Lethal Skeletal Dysplasia

Recommendations of Practice

Background

- Lethal skeletal dysplasias/ osteochondrodysplasias are fetal abnormalities. They refer to the abnormal formation and remodelling of bone manifesting in diffuse skeletal deformity, bone shortening, abnormal bone shape, density and number of bones
- Each skeletal dysplasia is the result of an abnormal cellular product/process, resulting from defective single gene disorder or chromosomes. Over 90% result from new spontaneous mutations
- The prevalence of lethal skeletal dysplasia ranges from 0.95 to 1.51 per 10000 live births, with 23% stillborn and 32% passing away after birth
- There are >456 types of skeletal dysplasia which are classified as lethal or non-lethal
- Lethality is generally based on pulmonary hypoplasia that results from restrictive thorax
- Lethal skeletal dysplasias typically have an earlier presentation than the non-lethal group.

Objective

- To ensure correct evaluation of fetuses when there is a suspicion of skeletal dysplasia, when referred with short or abnormally shaped limbs
- To guide accurate diagnosis and investigation
- When diagnosis unclear, the most important distinction in early antenatal period is that of lethality
- To facilitate appropriate care planning for women.

Differential Diagnosis

- Error in measurement
- Placental insufficiency
- Fetal growth restriction
- Aneuploidy
- Constitutional

Important History

- Family history
- Ethnicity
- Consanguinity
- Parental heights
- Obstetric history: perinatal deaths, aneuploidy
- Uncontrolled diabetes
- Medication: Warfarin, Glucose, Alcohol, Phenylalanine, Thalidomide
- Prenatal screening : increased nuchal translucency

Practical Approach and USS Features

1. Establish Lethal vs Non-Lethal

Lethality: Prenatal ultrasound has high sensitivity to detect lethality (81-99%)

1. Significant thoracic narrowing
    a. Small chest (<5th centile for GA), short ribs, increased cardiothoracic ratio (CTR)
2. Severe micromelia (<4SD)
    a. Early and severe shortening of long bones
3. Marked bowing, multiple fractures, beaded &/- fractured ribs
4. Reduced bone echogenicity
5. FL:AC<0.16
6. Hydrops

Ratios

FL:AC	<0.16
FL:foot	<0.9
TC:AC	<0.79
TC	<5th centile for GA
Cardiac Circumference: TC	>0.6

Top 3 Prenatally Diagnosed Lethal Dysplasias

1. Thanatophoric Dysplasia (Type 1 and 2)
    - Severe rhizomelic micromelia, small thoracic circumference, macrocrania, normal trunk length, normal mineralisation, no fractures, redundant skin folds, flat vertebral bodies, trident hands
2. Achondrogenesis
    - Severe micromelia, small thoracic circumference, macrocrania, short trunk length, decreased mineralisation, occasional fractures
3. Osteogenesis Imperfecta Type II
    - Severe micromelia, small thoracic circumference, normal cranial size, short trunk length, decreased mineralisation, multiple fractures

Also

Short rib polydactyly
Campomelic dysplasia
Asphyxiating thoracic dysplasia

2. Long Bones

- Measure all long bones and chart
  - Femur:Foot Length <1:1 is suggestive of short long bones
- Presence/Absence
  - Eg Radial Ray (absent radius)
    - T18
    - Holt Oram (cardiac/no thumb)
    - TAR Syndrome (has thumb)
- Shape
  - Angulated/Fractured eg Osteogenesis Imperfecta
  - Telephone receiver eg thanatophoric dyplasia
  - Dumb-bell eg metatropic dysplasia
- Angulation/fractures
- Mineralisation
  - Clear brain view (especially near field)
    - Reduced attenuation/absorption
  - Ossification of Epiphyseal centres
    - Proximal femur 32-33 weeks
    - Distal femur 35 weeks
    - "absent" ossification centres
      - Same echotexture as surrounding structures
      - Eg hypophosphatasia

Micromelia	all
Rhizomelia	proximal shortening
Mesomelia	intermediate shortening
Acromelia	distal shortening

3. Hands/Feet

- Polydactyly eg Short rib polydactyly
  - Preaxial
  - Postaxial
- Syndactyly fused
- Clinodactyly bend of finger eg T21
- Brachydactyly short fingers
- Ectrodactyly lobster hands
  - Widely spaced, fused 2/3, 4/5
  - Look at feet
    - Split hand and foot syndrome EEC
- Trident fingers
- Ulnar deviated thumb "hitch hiker's thumb"
  - Eg diastrophic dysplasia, type II atelosteogenesis
- Rockerbottom feet
- Clubbing of hands eg T18, Holt-Oram, Neu-Laxova
- Talipes Club feet
- Apert Syndrome mitten hands (and craniosynostosis)
- Pfiffer Syndrome broad thumbs (and craniosynostosis)

