In-Utero

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Introduction: Prenatal Ultrasound

Development

The evaluation of fetuses in the second trimester for the detection of abnormalities represents a standard of care in many communities [1].

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Morphogenesis of the skeletal systems occurs from the third to the eighth week intra utero, and therefore, prenatal diagnosis of some skeletal disorders is possible.

Week	Development	Activity
8	Limb buds, clavicle, mandible	
9	Femur, humerus	Body movements
10	Tibia/fibula, radius/ulna	
11–12	Accurate measurements can be performed	Limb movement
20	Epiphyseal ossification centers visible (long bones)	

Summarized from Chitty and Altman [2] and van Zalen-Sprock et al. [3]

The appendicular and axial skeleton follow a pattern of endochondral ossification. The calvarium, portions of the clavicle, and pubis follow a pattern of membranous ossification [4].

The measurement of fetal limbs has been used to date pregnancies and constitutes and important part of the assessment of fetal anatomy [5].

The femur length is the most commonly used limb measurement and is also included in the regular growth scans, as one of the parameters to assess growth, and to obtain an estimate on fetal weight [6]. The increase in size of long bones is linear throughout gestation [7].

Imaging Workup When a Skeletal Dysplasia Is Suspected in Utero (Prenatal Ultrasound)

When the femoral or humeral measurements are less than the fifth percentile or less than two standard deviations (SD) from the mean in the second trimester, fetal medicine referral and complete evaluation of the skeleton should be made.

When measurements of the long bones are less than three SD from the mean, suspicion of skeletal dysplasia should be very high, especially if the head circumference is above the 75th centile.

Specific views to obtain in the suspicion of skeletal dysplasia	
All long bones	Length measurement
	Shape
	Echogenicity
	Femur-to-foot ratio
Other bones	Scapula
	Clavicle
	Mandible
Abdominal	Circumference measurement
Chest	Circumference measurement
Fetal cranium	Biparietal diameter measurement
	Occipitofrontal diameter measurement
	Head circumference measurement
Facial profile	Glabellar bossing
	Flattened nasal ridge
	Assessment of micrognathia
Vertebral bodies	Number Shape
Hands and feet	Extra digits Missing digits Malformations
Mineralization	Calvarium Skeleton Ectopic mineralization

The accuracy of diagnosis of dysplasias in prenatal ultrasound ranges between 40% and 60% [8, 9]; therefore, subsequent radiological evaluation (or in cases of demise autopsy and histomorphic analysis) is very important.

The obtention of an accurate diagnosis is important, to offer counseling to avoid the possibility of recurrence (many dysplasias have a high recurrence risk) [10].

Low-dose and ultralow-dose CT allow the exquisite depiction of fetal bones and the possibility of complete 3D rendering of the skeleton. Images can be rotated in space and postprocessed to focus on sections and obtain adequate detail. This is an important advantage with respect to dedicated ultrasound, in which the maternal habitus and the position of the fetus have a great impact on visualization.

Assessment of Characteristics of Long Bones

Bone Length

- The bones are measured in a plane as close as the orthogonal plane to the ultrasound beam.
- The full length of the bone has to be visualized, and the view should not be obscured by shadowing from adjacent body parts [7].
- Calipers are placed from the greater trochanter to the end of the ossified shaft (femur) (Fig. 1a, b). End-to-end of ossified shafts in other bones (Fig. 2a–d).

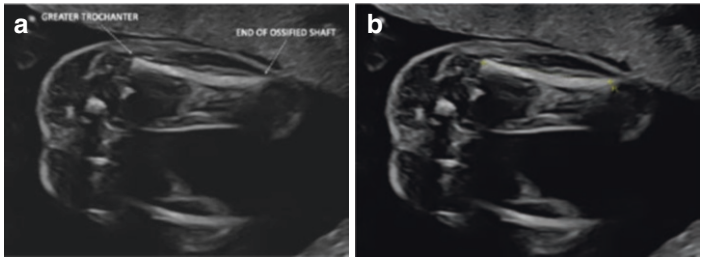

FIGURE 1 (**a**, **b**) Femur length measurement (landmarks)

