There’s a Short Long Bone, What Now?
Fetal Skeletal Dysplasias
Over 450 types of Skeletal Dysplasias

<table>
<thead>
<tr>
<th>X-linked Spondyloepiphyseal Tarda</th>
<th>Thanatophoric dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Osteogenesis Imperfecta</strong></td>
<td></td>
</tr>
<tr>
<td>Achondrogenesis</td>
<td>Hypochondrogenesis</td>
</tr>
<tr>
<td>Achondroplasia</td>
<td></td>
</tr>
<tr>
<td>Otospondylomegaepiphyseal dysplasia (OSMED)</td>
<td>Fibrochondrogenesis</td>
</tr>
<tr>
<td>Hypochondroplasia</td>
<td>Campomelic dysplasia</td>
</tr>
<tr>
<td>Spondyloepiphyseal dysplasia congenita (SEDC)</td>
<td></td>
</tr>
</tbody>
</table>
How will we come across this diagnosis?

- Third trimester size less than dates ultrasound at 33 4/7 weeks shows:

```markdown
Ultrasound Measurements mm GA
Biparietal diameter (BPD) 88 35w5d
Head circumference (HC) 299 33w0d
Abdominal circumference (AC) 281 32w1d
Femur length (FL) 54 28w3d
Humeral length (HL) 48 28w0d
Cerebellar Diameter 44
Ultrasound Age 31w3d
```

```markdown
Rt radius 3.6 mm <1%
Rt ulna 43 mm <1%
Left radius 39 mm <1%
Left ulna 43 mm <1%
Rt tibia 48 mm <1%
Rt fibula 45 mm <1%
Left tibia 48 mm <1%
Left fibula 49 mm 1%
```
What should our goal be at the initial visit?

A. Genetic definitive diagnosis
B. Termination of pregnancy
C. Detailed anatomic survey including all long bones
D. Assessment of likely lethality from pulmonary hypoplasia
E. Amniocentesis or Serum Testing/Genetics Referral
F. Referral to a Fetal Care Center
What should our goal be at the initial visit?

A. Genetic definitive diagnosis
B. Termination of pregnancy
C. Detailed anatomic survey including all long bones
D. Assessment of likely lethality secondary to pulmonary hypoplasia
E. Amniocentesis or Serum Testing/Genetics Referral
F. Referral to a Fetal Care Center
Detailed Ultrasound Technique

- Long bones
- Thorax
- Hands/feet
- Skull
- Spine
- Face
Long bones

- Measure all including distal
- Look for missing bones
- Mineralization, curvature, fractures
If limbs disproportional....

Does the abnormality effect:

- Proximal (rhizomelic)
- Middle (mesomelic)
- Distal (acromelic)
Long bones

- Measure all extremities
  - If limb shortening present: define involved segments
  - Femur length-foot length ratio
    - Normal = 1
    - < 1 suggests skeletal dysplasia

- Presence of bones
- Curvature/bowing
  - Campomelic dysplasia, thanatophoric dysplasia, AD OI, achondrogenesis, hypophosphatasia

- Degree of mineralization
  - ↓: hypophosphatasia
  - Pronounced at spine, cranium

- Fractures
  - OI

Long bones

- **Timing of limb shortening**
  - If found second trimester at anatomic survey: 18-20 weeks
    - OI II, achondrogenesis, thanatophoric dysplasia, diastrophic dysplasia, chondroectodermal dysplasia
  - Serial measurements: later appearing (22-30 weeks)
    - Achondroplasia more likely
Putting it in perspective...

Figure 1. Prenatally diagnosed skeletal dysplasias: numbers of cases by gestational age groups for the 10 most common dysplasias: thanatophoric dysplasia (types 1 and 2) (■), osteogenesis imperfecta (all types) (□), short rib dysplasias (■), Ellis van Creveld (■), achondroplasia (■), achondrogenesis (■), campomelic dysplasia (■), asphyxiating thoracic dysplasia (■), hypochondrogenesis (■), and diastrophic dysplasia (■). The peak of diagnoses is between 15 and 29 weeks, but some types are often first apparent in the third trimester.
Thorax

- **Pulmonary hypoplasia**
  - TC < 5\(^{th}\) percentile
  - FL/AC < 0.16
  - TC/AC < 5\(^{th}\) percentile
  - Chest-trunk length ratio < 5%

- **Ribs**
  - Size, number
  - Fracture, mineralization, length

- **Clavicle**
  - Absent/hypoplastic: cleidocranial dysplasia

- **Scapula**
  - Absent: camptomelic dysplasia

Image from Dighe et al Radiographics 2008
Thorax

- **Short**
  - OI type II
  - Kniest’s dysplasia
  - Pena-Shokeir syndrome

- **Long narrow**
  - Asphyxiating thoracic dysplasia (Jeune)
  - Chondroextodermal dysplasia (Ellis-Van Creveld)
  - Campomelic dysplasia
  - Jarcho-Levin syndrome

- **Hypoplastic**
  - Short-rib polydactyly syndrome (I and II)
  - Thanatophoric dysplasia
  - Cleidocranial dysostosis syndrome
  - achondroplasia
Hands and feet

- **Digits**
  - Preaxial polydactyly
    - Radial/tibial
  - Postaxial polydactyly
    - Ulnar/fibular
- **Deformities**
  - Syndactyly (soft-tissue or bone fusion of adjacent digits)
  - Clinodactyly (deviation of finger)
- **Foot length**
- **Missing bones**
  - Absence of radius, hand
- **Postural deformities**
  - Hitchhiker’s thumb
  - Rocker bottom feet
  - Club feet/hand
Fetal Head

