

Evaluating skeletal dysplasias on prenatal ultrasound: an emphasis on predicting lethality

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Abstract Lethal skeletal dysplasias can be diagnosed by prenatal ultrasound (US) using several sonographic parameters. Degree of femoral shortening, lung volumes, femur length to abdominal circumference ratio, and chest circumference to abdominal circumference ratio are the most sensitive and specific predictors. Although there are more than 450 different skeletal dysplasias, only a few are lethal in the perinatal period. We review current fetal US literature and present an updated algorithmic approach to first establish lethality and, second, evaluate for hallmark sonographic features to help determine a specific diagnosis.

Keywords Bone · Chondro-osseous disorder · Fetus · Lethal · Skeletal dysplasia · Ultrasound

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Introduction

Skeletal dysplasias represent a heterogeneous group of more than 450 chondro-osseous disorders, the more severe of which can be detected prenatally [1, 2]. Birth incidence is nearly 1/5,000 overall, though each individual skeletal dysplasia is relatively rare [3]. Although family history plays an important role in assessing risk of skeletal dysplasias, as many as 90% of dysplasias occur in the absence of any known parental risk factors [4]. Thus, it is important to consider the diagnosis in any fetus with significantly shortened limbs. Currently, the gold standard for diagnosis of a skeletal dysplasia includes a combination of antenatal ultrasound (US), postnatal radiologic features, pathology and cytogenetic evaluation. Of these, the fetal sonologist is often the first to suggest the presence of a skeletal dysplasia by US and should be able to determine lethality. Prenatal US has only a 65–68% accuracy rate for diagnosis of a particular skeletal dysplasia [5, 6]. Antenatal prediction of a lethal skeletal dysplasia, however, approaches 100% with knowledge of the appropriate diagnostic criteria [7, 8]. A dysplasia may be considered perinatal lethal if it results in death, with or without heroic measures, between the second trimester and 4 weeks of postnatal life [9]. Many predictors of lethality in skeletal dysplasias have been previously described and the supporting literature is vast; however, the fetal sonologist need not memorize all of these to predict with a high degree of accuracy those dysplasias that consistently take a lethal course. Skeletal dysplasias that do not meet criteria for lethality can then be further assessed and risk stratified at a specialized fetal care center. We describe a simplified algorithm for determining lethality of a suspected skeletal dysplasia by prenatal US for radiologists and obstetricians practicing general fetal sonology.

Approaches

First, the short femur

The first step in diagnosing a skeletal dysplasia is detecting significant shortening of the long bones. Anatomical fetal US is performed between 18 and 22 weeks' gestation. Evaluation of fetal structures during this examination includes femur length measurement, an important assessment of the fetal skeletal system. Of note, the long bones, vertebrae and calvarium begin ossifying by 12 weeks, so the presence of a skeletal dysplasia can be suggested as early as the first trimester. The earlier it is detected, the more severe the dysplasia. There are a number of causes of short femur, including inaccurate gestational dating, intrauterine growth restriction, small for gestational age, and Down syndrome, so the second task is to exclude the many more common causes of short femur. Although this is a crucial step, it is rarely a diagnostic dilemma, because fetuses with lethal skeletal dysplasias have marked and early shortening of the long bones, disproportionate to fetal abdominal and calvarial growth. The pattern of growth in lethal dysplasias continues to decelerate throughout fetal life, with slightly slowed or delayed growth indicative of other entities. If there is doubt regarding the etiology of a shortened femur, a 3-week-interval follow-up US will demonstrate persistent reduced femur growth [10]. The diagnosis of a skeletal dysplasia should be considered when limb shortening is detected early and is relatively severe, falling at least two standard deviations below the mean relative to the biparietal diameter; however, this alone is not diagnostic for a skeletal dysplasia [11–13]. If during follow-up, the femur length is more than 5 mm below 2 standard deviations (equivalent to greater than 4 standard deviations below the mean), the sonologist can be certain he or she is dealing with a significant skeletal dysplasia (Fig. 1) [12]. Kurtz et al. [12] looked at 27 fetuses with shortened femurs and compared femur length with biparietal diameter to determine degree of femoral shortening, thus correcting for discrepancies in gestational dating [12, 14]. Of the 12 fetuses with femoral shortening greater than 5 mm below 2 standard deviations (range: 4.3–31 standard deviations below the mean), all 12 had a skeletal dysplasia, 8 of which were lethal. Of the 15 fetuses with less severe femoral shortening (range: 2–4 standard deviations below the mean), only one had a skeletal dysplasia, which was nonlethal (heterozygous achondroplasia). This suggests the degree of femoral shortening can also help predict lethality [12]. In this study, femoral shortening that is not four or more standard deviations below the mean represents either a nonlethal dysplasia or other growth aberration, but a lethal skeletal dysplasia can be excluded [12].

Ultrasound versus MRI for calculation of fetal lung volumes

Mortality in the skeletal dysplasias is determined largely by the degree of pulmonary hypoplasia [15]. A recent study suggests fetal lung volumes can be calculated using 3-D US and that it may prove an accurate sonographic tool for determining lethality in skeletal dysplasias [16, 17]. Barros et al. [16] prospectively evaluated 27 fetuses with skeletal dysplasia, 18 of whom were ultimately found to have a lethal dysplasia, as proven by postnatal clinical and radiologic criteria. Lung volumes were calculated on each fetus between 20 and 32 weeks' gestation. Measurements after 32 weeks were not performed due to technical limitations of late gestational sonography, including robust fetal breathing movements and shadowing from spine and rib ossification, previously shown to result in measurements that are not reproducible [17]. Contour measurements outlining the margins of each lung were obtained in axial, sagittal and coronal planes and a virtual organ computer-aided analysis method was used to compute volumes, which were compared to normative values based on gestational age [17]. Lung volumes were determined to be hypoplastic if one or both lungs fell below the fifth percentile of expected for gestational age as presented by Peralta et al. [17]. Fifteen of the 18 fetuses diagnosed with lethal pulmonary hypoplasia secondary to a skeletal dysplasia demonstrated abnormally low lung volumes, representing a sensitivity of 83%. No fetus with pulmonary hypoplasia by US survived the postnatal period (specificity 100%). Given that there was no postnatal autopsy in the study by Barros et al. [16], it is uncertain if the three false-negative cases were a result of pulmonary hypoplasia, though this is the assumption of the authors. Other 2-D sonographic parameters were assessed alongside 3-D lung volumes, including thoracic circumference, thoracic circumference to abdominal circumference ratio, thoracic area to cardiac area ratio, and femur length to abdominal circumference ratio, all of which had lower sensitivities and specificities when evaluated alone than total lung volume [16].

