia primary & secondary ossification centers bodies
- associated narrow chest, short limbs, decreased joint mobility
- DNA testing for Heparan Sulfate Perlecan Gene 2 positive



Campomelic Dysplasia

- "Bent bone dysplasia" Gene: Sox9, generally AD
- May have only mild femoral shortening with mild or no bowing thus may be overlooking (acampomelic form no bowing)
- Important clues:
  - Hypoplastic scapulae (bodies very short)
  - Cervical spine vertebral body hypoplasia with exaggerated lordosis
  - Facial dysmorphism
  - Sex reversed (XY) females
- Chest – typically borderline slightly small with normal rib length however laryngo-tracheomalacia common leading to neonatal demise in ~ 75%
- Other bent bones with angulated femurs include kyphomelic dysplasia, Schwartz jampel, widemen, OI, scapuloiliac dysplasia…

Early Diagnosis

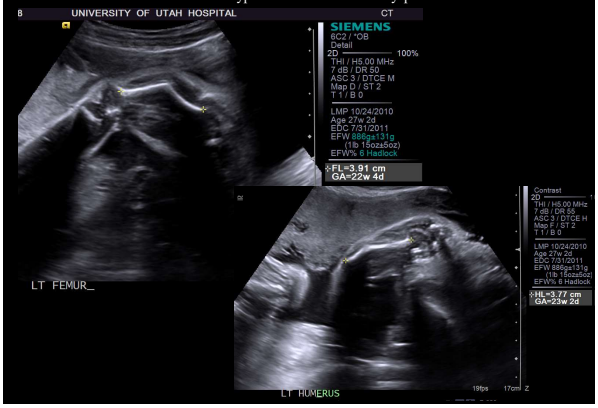


11 wks	13.7 weeks	
Large NT	Severe micrognathia Small Chest	Curved short long bones Femur & Tibia

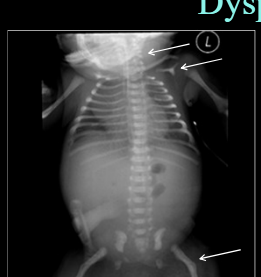
Final Diagnosis:Campomelic dysplasia

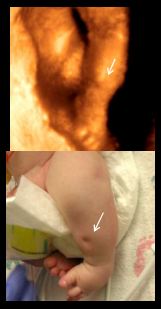
Courtesy Anne Kennedy

Kyphomelia – Bent Bone Dysplasia



Additional Features Campomelic Dysplasia





Analysis of *SOX9* provides molecular confirmation

Courtesy Anne Kennedy

Severe Micromelia, Macrocranium

MEASUREMENTS(mm)			MEAN		MA(wks)
BPD	100	100	100.0	mm	41.1±3
HC	361	358	359.3	mm	
AC	298	299	298.5	mm	33.8±3
FL	39	38	38.7	mm	22.4±2
CRL					
HUM	38	39	38.3	mm	23.5±3
BD					

EFW=1897±330g ULTRASOUND%=71 LMP%=18

CI NOT VALID FL/BPD NOT VALID
FL/AC 13.0 (20-24) HC/AC 1.20(0.97-1.16)

Delete from MA: BPD HC AC FL CRL HUM BD

CLINICAL	ULTRASOUND
LMP=~~14-AUG-91~~	ACUSON
MA =34.1wks	MA =30.2±SD wks
EDC=~~28-MAY-92~~	EDC=17-JUN-92

HOMOZYGOUS ACHONDROPLASIA

Both parents affected with heterozygous non lethal form
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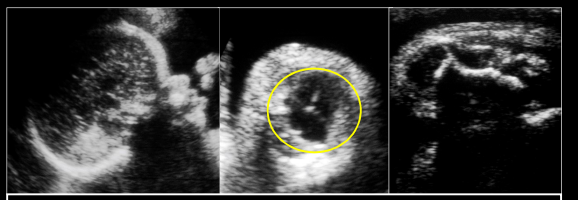
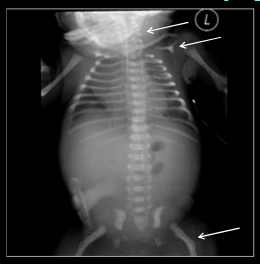
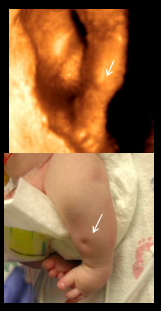


Presumptive diagnosis is thanatophoric dysplasia

Additional Features Campomelic Dysplasia





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Feature: Temporal Lobe Dysplasia in Thanatophoric Dysplasia

- 11 year retrospective to determine incidence of TLD in TD
  - 31 /2501 cases with perinatal autopsy had TD
  - 24/ 31 cases with corresponding US
  - Mean GA 21.3 wks
    - Prospective ID 25% (all after 2007)
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UOG 2014 by Glanc et al

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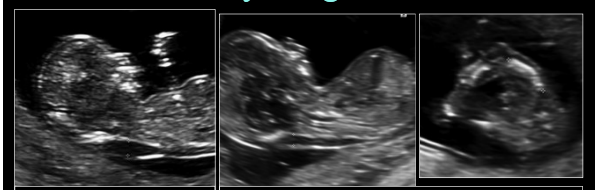

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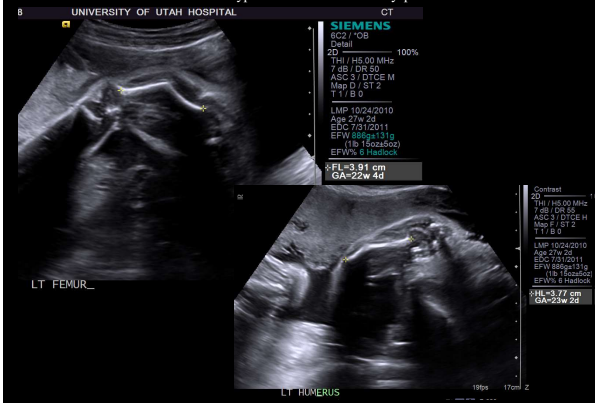
Kyphomelia – Bent Bone Dysplasia



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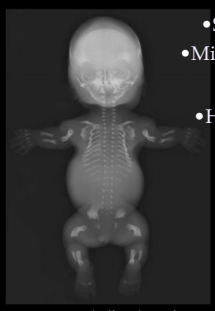
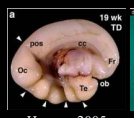
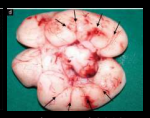


- Severe
- Micromelia
- Rib
- Hypoplasia

- Pathophysiology
- *FGFR3* gene
- 4p16



•Hevner, 2005



•Blaas et al.2012

- Lethality detection: ~100%
- Accuracy of specific diagnosis: 40-87.5%

1. Veh et al. Prenatal Diagnosis. 2011; 31:515-518.
2. Schramm et al. Ultrasound in Obstetrics & Gynecology 2009;34(2):160-170.

