A short review of antenatal imaging of the common skeletal dysplasias

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Learning Objectives

1. To understand the salient features of skeletal dysplasias at antenatal ultrasound.
2. To differentiate between the lethal and non-lethal skeletal dysplasias at morphology scanning.
3. To review the classification of skeletal dysplasias, and features seen in the most common and recognizable dysplasias.

Background

Skeletal dysplasias are characterized by abnormalities of cartilage and bone growth, resulting in abnormal shape and size of the skeleton, and disproportion of the long bones, spine, and head. The prevalence of skeletal dysplasias is 1 in 2000 to 1 in 5000 births\(^1\). While there are many skeletal dysplasias, four disorders comprise almost 70%: achondroplasia, thanatophoric dysplasia, osteogenesis imperfecta, and achondrogenesis. Around 25% of neonates with a skeletal dysplasia are still born, and one third die in the first week of life\(^2\), causing enormous stress to the affected families.

This presentation reviews the imaging findings of the most common skeletal dysplasias seen at antenatal ultrasound, with x-ray and pathologic correlation. Some of the less common, but characteristic dysplasias are also discussed.

Imaging Findings OR Procedure Details

*The Diagnosis of a Skeletal Dysplasia.*

A skeletal dysplasia is usually suspected when the antenatal ultrasound shows disproportionately short limbs compared with the size of the head and body. There are over 350 different types of skeletal dysplasias\(^3\), and there are other conditions such as aneuploidies that can mimic these diseases. Investigation of a suspected skeletal dysplasia should begin with a detailed ultrasound scan, including measurements of all the long bones, the head, chest and abdomen, as well as detailed imaging of the spine and organs for any associated abnormalities. It is very difficult to correctly diagnose a specific skeletal dysplasia on the basis of ultrasound alone. It has been shown that ultrasound can predict with high accuracy the lethality of a skeletal dysplasia\(^1,4,5\). The ability to counsel on the basis of whether the unborn child will survive or not is very useful to the
parents. A definite diagnosis is obtained in only 70 - 80% of cases, even after clinical, radiological, pathological, biochemical and genetic investigations\textsuperscript{1, 4}. In our experience, the parental relationship has been consanguineous in a number of cases.

There are several indicators of a poor prognosis in skeletal dysplasias\textsuperscript{1, 2, 6}. These are listed below.


Death as a result of a skeletal dysplasia is usually due to a small chest and associated pulmonary hypoplasia. A chest circumference $< 5^{\text{th}}$ percentile for gestational age is an indicator of pulmonary hypoplasia\textsuperscript{2}. A chest-to-abdominal circumference ratio of $< 0.6$ is strongly suggestive of a lethal disorder\textsuperscript{3}.

2. Severely Shortened Long Bones.

The shorter the fetal long bones, the higher the likelihood of a lethal disorder. A femur length that is less than 2 standard deviations below the mean for gestational age should provoke measurements of all the long bones to investigate a potential skeletal dysplasia.

3. Abnormally Bent or Curved Bones.

Bending is a feature of many lethal skeletal dysplasias including thanatophoric dysplasia, or can be the result of fractures in conditions such as osteogenesis imperfecta or hypophosphatasia. Very few non-lethal dysplasias show bent or curved bones antenatally.

4. Evident at an Early Age.

The most severe dysplasias such as achondrogenesis are evident in the first trimester, whereas the less-severe, non-lethal conditions such as achondroplasia may not become obvious until the 3\textsuperscript{rd} trimester. Hence, the earlier a condition can be detected antenatally, the poorer the long term prognosis.

5. Low Femur Length-to-Abdominal Circumference Ratio.
This ratio was introduced into the literature in 1997\(^6\).\(^7\). It has been shown that a femur length-to-abdominal circumference ratio of < 0.16 results in a lethal outcome in almost all cases, whereas a ratio of > 0.16 resulted in survival\(^6\),\(^7\).

6. Fetal Hydrops.

Hydrops occurs in the most severe of the skeletal dysplasias, as well as aneuploidies which can mimic a skeletal disorder.