Although results are favorable for 3-D US calculation of lung volumes, the small study size and lack of pathological correlation for cause of death limit the authors' conclusions. Other limitations include the inability to be reproduced at later gestational ages due to excessive fetal motion and shadowing from the thoracic cage. Important pitfalls inherent to US imaging include poor soft-tissue contrast between lung and liver as compared with MRI, which can result in measurement inaccuracies. Decreased sonographic windows in the setting of oligohydramnios or maternal obesity can also limit US capabilities. MRI is not, however, limited by maternal body habitus, oligohydramnios or fetal positioning and can be complementary in difficult or equivocal US cases. MRI is not ideal for early gestational (prior to 18–20 weeks) imaging, mostly due to fetal motion, and likely offers more accurate lung volume

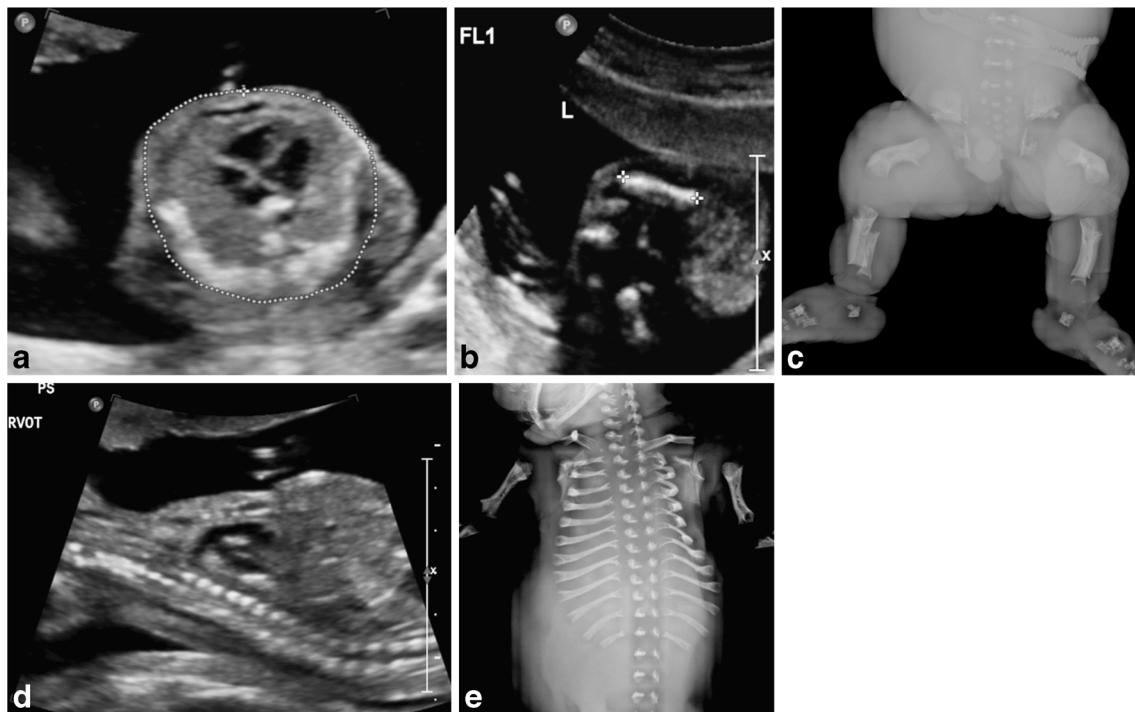


Fig. 1 A 22-week-old fetus with thanatophoric dysplasia. **a** Axial US image of the chest shows markedly shortened, irregular ribs and small chest. The *dotted circle* outlines the chest circumference. **b** US image of the femur (*calipers*) with severe shortening. Bowing is less apparent (*L* left). **c** Postnatal image of the same fetus on day of life 1. Appreciate the severely shortened and bowed femurs typical of type I thanatophoric

dysplasia that earned them the nickname “telephone receiver” femur. Also evident is rounded metaphyseal cupping, platyspondyly and an abnormally shaped pelvis. **d** Parasagittal US shows a bell-shaped chest and protuberant abdomen, indicative of thoracic hypoplasia. **e** Frontal chest radiograph in the same fetus on day of life 1. Thoracic hypoplasia is striking. The lungs are not aerated

calculations in the late second to third trimester, when US is limited. Additionally, normative lung volumes are published in US for fetuses as young as 12 weeks of age, whereas normative data for MRI is not available before 21 weeks [17, 18]. This can be problematic if elective termination is desired, given most states do not allow termination after 24 weeks.

Most 2-D US measurements are inferior to 3-D US and MRI in predicting lung volumes and pulmonary hypoplasia [19]. This is in part because fetal lung size is being indirectly estimated by thoracic circumference, thoracic area and thoracic area minus heart area, and these measurements are dependent on accurate gestational age. The observed-to-expected US lung-to-head ratio (o/e LHR) is the only 2-D US measurement that predicts pulmonary hypoplasia, and this has only been proven in fetuses with congenital diaphragmatic hernia [20]. Kastenholz et al. [20] showed that the observed-to-expected MRI fetal lung volume (o/e TLV) is a statistically significant prognostic parameter for the prediction of neonatal survival in congenital diaphragmatic hernia as is US o/e LHR, and that the two measurements are highly correlated ($P < 0.0001$). The same has been shown to be true for o/e LHR measurements made by fetal MRI [21]. Added prognostic value of this 2-D measurement over others is likely in part because it is independent of gestational age.

