Fetal Musculoskeletal System & Skeletal Dysplasias

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Let me Count the Whys

1. Rare (2.4 per 10,000)
2. Most die (23% still born & 32% in 7 days)
3. Nearly 300 different types
4. Only a few can be accurately diagnosed with targeted ultrasound
5. It’s life & death if you make a mistake

Normal Skeletal Development

• 6 weeks
  - Vertebral bodies
• 7 weeks
  - Skull
• 8th weeks
  - Limb buds, Mandible, clavicle
• 9th weeks
  - Femur, humerus
• 10 weeks
  - Tibia / fibula, radius / ulna
• 11 weeks
  - Digits of hands & feet

Skeletal Dysplasias

• Why do we dread them?
There’s more to musculoskeletal evaluation than diagnosing skeletal dysplasia...

What to Look For?
- Length of extremities
- Shape of extremities
- Mineralization
- Movement
- Associated abnormalities in other systems

What to Look For?
- Length of extremities

Length of Extremities
- Possible causes of long bone length less than 2 SD below the mean for gestational age
  - Incorrect dates
  - Abnormal karyotype
  - IUGR
  - Constitutionally short stature
  - Isolated skeletal anomaly
  - Skeletal dysplasia

Ratio Between the FL & Other Body Measurements
- The femur length & foot are of comparable length in the normal fetus

Initial Questions
- What has been the interval growth of the femur length?
Interval Growth of the Femur

- From 16 to 22 weeks gestation the mean length of all long bones increases by between 2.5-2.7 mm/week.
- A fetus with OI type II may have an abnormal FL at 15 weeks gestation.
- A fetus with heterozygous achondroplasia may not have abnormally short until 21-27 weeks gestation.

Initial Questions

- Is the ratio between the femur length and other body measurements appropriate?

What to Look For?

- Length of extremities
- Shape and fractures of extremities

Ratio Between the FL & Other Body Measurements

- Femur length-HC ratio more than 3 SD below the mean suggests a skeletal dysplasia.
- Femur length-AC ratio < 0.16 suggests lung hypoplasia.
- Femur length-foot length ratio of <1 suggests skeletal dysplasia.
- Chest circumference/abdominal circumference ratio < 0.8 suggests lethality.

What to Look For?

- Length of extremities
- Shape and fractures of extremities
- Mineralization
Hypophosphatasia

- Demineralized segment where the vertebral bodies have a “ghost” outline and no acoustic shadowing

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- Movement

What to Look For?

- Length of extremities
- Shape and fractures of extremities
- Mineralization
- Movement
- Associated abnormalities in other systems
  - Head, Thorax & spine

Narrow Chest

- Hypoplastic thorax occurs in many skeletal dysplasias
  - Thanatophoric dysplasia
  - Achondrogenesis
  - Hypophosphatasia
  - Camptomelic dysplasia
  - Osteogenesis imperfecta
  - Chondroectodermal dysplasia
  - Short rib polydactyly

Shortening of the Extremities

- Rhizomelia
- Mesomelia
- Micromelia
- Acromelia

Rhizomelia

- The proximal portion of the limb is reduced in size (humerus or femur)
**Rhizomelia – Associated Findings**

- Thanatophoric dysplasia
- Atelosteogenesis
- Chondrodysplasia punctata (rhizomelic type)
- Diastrophic dysplasia
- Congenital short femur
- Achondroplasia

**Mesomelia**

- The mid-limb (ulna/radius and or tibia/fibula) is reduced in size

**Micromelia**

- The entire limb is reduced

**Micromelia – Associated Findings**

- Achondrogenesis
- Atelosteogenesis
- Short-rib polydactyly syndrome (types I & III)
- Diastrophic dysplasia
- Fibrochondrogenesis
- Osteogenesis imperfecta (type II)
- Kniest dysplasia
- Dyssegmental dysplasia

**Acromelia**

- The hands or feet are reduced in size
Hands & Feet Abnormalities

- Polydactyly
- Oligodactyly
- Syndactyly
- Clinodactyly
- Amelia
- Meromelia
- Club Hand / Foot
- Rockerbottom Feet
- Sandal Toes