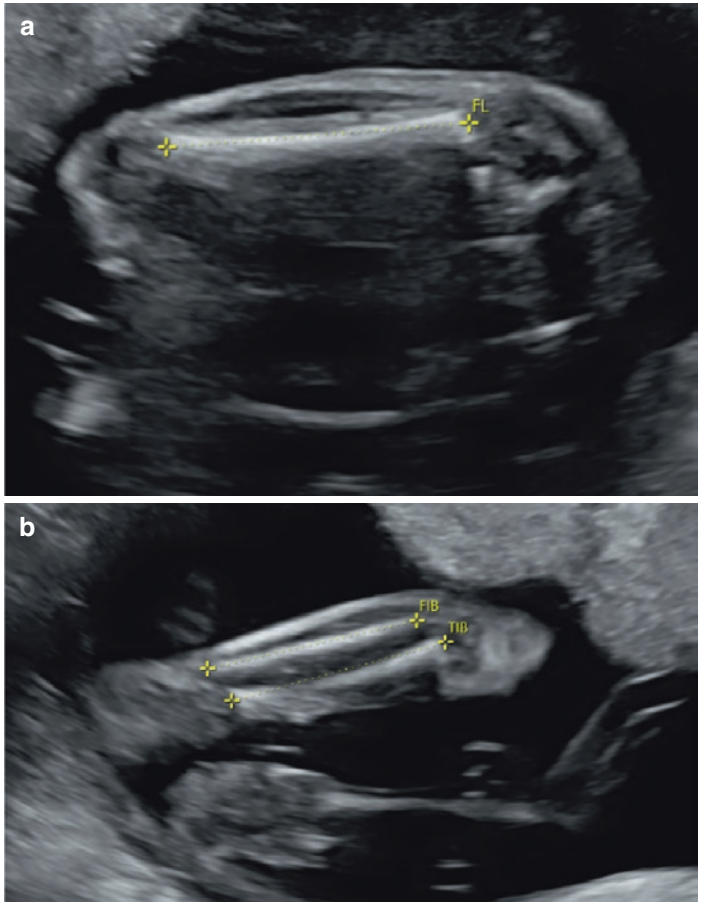

FIGURE 2 Measurements of long bones. (**a**) Femur measurement. (**b**) Tibia and fibula measurement. (**c**) Humerus measurement. (**d**) Radius and ulna measurement

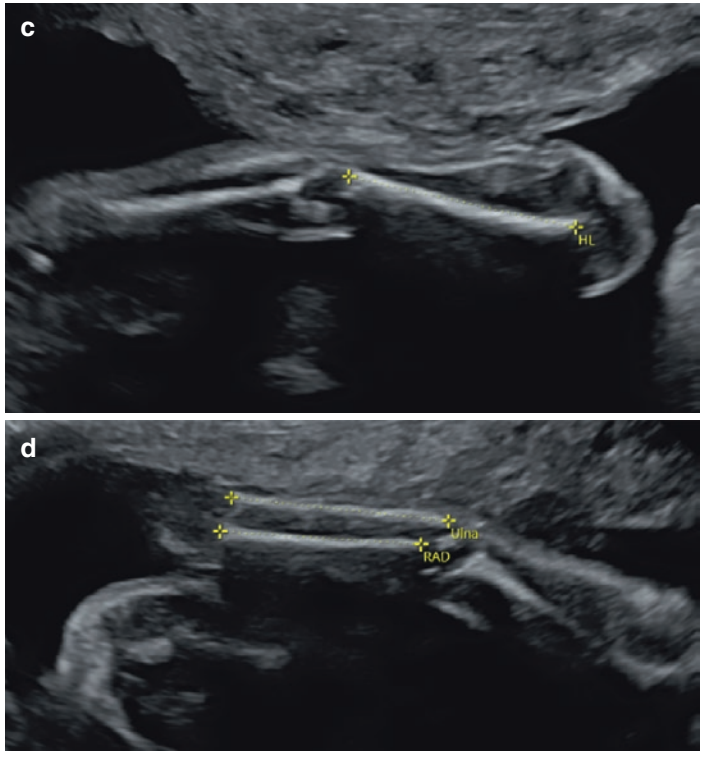

Figure 2 (continued)