Weaver et al. [22] evaluated fetal lung volumes by MRI on 23 skeletal dysplasias diagnosed between 21 and 36 weeks’ gestation. Authors confirmed not only the association between lethality and reduced femur length to abdominal circumference ratios, further discussed below, but also showed a correlation between reduced fetal lung volumes and increased lethality. The most interesting finding, though, was the unexpectedly high cutoff for lung volumes associated with an increased risk of a lethal dysplasia. Weaver et al. [22] found that an o/e TLV ratio of less than or equal to 47.9% was associated with lethality (sensitivity: 75% and specificity: 82%), with two falsely predicted lethal dysplasias. This is in contrast to fetuses with pulmonary hypoplasia secondary to congenital diaphragmatic hernias, in which decreased survival was not statistically different until o/e TLV fell below 25% [23]. Thus, a single lung volume threshold alone cannot predict lethality across all fetal diseases. The higher cutoff in fetuses with skeletal dysplasias suggests a more complex, multifactorial cause of death, not fully explained by pulmonary hypoplasia alone. Of note, both fetuses falsely predicted to have a lethal dysplasia based on lung volumes in the study by Weaver et al. [22] survived the neonatal period but only with continuous ventilator support.

Femur length to abdominal circumference ratio

Femur length to abdominal circumference ratio is a reliable predictor of lethality in skeletal dysplasias [24]. Femur length to abdominal circumference ratio of less than 0.16 represents a lethal skeletal dysplasia in 92–96% of cases [24]. When combined with the presence of polyhydramnios, the ability to predict lethality has been reported to be as high as 100% in one series by Nelson et al. [24], owing in part to compressive effects of increased amniotic fluid volume on pulmonary hypoplasia. Nelson et al. [24] retrospectively reviewed 45 pregnancies with suspected skeletal dysplasias determined by prenatal US and found that those who had a lethal skeletal dysplasia were more likely to have polyhydramnios than those who had a nonlethal dysplasia (83% versus 27%). Those with lethal dysplasias had a significantly lower femur length to abdominal circumference ratio, less than 0.16, than those with a nonlethal dysplasia (91% versus 11%) [24]. All seven fetuses (100%) in this study who had both a femur length to abdominal circumference ratio less than 0.16 and polyhydramnios had a lethal skeletal dysplasia [24]. Supporting literature includes work by Ramus et al. [25], who reviewed 30 sonograms of fetuses with suspected skeletal dysplasia and found neonatal death occurred in 12 of 13 patients (92%) with a femur length to abdominal circumference ratio <0.16 . Severe bowing deformity was noted in the single case of nonlethal dysplasia with femur length to abdominal circumference less than 0.16 [25]. Rahemtullah et al. [26] found all nine lethal skeletal dysplasias in their series to have a femur length to abdominal circumference ratio of less than 0.16 and all nonlethal dysplasias to have a ratio greater than 0.16. These studies suggest no more than 8% of fetuses with a femur length to abdominal circumference ratio of less than 0.16 may still have a nonlethal dysplasia. One example of this is in the nonlethal dysplasia Grebe chondrodysplasia, characterized by marked long bone shortening but normal chest measurements. Variability between studies has also been related to differences in femur measurements in fetuses with bowing deformities, since a linear measurement in such cases does not accurately reflect the true femur length [24, 25]. Thus, limb measurements should be made with care in fetuses with bowing deformities, and measurement of the hypotenuse avoided rather than the true limb length, as this could result in falsely shortened measurements and a spuriously low femur length to abdominal circumference ratio.

Femur length to abdominal circumference ratio has utility not only for including, but also for excluding, the presence of a lethal dysplasia. Ramus et al. [25] and Rahemtullah et al. [26] found no fetus with a ratio >0.16 to have a lethal skeletal dysplasia, while Nelson et al. [24] had one case of lethal dysplasia with a femur length to abdominal circumference ratio of greater than 0.16, which was only slightly increased at 0.17. Of the 45 fetuses evaluated for suspected skeletal dysplasia by Nelson et al. [24], there was no difference between the

gestational age at which nonlethal (median: 34 weeks' gestational age) versus lethal (median: 28 weeks' gestational age) skeletal dysplasias were diagnosed using abnormal femur length to abdominal circumference ratio or thoracic circumference to abdominal circumference ratio. Thus, the predictive value of this ratio is retained regardless of the gestational age at which measurements are made, further strengthening its clinical utility [24].

Chest circumference to abdominal circumference ratio

Chest circumference to abdominal circumference ratio of less than 0.6 represents a lethal skeletal dysplasia in 86.4% of cases [27]. Only 7% of fetuses with a chest circumference to abdominal circumference ratio of greater than 0.6 may still have a lethal skeletal dysplasia. The false-negatives are likely related to body wall edema or disorders in which edematous or redundant skin distorts measurements [27]. Sonographic measurement of chest circumference alone has also been shown to be a useful predictor of pulmonary hypoplasia in cases of premature rupture of membranes and oligohydramnios [28–30]. This, however, requires knowledge of the gestational age and cannot be used in fetuses with suspected intrauterine growth restriction. Yoshimura et al. [27] studied 21 fetuses with lethal pulmonary hypoplasia that resulted in death within the first 24 h after birth with autopsy confirming a diagnosis of pulmonary hypoplasia by lung weight to body weight ratios and radial alveolar counts. Eight different sonographic chest-related measurements and ratios were made on these fetuses and, of these, the thoracic to abdominal circumference ratio was most closely related to the lung weight to body weight ratio, which is the gold standard used at necropsy to diagnose pulmonary hypoplasia postmortem [31, 32]. Of the eight measurements studied, chest circumference to abdominal circumference ratio also had the highest diagnostic accuracy for antenatal diagnosis of pulmonary hypoplasia (sensitivity: 93.5% and specificity: 90.3%) independent of gestational age [27].