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Result in fetus with Homozygous lethal form
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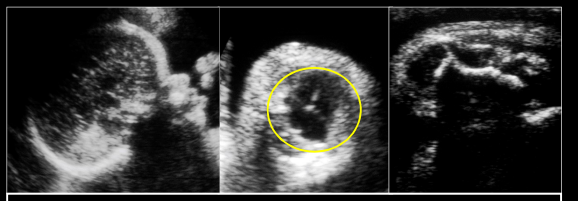


Presumptive diagnosis is thanatophoric dysplasia

Methods

- Retrospective review of all perinatal autopsies from 2002-2013 at tertiary referral centre in Toronto, ON
- Reviewed prenatal ultrasound reports to determine prospective detection of TLD
- Conducted retrospective reinterpretation of prenatal ultrasound for sonographic evidence of TLD

	24 (%)
Total number of perinatal autopsies	**2501**
# Cases of Confirmed TD	**31 (1.2%)**
# TD cases with U/S Imaging available for review	**24 (77%)**
TD Classification	**24 (Total)**
• TD Type 1	**20**
• TD Type 2	**4**

Feature: Temporal Lobe Dysplasia in Thanatophoric Dysplasia

- 11 year retrospective to determine incidence of TLD in TD
  - 31 /2501 cases with perinatal autopsy had TD
  - 24/ 31 cases with corresponding US
  - Mean GA 21.3 wks
    - Prospective ID 25% (all after 2007)
    - Retrospective ID 67% (throughout time)
  - Conclusion: Need dedicated views in MSK dysplasias

UOG 2014 by Glanc et al

Results

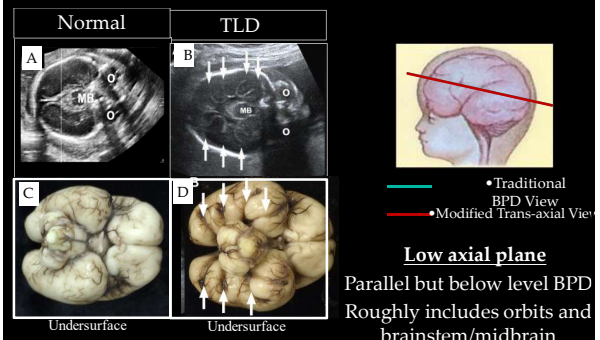
- Despite being virtually pathognomonic for TD, TLD was only initially reported in 6/24 TD cases; retrospective interpretation found 10 additional cases with TLD

	2002-2006 N=10		2007-2013 N= 14		2002-2013 N=24
Interpretation	**Yes**	**No**	**Yes**	**No**	**Total**
Original	0	10	6	8	6
Retrospective	5	5	11	3	16

- Factors that contribute to low sonographic detection
  - Lack of awareness of feature (1st case report 2007[1])
  - Ultrasound views that optimally display TLD are not included in the standard views taken
  - Overshadowing of TLD by the overwhelming abnormality in fetal skeletal structure

1. Malinger G, et al. Ultrasound in Obstetrics & Gynecology. 2007;29(2):178-191.

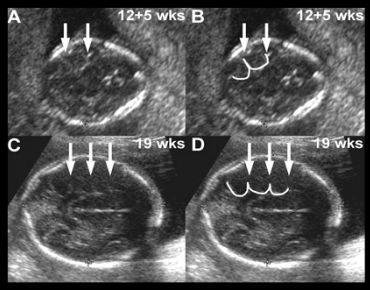
Examples – Low axial plane



Low axial plane

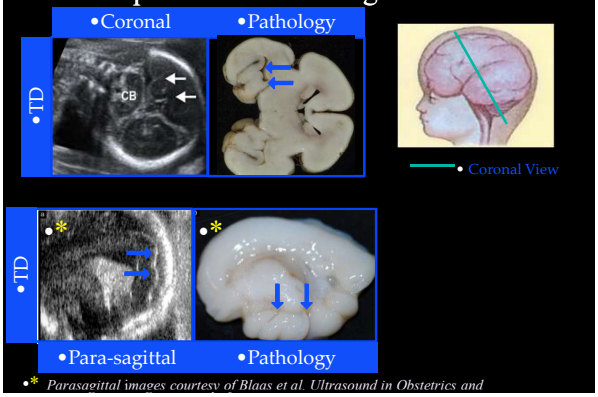
Parallel but below level BPD

Roughly includes orbits and brainstem/midbrain but lower plane



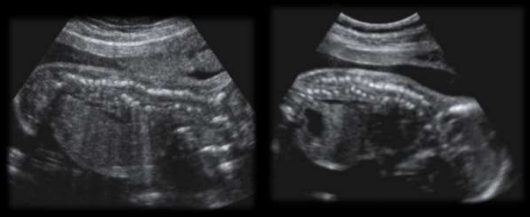
- Using the modified low axial views
  - TLD could potentially be detected as early as 16, or even possibly 12 weeks

Example – Coronal & Sagittal Plane



•* *Parasagittal images courtesy of Blaas et al. Ultrasound in Obstetrics and*

Case 4 Courtesy Charlotte Henningsway

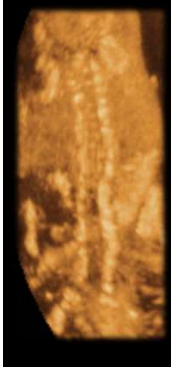


Referred for abnormality - 22wk 4days
Amnio 46XX
27 yo G5P1 SA3
NT 1.2mm, NB present.

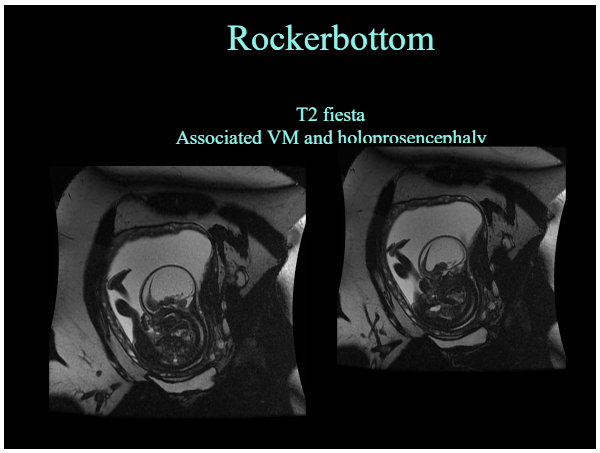
ID TLD

- Modified axial/coronal views
- Presence TLD help to distinguish from other skeletal dysplasias
- Guide specific molecular investigation for FGFR3 mutation for definitive analysis

