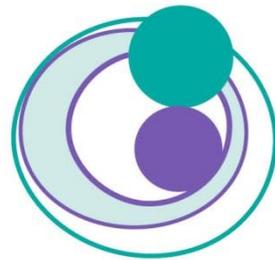




Lethal Skeletal Dysplasia



New Zealand
Maternal
Fetal
Medicine
Network

This guideline was updated in August 2015 by Dr Joana De Sousa with input from members of the New Zealand Maternal Fetal Medicine Network, Clinical Directors in Obstetrics and in Neonatology.



Background

Lethal skeletal dysplasias/ osteochondrodysplasias are rare and until recently poorly understood. They refer to 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. >90% result from new spontaneous mutations.

Prevalence of lethal skeletal dysplasia ranges from 0.95 to 1.51 per 10000 live births. 23% are stillborn, 32% die post-delivery.

There are >456 types of skeletal dysplasia which are classified as lethal or non-lethal. Lethality is based on pulmonary hypoplasia that results from restrictive thorax.

Three most common prenatally diagnosed lethal skeletal dysplasias:

- **Thanatophoric dysplasia (29%):** Severe rhizomelic micromelia, small thoracic circumference, macrocrania, normal trunk length, normal mineralization, no fractures, redundant skin folds, flat vertebral bodies
- **Achondrogenesis (9%):** Severe micromelia, small thoracic circumference, macrocrania, short trunk length, decreased mineralization, occasional fractures
- **Osteogenesis imperfecta type 2 (14%):** Severe micromelia, small thoracic circumference, normal cranial size, short trunk length, decreased mineralization, multiple fractures

Lethal group of skeletal dysplasia typically have an earlier onset than the non-lethal group.



Objective

- To ensure correct evaluation of fetuses when there is a suspicion of skeletal dysplasia, by virtue of 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

Definition

Micromelia: shortening of the entire limb

Rhizomelia: shortening of the proximal segment

Mesomelia: shortening of the intermediate segment

Acromelia: shortening of the distal segment

Differential Diagnosis

- Severe early growth restriction
- Aneuploidy

• 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

Ultrasound

Skull

- shape, softness, sutures, mineralization
- frontal bossing, clover leaf skulls, craniosynostosis

Face

- profile and coronal views with 3D if possible
- Micrognathia, hyper/hypotelorism

Spine

- sagittal, transverse and coronal views

All Long Bones

- Lengths: correlate with long bone charts
- Shape, bowing, fractures

Femur and Humerus

- sagittal and coronal views

Clavicles

- Length and transverse views
- First bone to fuse in fetus
- Growth 1mm/week gestational age

Scapulae

- length and sagittal views

Ribs

- length and shape
- should extend 2/3 circumference of thoracic cavity





Chest and Abdomen

- Midline sagittal view of chest and abdomen on same image

Circumferences – TC: AC

- Thoracic circumference: Abdominal circumference
 - At level of 4CH view of heart
 - Ratio should be 80-100%
 - Lower values suggest pulmonary hypoplasia

Hands

- Number of digits
- Clenched or trident hands

Feet

- Axial views and length
- Length of foot = length of femur
- Talipes and rocker bottom feet

Lethal Skeletal Dysplasia

Criteria for lethal skeletal dysplasia: based on pulmonary hypoplasia. Prenatal ultrasound has high sensitivity to detect lethality (81-99%)

Findings suggestive of pulmonary hypoplasia include:

- Early severe micromelia ($\geq 4SD$ below mean for gestational age)
- Femur length: abdominal circumference < 0.16
- Thoracic circumference $< 5\%$ tile
- Thoracic circumference : abdominal circumference < 0.79
- Cardiac circumference : thoracic circumference > 0.60

- Ribs around less than 70% of thoracic circumference at level of 4-chamber view
- Concave or bell-shaped thorax (coronal view)
- Thoracic length (from neck to diaphragm)

Investigation

Consider (pre or postnatally)

- Karyotype
- Biochemical : hypophosphatasia

There is a large and rapidly growing list of single-gene disorders, need 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 suggesting lethality.



On-going Management

Consultation with radiologist, geneticist, neonatologist, fetal medicine panel.

If pregnancy is terminated, or fetal death:

- Advise post-mortem evaluation
- 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

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