- Macrocephaly
  - Thanatophoric dysplasia, camptomelic dysplasia, Jarcho-Levin
- Hydrocephalus
  - Thanatophoric dysplasia, camptomelic dysplasia, OI II
- Microcephaly
  - Rhizomelic chondrodysplasia punctata
- Frontal bossing
  - TD, achondroplasia, cleidocranial dysplasia, osteopetrosis
- Cloverleaf
  - TD

Image from Dighe et al Radiographics 2008
Skull

- HC and BPD
- Shape
  - Brachycephaly
  - Scapocephaly (lateral flattening)
  - Craniosynostosis
- Mineralization, ossification
- BOD, IOD
- Micrognathia
- Cleft lip/palate
Spine

- Length/scoliosis
- Mineralization
- Vertebral height
  - Platyspondyly
    - Flattened body shape with reduced distance between the end plates
    - Tough diagnosis
Pelvis

• **Shape**
  - Femoral hypoplasia-unusual face syndrome
    - Hypoplastic acetabulae, constricted iliac base w/vertical ischial axis, large obturator foramina
  - Achondroplasia
    - Flat, rounded iliac bones  no iliac flaring
    - Broad horizontal superior acetabular margins
    - Small sacrosciatic notches

• **Evaluate genitalia**

• **3D u/s especially face and spine**
  - Improve diagnostic accuracy\(^1\)
  - Identify additional phenotypic features\(^2\)

---

Importance of Full Survey

Additional findings include

**Internal anomalies**
- Cardiac (Ellis-van Creveld syndrome)
- Urinary tract abnormalities (short-rib polydactyly type 2)
- Genital abnormalities (Robert syndrome, camptomelic dysplasia [ambiguous genitalia])
- GI tract abnormalities (achondrogenesis type 1)
- Skull abnormalities (asymmetry, basilar invagination, cloverleaf skull, craniosynostosis, defective ossification, macro or micro cephaly)

**External anomalies**
- Abnormally shaped ears
- Caudal appendate
- Facial deformities: cleft palate, micrognathia, short nasal bridge
What should our goal be at the initial visit?

A. Genetic definitive diagnosis
B. Termination of pregnancy
C. Detailed anatomic survey including all long bones
D. **Assessment of likely lethality**
E. Amniocentesis or Serum Testing/Genetics Referral
F. Referral to a Fetal Care Center
Lethality Assessment
Typically secondary to Pulmonary Hypoplasia

- Specific diagnosis when possible
- *FL/AC <0.15
- *Thoracic circumference ((AP + Transverse) * 1.57)
  - TC/AC normal: 0.77 – 1.01
  - <5% or less than 0.6 concerning
- FL <1%
- *Polyhydramnios
- 3D US versus MRI lung volumes (<5%)

Evaluating skeletal dysplasias on prenatal ultrasound: an emphasis on predicting lethality

Kathryn S. Milks¹ - Lyndon M. Hill² - Keyanoosh Hosseinzadeh³
What should our goal be at the initial visit?

A. Genetic definitive diagnosis  
B. Termination of pregnancy  
C. Detailed anatomic survey including all long bones  
D. Assessment of likely lethality  
E. Amniocentesis or Serum Testing/Genetic Referral  
F. Referral to a Fetal Care Center
### Prenatal Genetic Testing for Skeletal Dysplasia

#### NIPT – Genetic Screening Panel

- Tests **30** genes, **4** related to skeletal dysplasia:
  - FGFR3, FGFR2, COL1A1, COL1A2
- Need to have both biological parents (trio analysis).
- For *de novo* or paternally inherited diseases.

#### Prenatal Genetic Testing Panels

<table>
<thead>
<tr>
<th>Panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>natera</td>
</tr>
<tr>
<td>vistara</td>
</tr>
<tr>
<td>ARUP Laboratories</td>
</tr>
<tr>
<td>GeneDx</td>
</tr>
<tr>
<td>Connective Tissue Gene Tests</td>
</tr>
<tr>
<td>Greenwood Genetic Center</td>
</tr>
</tbody>
</table>

And others...

***Also the option for prenatal WES, but many of these panels are likely exhaustive enough***
# Genetic Testing

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Skeletal Dysplasia Sequencing Panel</th>
<th>Prenatal Skeletal Dysplasia Panel</th>
<th>Skeletal Dysplasia Panel, Sequencing (39 Genes) and Deletion/Duplication (36 Genes), Fetol</th>
<th>Skeletal dysplasia core &amp; extended NGS Panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab Name</td>
<td>Greenwood Genetic Center - Molecular Diagnostic Laboratory</td>
<td>GeneDx</td>
<td>ARUP Laboratories</td>
<td>Connective Tissue Gene Tests</td>
</tr>
<tr>
<td>Category</td>
<td>Skeletal Disorder and Skeletal Dysplasia Panel Tests</td>
<td>Skeletal Disorder and Skeletal Dysplasia Panel Tests</td>
<td>Skeletal Disorder and Skeletal Dysplasia Panel Tests</td>
<td>Skeletal Disorder and Skeletal Dysplasia Panel Tests</td>
</tr>
<tr>
<td>Test Code</td>
<td>SKELETAL-DYSPLASIA-SEQUENCING-PANEL</td>
<td>949</td>
<td>20121010</td>
<td>5118</td>
</tr>
<tr>
<td>Source</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Price</td>
<td>$2,400.00</td>
<td>$850.00</td>
<td>$3,720.00</td>
<td>$1,620.00</td>
</tr>
<tr>
<td>TAT</td>
<td>56 days</td>
<td>21 days</td>
<td>28-42 days</td>
<td>14-28 days</td>
</tr>
<tr>
<td>Techniques</td>
<td>Sequencing</td>
<td>Deletion/Duplication, Sequencing</td>
<td>Deletion/Duplication, Sequencing</td>
<td>Sequencing</td>
</tr>
<tr>
<td>Mechanisms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overlapping Genes</td>
<td>COL1A1, COL1A2, COL2A1, FGFR3, HSPG2, SLC26A2, SOX9, TRPV1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unique Genes</td>
<td>COL1A1, COMP, FLNA</td>
<td>AGPS, ALPL, ARSE, BMP1, CEP120, COL1A1, COL1A2, COMP, CRFAP, DLL3, DYN2C3H1, EVC2, FGFR1, FGF2, FKBPLD, FLNA, FLNB, GNAT1, IFTM5, IFT172</td>
<td>AGPS, ALPL, ARSE, BMP1, CEP120, COL1A1, COL1A2, COMP, CRFAP, DLL3, DYN2C3H1, EVC2, FGFR1, FGF2, FKBPLD, FLNA, FLNB, GNAT1, IFTM5, IFT172</td>
<td>ALPL, ARSE, COL1A1, COL1A2, DDX2, FKBPLD, FLNA, FLNB, GNAT1, IFTM5, IFT172</td>
</tr>
</tbody>
</table>