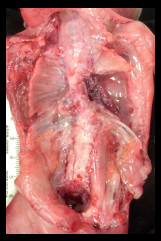
Group 35: Dysostoses with predominant vertebral involvement with and without costal involvement



- Heterogenous group with multiple spinal malsegmentation may be AR, AD, sporadic, may short thorax, pulm hypoplasia
- Spondylothoracic dysostosis : vertebral body malformations and ribs which flare in a fanlike pattern but which are not significantly malformed (thoracic asymmetry)
  - AR, > mortality rate , > neural tube defects.
- Spondylocostal dysostoses: vertebral malformations, frequent dramatic rib malformations, and short thorax
  - Most AR but familial ADF form with better survival
    - Mortality due respiratory insufficiency
- Short neck and trunk with relatively normal length limbs, scoliosis
- Extraskeletal: NTD, hindbrain, CVS, GU
- Most prevalent in Puerto Rican families

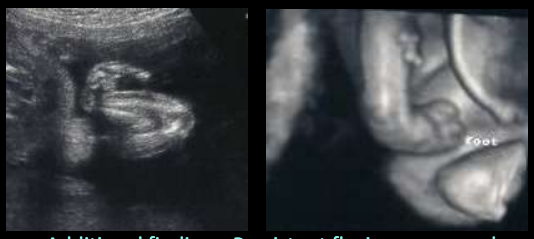


Spondylocostal dysostosis



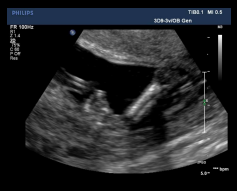
- Low-set posteriorly rotated ears
- Neck short, webbed
- Short torso
- Vertebral segmentation defects and rib anomalies
- Left-sided diaphragmatic hernia
  - Stomach, spleen and pancreas in thorax
  - Malrotated bowel
  - Midline liver
- Neuropathology:
  - Multiple Segmentation Anomalies, Spine
  - Ectopic Adrenal, Renal, Mullerian and Spinal Cord Elements, Left Paravertebral Soft Tissue.
  - Dorso-Ventral Duplication of Central Canal, Lumbar Spinal Cord.
- Bilobed right lung
- Absent left umbilical artery

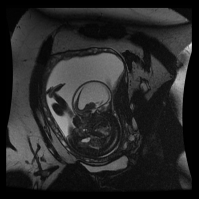
CASE: G1PO @ 24 WKS
Indication: Size > Dates

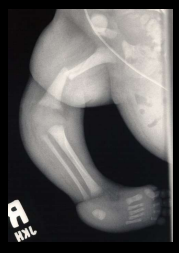


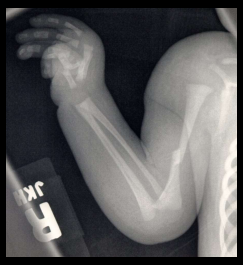
- Additional findings: Persistent flexion upper and lower limbs, limited movement, polyhydramnios
  - Small VSD

- 14 week with clubfoot, congen diaphr hernia, cardiac…etc.









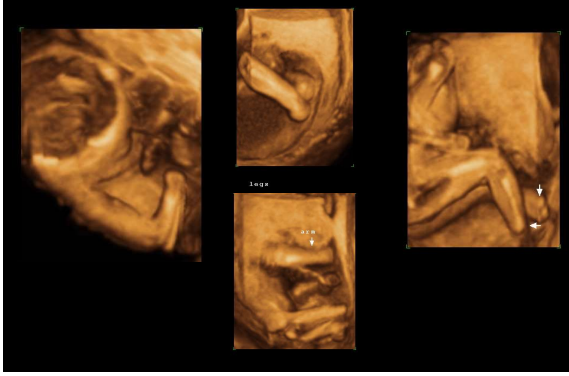
- Arthrogryposis of the upper and lower extremities
  - Small mouth, short neck, hypertelorism, edematous tissues
  - Contracted limbs with fractures humerus and femurs from delivery

Suspect Fetal Akinesia

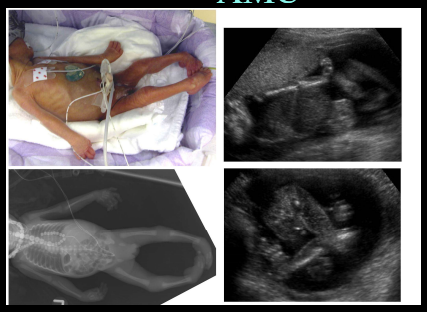
AMC vs Pena-Shokeir Phenotype

- PSP- lethal, multiple ankyloses, facial anomalies,pulmonary hypoplasia, IUGR, poly
  - Intercostal and diaphragmatic muscle dysfunction in combination with small thorax = lethal
- AMC – multiple extremitity contractures (≥ 2) but otherwise heterogenous
  - Pulmonary hypoplasia not obligatory
  - Variable outcome
- DDX: Trisomy 18 , multiple ptergyium syndrome,
- Variable genetic etiology

Acheiropodia: Absent hands/feet



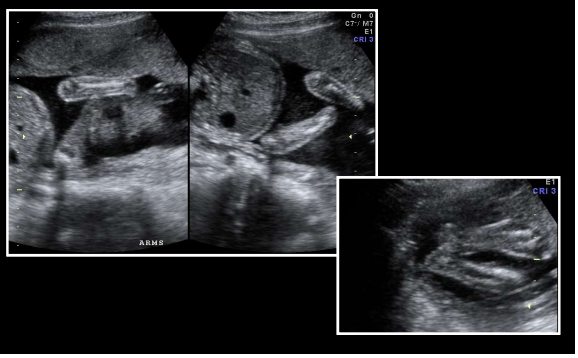
AMC



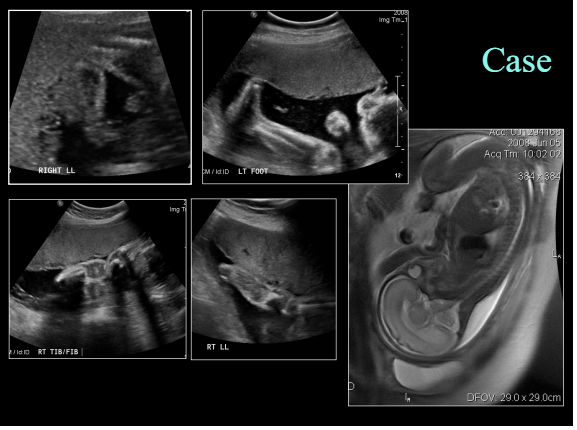
Case

Case: 35 yo G2P1

Maternal PMH: Congenital nystagmus

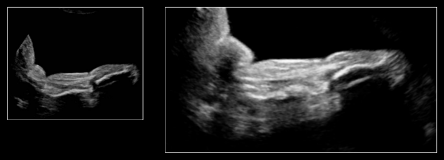


Case



Case

Femur- tibia



- Marked polyhydramnios
- Bones angulated with ? Fractures
- Bones poorly defined, angulations and curvatures with step deformitites