Diagnosis of lethal dysplasias

Three-dimensional fetal lung volumes, femur length to abdominal circumference ratio, and chest circumference to abdominal circumference ratio are the three most accurate predictors of a lethal skeletal dysplasia when evaluated in conjunction with fetal amniotic fluid volume. The degree of femoral shortening is necessary in initial sonographic diagnosis of a skeletal dysplasia, and also has predictive capacity in terms of lethality. Evaluation of the fetus is not complete with these measurements alone, though, and sonographic assessment for associated features can aid in making a specific diagnosis. Although not necessary to predict outcome, a specific prenatal diagnosis helps anticipate guidance for the family, genetic

counseling, molecular testing and reproductive options. A few common in utero diagnoses make up the majority of all lethal skeletal dysplasias, and knowledge of hallmark features of each is a powerful tool for any sonologist. The most common lethal skeletal dysplasias include thanatophoric dysplasia, osteogenesis imperfecta type II, achondrogenesis, atelosteogenesis, short rib polydactyly and perinatal lethal hypophosphatasia. Additionally, homozygous achondroplasia and camptomelic dysplasia are occasionally fatal in the perinatal period [33, 34].

Bowing or fractures

In utero fractures and severely bowed limbs are ominous signs of a lethal skeletal dysplasia. The presence of one or the other can help distinguish the specific type of dysplasia. If the limbs are bowed without evidence of fracture, the differential is thanatophoric dysplasia, camptomelic dysplasia, atelosteogenesis, achondrogenesis or homozygous achondroplasia [35–38].

Thanatophoric dysplasia is by far the most common of these, although it does not always have limb bowing. A large scale study by Chitty et al. [39] reported bowing deformity in 67% of cases of thanatophoric dysplasia. Type I thanatophoric dysplasia is characterized by symmetrical bowed femurs, termed the “telephone receiver” femur, with characteristic metaphyseal broadening (Fig. 1). Skull deformity may or may not be seen with type I. Type II thanatophoric dysplasia is less common. Affected fetuses have a straight femur and most have a “cloverleaf” skull deformity. Cloverleaf describes the bulbous, triradiate outward bowing of the cranium that occurs to accommodate the growing brain despite in utero craniosynostosis of the coronal and lambdoid sutures. Concomitant hypertrophy of the temporal lobes may also contribute to the cloverleaf shape of the skull (Fig. 2) [40, 41]. Both type I and type II thanatophoric dysplasia

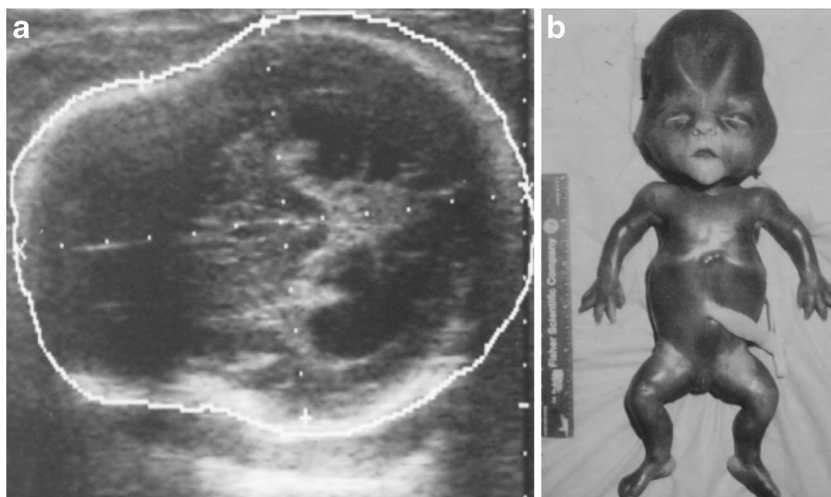
demonstrate flattened vertebral bodies with relative enlargement of the disc spaces (platyspondyly) [42].

Camptomelic dysplasia fetuses have bowed lower extremity long bones, most classically affecting the tibia but often the femora are bowed as well. Cutaneous skin dimpling is typically seen along the anterior lower leg (Fig. 3) [34, 43]. It is distinguished from the other conditions with long bone bowing by the absence of fractures and the presence of a hypoplastic or absent scapula, which is unique to this dysplasia [44].

Homozygous achondroplasia is suspected prenatally in an affected set of achondroplastic parents, raising prenatal apriorism. A newly described feature unique to achondroplasia was widening of the femoral proximal diaphysis—metaphysis angle (or femoral angle) to greater than 130°. This angle, measured in utero, was the most consistent sonographic finding predictive of achondroplasia, seen in 83% of fetuses with achondroplasia, when compared with other findings such as frontal bossing (67%), trident hand (33%), polyhydramnios (50%), depressed nasal bridge (17%), and macrocephaly (17%) in a recent paper by Khalil et al. [45]. This relationship has only been studied in third trimester fetuses with long bone shortening [45, 46]. Characteristic features of homozygous achondroplasia include those seen with heterozygous achondroplasia including trident hand and frontal bossing; however, long bone shortening is identified earlier, in the first trimester or early second trimester, as it is more severe (Fig. 4). Heterozygous achondroplasia may not be diagnosed until after birth since limb shortening is not apparent until the third trimester [47].

Atelosteogenesis may have bowed long bones with delayed segments of spinal ossification, similar to achondrogenesis. Fetuses with atelosteogenesis also have characteristic distal long bone tapering, particularly affecting the humeri and femurs, in contradistinction to achondrogenesis, which does not have tapering of the long bones. Micrognathia is common. Evaluation of the hands and feet may help substantiate a diagnosis of

Fig. 2 A 16-week-old fetus with type II thanatophoric dysplasia. **a** Gray-scale axial sonographic image of the abnormally shaped skull seen in type II thanatophoric dysplasia is likely due to in utero craniosynostosis and temporal lobe enlargement. Ventriculomegaly is also evident. **b** Postmortem photograph of the same fetus at 18 weeks illustrates the lobulated calvarium termed “cloverleaf” skull