*The Most Common Skeletal Dysplasias.*

**Thanatophoric Dysplasia.**

There are 2 subtypes thanatophoric dysplasia (TD), the most common of the lethal skeletal dysplasias. Both result from a new autosomal dominant mutation on chromosome 4\(^8\). Almost all affected neonates die within days of birth due to respiratory insufficiency. The ultrasound features are (Fig. 1 on page 9, Fig. 2 on page 10):

- severe micromelic limb shortening
- pronounced curvature of the limb bones
- relatively large head
- small thoracic cage
- polyhydramnios

The radiological manifestations include (Fig. 3 on page 11):

- macrocephaly with small face, "clover-leaf" skull in some
- long narrow thoracic cage with short ribs
- severe platyspondyly, "U" or "H" shape vertebra on AP projection
- short, bowed long bones, "French telephone receiver" femurs (TD I), straight femurs (TD II)
- short, small iliac bones with horizontal acetabular roofs
- increased subcutaneous tissues

**Achondroplasia.**

Achondroplasia is the most common non-lethal skeletal dysplasia with an incidence of about 1 in 25 000 births\(^8\). It has an autosomal dominant inheritance on chromosome 4, with 80% of cases due to new mutations\(^8\). It is usually diagnosed postnatally, or antenatally in the third trimester, when polyhydramnios causes the pregnancy to seem
large for dates. Homozygous achondroplasia can be diagnosed much earlier in the pregnancy, and is usually hereditary. The ultrasound features are (Fig. 4 on page 12, Fig. 5 on page 13, Fig. 6 on page 14):

- normal 19 week morphology scan
- drop off in growth of the long bones in the 3rd trimester
- relative macrocephaly
- frontal bossing
- saddle nose
- polyhydramnios

The radiological manifestations include (Fig. 7 on page 15):

- large cranium with a narrow foramen magnum and J-shaped sella
- short, flat vertebral bodies with short pedicles and narrow vertebral canal
- pronounced lumbar lordosis
- "champagne glass" pelvis with narrow sciatic notches
- micromelic shortening of the long bones with flared metaphyses
- mildly shortened ribs

**Osteogenesis Imperfecta.**

There are 4 main subtypes of osteogenesis imperfect (OI) which range from the clinically mild types I and IV which are usually diagnosed in childhood, to the lethal type II. *Only the severe types are diagnosable on imaging antenatally.* As a group, they are one of the most common of all skeletal dysplasias, most resulting from a gene defect on chromosome 17. The incidence is about 1 in 25 000 births\(^8\), although this may be higher as around 10% are subclinical. The frequency and inheritance are summarised in Table 1\(^8\).

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency</th>
<th>Inheritance</th>
<th>Clinical Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>~50%</td>
<td>autosomal dominant</td>
<td>mild to moderate</td>
</tr>
<tr>
<td>II</td>
<td>~25%</td>
<td>usually autosomal recessive</td>
<td>perinatal lethal</td>
</tr>
<tr>
<td>III</td>
<td>~21%</td>
<td>autosomal, 75% dominant, 25% recessive</td>
<td>progressive deforming</td>
</tr>
<tr>
<td>IV</td>
<td>rare</td>
<td>autosomal dominant</td>
<td>mild to moderate</td>
</tr>
</tbody>
</table>
Table 1. Subtypes of Osteogenesis Imperfecta.

The ultrasound features are (Fig. 8 on page 16, Fig. 9 on page 17, Fig. 10 on page 18):

- "too-well seen" anatomy - the poor mineralization allows sounds waves to pass through the bones easily
- short, bent or crooked bones, as a result of multiple fractures
- compressible skull

The radiological manifestations include (Fig. 11 on page 19):

- very poorly ossified bones, especially the skull
- wormian bones
- crumpled long bones
- short, beaded ribs
- flattened acetabulae and iliac wings

Achondrogenesis.

Achondrogenesis is one of the most severe skeletal dysplasia and can be diagnosed as early as the late first trimester. There are several subtypes although the radiological features are similar. The incidence is around 1 in 50 000 live births\(^8\), although most fetuses are stillborn. The ultrasound features are (Fig. 12 on page 20):

- severe micromelia
- fetal hydrops
- very short beaded ribs
- deficient or absent vertebral ossification
- barrel-shaped chest and distended abdomen
- polyhydramnios

The radiological manifestations include (Fig. 13 on page 21):

- poorly mineralized skull
- short, splayed ribs
- short, broad, bowed tubular bones
- minimal vertebral body ossification
- short, deformed iliac wings
- increased soft tissues (hydrops)

Other Interesting Skeletal Dysplasias.
Hypophosphatasia.

This lethal skeletal dysplasia can be overlooked antenatally due to subtle ultrasound findings. The disease is uncommon, with an incidence of 1 in 100 000 live births\textsuperscript{8}, and results from a defect on chromosome 1 that is inherited in an autosomal recessive fashion. The ultrasound features are (Fig. 14 on page 22):

- "too-well-seen" anatomy - due to lack of bone mineralization
- shortened, deformed limbs
- polyhydramnios

The radiological manifestations include (Fig. 15 on page 23):

- very poor mineralization of bones - "jelly-baby"
- almost no calvarial ossification (cranium membranosum)
- marked retardation of skeletal ossification
- very small chest, with small ribs
- abnormally shaped vertebral bodies - clefting, platyspondyly

Atelosteogenesis.