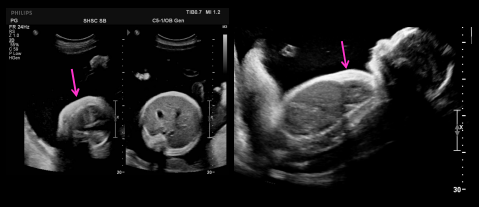
Case

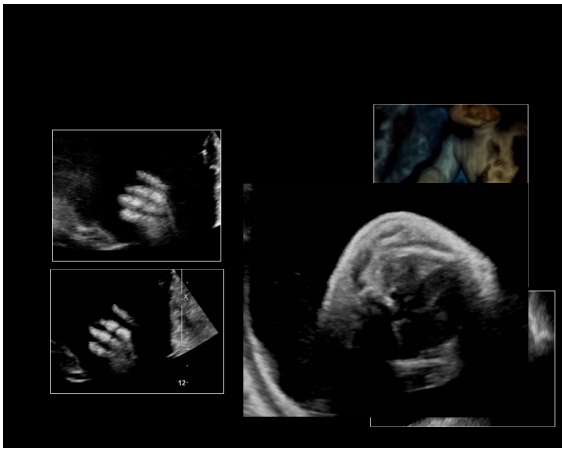
- History
  - 28yo G2P1 (4 yo male A&W), No family history
  - Meds: synthroid, materna, iron, otherwise no FH.
- Normal routine 18-20 wk but comment "NWS, rec repeat"
  - Admitted back pain , US shows poly, short limbs
  - Transferred to MSH @ 30wk4D
- Biometry:
  - BPD 79mm/32 wks;
  - HC 283/30wks 5d;
  - AC 289/33 wk
  - FL 44mm/24wk5days **

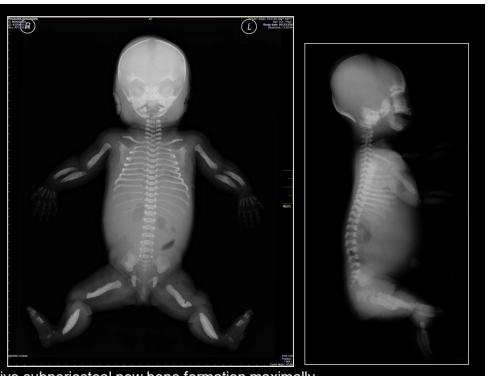
Facial & Extremities

Chest: Abd.

- Chest appeared visually small but thoracic circumference measured within normal for GA
  - Narrow AP diameter; heart fills > 50% thorax, ribs bit short





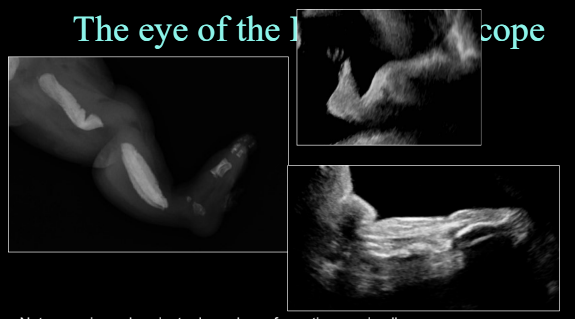


•Note massive subperiosteal new bone formation maximally involving long bones, irregular surface diaphysis, "reverse curvatures"

Caffey Disease or infantile cortical hyperostosis

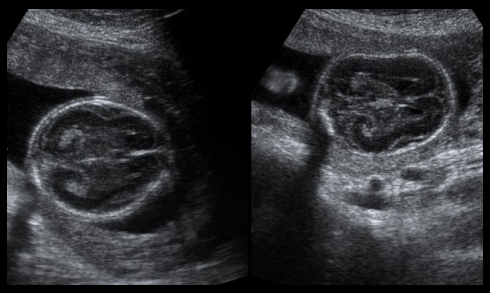
- Massive subperiosteal new bone formation
  - max involve diaphyses long bones and ribs, also mandible,s capulae, clavicles with sparing epiphyses
- Assoc fever, joint swelling pain around age 2 months and spont resolution by age 2 years.
- Occasion detect in T3 on US
- *COL1A1*mutation c.3040C>T (p.Arg1014Cys;
- Genetic counsel- inherit AD manner, may new mutation.

The eye of the I cope



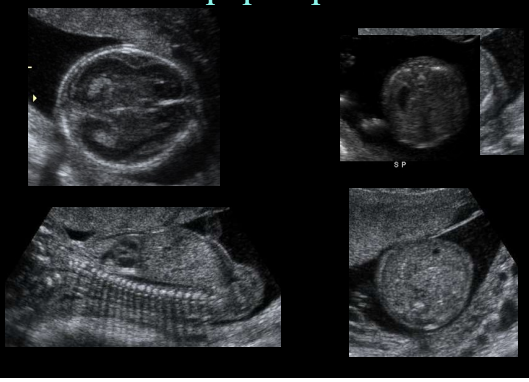
•Note massive subperiosteal new bone formation maximally involving long bones, irregular surface diaphysis, "reverse curvatures"