Polydactyly

- Presence of additional digit
- Range from a fleshy nubbin to a complete digit with controlled flexion and extension

Polydactyly

- More common in hands than feet

Polydactyly

- Postaxial polydactyly
  - ulnar side of the hand & fibular side of the foot
- Preaxial polydactyly
  - Radial side of the hand & tibial side of the foot

Polydactyly

- Preaxial
  - Chondroectodermal dysplasia
  - Short-rib polydactyly syndrome type II
  - Carpenter syndrome
- Postaxial
  - Chondroectodermal dysplasia
  - Short rib-polydactyly syndrome (type I, type III)
  - Asphyxiating thoracic dysplasia
  - Otopalatodigital syndrome
  - Mesomelic dysplasia Werner syndrome (no thumbs)

Oligodactyly

- Fewer than 5 digits per extremity
**Syndactyly**

- Fused digits, either cutaneous or osseous

**Poland syndrome**
- Carpenter syndrome
- Aper syndrome
- Otopalatodigital syndrome (type II)
- Mesomelic dysplasia Werner type
- TAR syndrome
- Jarcho-Levin syndrome
- Roberts syndrome
- Triploidy

**Clinodactyly**

- Permanent bend in one or more digits or persistently overlapping digits
- Associated with trisomy 18

**Amelia**

- Absence of the limbs

**Meromelia**

- Absence of the hands and most of the forearm

**Club Hand**

Classified into two categories:

- Radial club hand
  - Absent thumb
  - Thumb hypoplasia
  - Thin first metacarpal
  - Absent radius

- Ulnar club hand (less common)
  - Mild deviations of the hand of the ulnar side of the forearm
  - Complete absence of the ulna
**Club Hand**

Clubbing of the hand and webbing at the wrist and elbow consistent with early onset of fetal akinesia.

**Club Foot**

- All metatarsals (& toes) are visible in the same plane as the tibia & fibula, roughly perpendicular to them.

**Club Foot**

- Medial deviation and inversion of the sole
- Familial history 15%
- Twice as frequent in males

**Club Foot: Associated Findings**

- Chromosomal abnormalities (tri 18 > 13)
- Neural tube defect; CNS disorders
- Neuromuscular disorders
- Crowding: oligohydramnios, multiples, fibroids, amniotic bands
- Other skeletal abnormalities
  - arthrogryposis, skeletal dysplasia, genetic syndromes
- Heart defects, cleft lip, renal abnormalities

**Club Foot - Types**

Types of club foot and associated ultrasound images.
**Rocker-bottom Feet**

- Characterized by a prominent heel and a convex sole
- Associated w/ >30 malformation syndromes, especially trisomy 18

**Sandal Toes**

- Space between 1st & the 2nd toe (trisomy 21)

**Arthrogryposis**

- Contractures of the extremities
  - Hand is persistently flexed
  - Contracture of the ankle

**Arthrogryposis**

- Due to:
  - Neuropathic abnormalities
  - Muscular abnormalities
  - Connective tissue abnormalities
  - Space limitations within the uterus
  - Intrauterine vascular compromise

- Associated with:
  - Bilateral renal agenesis
  - Spina bifida
  - Sacral agenesis
  - Metatrophic or diastrophic dwarfism

**Abnormal skull Contour**

- Frontal bossing
  - Thanatophoric dysplasia
  - Osteogenesis imperfecta

- Cloverleaf skull
  - Homozygous achondroplasia
  - Thanatophoric dysplasia
**Frontal Slanting**

- Scaphocephaly
- Microcephaly

**Sagittal View – Facial Profile**

- Mandible Anomalies
  - Part of more than 100 genetic syndromes
  - Micrognathia *
    - Insufficient size
  - Retrognathia
    - Recession of the chin

**Facial Profile View**

- Prognathia
- Micrognathia
- Retrognathia

- Micrognathia
  - small chin – prominent upper lip
    - Otocephaly
    - Pierre Robin sequence
    - Fetal alcohol syndrome
    - Achondrogenesis
    - Triploidy & trisomy 18 & 13
• Severe Kypho-scoliosis
• Abnormal Neck/Chin
• Webbing from arms to chest