Most subtypes of this severe skeletal dysplasia are neonatally lethal. Cases have been reported of both dominant and recessive types, with defects on chromosomes 3, 4 and 5\textsuperscript{9}. All types show severe rhizomelic limb shortening and facial abnormalities. The ultrasound features are (Fig. 16 on page 24):

- very short tubular bones, including hypoplastic femurs and, sometimes, absent humeri
- boomerang-shaped tibia
- clefted vertebrae
- cleft lip and palate
- micrognathia
- omphalocoele

The radiological features include (Fig. 17 on page 25):

- absent, short or clubbed humeri
- short, flared femurs
- short, bowed radius, ulna and tibia, hypoplastic fibula
- hypoplastic vertebra, vertebral clefting, platyspondyly
- 11 - 12 short ribs
- hypoplastic maxilla and mandible
- "hitch-hiker thumb" - characteristic feature of Type II\textsuperscript{8,9}
Short-Rib Polydactyly Syndrome.

This is an autosomal recessive disorder with several subtypes\(^8\). Despite the name, polydactyly is not always present, especially in subtypes III and IV. The condition is almost universally lethal in the neonatal period. The ultrasound features are (Fig. 18 on page 26, Fig. 19 on page 27):

- short ribs and long bones
- polydactyly
- narrow chest
- cystic hygroma
- choroid plexus cysts
- brain and renal abnormalities in type II and IV (vermian hypoplasia, arhinencephaly, cystic kidneys)
- hydrops

The radiological features include (Fig. 20 on page 28):

- very short, horizontal ribs
- micromelia, hypoplastic tubular bones with ragged ends, pointed femoral ends
- polydactyly
- dolichocephaly with poorly mineralized frontal bones
- micrognathia
- misshapen vertebral bodies with coronal clefting

Arthrogryposis.

Arthrogryposis refers to a heterogeneous group of disorders characterised primarily by joint contractures. The clinical features are very varied depending on the underlying cause, but the antenatal ultrasound features are similar in all these disorders. Final diagnosis is obtained via muscle biopsy and genetic investigations. The ultrasound features are (Fig. 21 on page 29, Fig. 22 on page 30):

- absent or severely reduced fetal movements during scanning
- failure of fetus to change position during scanning
- fixed flexion/extension of limbs
- clasped thumbs
- cystic hygroma

The radiological features include (Fig. 23 on page 31):

- slender, osteoporotic bones
- fixed flexion deformities, joint dislocations
• vertical talus with rocker-bottom feet
• brachycephaly

*Important Mimics of Skeletal Dysplasias.*

**Severe Intrauterine Growth Restriction (IUGR).**

In cases of severe IUGR, the fetal long bones may be quite short, mimicking a skeletal dysplasia$^{10}$. As such, we recommend that an examination of fetal well-being including Doppler ultrasound be performed as well as a detailed examination of the placenta. IUGR is defined as being present if the fetal weight is below the 10$^{th}$ percentile for gestational age. The prevalence of IUGR is 3 - 5%, and is higher in women with hypertension or IUGR in a previous pregnancy$^{11}$. The ultrasound features are (Fig. 24 on page 32, Fig. 25 on page 33, Fig. 26 on page 34):

• abnormal fetal biometry - small abdomen with poor growth, shortened long bones, head measurement may be normal or small
• oligohydramnios
• abnormal umbilical artery dopplers - elevated SD ratios, absent or reversed end diastolic flow
• abnormal middle cerebral artery dopplers - increased diastolic flow and abnormal resistive indices
• abnormal placenta in many cases - small or calcified placenta, marginal or velamentous cord insertion
• echogenic bowel in up to 20%

**Chronic Intervillous Histiocytosis.**

Chronic intervillous histiocytosis (CIH) or chronic intervillositis is a rare inflammatory disorder of the placenta resulting in extreme IUGR and recurrent pregnancy losses$^{12}$. The skeletal findings can be striking, mimicking a severe skeletal dysplasia (Fig. 27 on page 35, Fig. 28 on page 36, Fig. 29 on page 37).