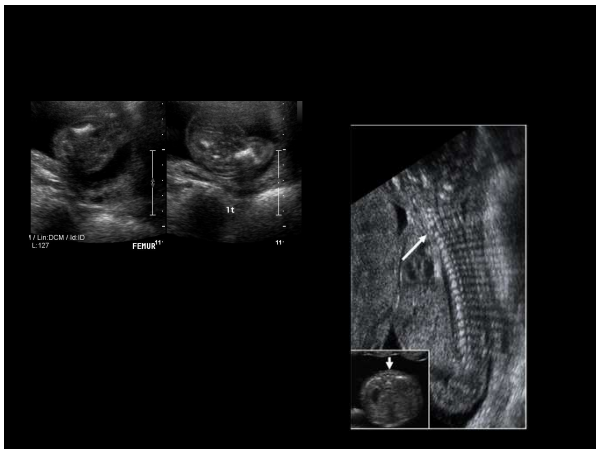
Case

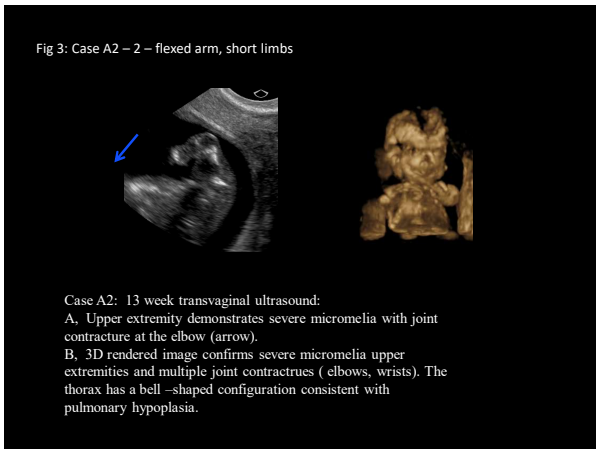


Clue in retrospect

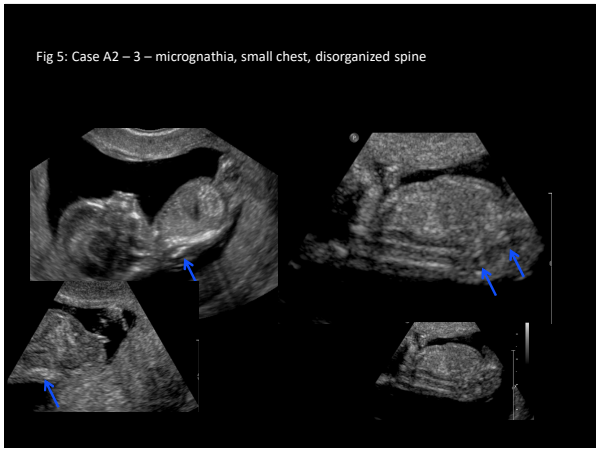
HYpophosphatasia

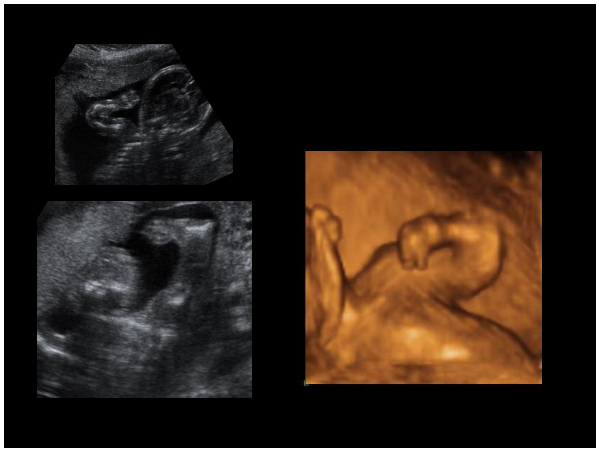






Case T1





Dyssegmental Dysplasia

- Rare ,AR
- Characteried by differences in size/shape vertebral bodies anisospondyly resulting in spine disorganization
  - Severe is Silverman-Handmaker DD SH
  - Milder Rolland Desbuquos DD RD type
  - Mutation in heparan sulphate perlecan gene (HSPG2)
    - Abn cartilage development

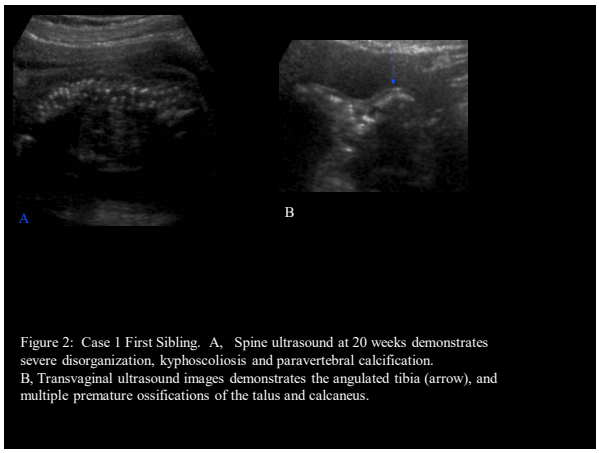


Figure 2: Case 1 First Sibling. A, Spine ultrasound at 20 weeks demonstrates severe disorganization, kyphoscoliosis and paravertebral calcification.
B, Transvaginal ultrasound images demonstrates the angulated tibia (arrow), and multiple premature ossifications of the talus and calcaneus.

Sibling tvs 13 weeks

Fig 1: Case A1 – Autopsy images 22 yo normal history. Initial US 23 weeks multiple Segmentation anomalies, markedly shortened long bones and small chest

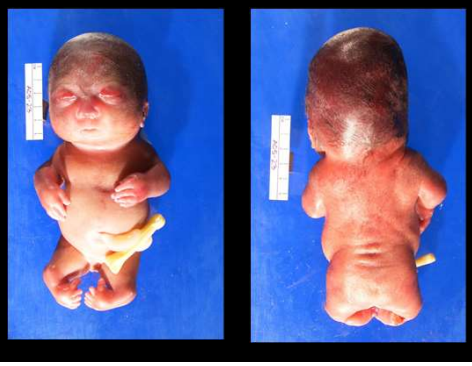
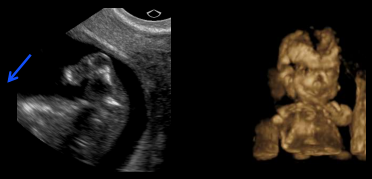


Fig 3: Case A2 – 2 – flexed arm, short limbs



Case A2: 13 week transvaginal ultrasound:
A, Upper extremity demonstrates severe micromelia with joint contracture at the elbow (arrow).
B, 3D rendered image confirms severe micromelia upper extremities and multiple joint contractrues (elbows, wrists). The thorax has a bell –shaped configuration consistent with pulmonary hypoplasia.