Type of shortening	Involvement	
Micromelia	Entire limb	
Rhizomelia[a]	Proximal segment	Femur, humerus
Mesomelia[a]	Intermediate segment	Tibia, fibula, radius, ulna
Acromelia	Distal segment	Hands, feet

[a]The diagnosis of rhizomelia or mesomelia requires comparison of the length of the bones of the leg or forearm (tibia/fibula and radius/ulna) with those of the thigh and arm (femur and humerus). Plotting against normal values (population charts) is helpful to determine whether both segments may be involved [1]

- The femur-to-foot ratio approaches 1.0 throughout gestation (in our experience, the foot is almost always slightly larger than the femur) (Fig. 3). Many skeletal dysplasias show obvious disproportion of the femur-to-foot ratio: the dysplasias in which rhizomelia is predominant will show <1.0 femur-to-foot ratio [11].
- The foot is measured in the plantar view, from the heel to the end of the longest toe [2] (Fig. 4a, b).
- The more severe the reduction, the earlier it can be detected:
  - 16–18 weeks—severe limb reductions (osteogenesis imperfecta type II, achondrogenesis, thanatophoric dysplasia, diastrophic dysplasia, chondroectodermal dysplasia);
  - 22–24 weeks—less severe reductions (achondroplasia) [1].

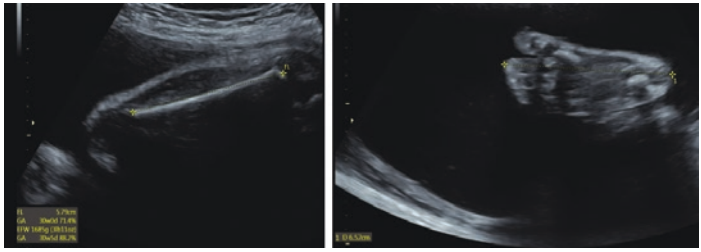

FIGURE 3 Femur-to-foot ratio

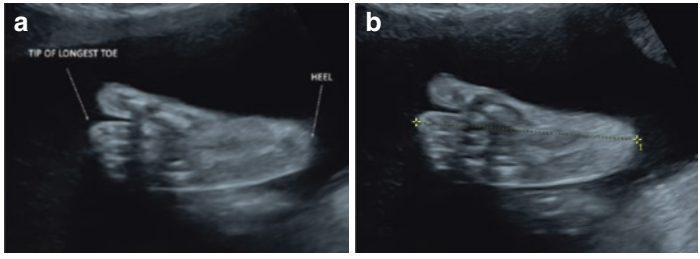

FIGURE 4 (**a**, **b**) Foot measurement (landmarks)

Isolated reduction of limbs is often inherited as part of a syndrome: Holt-Oram, Fanconi pancytopenia, and thrombocytopenia with absent radii.

- Amelia—complete absence of an extremity.
- Acheiria—absence of the hand.
- Phocomelia—absence of proximal segments: seal limb.
- Aplasia—hypoplasia of the radius or ulna.

Other causes are amniotic bands, exposure to thalidomide, and caudal regression.

Bone Shape

A small degree of curvature of the femur is a normal finding.

- Bowing: campomelic dysplasia, thanatophoric dwarfism, osteogenesis imperfecta (autosomal dominant), achondrogenesis, and hypophosphatasia.
- Fractures and callus formation: osteogenesis imperfecta (autosomal dominant), achondrogenesis, and hypophosphatasia [12].

Echogenicity

When the bones are hypomineralized, the echogenicity on ultrasound is be reduced.

Hypomineralization can be seen in conditions such as osteogenesis imperfecta, hypophosphatasia, and achondrogenesis [12].

Evaluation of Hands and Feet

- Polydactyly—more than five digits.
  - Postaxial if the additional digits are on the ulnar/fibular aspect.
  - Preaxial if they are on the radial/tibial aspect.

- Brachydactyly—missing fingers.
- Syndactyly—fusion of soft tissues or bones of adjacent digits.
- Clinodactyly—deviation of the fingers.
- Disproportion—between the hands and feet and other parts of the limb.
- Deformities—equinovarus (talipes) [13].

