OBJECTIVE

- Identify key features on prenatal imaging that aid in diagnosis of skeletal dysplasias (SD).
- Develop an organized approach in assessing lethal vs nonlethal SD.
Need to

- Recognize normal musculoskeletal development
- Know when a finding is abnormal
- Accurate knowledge of gestational age
  - Best: early 1st trimester US
  - IVF dates

- Appearance of the bony skeleton
  - Entire limb = micromelia
  - Proximal segment = rhizomelia
  - Intermediate segment = mesomelia
  - Distal segment = acromelia
Multiple tables

- Use ossified fetal skeleton to determine GA
- Tables based on specific population
  - may not apply (Japanese)
- **Early** gestation: all fetuses are same size
- **Later** gestation: great range of variability
Modalities - US

- Useful throughout pregnancy
- Only tool in 1\textsuperscript{st} trimester
- 3D advances
- \textbf{BUT} poor at determining degree of mineralization
Modalities - Fetal MRI

- 2nd and 3rd trimesters
- Global view of fetus
- Better
  - Intracranial anomalies
  - Chest abnormalities
  - Cleft palate
- **BUT** Limited skeletal imaging
Modalities - Fetal CT

- 2\textsuperscript{nd} and 3\textsuperscript{rd} trimesters
- Best to visualize bone
- \textit{BUT} Radiation exposure
Skeletal Dysplasia

- 80-90% lethal or severe SD detectable prenatally

- But only ~50% given accurate diagnosis
Early 1\textsuperscript{st} trimester-
Nuchal Translucency
Second trimester US clues suggesting **lethal** Skeletal Dysplasia:

- Long bone measurements <3rd % (particularly early second trimester)
- Femur/Foot ratio < 1.
- Chest/abdominal circumference <0.6
- Chest circ <5%, Cardiac:thoracic ratio
- Femur length/abdominal circumference <0.16
- Polyhydramnios
**Lethal THANATOPHORIC DYSPLASIA**

- Most common lethal dysplasia.
- Defect in fibroblast growth factor receptor 3 \( \text{FGFR}3 \)
- Usually autosomal dominant de novo mutation.
- First trimester - nuchal translucency
- Type I more common.
- Type II assoc with less femoral bowing and cloverleaf skull.
Long Bones: severe micromelia
 THANATOPHORIC DYSPLASIA

- Hands/Feet:
  - Brachydactyly
  - Trident hand

Short Femur/Foot ratio: 0.4 (Normal 1)
THANATOPHORIC DYSPLASIA

- **Head:** macrocrania, frontal/parietal bossing - cloverleaf skull; temporal lobe anomalies
- **Face:** flat /depressed nasal bridge

MR-Macrocephaly. delayed sulcation
abnormal cortical gyration
loss of pial lamination inferior medial temporal lobes.
**THANATOPHORIC DYSPLASIA**

- **Thorax:** narrow short ribs
  - CC/AC: < 0.6
- **Spine:** platyspondyly

Small, bell-shaped thorax,
Lethal ACHONDROGENESIS

- Ribs short, thin, hypomineralized
- Vertebral bodies absent; parallel pedicles
- Ilia short crescentric; absent ossification ischia / pubis
- Severe micromelia - flared, cupped metaphyses
Lethal ACHONDROGENESIS

- First trimester - increased nuchal translucency
- **Head**: hypomineralized skull
- **Face**: flat nasal bridge, short nose
  
  Short neck

Clarity of intracranial structures is a sign of decreased mineralization.

Flat nasal bridge

27 weeks 2 days
ACHONDROGENESIS

- **Chest:** short slender ribs +/- fractures; normal scapulae
- **Abdomen:** protruberant
- **Spine:**
  - vertebral bodies not mineralized
  - pedicles parallel

Rib short with beaded appearance suggestive of fractures

Parallel pedicles; hard to see vertebral bodies
ACHONDROGENESIS

- **Pelvis**: ilia short and crescentric; absent ossification of ishia and pubi
- **Long Bones**: severe micromelia
- **Hands/Feet**:  
  - Short Femur/Foot ratio <1  
  - Low FL/AC <0.6
Lethal
Type II OSTEOGENESIS IMPERFECTA
OSTEOGENESIS IMPERFECTA

- Type I collagen gene
- Types I-IX: type II lethal, III severe; I / IV mild.
- Auto dom (I-V); Auto recessive (VI-IX)
  - II and III may also be autosomal recessive.
- Type II - nuchal translucency.
- Multiple asymmetric fractures.
Lethal type II
OSTEOGENESIS IMPERFECTA

- **Head:** hypomineralization, compressible
Lethal Type II
OSTEOGENESIS IMPERFECTA

- **Thorax**: bell-shape, deformed, beaded ribs
- **Spine**: platyspondyly
Lethal Type II
OSTEOGENESIS IMPERFECTA

- **Long Bones**: short broad, irregular bowing, angulation, asymmetric FL/AC, Femur/Foot abnormal
Type III