Fig 2: Case A1 – Postnatal radiographs

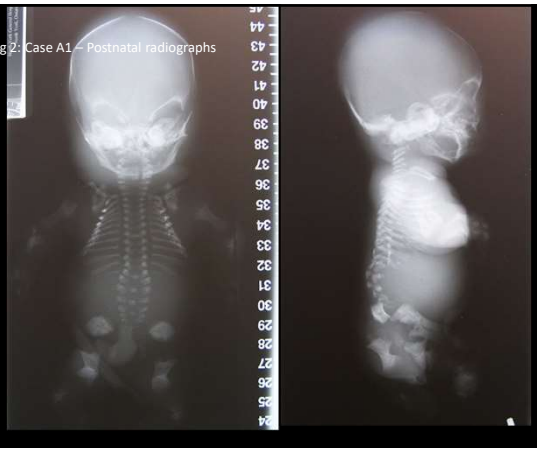


Fig 5: Case A2 – 3 – micrognathia, small chest, disorganized spine

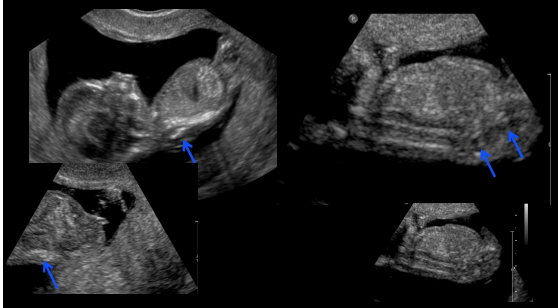


Fig 9: Case B

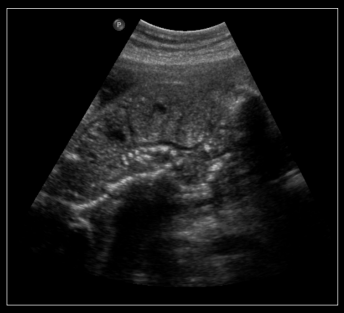
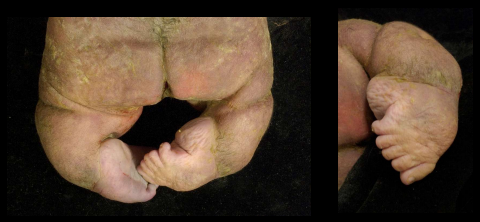


Figure Family B1, DD-SH at 19.9 weeks gestation age.
B, Sagittal ultrasound spine demonstrates marked vertebral disorganization. The vertebral bodies demonstrate a range of abnormalities from lack of ossification to varying sizes consistent with anisospondyly.

Fig 11: Case B – autopsy: short limbs, talipes



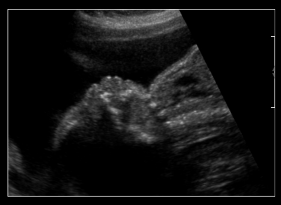


Figure Family B1, DD-SH at 19.9 weeks gestation age.
C, Sagittal ultrasound of the profile demonstrates flat facies with micrognathia

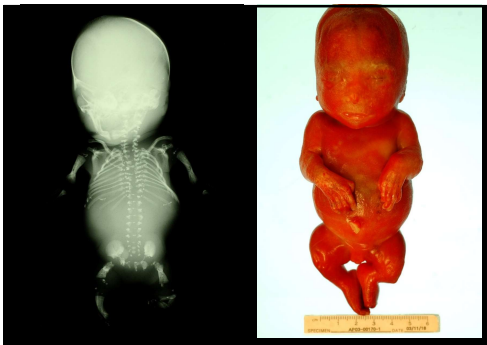


Figure 1: First sibling at 20 weeks gestation. A, Radiograph (AP view) demonstrates chondrodysplasia punctata with foci of multiple punctate epiphyseal calcifications, ectopic cartilaginous calcifications, severe asymmetric shortening and bowing of long bones, angulated fracture of the left tibia, profound platyspondyly, bell shaped thorax and hypoplastic gracile ribs. B, AP photograph confirms radiographic findings, and demonstrates midface hypoplasia.

Fig 10: Case B – autopsy: flat facies, micrognathia

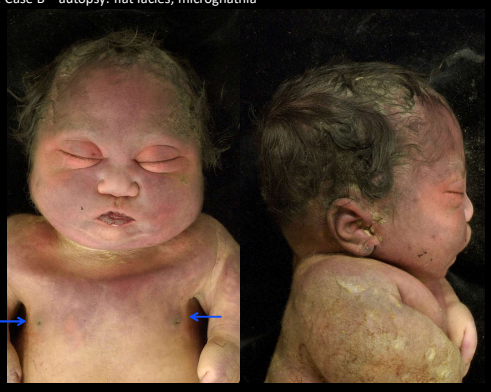
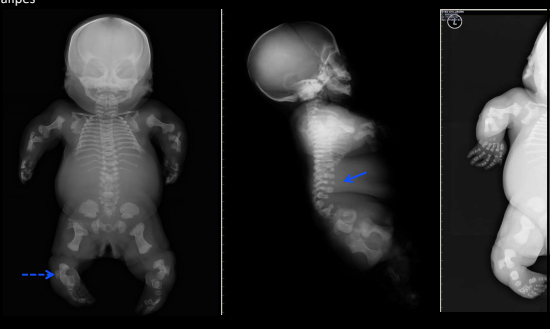
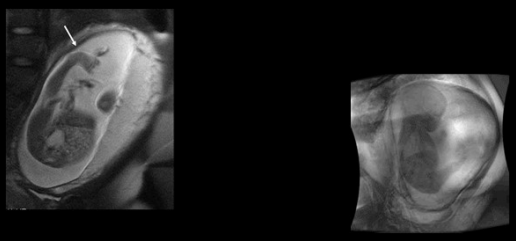


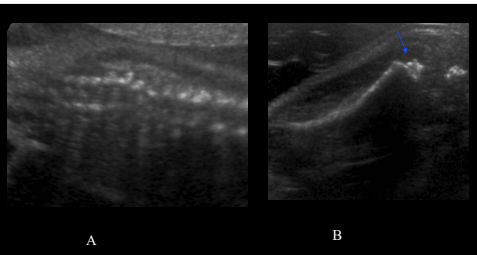
Fig 12: Case B radiographs

- Irregular sized vertebral bodies with single or multiple ossification centres
- Small thorax and short horizontal ribs
- Shortened, widened, angulated tubular bones
- Bony protrusions at joints
- Talipes



Club foot and amputation





A B

Figure 4: Second sibling at 24 weeks A,: Spine ultrasound at 24 weeks demonstrates mild vertebral disorganization and scoliosis. B, Radiograph femur: mild bowing of the femur with premature proximal epiphyseal stippling (Arrow).

Case

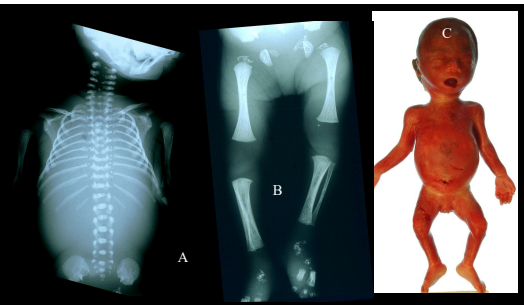
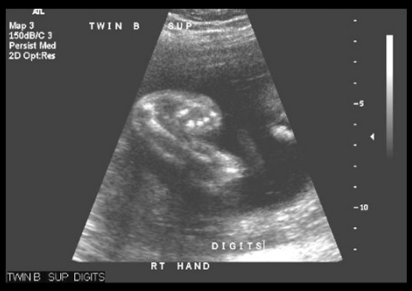
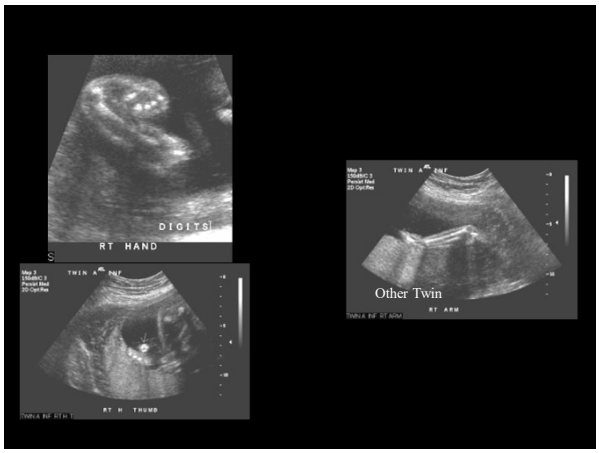