- **Genes:** COL1A1, COL1A2, COL2A1, FGFR3, HSPG2, SLC26A2, SOX9, TRPV1
- **Unique Genes:** COL1A1, COMP, FLNA, AGPS, ALPL, ARSE, BMP1, CEP120, COL1A1, COL1A2, COMP, CRFAP, DLL3, DYN2C3H1, EVC2, FGFR1, FGF2, FKBPLD, FLNA, FLNB, GNAT1, IFTM5, IFT172

- **Overlapping Genes:** ALPL, ARSE, COL1A1, COL1A2, DDX2, FKBPLD, FLNA, FLNB, GNAT1, IFTM5, IFT172

- **Other Genes:** MMP9, NIK2, NSOHL, PEX7, PTH1R, RBM1, SBD5, SLC25A1

- **Techniques:** Sequencing, Deletion/Duplication

- **Mechanisms:** Deletion/Duplication, Next Generation Sequencing

- **TAT:** 56 days, 21 days, 28-42 days, 14-28 days

- **Source:** Greenwood Genetic Center - Molecular Diagnostic Laboratory, GeneDx, ARUP Laboratories

- **Price:** $2,400.00, $850.00, $3,720.00, $1,620.00
### Table 2

<table>
<thead>
<tr>
<th>Disease Entities</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple epiphyseal dysplasia, pseudoachondroplasia</td>
<td>COMP, COL9A1, COL9A2, COL9A3, MATN3</td>
</tr>
<tr>
<td>Ellis–van Creveld syndrome</td>
<td>EVC</td>
</tr>
<tr>
<td>Osteogenesis imperfecta types I–IV, Ehlers-Danlos syndrome</td>
<td>COL1A1, COL1A2</td>
</tr>
<tr>
<td>Achondrogenesis type II, hypochondrogenesis, Kniest dysplasia, spondyloepiphyseal dysplasia, spondyloepimaphyseal dysplasia, Stickler dysplasia</td>
<td>COL2A1</td>
</tr>
<tr>
<td>Thanatophoric dysplasia types 1 and 2, achondroplasia, hypochondroplasia, other FGFR3 disorders, SADDAN dysplasia</td>
<td>FGFR3</td>
</tr>
<tr>
<td>Diastrophic dysplasia, achondrogenesis type 1B, atelosteogenesis type II, multiple epiphyseal dysplasia (recessive), other diastrophic dysplasia variant disorders</td>
<td>DTDST (SLC26A2)</td>
</tr>
<tr>
<td>Cleidocranial dysplasia</td>
<td>RUNX2</td>
</tr>
</tbody>
</table>

Note.—For a more detailed list of biochemical and molecular tests available for the diagnosis of skeletal dysplasia, see the University of Washington–sponsored World Wide Web page GeneTests (http://www.genetests.org). COL1A1 = collagen, type I, alpha 1; COL1A2 = collagen, type I, alpha 2; COL2A1 = collagen, type II, alpha 1; COL9A1 = collagen, type IX, alpha 1; COL9A2 = collagen, type IX, alpha 2; COL9A3 = collagen, type IX, alpha 3; COMP = cartilage oligomeric matrix protein gene; EVC = Ellis–van Creveld; DTDST (SLC26A2) = diastrophic dysplasia sulfate transporter (solute carrier family 26 [sulfate transporter] member 2); MATN3 = matrilin 3; RUNX2 = runt-related transcription factor 2; SADDAN = severe achondroplasia with developmental delay and acanthosis nigricans.

www.genetests.org
Table 2
Genes That Can Be Screened or Diagnosed In Utero

<table>
<thead>
<tr>
<th>Disease Entities</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple epiphyseal dysplasia, pseudoachondroplasia</td>
<td>COMP, COL9A1, COL9A2, COL9A3, MATN3</td>
</tr>
<tr>
<td>Ellis–van Creveld syndrome</td>
<td>EVC</td>
</tr>
<tr>
<td>Osteogenesis imperfecta types I–IV, Ehlers-Danlos syndrome</td>
<td>COL1A1, COL1A2</td>
</tr>
<tr>
<td>Achondrogenesis type II, hypochondrogenesis, Kniest dysplasia, spondyloepiphysyal dysplasia, Stickler dysplasia</td>
<td>COL2A1</td>
</tr>
<tr>
<td>Thanatophoric dysplasia types 1 and 2, achondroplasia, hypochondroplasia, other FGFR3 disorders, SADDAN dysplasia</td>
<td>FGFR3</td>
</tr>
<tr>
<td>Diastrophic dysplasia, achondrogenesis type 1B, atelosteogenesis type II, multiple epiphyseal dysplasia (recessive), other diastrophic dysplasia variant disorders</td>
<td>DTDST (SLC26A2)</td>
</tr>
<tr>
<td>Cleidocranial dysplasia</td>
<td>RUNX2</td>
</tr>
</tbody>
</table>