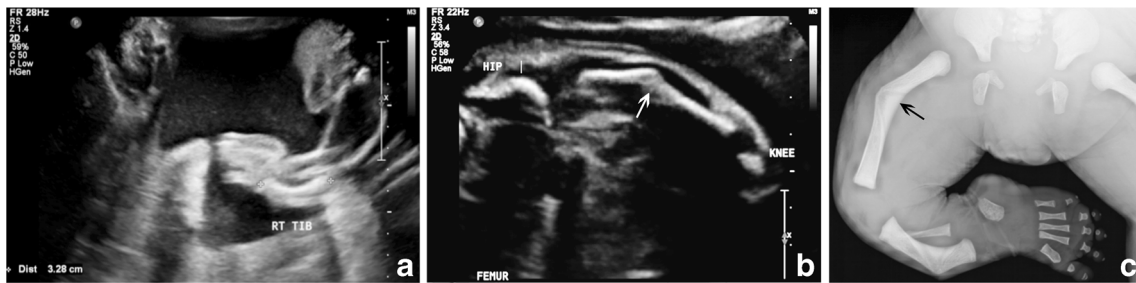


Fig. 3 A 28-week-old fetus with camptomelic dysplasia. **a** Gray-scale US image of the right tibia shows marked bowing and foreshortening, measuring 23 weeks by length. **b** Image of the same fetus’ femur also at 28 weeks demonstrates an angulated midshaft deformity (*arrow*). **c**

Postnatal radiograph on day of life 3 shows the right lower extremity in the same fetus with camptomelic dysplasia. Cross-modality comparison illustrates the angulated femoral deformity (*arrow*), marked tibial bowing and hypoplastic fibula. Skin dimpling is also noted

atelosteogenesis, as these fetuses often have a “hitchhiker”-type deviated thumb or toe as well as deficient ossification of the metacarpals and proximal and middle phalanges. Peculiarly, the distal phalanges are normally ossified (Fig. 5) [38, 48].

Multiple long bone fractures are characteristic of osteogenesis imperfecta. As many as 16 different types of osteogenesis imperfecta have been described based on unique gene mutations, though Sillence et al. [49] more simply classifies them

based on the 4 types of clinical and radiographic presentations [50]. Types I and IV, the mild to moderate forms, present with fractures in childhood and rarely type IV can present with in utero fractures. Type II lethal osteogenesis imperfecta fetuses invariably have in utero fractures and 50% of type III fetuses have in utero fractures [51]. The importance of distinguishing osteogenesis imperfecta type II from types III and IV is that type II is lethal and types III/IV are nonlethal. In utero evaluation of

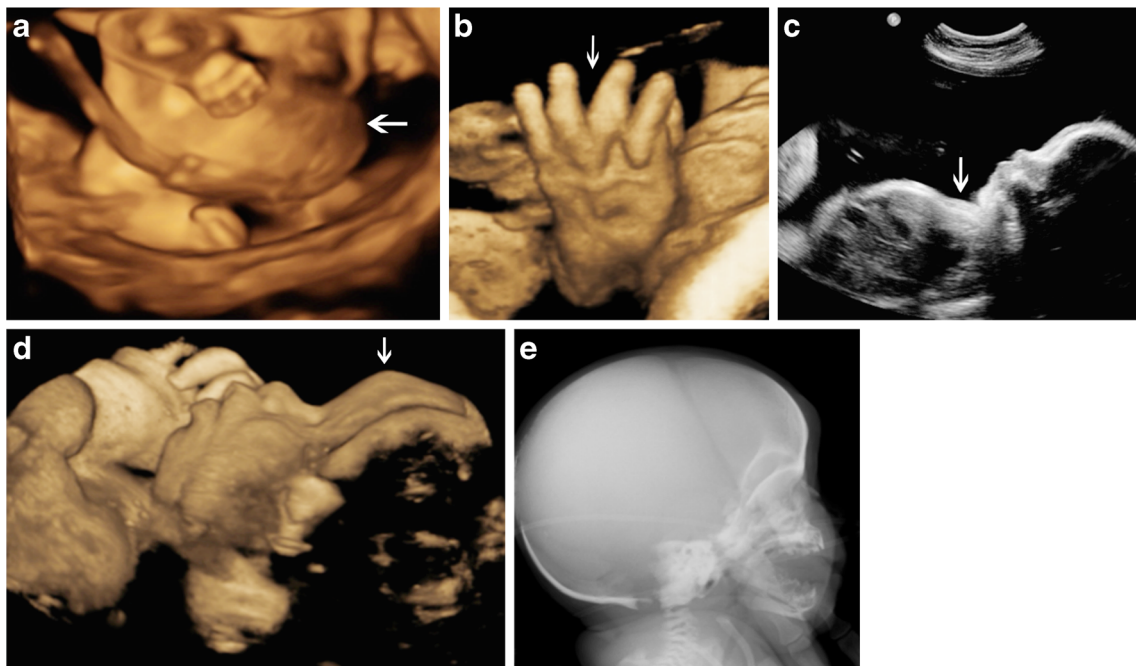


Fig. 4 A fetus with homozygous achondroplasia at 19 weeks. **a** Three-dimensional US image shows severe long bone shortening, protuberant abdomen (*arrow*) and small thoracic cage. **b** Three-dimensional image of the fetal hand demonstrates a “trident” configuration, typical for achondroplasia. A trident hand has digits that are similar in length with an exaggerated separation between the third and fourth digits (*arrow*). **c**

Sagittal gray-scale image of the fetus demonstrates multiple features of homozygous achondroplasia including polyhydramnios, depressed nasal bridge with frontal bossing and thoracic hypoplasia (*arrow*). **d** Parasagittal 3-D image of the fetal head better illustrates the frontal bossing (*arrow*). **e** Postnatal lateral skull radiograph on day of life 7. Note the macrocephaly, depressed nasal bridge and frontal bossing