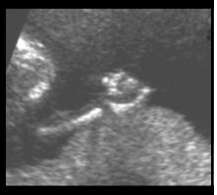
Figure 3: Sibling 2 at 24 weeks. A, AP Radiograph at 24 weeks demonstrates premature proximal femoral epiphyseal stippling, mild vertebral abnormalities (sagittal clefting of the thoracic vertebrae, mild platyspondyly).
B, AP radiogragph . Premature epiphyseal stippling is present at multiple locations including the femurs, calcaneus, talus, and paravertebral. Borderline mild shortening of the long bones is noted.
C, Photograph of the stillborn infant.

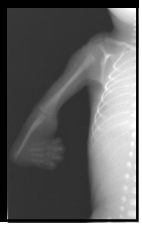
What do you want to know?



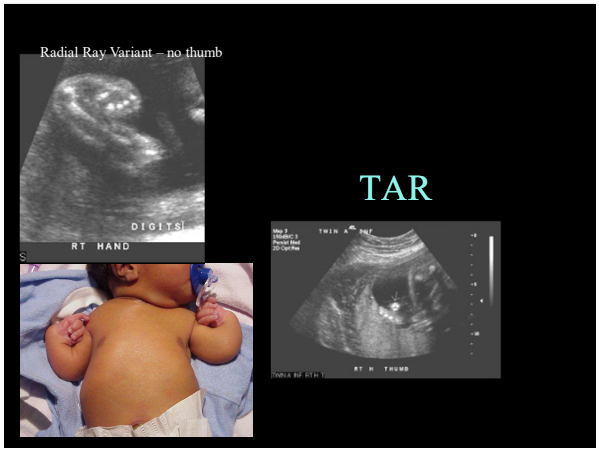


Radial clubhand





The most frequent
Rarely isolated and sporadic
Usually syndromic or associated with
- aneuploidy (T18)
- radial hypoplasia sequence
  (mild thumb hypoplasia- absence of radius)
- hematologic disorders (Fanconi, TAR,…)



TAR

Radial clubhand & hematologic disorders

Fanconi	AR, pancytopenia, chromosomal instability radial clubhand, no thumb, radial hypoplasia microcephaly, scoliosis,… ! 25 % no limb reduction anomaly
TAR	thrombocytopenia-absent radius, AR thumb & metacarpals present 33 % heart defects (Fallot, septal defects) C/S recommended
Aase S	AR, hypoplastic anemia, triphalangeal thumb cardiac defects (VSD, Coarctation)

Thrombocytopenia absent Radius TAR

- Rare – AR – chromosome 1q21 harbor a 200kb deletion multigene include rmb8 gene
- Characterize :
  - Absent radius BUT HAVE THUMB
  - Thrombocytopenia/platelet deficiency
    - May normalize with age
- Associated short stature, multisystem malformation, dysmorphic facies/microgthania…

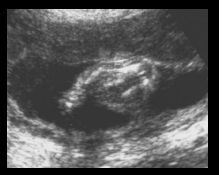
Radial clubhand & hematologic disorders

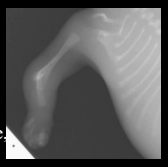
Fanconi	AR, pancytopenia, chromosomal instability radial clubhand, no thumb, radial hypoplasia microcephaly, scoliosis,… ! 25 % no limb reduction anomaly
TAR	thrombocytopenia-absent radius, AR thumb & metacarpals present 33 % heart defects (Fallot, septal defects) C/S recommended
Aase S	AR, hypoplastic anemia, triphalangeal thumb cardiac defects (VSD, Coarctation)

Radial clubhand & …

- Scoliosis VACTERL
  Goldenhar
  Klippel-Feil
- Cleft lip / palate
- Chromosomal anomaly: T18, T21
  13p del, ring 4

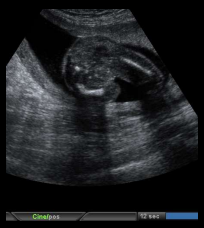
Ulnar clubhand





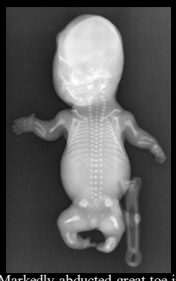
- rare
- ulnar deficiency
- usually non syndromic
- frequently isolated
- may be associated with:
  radial fingers anomalies! ,
  other: lobster claw, Cornelia de Lange, mesomelic dwarfism

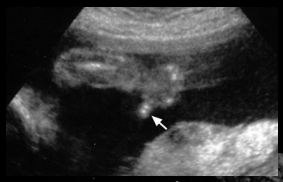
Once we are talking thumbs

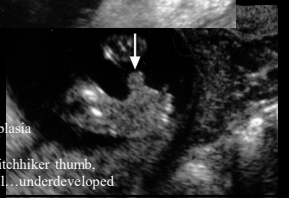


- Focal Femoral Deficiency
  - Proximal type Classify A-d (D is worst involving aceteabulum)
  - Rare, non-hereditary
  - Uni or bilateral
  - Etiology
    - Thalidomide
    - Associated with other syndromes included femoral hypoplasia-unusual facies, femur-fibula-ulna syndrome
    - May association diabetes

Diastrophic Dysplasia



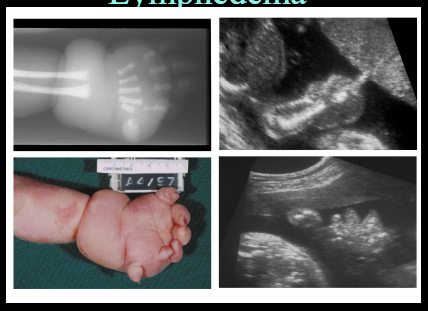




Markedly abducted great toe in diastrophic dysplasia
Wax et al JUM 22:805-808 2003
Note proximal micromelia, externally rotated hitchhiker thumb, hypoplastic vertebral bodeies especially cervical, underdeveloped

- Focal Femoral Deficiency
  - Proximal type Classify A-d (D is worst involving aceteabulum)
  - Rare, non-hereditary
  - Uni or bilateral
  - Etiology
    - Thalidomide
    - Associated with other syndromes included femoral hypoplasia-unusual facies, femur-fibula-ulna syndrome
    - May association diabetes