Evaluation of Fetal Movements

Limitation of flexion or extension of the limbs may be associated to arthrogryposis and multiple pterygium syndrome [14].

Evaluation of the Fetal Head

Many dysplasias, some of them severe, involve abnormalities of the shape or ossification of the skull bones.

Most dysplasias with a prenatal onset demonstrate a relative disproportion of the skeletal measurements compared to the measurements of the fetal head [15].

- Head measurements are obtained in a symmetric axial plane, at the level of the thalami and the cavum septum pellucidum (the cerebellum should not be included in the plane) (Fig. 5a).
  - Biparietal diameter: calipers are placed at the outer edge of the near calvarial wall and the inner edge of the far calvarial wall (Fig. 5b).
  - Head circumference: ellipse should be drawn around the outside of the calvarium (Fig. 5c).
- The face also needs to be evaluated: hypertelorism, micrognathia, short philtrum, and abnormal morphology or location of the ears.

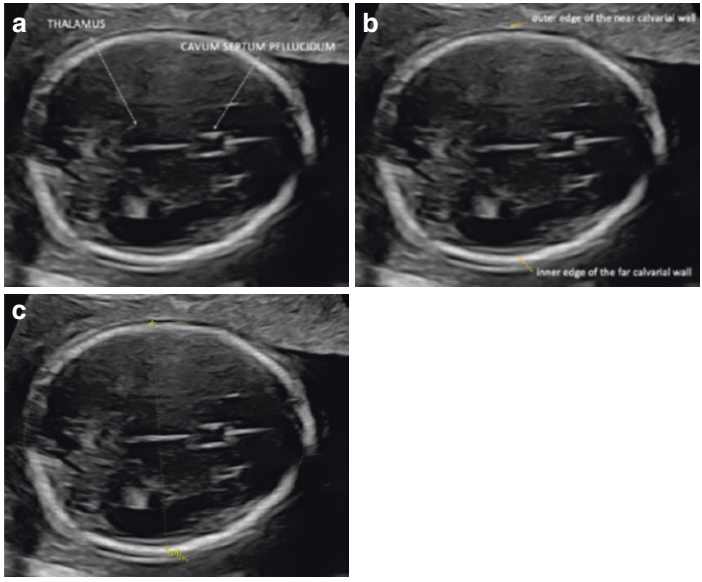

FIGURE 5 (**a**, **b**, **c**) Head measurements (landmarks and measurements)

Abdominal Circumference

Abdominal circumference is measured at a level including the fetal stomach, umbilical vein, and adrenal glands (Fig. 6a). The descending aorta should appear in true cross section (completely round). Kidneys should not be visible. The calipers should be placed in the skin line (Fig. 6b).

Evaluation of the Fetal Thorax

Severe skeletal dysplasias are associated with a small thorax, which is linked to pulmonary hypoplasia, and associated with neonatal death [16].

- The bony thoracic circumference is measured at the level of the four-chamber view. The whole thorax should be vis-

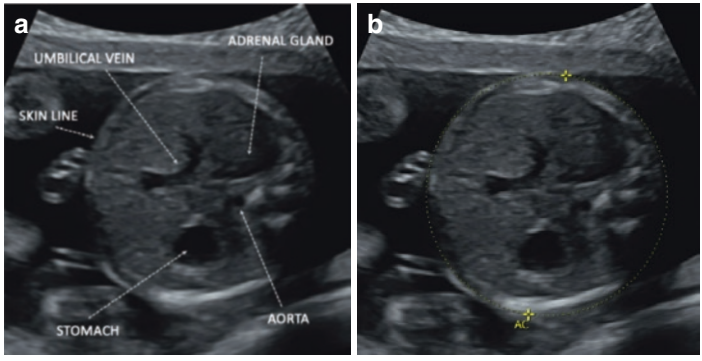

FIGURE 6 (**a**, **b**) Abdominal circumference measurement (landmarks and measurements)