Note.—For a more detailed list of biochemical and molecular tests available for the diagnosis of skeletal dysplasia, see the University of Washington–sponsored World Wide Web page GeneTests (http://www.genetests.org). COL1A1 = collagen, type I, alpha 1; COL1A2 = collagen, type I, alpha 2; COL2A1 = collagen, type II, alpha 1; COL9A1 = collagen, type IX, alpha 1; COL9A2 = collagen, type IX, alpha 2; COL9A3 = collagen, type IX, alpha 3; COMP = cartilage oligomeric matrix protein gene; EVC = Ellis–van Creveld; DTDST (SLC26A2) = diastrophic dysplasia sulfate transporter (solute carrier family 26 [sulfate transporter] member 2); MATN3 = matrilin 3; RUNX2 = runt-related transcription factor 2; SADDAN = severe achondroplasia with developmental delay and acanthosis nigricans.
What should our goal be at the initial visit?

A. Genetic definitive diagnosis
B. Termination of pregnancy
C. Detailed anatomic survey including all long bones
D. Assessment of likely lethality
E. Amniocentesis or Serum Testing/Genetics Referral
F. Referral to a Fetal Care Center
Fetal MRI

- 89 women referred for skeletal dysplasia
  - 43 excluded with different diagnosis
- 46 cases of skeletal dysplasias
  - 20% no diagnosis given
  - 17 cases had reported diagnosis (82% correct)
Postnatal evaluation

- High rate of fetal/neonatal demise/pregnancy termination
- Establishment of correct diagnosis is key
- Postmortem (autopsy) work-up
  - External examination with photographs
  - Whole-body radiographs
  - Skin or other tissue biopsy specimen
    - Chromosomes
    - Fibroblasts for biochemical/genetic/enzymatic studies

Figure 1. Classification of the fetal skeletal dysplasias.

Fetal Skeletal Dysplasias: Radiologic-Pathologic Classification of 72 Cases

Sihem Darouich, Aida Masmoudi
Postnatal evaluation

• Goals
  ○ Counseling re recurrence risk
  ○ Design strategies for prenatal monitoring future pregnancies
    ▪ Achondroplasia: definite diagnosis
      ○ >99% have either a GLY380Arg substitution
      ○ Point mutation in FGFR3 gene or a mutation at nucleotide 1138;
    ▪ Osteogenesis Imperfecta:
      ○ Mutations in either COL1A1 or COL1A2 gene results in
      ○ abnormal procollagen type I.
      ○ Confirm
        • biochemical analysis of collagen or
        • DNA sequencing of COL1A1 and COL1A2.
Case I

- 24 y/o G1P0 at 20 weeks with
  - Extremities: severely shortened, mesomelic, normal mineralization, no bowing
  - Thorax: shortened ribs, TC <5%, FL/AC Ratio = 0.14
  - Face: normal
  - Head: irregular shape, “large cheeks”

- Is it lethal? What is the diagnosis? Is there testing? What’s the likely recurrence?
Case 1
Thanatophoric dysplasia

- Most common lethal dysplasia
  - Birth Prevalence 1:10,000
  - 40/162 (Schramm et al 2009)
Thanatophoric dysplasia

- **Characterized by**
  - Very short extremities
  - Polyhydramnios (50%)
  - Trunk length: normal
  - Thorax: narrow
  - Vertebral ossification centers: distinct flattening (platyspondyly)
  - **Head**
    - disproportionately large
    - Cloverleaf skull deformity (secondary; due to premature closure of sutures) (Type II)
  - **Legs**
    - Type I: curved femurs
    - Type II: straight femurs, cloverleaf skull
  - **Face:**
    - Depressed nasal bridge
    - Prominent forehead
    - Protruding eyes
Thanataphoric Dysplasia

- **Summary:** Most common lethal (40/162)
- **SEVERE early onset shortening**
  - Third trimester polyhydramnios
  - Little long bone growth
  - Small thorax (normal length) big AC
- **2 types**
  - Type 1: bowed,
  - Type 2: straight
Genetics thanatophoric dysplasia

- Genetics
  - Autosomal dominant
    - Vast majority are new mutations
  - FGFR3 Mutation (fibroblast growth factor receptor 3 gene)
    - Mapped to chromosome band 4p16.3
Case 2

- **37 y/o G2P1001 at 28 weeks**
  - Extremities: late shortening (mild), rhizomelic, normal mineralization, trident hand
  - Thorax: normal TC, FL/AC = 0.23
  - Face: frontal bossing
  - Head: macrocrania
  - Normal 20 week ultrasound on review

- Is it lethal? What is the diagnosis? Is there testing? What’s the likely recurrence?
Achondroplasia

- Most common form of short-limb dwarfism
  - achondroplasia (total absence of cartilage)
- Non-lethal
- Incidence: 1:26,000 live births
Achondroplasia

- **Features**
  - Short limbs (rhizomelic)
  - Lumbar lordosis
  - Short hands and fingers
  - Macrocephaly
    - Frontal bossing
    - Depressed nasal bridge
Achondroplasia: ultrasound findings