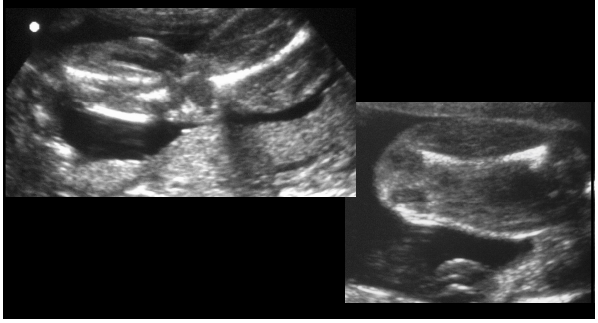
Constricting Bands with Lymphedema

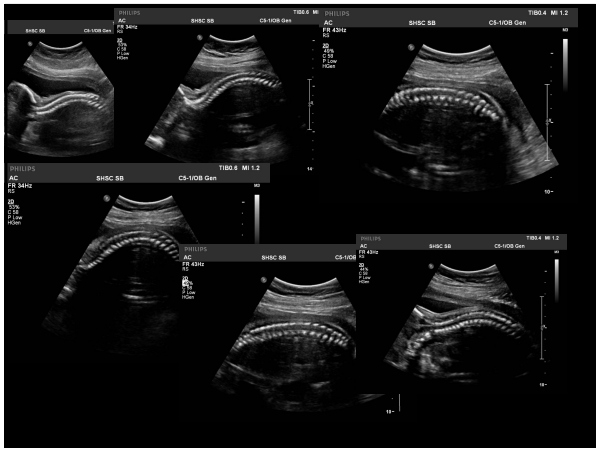


We Fail

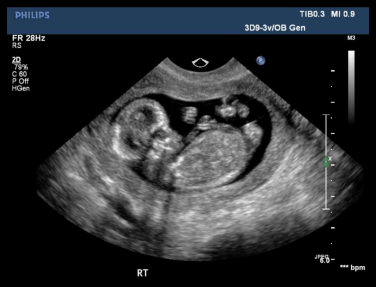
- 19 wk G1P0 Routine
  - Repeat anatomy for "limited views sagittal spine due to breech position".

Easy to Miss – lymphedema lower extremitiy

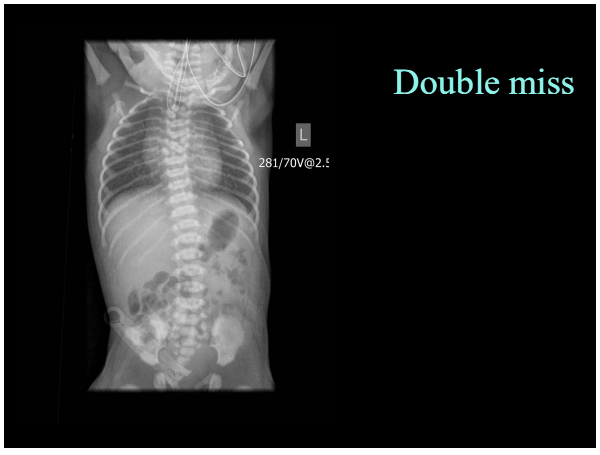


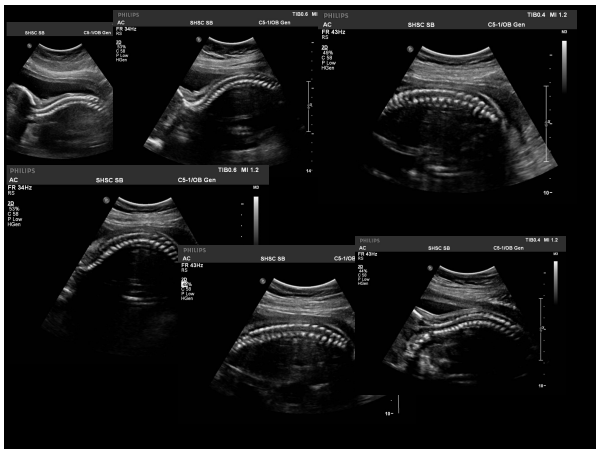


Right arm radial hypoplasia – T1



Double miss



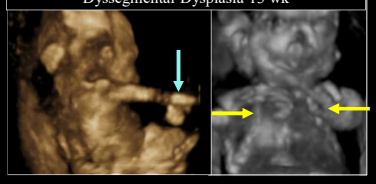


Thank you

Timing Onset Limb Shortening

- T1 diagnosis generally lethal - Earlier diagnosis the worse the prognosis

Dyssegmental Dysplasia 13 wk



- T3 onset want to consider
  - Familial, constitutional, normal variation, FGR, nonlethal (Htz achondroplasia)

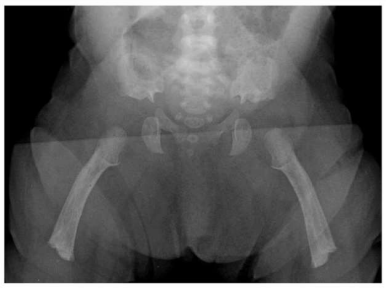
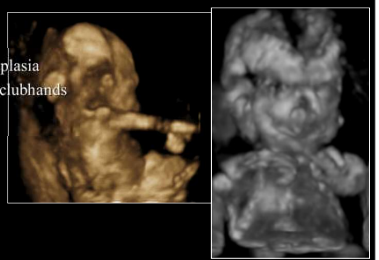


Fig. 4
Anteroposterior radiograph of the pelvis and femora in an infant with achondroplasia. Characteristic findings include a squared-off pelvis, horizontal acetabula, very narrow sacrosciatic notch, characteristic proximal femoral radiolucency, and short and robust femora

Timing Onset Limb Shortening

- **T1 diagnosis generally lethal - Earlier diagnosis the worse prognosis**

13 weeks Dyssegmental Dysplasia
Note Radial ray hypoplasia, clubhands
Note pulmonary hypoplasia



- **T3 onset want to consider**
  - Familial, constitutional, FGR, nonlethal (Htz achondroplasia)

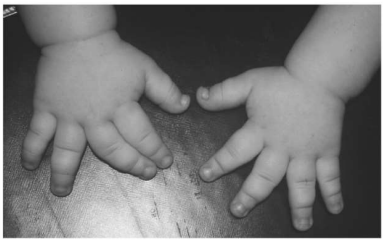


Fig. 6
Hands in achondroplasia, well illustrating brachydactyly and (here, asymmetric) trident configuration – excess separation between the third and fourth fingers. Originally published in Pauli RM (2010) Achondroplasia. In Cassidy SB, Allanson JE: Management of Genetic Syndromes, 3rd ed. Wiley-Blackwell