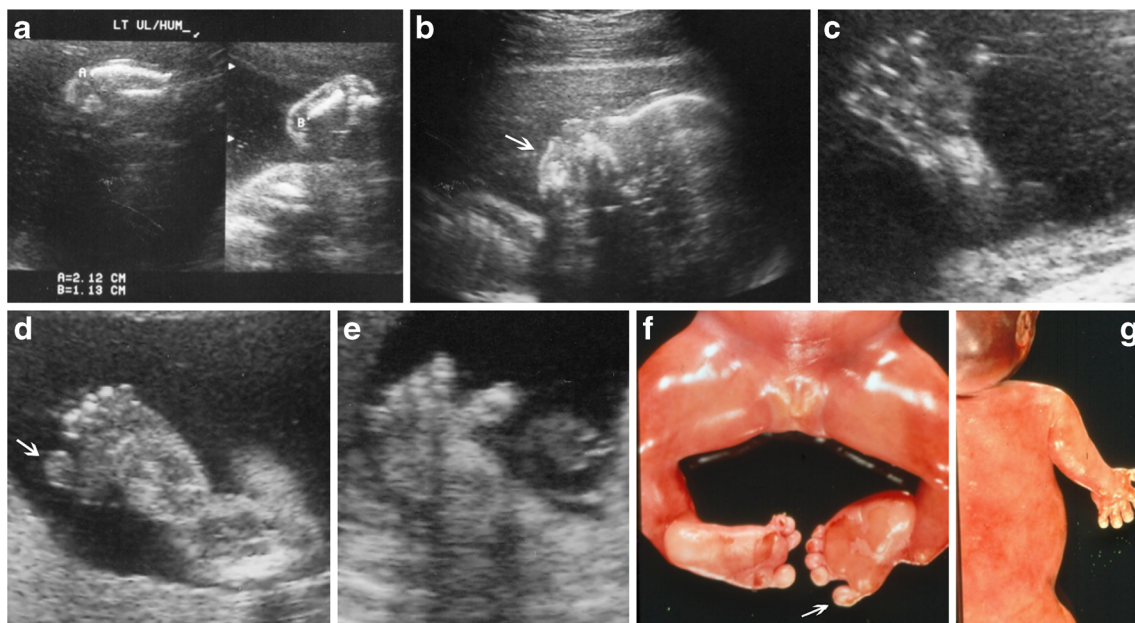


Fig. 5 A fetus with atelosteogenesis at 17 weeks. **a** Ultrasound images show bowed ulna (A) and shortened humerus (B). **b** Sagittal US profile of the face illustrates the hypoplastic mandible seen with micrognathia (arrow). **c** Coronal image of the hand with absent ossification of the metacarpals and proximal and middle phalanges with ossification of the distal phalanges, characteristic of atelosteogenesis. **d** Coronal image of an angulated lower limb coronal to the foot demonstrates the preaxial widening between the second digit and great toe reminiscent of a

“hitchhiker” toe (arrow). **e** Coronal image of a hand in a different patient shows the abducted thumb typical of “hitchhiker” thumb. **f** Postmortem photograph of the same fetus at 21 weeks with atelosteogenesis shows the “hitchhiker-like” toe (arrow) and extreme bowing deformities of the lower limbs. **g** Hand of same fetus shows with absent ossification of the metacarpals and proximal and middle phalanges

long bone shortening and bone mineralization can differentiate the lethal from nonlethal forms, as described by Bulas et al. [52]. In their study, prenatal sonographic evaluation of six fetuses with osteogenesis imperfecta revealed severe demineralization in the two fetuses with type II. Ultrasound manifestations of demineralization were brain parenchyma “too well seen” due to a nearly unmineralized skull and little to no posterior acoustic shadowing from long bones (Fig. 6). Additionally, the degree of long bone shortening is severe in osteogenesis imperfecta type II due to the multitude of fractures, which results in beaded ribs and crumpled long bones, not seen with types III/IV. Rib fractures result in a small thorax and serve as the prerequisite for lethal pulmonary hypoplasia in type II. Bulas et al. [52] found the remaining four fetuses with types III/IV had fewer fractures, predominantly of the long bones not the ribs, and normal bone mineralization. Three-dimensional US capabilities have been shown to improve diagnostic capabilities over 2-D in the diagnosis of osteogenesis imperfecta [53, 54]. Of note, perinatal lethal achondrogenesis can rarely present with in utero fractures, though much more impressive is nonossification of the axial skeleton seen in this disease.

Abnormal number of bones

In the assessment of skeletal dysplasias, it is essential to catalog the presence or absence of all bones and the degree of

ossification. Underossification can be defined as the lack of posterior acoustic shadowing when scanning in a plane perpendicular to the bone of interest. Although several of the lethal skeletal dysplasias manifest with an underossified spine, whether the affected portion is cervical, thoracic or lumbosacral spine can help differentiate one dysplasia from another, so close attention should be paid to the spinal levels affected during sonographic evaluation.

Diffuse underossification of the fetal skeleton with many absent bones and no posterior acoustic shadowing from the sonographically visible bones is characteristic of the perinatal lethal form of hypophosphatasia [55]. In particular, absent or poorly ossified neural arches and absent ossification of the thoracic spine may be noted [56]. Deep, angulated cupping of the metaphyses of the long bones, giving them a Y-shaped appearance similar to pediatric rickets, has also been described as a unique feature of perinatal lethal hypophosphatasia [56]. In contrast to fetuses with osteogenesis imperfecta type II, who also demonstrate poor ossification, fetuses with congenital hypophosphatasia do not have fractures. Underossification of the spine is also typical of lethal achondrogenesis type II (Langer-Saldino type), although in achondrogenesis type II underossification is most pronounced in the cervical and sacral regions, not the thoracic spine [56]. Fetuses with achondrogenesis type II typically have underossification of the skull and absent or deficient sacrum and pubic bones, with sparing of the iliac bones [57].