- Virtually all long bones affected
- 3rd trimester Shortening
- Mild to moderate shortening (rhizomelic)
- Protuberant abdomen
- Trident shaped hand
Findings, con’t

- **Macrocrania**
- **Abnormal profile**
  - Frontal bossing
  - Flattened nasal bridge
  - Elongated philtrum
- **Flattened vertebral bodies with increased intervertebral space, cupped anterior ends to ribs**
Achondroplasia: outcome, interventions

- At birth: most do not require special medical treatment
  - 75% are missed at birth, 60% diagnosed by 1 year

- Growth
  - Normal growth 1st year
    - adult male 52 in, 120 pounds
    - adult female 48.6 in, 100 pounds

- Cognitive development: Normal
  - Delayed motor milestones

- Potential problems:
  - Cervicomedullary junction compression due to small foramen magnum
    - 10% respiratory complications due to foramen magnum compression
  - Spinal stenosis
  - Recurrent ear infections

- Potential interventions:
  - 25% treat leg bowing with corrective osteotomies of tibia (leg lengthening)
  - Recombinant growth hormones
Achondroplasia: genetics/recurrence risk

- 80% sporadic new mutations
- Heterozygous or homozygous (lethal)
- 20% Autosomal dominant
  - Phenotype: 100% penetrant
  - Chromosome 4, band p16.3
    - Fibroblast growth factor receptor 3 (FGFR3)
    - Rapid PCR based diagnosis
Summary

- Detailed anatomic survey will get the most clues
- Referral for genetics consultation is useful
- Many/most will present third trimester and mimic IUGR
- You will miss and misdiagnose some

A precise prenatal diagnosis is frequently difficult and often inaccurate. Prediction of lethality is much easier and often possible with accuracy. Parents need to be aware that the outcome of many skeletal dysplasias is poor.”

- Yeh et al. Prenatal Diagnosis 2011
Good review, good approach

Fetal Skeletal Dysplasia: An Approach to Diagnosis with Illustrative Cases

Manjiri Dighe, MD • Corinne Fligner, MD • Edith Cheng, MD • Bill Warren, MD • Theodore Dubinsky, MD

©RSNA, 2008 • radiographics.rsna.org
Figure 8. Diagram illustrates a diagnostic algorithm for use in fetuses with suspected skeletal dysplasia and skull abnormalities. *OI* = osteogenesis imperfecta.
THERE’S A SHORT BONE, WHAT NOW?

- Option 1: Download excel worksheet and macro for norms, MOM from J Ultrasound Med 2012; 31:1140-1141 letter to the editor
- Option 2: copy the form from RSNA article and fill in

My theory: you may (likely) not walk a way with the diagnosis that day but if you have everything measured, you can piece it together...
The End!

THANKS TO DR HONOR WOLFE!
Figure 2. Diagram illustrates a diagnostic algorithm for use in fetuses with severe limb shortening and normal mineralization. OI = osteogenesis imperfecta.

Figure 3. Diagram illustrates a diagnostic algorithm for use in fetuses with moderate limb shortening and normal mineralization. OI = osteogenesis imperfecta.
Figure 4. Diagram illustrates a diagnostic algorithm for use in fetuses with mild limb shortening and normal mineralization and in fetuses with partial or complete limb agenesis. OI = osteogenesis imperfecta.

Figure 5. Diagram illustrates a diagnostic algorithm for use in fetuses with normal or shortened limbs and decreased mineralization. OI = osteogenesis imperfecta.
Figure 7. Diagram illustrates a diagnostic algorithm for use in fetuses with suspected skeletal dysplasia and facial abnormalities. OI = osteogenesis imperfecta.
A word on MRI
Case 3

- 26 y/o G4P2012 at 20 weeks
  - Extremities: Severe shortening, decreased mineralization, fractures
  - Thorax: TC <5%, FL/AC = 0.11
  - Face: Normal
  - Head: normocephalic, decreased mineralization

- Is it lethal? What’s the likely diagnosis? What is the recurrence rate?
Case 3
Osteogenesis Imperfecta

- 1/28,500 live births
  - 2nd most common (35/162)
- Heterogeneous group
- Mutations in genes for Type I collagen
  - Resultant bone fragility
Osteogenesis Imperfecta

- **Disordered collagen maturation**
  - abnormal skeletal, ligament, skin, sclera, and dentin formation
  - fragile bones, blue sclerae, loose joints and growth deficiency
  - 4 clinical subtypes
    - Type I: abnormal quantity of collagen
    - Type II, III, IV: abnormal quality of collagen
Osteogenesis Imperfecta: Ultrasound

**Long Bones:**
Fractures (femoral irregularity & angulation)

**Skull:** Decreased skull ossification (easy to see inside)
Probes may deform
May have “wavey” outline

**Ribs:** Decreased echogenicity with fractures
Osteogenesis Imperfecta

- **Type I**
  - 1:60,000 birth prevalence
    - mildest form
  - Normal collagen, but less bones easily broken
  - Loose joints, muscle weakness, and bluish, purplish or grayish tinting of the sclera
  - Some brittle teeth and hearing loss
  - Characterized by:
    - Early prenatal onset of severe bone shortening and bowing
    - multiple fractures long bones and ribs
    - Poor mineralization of skull
Osteogenesis Imperfecta

- **Type II**
  - most severe form. lethal
  - 1: 60,000 live births
  - ±fractures in utero (ribs, long bones)
  - severe micromelia, narrow thorax
  - Compressible translucent skull
  - Many affected die before birth or shortly after
  - Survivors numerous fractures, severe bone deformity and small stature