AUA 19w2d
GA (LMP) 19w4d

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<tr>
<th>Measurement</th>
<th>GA</th>
<th>Range</th>
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<td>BPD</td>
<td>4.49 cm</td>
<td>19w5d (±1w6d)</td>
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<tr>
<td>HC</td>
<td>16.43 cm</td>
<td>19w2d (±1w4d)</td>
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<tr>
<td>AC</td>
<td>15.23 cm</td>
<td>20w4d (±2w1d)</td>
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<td>FL</td>
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<td>17w1d (±1w3d)</td>
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<td>&lt;2 %</td>
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<td>Heart Rate</td>
<td>146 bpm</td>
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OSTEOGENESIS IMPERFECTA Type III

- 3D CT 22 wk 2 days
- Skull-demineralized
- Chest-ribs thin, demineralized, and irregular
- Long Bones-bowed femurs
Type III OI

Bell-shaped, thin ribs, beading; vertebral bodies flat.
19 week fetus with multiple fractures
Hypophosphatasia
New Case
Hypophosphatasia

Alkaline phosphatase < 10

Neg OI testing
Chondroectodermal dysplasia
Common in Amish
Autosomal recessive; mutations in EVC1 or EVC2, located on chromosome 4p16.
Same gene mutation causing Curry-Hall syndrome, autosomal dominant.
ELLIS-VAN CREVELD SYNDROME

- Head/face: normal
- Thorax: narrow thorax with short ribs
- Abdomen: protuberant

Bell-shaped, small thorax; apparent cardiomegaly; protuberant abdomen
ELLIS-VAN CREVELD SYNDROME

- **Long Bones:** short, bowed round metaphyses
- **Hands/Feet:** postaxial polydactyly (100% hands; 10% feet)
ELLIS-VAN CREVELD SYNDROME

- cardiac defects
- handlebar clavicles

DDX: Jeune syndrome, short-rib polydactyly
Lethal and nonlethal CHONDRODYSPLASIA PUNCTATA

- heterogeneous - 4 types
- Conradi-Hunermann type (2) X-linked dominant involves cholesterol synthesis enzymes.
- Brachytelephalangic and Rhizomelic types autosomal recessive, respectively involving sulphate ester bonds and peroxisomal protein import.
- Rhizomelic type is usually lethal.
- Subtypes have punctate calcification of the epiphyseal cartilage and flat midface and nose.
CHONDRODYSPLASIA PUNCTATA

- **Head:** microcrania
- **Face:** dysmorphic, flat, saddle nose, cataracts
- **Thorax:** stippling costochondral junction

![Image of ultrasound with measurements and notes: HC <3rd %, Flat face and nose.]
CHONDRODYSPLASIA PUNCTATA

- **Spine**: stipled epiphyses
- **Long Bones**: short femora and humeri

Stipling of vertebral bodies with more than 3 ossification centers
CHONDRODYSPLASIA PUNCTATA

- Hands/Feet: stippled epiphyses, carpal and tarsal
- contractures, polyhydramnios
CHONDRODYSPLASIA PUNCTATA

Small head facial flattening; stipling of cervical, lumbar, and sacral vertebral bodies.
Nonlethal

- Normal growth in first and early second trimester.
- Skeletal growth starts to drop late 2nd/early 3rd trimester
Nonlethal ACHONDROPLASIA

- **Head:** Macrocephaly
- **Face:** small midface, depressed nasal bridge (saddle nose) Frontal bossing
- **Thorax:** +/- small; normal scapula and clavicle
Nonlethal ACHONDROPLASIA

- **Pelvis:** hard to see prenatally
- **Long Bones:** rhizomelic shortening; metaphyseal flaring/overgrowth (femur-collar hoop sign)

Left femur (7 wks behind <3rd) and left tibia (measured only 5 wks behind) consistent with rhizomelia.

- Femur/Foot ratio: 0.67 (< 1).
Nonlethal
ACHONDROPLASIA

- Hands/Feet: brachydactyly, trident hand

- DDX: hypochondroplasia

- thanatophoric dysplasia,
- homozygous achondroplasia
ACHONDROPLASIA

- Postnatal imaging:
  - Frontal bossing
  - Small midface and saddle nose
  - Spine: thoracolumbar kyphosis, caudal narrowing of interpedicular distance, posterior scalloping, and bullet shape
  - Rhizomelia, flared metaphyses, redundant skin folds
  - Squared iliac bones, medial and/or lateral spurs, narrow sacrosciatic notch
  - Brachydactyly; trident hand
New case
Polyhydramnios, short limbs, wide metaphysis
Metatropic Dysplasia
With so many SD, specific diagnosis often not possible prenatally. Critical to differentiate lethal from nonlethal.

Key findings suggesting lethality include:

- Long bone measurements < 3rd percentile in the early second trimester
- Femur/Foot ratio < 1.
- Chest/abdominal circumference < 0.6
- Femur length/abdominal circumference < 0.16
CONCLUSIONS

- Complex group of SD with over 400 possible diagnoses and significant overlap of features on prenatal imaging.

- An organized US approach to determine lethality improves prenatal counseling and allows for appropriate delivery planning and postnatal management.

- Using specific criteria described, prenatal SD lethality detection can approach 100%.(Yeh et al Prenat Diagn 2011)
Thank you!

- Anna Blask
- Eva Rubio
- Kimberly Fagen
- Kadine Linden
- Linda Rebolo
REFERENCES