• The term *dysplasia* means
  – Intrinsic growth disturbance occurring during the early stages of fetal development

*Skeletal Dysplasia*

What is difficult?
• Precise diagnosis of bone dysplasia
**Skeletal Dysplasia**

**What is important?**
- Differentiation between a lethal and a non-lethal variety
  - Antenatal care
  - Prediction of fetal outcome

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**Clues to Lethal Skeletal Dysplasia**

1. Early onset severe limb shortening
2. Small chest with short ribs
3. Fractures or marked bowing
4. Clover leaf skull
5. Hydrops
6. Demineralization
7. Early severe polyhydramnios

- Femur/abdominal circumference ratio < 0.16 suggests lethality
- Chest circumference/abdominal circumference ratio < 0.8 suggests lethality

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**Lethal Skeletal Dysplasia is Not Subtle!**

**Thanatophoric Dysplasia**

- The most common lethal skeletal dysplasia
- Name means “seeking death”
- Birth prevalence of ~ 0.7-0.8 in 10,000
- Prenatal genetic testing
  - Mutation in FGFR3 gene

**Thanatophoric Dysplasia - Features**

- Long bones
  - Very short & curved
- Head
  - Macrophagy
  - Frontal bossing + depressed nasal bridge
  - Cloverleaf-shaped skull
- Chest
  - Narrow thorax
  - Short ribs
- Small short & wide iliac wings

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**Common Skeletal Dysplasias**

**Osteochondrodysplasias**

Abnormalities of cartilage or bone growth & development

1. Thanatophoric Dysplasia (lethal)
2. Acondroplasia (usually not lethal)
3. Osteogenesis Imperfect (type II lethal)
4. Achondrogenesis (lethal)
5. Hypophosphatasia (some types lethal)
Thanatophoric Dysplasia

- Narrow chest, protuberant abdomen, abnormal chest/abd ratio, bell-shaped

- Short ribs

- Micromelia (short limbs)

- Macrococania, frontal bossing, depressed nasal bridge, cloverleaf shape (14% (type II))

- "Type I" (sporadic)
  - Telephone receiver femurs
**Thanatophoric Dysplasia**

- **Type II** (autosomal recessive)
  - Femurs are straight but the skull is Cloverleaf shaped

- Small Thorax + short ribs
- Micromelia
- Large head with a prominent forehead
- Type I (sporadic)
  - Telephone receiver femurs
- Type II (autosomal recessive)
  - Femurs are straight but the skull is Cloverleaf shaped
  - Severe polyhydramnios – early onset

**Associated anomalies**
- Holoprosencephaly
- Agenesis of the corpus callosum
- Ventriculomegaly
- Horseshoe kidney
- Hydronephrosis
- Congenital heart disease

**US Findings**
- Disproportionately large head
- Prominent forehead
- Depressed nasal bridge
- Small nose with anteriorly deviated nostrils
- Increased distance between tip of nose and lower edge of chin
- Short neck
- Narrow and short thorax
- Very short limbs, dwarfism
- Distended abdomen
- Polyhydramnios, early onset

**Achondrogenesis**

- Lethal skeletal dysplasia
- Birth prevalence of about 1 in 40,000

**US Findings**
- Severe micromelia
- Redundant soft tissue
- Mimics hydrops
Achondrogenesis

- Type I (autosomal recessive) – 20%
  - Poor ossification of spine & skull
  - Short fractured ribs
- Type II (sporadic) – 80%
  - Hypo-mineralization of the vertebral bodies
  - Normal mineralization of the skull
  - No rib fractures

Achondroplasia

- Most common heritable non-lethal skeletal dysplasia
- Most common cause of short stature with disproportionately short limbs
- An autosomal dominant condition
- Birth prevalence of about 1 in 40,000
- Normal intellect and life span
- Mean adult height 52” for men, 49” for women
- Orthopedic, orthodontic, neurologic sequelae
- Diagnosis may not become obvious until 22–24 weeks