- **Type III**
  - progressive form
  - 1:70,000 births
  - + in utero fractures,
  - spinal deformities, bone deformities, a barrel-shaped rib cage and short stature
  - sclera are tinted
  - brittle teeth and hearing loss

- **Type IV**
  - rarest form
  - moderately severe symptoms
  - Bones fracture easily, with most fractures occurring before puberty, leading to short stature
  - Some patients have brittle teeth and hearing loss
Nonlethal OI

- Normal thoracic and head circumference
- Progressive slowing of long bone growth with advancing GA
- May look like hypophosphatasia
Osteogenesis imperfecta

- **Genetics**
- **Underlying defect: dominant negative mutation**
  - Affecting COL1A or COL1A2 alleles which encode type I collagen
  - New mutations
    - AD inheritance
  - OI Type III
    - Rare cases AR
<table>
<thead>
<tr>
<th>Type</th>
<th>Mode of inheritance</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Dominant</td>
<td>Mild fragility w/o deformity, short stature</td>
</tr>
<tr>
<td>II</td>
<td>Dominant or recessive</td>
<td>Perinatal lethal</td>
</tr>
<tr>
<td>III</td>
<td>Dominant or recessive</td>
<td>Severe, progressive deformity.</td>
</tr>
<tr>
<td>IV</td>
<td>dominant</td>
<td>Skeletal fragility and osteoporosis, bowing</td>
</tr>
</tbody>
</table>

**Table 1**

**Features of Various Types of Osteogenesis Imperfecta**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Generalized demineralization; increased bone fragility, sometimes with secondary deformities; retarded ossification of the cranial vault</td>
</tr>
<tr>
<td>II</td>
<td>Generalized demineralization with multiple fractures; thick, short crumpled shafts of the long bones; rectangular femora with a wavy appearance; severe retardation of calvarial bone formation; short, thick ribs with continuous beading</td>
</tr>
<tr>
<td>III</td>
<td>Generalized osteopenia; short, deformed long tubular bones with broad metaphyses and thinner diaphyses; retarded calvarial ossification; thin ribs with discontinuous fractures</td>
</tr>
<tr>
<td>IV/V</td>
<td>Generalized demineralization; increased bone fragility, sometimes with secondary deformities; bowed long bones; retarded ossification of the cranial vault</td>
</tr>
</tbody>
</table>

*Perinatal lethal.*
- **Achondroplasia**
  - 80% sporadic new mutations, 20% Autosomal dominant
  - Chromosome 4, band p16.3
  - Coding sequences for fibroblast growth factor receptor 3 (FGFR3)

- **Camptomelic dysplasia**
  - Most are new mutations, autosomal dominant
  - Map to chromosome 17
  - SOX 9 mutation

- **Thanatophoric dysplasia**
  - Majority are de novo mutations; Autosomal dominant mutations
  - Fibroblast growth factor receptor 3 gene (FGFR3)
  - Chromosome band 4p16.3

- **Achondrogenesis**
  - **Type I**
    - Autosomal recessive
    - Mutations in the SLC26A2 cause type IB
    - Genetic causes of type IA unknown SLC26A2 and COL2A1 genes cause types 1B and 2
  - **Type II**
    - Autosomal dominant (sporadic, new mutations)
    - Mutations in COL2A1 gene cause type 2

- **Hypophosphatasia**
  - Perinatal type
  - Autosomal recessive
  - Chromosome 1p36.1-34 (TNSAP gene missense mutations)
**Slide 25: Thanatophoric dysplasia type 1**

- A-transverse u/s image showing a normal shaped but enlarged head
- B-sagittal u/s showing depressed nasal bridge (arrowhead), a prominent forehead (double arrows) and an undersized thorax (single arrow) compared with the abdomen
- C—u/s image showing a telephone receiver shaped femur (arrows). Normal limb echogenicity with severe shortening and bowing of the limbs, a narrow chest and macrocephaly suggest thanatophoric dysplasia 1 (look at flow chart 2,6,8)
- D—postmortem radiograph shows bowed long bones (white arrows) a narrow chest and platyspondylyl (black arrow)
- E,f—autopsy show shortened limbs, depressed nasal bridge (arrowhead in figure f), a short trunk, an enlarged abdomen and prominent forehead (f)
Thanatophoric Dysplasia
Chondroectodermal dysplasia (Ellis-Van Creveld syndrome)

- Rare, mostly lethal
- Characterized by
  - Acromelic and mesomelic shortness of limbs
  - Postaxial polydactyly
  - Small chest
  - Ectodermal dysplasia
  - Congenital heart defects: ASD, VSD (>50%)
  - Some Dandy walker malformation
Short Rib Dysplasias

- Lethal, autosomal recessive
- Micromelia, + postaxial polydactyly
  - Narrow thorax, short ribs, protuberant abdomen
- Type I
  - Polydactyly, heart defects, facial clefts, anomalous brain, kidneys, genitalia
- Type 2
  - Polydactyly (pre/post)large head, depressed nasal bridge, micrognathia, clefts, hypoplastic cerebellar vermis, cystic kidneys
- Type 3
  - Polydactyly (hands/feet), GI, GU defects
- Type 4
  - Bowed limbs, polydactyly, 100% facial clefts, less commonly cardiac, cerebral, GI, renal anomalies, omphalocele
Jeune asphyxiating thoracic dystrophy

- Short – rib dysplasia
- Thorax long/narrow
- Mild rhizomelia, some polydactyly
- Most – cystic dysplastic kidneys
Genetics Ellis-van Creveld