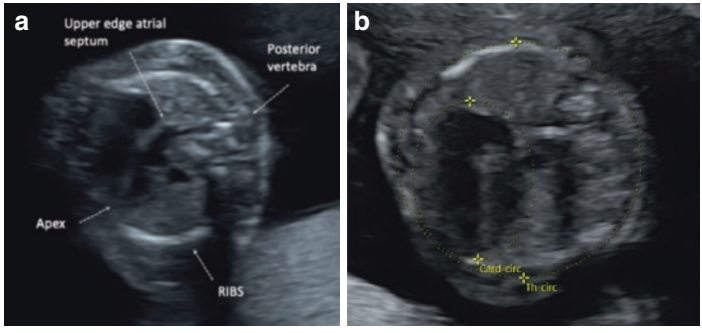

FIGURE 7 (**a**, **b**) Thoracic measurements (landmarks and measurements of the cardiac and thoracic circumferences)

ible in the screen, with ribs on both sides, and no abdominal contents. The points of reference for the circumference are the anterior thoracic wall and the posterior edge of the fetal vertebra. Measurements are performed with the heart in diastole. Reference points for the heart are the cardiac apex and the upper edge of the atrial septum [17, 18] (Fig. 7).

Determination of Lethality

One of the most important tasks for prenatal ultrasound in the context of a skeletal abnormality is to determine the neonatal or infantile lethality of the condition.

Lethality is normally linked to small chest circumference and subsequent pulmonary hypoplasia, which leads to early postnatal death. Not all skeletal dysplasias with small chests will result in immediate death.

Strongly linked to lethality:

- Chest-to-abdominal circumference ratio <0.6 [19] (Fig. 8).
- Femur length-to-abdominal circumference ratio <0.16 [20].
- Evaluate the occurrence of other abnormalities in other systems (heart, urogenital).
- Other markers of lethality:
  - Severe long bone shortening (more than three SD from mean).
  - Hydrops.
  - Markedly decreased bone echogenicity and prominent bowing or fractures [16, 21].

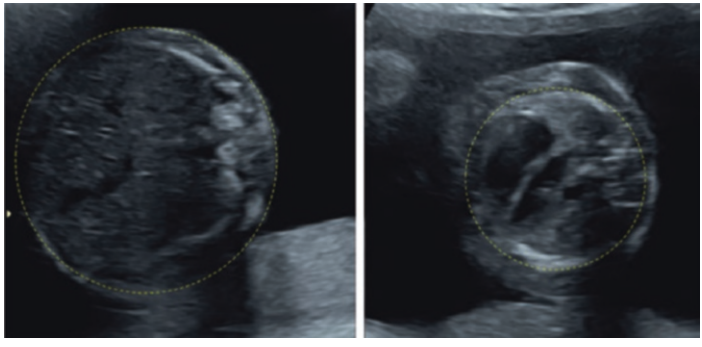

FIGURE 8 Comparison in size of abdomen and thorax

Imaging Workup When a Skeletal Dysplasia Is Suspected Postnatally (Radiographs)

If a skeletal dysplasia is suspected, a skeletal survey needs to be performed. This consists of a series of radiographs that will sample the structure and morphology of a wide range of bone structures.

Early radiographs are very useful. The ideal age for recognition of most dysplasias is before the closing of the growth epiphyses. After this, radiological diagnosis may be impossible [22].

Ideally, the skeletal survey should include [23, 24]:

- Skull (AP and lateral).
- Thoracolumbar spine (AP and lateral).
- Chest (AP).
- Pelvis (AP).
- One upper limb (AP).
- One lower limb (AP).
- Left hand (AP)*.

*The left hand is included to assess bone age. This is important in some cases in which it is necessary to relativize findings to the stage of normal growth [25]. Bone age may also be obtained from the foot and ankle, or the knee (especially in children younger then 2 years).

Specific Considerations

- If the limbs are visibly asymmetrical, or if there is the suspicion of epiphyseal involvement or stippling, views of both limbs (upper and lower) should be obtained for more accurate assessment.
- May be useful to obtain dedicated views (dedicated projections) that would better display the abnormality.

- Radiological surveys (and previous imaging) from affected family members may give an insight on future appearances, aid with diagnosis and prognosis, and help with the pattern of inheritance.
- Serial evaluation. This should not be done too early though—most centers would not repeat in less than 12 months [24].

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