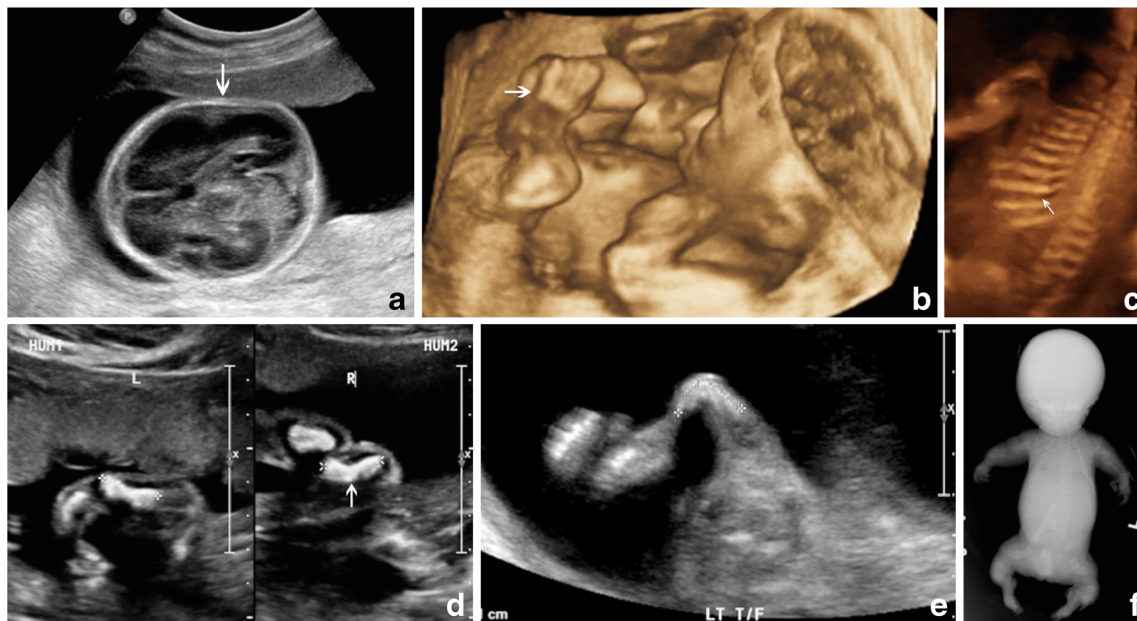


Fig. 6 Osteogenesis imperfecta type II in an 18-week-old fetus. **a** Axial gray-scale image of the skull shows deformation of the skull by the transducer (*arrow*). Also note the brain parenchyma is “too well seen” for an 18-week fetus, indicating abnormal mineralization of the skull. **b** Three-dimensional sonographic profile of the same fetus shows multiple long bone fractures involving the tibia, fibula, humerus and foot. Arrow on foot fracture. **c** Three-dimensional coronal image of the spine and ribs from posterior highlights the beaded appearance of foreshortened ribs with multiple fractures (*arrow*). **d** Gray-scale sonographic images of the

bilateral humeri (*calipers*) in a fetus with osteogenesis imperfecta. The humeri are short and the right humerus has an angulated fracture (*arrow*) (*L* left, *R* right). **e** Bowing deformity of the left tibia is secondary to an in utero fracture. **f** Postmortem radiograph of the fetus with osteogenesis imperfecta type II at 20 weeks. Note the shortened, angulated long bones with fractures giving them a crumpled appearance. There is also an underossified calvarium and hypoplastic thorax with bilateral rib fractures

Polydactyly, typically postaxial, differentiates the short rib polydactylies from other micromelic skeletal dysplasias (Fig. 7). Notably, short rib polydactylies have, as the name implies, the shortest ribs of all the lethal dysplasias and a resultant very narrow thorax [58, 59].

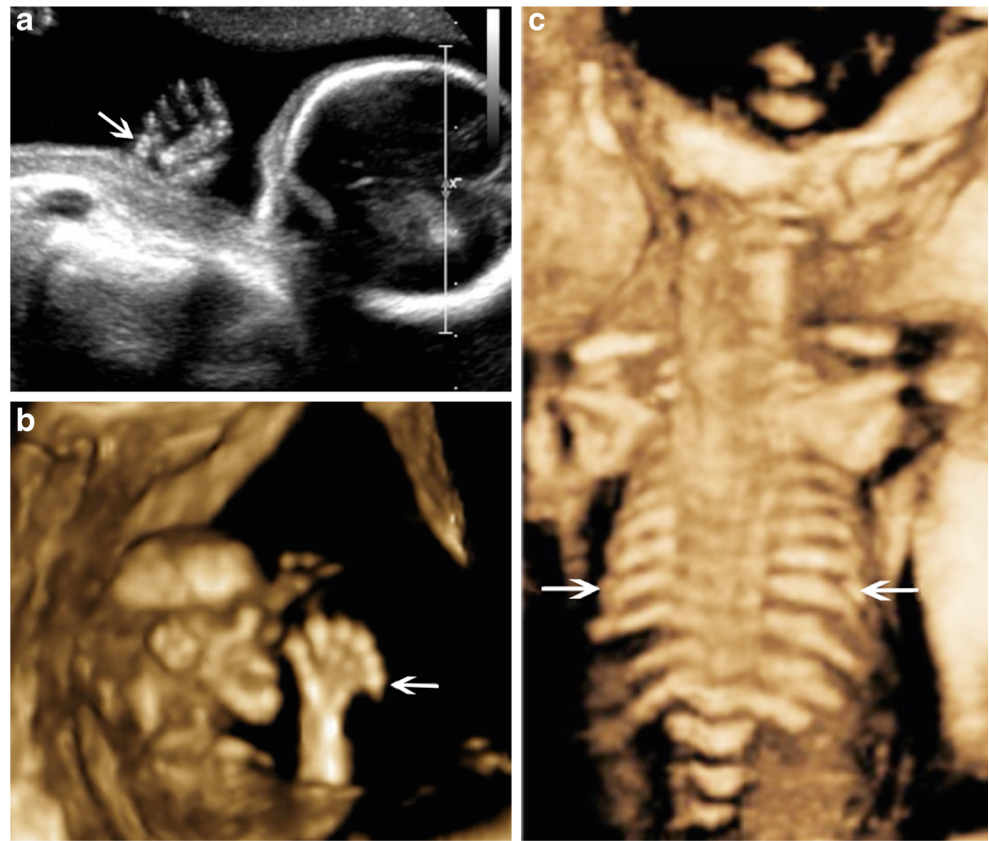
Genetic counseling and outcomes

Genomic sequencing and specific genetic tests for skeletal dysplasias continue to expand, offering parents more definitive diagnosis and counseling [60]. Skeletal dysplasia sequencing panels are available on the market today, testing anywhere from 10 to 173 genes (for example, Greenwood Genetic Center in Greenwood, S.C., and Emory Genetics Lab in Decatur, GA). Testing is widely available for FGFR3 gene mutations (seen in achondroplasia, hypochondroplasia and thanatophoric dysplasia) and COL1A1 and COL1A2 gene mutations (seen in osteogenesis imperfecta, achondrogenesis and hypochondrogenesis). Testing can be performed prenatally with deoxyribonucleic acid (DNA) obtained from chorionic villi or amniotic fluid or postnatally from