- **Autosomal recessive**
  - **EVC2 gene**
    - makes a protein called limbin
    - chromosome 4p, between positions 16.2 and 16.1
Diastrophic dysplasia: Ultrasound

- Severe micromelia
- Other common findings
  - Micrognathia
  - Cleft palate
  - Normal skull and vertebral body ossification
  - Ulnar deviation of hands, abducted and proximally inserted thumbs and great toes
  - Club feet
Diastrophic Dysplasia

- Diastrophic = twisting
- Observed only in caucasians
- 160/300 patients described from Finland
- Incidence: 1: 32,6000 live births in Finland
  - Rare condition outside of Finland
  - Few prenatal u/s diagnosis
Diastrophic dysplasia
Ultrasound

**Long bones:** short broad metaphyseal

**Hands/feet:**
- Hitchhikers thumb
- Club feet

**Head:** sloping forehead micrognathia
Diastrophic dysplasia: outcome

- Normal intelligence, non lethal
- Wide variation in phenotype
  - 3ft 9 inches-6 feet (mean 3’ 11 “)
- No indication for c/s
- 12% respiratory difficulties (glossoptosis)
Genetics

- Autosomal recessive
  - Varied expressivity
- Mutation of novel sulfate transporter gene (diastrophic dysplasia sulfate transporter (DTDST))
  - Chromosome 5q32-q33.1
  - Undersulfated protoglycans in cartilage matrix
Camptomelic dysplasia

- .05-1.6:10,000 live births
- Lethal
  - Antenatal: 50% fetal demise
  - Postnatal: most are lethal during 1st year of life
  - Rare survivors
    - Complicated by respiratory distress
Camptomelic Dysplasia: Ultrasound

- **Common findings**
  - Absent/hypoplastic scapulae
  - Hypertelorism
  - Cleft palate
  - Ventriculomegaly
  - Marked bowing tibia, femur
  - Hypoplastic fibula
  - Bell shaped narrow chest
  - Polyhydramnios (25-48% of affected cases)

- **Occasional findings**
  - Heart defects (25%)
  - Large bpd, flattened nose, micrognathia
  - Large kidneys, hydronephrosis
  - Club feet
  - Sex reversal **
    - Over 50% apparently ♀ infants have a male, XY karyotype
Camptomelic dysplasia: genetics

- Although majority are new mutations, CD is now considered to be inherited as autosomal dominant
  - The various skeletal and extraskettelal manifestations: map to chromosome 17
    1. SOX 9 mutation analysis
       - the only gene known to be associated with CD
       - available in clinical laboratories
       - detects mutations or chromosome rearrangements in approximately 95% of affected individuals
What to do when suspected

- **Karyotype**
  1. For gender—prepare for sex reversal
  2. Screen for chromosome 17 abnormalities, rearrangements

- **Genetic counselor**
  1. Prognosis (lethality, rare survivors)
  2. Long term outcome
     Ray and Brown, 1984
     81 patients (61 stillborn/died 1st 2 months, 13 died 35d-1 year, 2 survived >2 years) all patients who survived >6 mo: profound hearing loss

- **If patient opts for termination**
  1. Get placental material→ fibroblast culture → SOX 9 mutation analysis
     - the only gene known to be associated with CD, is available in clinical laboratories and detects mutations or chromosome rearrangements in approximately 95% of affected individuals
  2. Autosomal dominant; majority occurring as new mutation
  3. Whole body radiographs!

- **Treatment of newborn**
  - Complete physical exam
  - Radiographs
  - Expect respiratory distress
Achondrogenesis

- Lethal
- Birth prevalence: 1:40,000
- Characteristic features
  - Severe shortening of limbs
    - Abnormal movement
  - Narrow thorax
  - Short trunk
  - Large head
  - Non-ossified spine
  - Thickened nuchal fold
Achondroplasia

- **Type I (Houston-Harris type)**
  - Autosomal recessive
  - Extremely short limbs, narrow chest, short ribs
  - Poor mineralization of skull, vertebral bodies, pelvis
  - Rib fractures

- **Type IB (Parenti-Fraccaro type)**
  - Sporadic (new autosomal dominant mutations)
  - Extremely short limbs, narrow chest, prominent rounded abdomen
  - Short fingers and toes, clubbed feet
  - Hypomineralization of vertebral bodies
  - Normal mineralization of the skull
  - No rib fractures

- **Type II (Langer-Saldino type)**
  - Short arms and legs
  - Narrow chest with short ribs, and underdeveloped lungs
  - Lack of ossification in the spine and pelvis
  - Distinctive facial features include a prominent forehead, micrognathia, cleft palate
  - Protruding abdomen
Achondroplasia: Genetics
Hypophosphatasia

- 1:100,000 birth prevalence
- Multiple forms
  - Perinatal: universally lethal
  - Infantile: 50% mortality rate
  - Adult: presents during middle age
    - recurrent stress fractures, loss of permanent teeth
- Ultrasound findings
  - Profound undermineralization
  - Lack of skull ossification
  - Severe rhizomelic shortening
  - Small thorax, absent/short ribs
  - Polyhydramnios
Hypophosphatasia

Osteochondral projections (Bowdler spurs) of the midshaft of the fibula and ulna may be present (skin-covered spurs that extend from forearms or legs)
Hypophosphatasia
Hypophosphatasia
Hypophosphatasia: genetics