Images for this section:
Fig. 1: Morphology scan of a 21 week fetus with thanatophoric dysplasia type I. There is severe micromelia with the long bones measuring around 15 weeks size.
Fig. 2: Morphology scan of a 21 week fetus with thanatophoric dysplasia type I. The head is relatively large compared with the body, measuring around 23 weeks size. The coronal body view shows the small chest compared with the abdomen. Note the excessive liquor on these images.
Fig. 3: Post-mortem skeletal survey of the same infant, and image of a thanatophoric femur post dissection.
Fig. 4: Growth scan of a 33 week fetus with achondroplasia. The bones are short but straight, and note the drop off in growth since the morphology scan.
Fig. 5: Growth scan of a 33 week fetus with achondroplasia. The cranium is relatively large, and frontal bossing is evident on the profile view. The 3D image clearly shows the short midface and saddle nose.
Fig. 6: Growth scan of a 33 week fetus with achondroplasia. The chest is a little small, but not to the extent seen in lethal dysplasia. Note the excessive liquor.
**Achondroplasia**

**Fig. 7:** Post natal chest and abdomen x-ray of the same infant, and skull x-ray from a 6 year old with achondroplasia, demonstrating the salient skeletal features.
Fig. 8: Morphology scan of a 20 week fetus with osteogenesis imperfecta type II. The forearm bones appear twisted, and there is a 90 degree bend in the right lower leg. The bones are only slightly shortened.
Fig. 9: Morphology scan of a 20 week fetus with osteogenesis imperfecta type II. The cranial anatomy is beautifully seen as a result of the poorly mineralized cranium. The head is normal in size.
**Fig. 10:** Video clip taken at morphology scan, demonstrating the marked compressibility of the skull, due to poor mineralization.
Fig. 11: Post-mortem skeletal survey of the same infant, and image of the lower limbs showing the bending.
Fig. 12: 14 week scan of a fetus with achondrogenesis type 1B. The thoracic cage is extremely narrow, and there is a large cystic hygroma. There was oligohydramnios in this case, as the woman presented with premature rupture of membranes.
Fig. 13: Post-mortem skeletal survey and photograph of the same infant.
Fig. 14: Morphology scan of a 19 week fetus with hypophosphatasia. The fetal biometry is within the normal range, the only indication of a problem in this case was the "twisted" appearance to the fibula. Polyhydramnios was mild and developed later in the pregnancy.
Fig. 15: Post natal x-rays of the same infant, who succumbed from respiratory failure within hours of birth.
**Fig. 16:** Early morphology of 16 week fetus with atelosteogenesis. The long bones are very short, already 3 - 4 weeks behind normal size. The profile is micrognathic.
Fig. 17: Post-mortem skeletal survey and photograph of the same infant.
**Fig. 18:** Morphology scan of a 20 week fetus with short rib polydactyly syndrome type III. The long bones are straight but very short.
Fig. 19: Morphology scan of a 20 week fetus with short rib polydactyly syndrome type III. The ribs are very short, ending only halfway around the chest. There are more than 5 toes on the feet.
Fig. 20: Post-mortem skeletal survey of the same fetus, and photographs of the feet.
Fig. 21: Morphology scan of a 21 week fetus with arthrogryposis. The bone length is normal, but the knees are fixed in extension, and wrists and hands are tightly flexed. Fetal movements were minimal during the scan.
**Fig. 22:** Morphology scan of a 21 week fetus with arthrogryposis. The fetus is hydropic with a cystic hygroma and pleural effusions.
**Fig. 23:** Post-mortem skeletal survey of the same infant, showing the flexion and extension deformities.
Fig. 24: Growth scan in a 29 week fetus being followed for severe IUGR. There has been almost no growth in the 5 week interval since the previous scan. The femur looks curved and there is very little liquor.
Fig. 25: Growth scan in a 29 week fetus being followed for severe IUGR. The flow in the umbilical arteries is now reversed in diastole. There is also reversal of flow in the ductus venosus, which is a "pre-terminal" sign.
**Fig. 26:** Post-mortem skeletal survey in the same infant which succumbed before delivery could be initiated. While the bones are osteopenic, the length is "normal" in relation to the rest of the body, which is globally small.
Fig. 27: Growth scan in a 30 week fetus. This woman had already terminated 2 previous pregnancies for "skeletal dysplasia". The baby is small but growing appropriately, the chest is a little small and there is oligohydramnios.
Fig. 28: Growth scan in a 30 week fetus. The placenta is sonographically normal, but the umbilical artery dopplers have an elevated SD ratio. At this stage, the advanced Doppler were still normal.
**Chronic Intervillous Histiocytosis**

**Fig. 29:** Post-natal chest x-ray of the same infant, and post-mortem x-ray of the previous pregnancy. The bones are osteopenic but otherwise normal. Placental histology confirmed the diagnosis.
Conclusion

The appropriate identification of skeletal dysplasias is important not only for current pregnancy management, but also for genetic counselling concerning future pregnancies.

Personal Information

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References