whole blood samples. Turnaround time is typically 4–6 weeks, making the information difficult to obtain in time for pregnancy management. Postnatal testing and subsequent first or early second trimester genetic testing can help guide families in future pregnancies. For example, if a mutation is determined to be spontaneous or de novo, the recurrence risk is low, usually around 2–5%, whereas for heritable autosomal recessive mutations, recurrence risk is 25%. Chorionic villous sampling and amniocentesis also carry a small risk of miscarriage and can only be performed after 11 weeks. Advances in cell-free DNA, which uses maternal blood to detect fetal DNA, offer promise for early, noninvasive detection of suspected cases of skeletal dysplasias either based on US findings or prior pregnancy abnormalities [61]. It is, however, less sensitive for detection of de novo mutations.

There are two major components to the postnatal diagnosis of a specific skeletal dysplasia if it is uncertain prenatally. The first is genotyping, testing anywhere from one specific gene to whole exome sequencing, where nearly the entire fetal DNA is analyzed. Unfortunately, there are often many mutations throughout various genes

Fig. 7 A 20-week-old fetus with short rib polydactyly. **a** Gray-scale US image coronal to the hand in the same fetus shows a hypoplastic sixth digit (*arrow*). **b** Three-dimensional image of the fetal face and hand better accentuates the postaxial supernumerary digit (*arrow*). **c** Three-dimensional coronal US image from the posterior perspective in a fetus with short rib polydactyly shows short, angulated ribs and a hypoplastic thorax (*arrows* on the small thorax)



active in skeletal development and maturation in any one fetal exome, suggesting the possibility of several different dysplasias. Thus, taken alone, genetic testing has a high rate of false-positives.

The second component of postnatal diagnosis, phenotyping, is crucial and involves the expertise of the clinical geneticist and sonologist/radiologist. Physical exam and possibly skin biopsy for collagen phenotyping are performed by the clinical geneticist. The geneticist must then scrutinize the various chondro-osseous genetic mutations present in the fetal DNA and exclude the unlikely. Once the diagnosis is narrowed to a few dysplasias, the sonologist and/or radiologist illustrates specific imaging features to help synthesize the single most concordant diagnosis.

Family counseling should also include a discussion of outcomes. Fetuses with suspected perinatal lethal dysplasias can sometimes survive with aggressive medical treatment. Severely affected infants who survive the perinatal period are most susceptible to respiratory infections, which can be life threatening. Weaver et al. [22] describes 11 patients with severe but nonlethal skeletal dysplasias of the 23 observed in their study. Of these 11 patients, two became ventilator

dependent and the others required supplemental oxygen and had a 2-week or longer stay in the neonatal intensive care unit. One passed away at home after multiple prior hospitalizations for respiratory distress and upper respiratory infections. Three are living with no additional history provided. Thus, severely affected neonates who survive are most susceptible to respiratory distress and failure with upper respiratory infections due to pulmonary hypoplasia.

Conclusion

An algorithmic approach to skeletal dysplasias with emphasis on predicting lethality organizes and simplifies fetal sonographic assessment in cases of disproportionate long bone shortening. Improvements in US allow for detection of these diseases as early as the late first or early second trimester. Fetal sonologists should be able to predict lethality of a skeletal dysplasia with a high degree of accuracy by prenatal US after evaluation of the following fetal parameters: femur length, lung volume, femur length to abdominal circumference ratio, chest circumference to abdominal circumference ratio, and the presence or absence of polyhydramnios. These findings have

the highest sensitivity and specificity for detection of a lethal skeletal dysplasia. Abnormal lung volume is the most sensitive predictor of a lethal skeletal dysplasia, in keeping with the primary cause of perinatal death, which is pulmonary hypoplasia, not the shortened limbs themselves. If lethal characteristics are present, knowledge of hallmark distinguishing features among the few most common dysplasias can suggest a specific diagnosis, guiding further prenatal cytogenetic testing and parental counseling.

Key concept review

- Short femur
 - >4 standard deviations below the mean
Highly specific for a skeletal dysplasia, likely lethal (assuming correct pregnancy dating)
 - <4 standard deviations below the mean
Suggestive of a skeletal dysplasia
- 3-D US calculated lung volumes as compared with normal fetuses up to 32 weeks
 - ≥5th percentile for gestational age
Unlikely to be lethal
 - <5th percentile for gestational age
Likely lethal.
- Femur length to abdominal circumference ratio
 - <0.16 highly likely to be lethal. If polyhydramnios is present, then all are lethal
 - >0.16 unlikely to be lethal
- Chest circumference to abdominal circumference ratio
 - <0.6 highly likely to be lethal
 - >0.6 unlikely to be lethal
- Bowing or fractures
 - Bowing seen with camptomelic dysplasia, thanatophoric dysplasia and homozygous achondroplasia
 - Fractures are seen in utero in osteogenesis imperfecta type II and III most commonly. Type II have

decreased mineralization and type III has normal mineralization

- Abnormal number of bones
 - Too many bones seen with short rib polydactyly
 - Absent or hypoplastic bones
Hypoplastic or absent scapula seen with camptomelic dysplasia
Underossification of the spine seen with atelosteogenesis, achondrogenesis and hypophosphatasia
- Underossification of the spine
 - Many absent bones including neural arches and thoracic spine seen with hypophosphatasia
 - Absent cervical and sacral ossification and absent/deficient pubis seen with achondrogenesis
 - Delayed spine ossification and absent metacarpals, proximal and middle phalanges seen with atelosteogenesis

Compliance with ethical standards

Conflicts of interest None

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