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Achondroplasia

- Homozygous condition, lethal
  - manifests in abnormally short limbs earlier than the heterozygous form

Achondroplasia

- Chest normal
- Disproportionally short limbs (rhizomelia)
  - Normal ossification
  - No fracture
  - No bowing or angulation
  - Upper extremity more affected than lower
- Cranium / Face
  - Enlarged head
  - Frontal bossing
  - Depressed nasal bridge

Proximal femoral diaphyseal-metaphyseal angle

- Normal angle
  - 22 weeks: 98.5 ± 6.8°
  - 32 weeks: 105.6 ± 7.3°
- Angle is increased in affected fetuses
- In 1 study, 5 of 6 affected fetuses had angle > 130°
**Achondroplasia**

“Trident Hand”

**Osteogenesis Imperfecta**

- Genetically heterogeneous group of disorders presenting with fragility of bones, blue sclerae, loose joints and growth deficiency
- Advanced paternal age is a risk factor for OI

- **Type I**
  - Most common
  - Autosomal dominant condition
  - Birth prevalence of about 1 in 30,000
  - 2nd & 3rd trimester ultrasound may demonstrate fractures of long bones
  - Skeletal hypoechogenicity & limb bowing are frequently not detected until after 24 weeks
  - Blue sclera
  - Progressive deafness, but life expectancy is normal

- **Type II**
  - Lethal disorder
  - Birth prevalence of about 1 in 60,000
  - Severe bone shortening and bowing due to multiple fractures affecting all long bones and ribs
  - Poor mineralization of the skull
  - Limited limb movement
Osteogenesis Imperfecta Type II

Severe bone shortening & angulation due to multiple fractures

Narrowly spaced ribs

“Beaded” ribs and “wrinkled” bones due to multiple fractures

Concave, bell-shaped chest due to rib fractures

Hypomineralization of the cranium

Compression of skull by transducer
**Osteogenesis Imperfecta Type III**

- **Nonlethal**, autosomal recessive, rare
- Progressively deforming condition
- Long bone shortening & deformity may not become apparent until 19-22 weeks gestation
- Multiple fractures present at birth
- Scoliosis, very short stature, progressive deformities from birth to adolescence

**Osteogenesis Imperfecta Type III**

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

**Osteogenesis Imperfecta Type IV**

- Mildest presentation of OI
- Autosomal dominant condition
- Not detectable on prenatal US
- Premature osteoporosis in 40’s & 50’s
- No associated hearing impairment

**Hypophosphatasia**

- **Lethal**, autos recessive condition
- Birth prevalence of about 1 in 100,000
- Severe shortening of the long bones
- Small thorax
- Hypominalization of the skull & long bones
- Abnormal alkaline phosphatase assays
- Polyhydramnios

**Hypophosphatasia**

- Poor mineralization

**Hypophosphatasia**

- Demineralized segment where the vertebral bodies have a “ghost” outline and no acoustic shadowing
Hypophosphatasia

- SEVERE demineralization
- Bones
  - Thin
  - Delicate
  - Absent
- Hypoplastic ribs
- Severe micromelia
- Fractures not typical;
  - thin bowed long bones

Sirenomelia
Mermaid Syndrome

- A lethal congenital anomaly associated with gestational diabetes
- Partial to total sacral agenesis
- Fusion of the lower extremities
- Bilateral renal agenesis (oligohydramnios, pulmonary hypoplasia)

Sirenomelia

- Single femur and tibia at midline and a deformed foot
- Iliac bones are abnormally located

Resources

- Skeletal Dysplasia Registry – NIH funded
  - [www.lpaonline.org](http://www.lpaonline.org)
  - [www.csm.edu/genetics/skeldys/nomenclature.html](http://www.csm.edu/genetics/skeldys/nomenclature.html)
  - [www.TheFetus.net](http://www.TheFetus.net)

Fetal Musculoskeletal System

- Cranium (shape, ossification)
- Facial profile
- Spine
- Bones
  - Severity & Type of Shortening
  - Morphology, Mineralization, Fractures
- Chest (Thoracic / abdominal circumference ratio)
- Polyhydramnios

Thank You