- mutation in gene (ALPL) that codes for tissue-nonspecific alkaline phosphatase
- *ALPL* gene: **located at band 1p36.1-34**
- Perinatal and infantile hypophosphatasia: **autosomal recessive**
- Prenatal diagnosis:
  - Absence/very low activity of TNSALP isoenzyme in CVS/amniocytes, low total alkaline phosphatase
  - DNA studies
Jarcho-Levin syndrome
(spondylothoracic dysplasia)

- Characterized by
  - Vertebral and rib abnormalities (misalignment of the cervical spine and ribs)
  - Rest of skeleton is unaffected
  - Protuberant abdomen
- Autosomal recessive
  - Short thorax
    - “crab-claw” or “fan-like” rib configuration (on xray)
  - Respiratory death at infancy
  - Rare
- Another autosomal recessive and dominant type
  - Short stature
  - Compatible with survival into adulthood with some degree of disability
Cleidocranial Dysplasia

- Cleidocranial Dysplasia (cleido = collar bone, + cranial = head, + dysplasia = abnormal forming)
- 1:1,000,000,000
- Also known as Cleidocranial Dysostosis and Marie-Sainton Disease
- Characterized by defective development of the cranial bones and by the complete or partial absence of clavicles
  - Delayed closure (ossification) of fontanels
  - Premature closing of the coronal suture
  - Protruding mandible, frontal bossing
  - Wide nasal bridge due to hypertelorism
  - High arched palate or possible cleft palate
  - Short stature
  - Scoliosis
Cleidocranial dysplasia: genetics

- Genetics: mutation in RUNX2 gene
  - Autosomal dominant
Limb deficiency

- Overall prevalence: 0.49/10,000
- Most: transverse reduction deficiencies of one forearm or hand w/o associated anomalies
- Remainder: multiple reduction deficiencies + additional internal anomalies/craniofacial structures
- Isolated extremity amputation: can be due to amniotic band sequence, teratogen, vascular accident (sporadic, negligible recurrence risk)
Limb deficiency, con’t

- Classified according to Swinyard and Marquardt system
  - Two basic terms used
    1. Amelia (complete absence of the limb)
    2. Meromelia (partial absence of the limb)
  - Additional classification terminology
    1. Terminal (absence of all skeletal elements along longitudinal ray beyond a given point)
    2. Intercalary (absence of the proximal or middle segment of a limb with all or part of the distal segment present)
  - Further subgrouping is based on axis of deficiency
    1. Transverse
    2. longitudinal
Fetal Head

- **Macrocephaly**
  - Thanatophoric dysplasia, camptomelic dysplasia, Jarcho-Levin

- **Hydrocephalus**
  - Thanatophoric dysplasia, camptomelic dysplasia, OI II

- **Microcephaly**
  - Rhizomelic chondrodysplasia punctata

- **Frontal bossing**
  - TD, achondroplasia, cleidocranial dysplasia, osteopetrosis

- **Cloverleaf**
  - TD

- **Brachycephaly**
  - Cleidocranial dysplasia, chondrodysplasia punctata, diastrophic dysplasia
Case 4

- **36 y/o G3P1011 at 19 weeks**
  - Extremities: Rhizomelic, moderate shortening with normal mineralization but stippled epiphyses
  - Thorax: Normal, FL/AC=0.27
  - Face: flat with micrognathia
  - Head: microcephaly

- Is it lethal? What is the diagnosis? What is the likely recurrence? Is there genetic testing?
Case 4
Chondrodysplasia punctata

- Locally disordered bone mineralization
  - X ray: bone stippling
- Incidence: 1:100,000
- Consanguinity: 8-10% of recessively inherited cases
## Nonrhizomelic vs rhizomelic

### Nonrhizomelic
- Asymmetric shortening extremities
- Spinal kyphoscoliosis
- Flattened face
  - Small nose, flat nasal bridge
- Prominent forehead, wide-set eyes, upslanting palpebral fissures
- Prematurely calcified femoral epiphyses

### Rhizomelic
- Symmetric Shortening (humerus>$\text{femur}$)
  - Height: 2-4 SD below mean
- Cataracts (75%)
- Hypertelorism
- Brachycephaly, ventriculomegaly
- Premature calcification epiphyses
- Developmental abnormalities
- More severe
  - Most die within 1st year of life
Chondroplasia punctata

- Profound limb shortening
  - Humerus and femur only
    - Rhizomelic: humerus < femur
- Expanded, punctate epiphyses
  - Multiple hyperechoic foci early 2nd trimester
- Facial abnormalities
  - Nasal hypoplasia, midface depression, frontal bossing
- 10%: congenital heart disease
Chondroplasia punctata: long term outcome

- **Rhizomelic**
  - Most die during 1st year of life

- **Nonrhizomelic (Conradi-Hunermann syndrome)**
  - Shorter than normal at birth; throughout life
  - Infancy: cataracts, growth failure, feeding problems, respiratory infections
  - After 1st year: skeletal deformities less pronounced; contractures disappear
Chondroplasia punctata

- Genetically heterogenous group of disorders
  - **Nonrhizomelic**: Conradi-Hunermann syndrome
    1. Autosomal dominant disorder that is lethal in males
    2. X-linked recessive disorder
    3. A disorder due to a deletion in short arm of the x chromosome
  - **Rhizomelic type**: Rare autosomal recessive condition with severe limb shortening (and has other abnormalities: face, skin, cataracts, calcification of trachea an larynx, failure to thrive, death in 1st year of life)
    - Disorder of peroxisomes (intracellular organelles that catalyze a number of metabolic functions)
    - Leads to ↑ phytanic acid and ↓ plasmalogens
    - Prenatal diagnosis: analyze plasmalogen levels in chorionic villi and erythrocytes
    - There are three classes of peroxisomal disorders (Group A,B,C)