4. Head/Face

- Measure BPD/HC
  - ?macrocephaly eg thanatophoric dysplasia, achondroplasia
- Skull shape
  - Craniosynostosis
    - Brachycephaly (AP short)
    - Scaphocephaly (lat short)
    - Clover leaf eg thanatophoric dysplasia type II, campomelic dysplasia. Pfieffer syndrome
- Mineralisation
  - Deformation of cranium with probe pressure
  - Clear brain views (near field)
  - Wormian bones eg T21, Osteogenesis Imperfecta
    - 3D imaging good for this
- Hypo/hyper- telorism
- Micrognathia
  - "Jaw index"
    - Mandible/BPD x100
    - <21 is predictive of micrognathia
- Frontal bossing, depressed nasal bone eg Osteogenesis Imperfecta, thanatophoric dysplasia, achondroplasia
- Cleft lip/palate

5.Clavicles

- Present
- Absent/hypoplastic eg cleidocranial dysplasia

6.Scapulae

- Present
- Absent/hypoplastic eg Campomelic dysplasia

7.Thorax

- CTR (>0.6 abnormal) eg Osteogenesis Imperfecta, thanatophoric dysplasia, achondrogenesis
- Shape of ribs
  - Short
  - Fractured
  - Beading
  - Stippling
- Shape of chest
  - Bell, champagne cork eg thanatophoric dysplasia
  - Barrel eg Campomelic dysplasia
  - NB: also note protuberant abdomen.

8.Spine

- Kyphosis, scoliosis
- Hemivertebrae
- Mineralisation
    - Ossification centres "absent" with hypophosphatasia
    - Absent/under ossification of vertebral bodies eg achondrogenesis
- 4 ossification centres "splitting of spinal cord" diastomyelia
- Reduced vertebral body height (subjective) platyspondyly
    - Intervertebral discs are greater than the height of the vertebrae.
    - Eg thanatophoric dysplasia

9. Pelvic Shape

- Flattened iliac bones with lack of iliac flaring eg achondrogenesis
    - (maybe best assessed by 3D)

10.Other abnormalities

- Ambiguous genitalia "tulip sign" eg Campomelic dysplasia
- Cardiac eg Holt-Oram
- Situs inversus eg Short rib polydactyly I-III
- Cataracts eg chondrodysplasia punctate

11.Polyhydramnios

Secondary to:

- Small chest
- Hydrops
- Reduced fetal movements

Investigation:

- Consider (pre or postnatally)
    - Microarray panel and specific gene mutation testing
    - Biochemical : hypophosphatasia
- There is a large and rapidly growing list of single-gene disorders. A genetics consultation if considering use of array or directed testing.
- Genetic abnormalities have been identified for about 70% of the >456 described skeletal dysplasias
- If a family has a known genotype, pre-implantation genetic diagnosis or directed testing early in gestation can be offered.

Resources:

If molecular testing is in consideration, current information can be obtained from:

- www.Genetests.org
- www.esdn.org European Skeletal Dysplasia Network
- www.pediatrics.ch/Frames.html University of Lausanne Division of Molecular Paediatrics
- www.skeldys.org International Skeletal Dysplasia

Prognosis:

- Depends on ultrasound features and suggestion of lethality.

On-going Management:

- Consultation with radiologist, geneticist, neonatologist, fetal medicine panel
- If lethal, but continuing, offer involvement of Paediatric Palliative Care team.

If pregnancy is stopped, or stillbirth:

- Consider involvement of Paediatric Palliative Care team.

Advise post-mortem evaluation and imaging:

- Full body skeletal survey radiographs, including at minimum, AP and Lateral views of the skull, body and all limbs (including the digits of the hands and feet).
- Post mortem CT should always be considered and discussed with a paediatric radiologist
    - Pathologic examination: histology of chondro-osseous tissue
    - Karyotype / DNA studies.

Post delivery:

- Paediatric and/or genetic assessment.

References

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- Warman ML et al, Nosology and classification of genetic skeletal disorders: 2010 revision. *Am J Med Genet A.* 2011 May; 155A(5):943-68. Epub 2011 Mar 15

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The most up to date version of this Recommendation of Practice can be found on Healthpoint Wāhi Rua: New Zealand Maternal Fetal Medicine Network (NZMFM) webpages: https://www.healthpoint.co.nz/public/wahi-rua-new-zealand-maternal-fetal-medicine/