SONOGRAPHIC DETECTION OF SEVERE SKELETAL DYSPLASIAS

INTRODUCTION

The prevalence of skeletal dysplasias is between 1 and 2000 and 1 and 4000 livebirths[1]. While there are over 125 skeletal dysplasias[2], approximately 4 disorders comprise 70% of the total: achondroplasia, thanatophoric dysplasia, osteogenesis imperfecta, and achondrogenesis. The appropriate identification of lethal skeletal dysplasias is important not only for current pregnancy management, but also for genetic counseling concerning future pregnancies. Table I provides the genetic inheritance for but a few of the more common skeletal dysplasias.

The severity of the effect on the skeletal system with lethal skeletal dysplasias makes 2nd trimester diagnosis possible. Additional testing is necessary to confirm or exclude a specific skeletal dysplasia. For example, amniocentesis can be used to confirm a diagnosis of achondroplasia[3]. Usually a definitive diagnosis cannot be made until a pediatric or pathologic evaluation of the neonate is undertaken.

Table I. Inheritance of skeletal dysplasias.

Usually Lethal Dysplasia	Mode of Inheritance
Achondrogenesis	AR
Short-rib polydactyly	AR
Osteogenesis imperfecta	AD*, AR
Congenital hypophasphatasia	AR
Usually Non-lethal Dysplasia	
Camptomelic dysplasia	AR
Achondroplasia	AD
Diastrophic dysplasia	AR
Asphyxiating thoracic dysplasia	AR

Derived from: Wigglesworth JS, Singer DB. Textbook of Fetal and Perinatal Pathology. Oxford:Blackwell Scientific, 1991;1176.

*Majority of cases are new mutations.

DIAGNOSTIC APPROACH

As with any suspected congenital anomaly, a detailed fetal anatomic survey is required whenever a skeletal dysplasia is suspected. Ancillary sonographic findings frequently provide the clues that are necessary to narrow the differential diagnosis.

FEMUR LENGTH

The measurement of the femur length (FL) is part of standard 2nd and 3rd trimester biometry. Since the long bones are invariably affected in the severe skeletal dysplasias, this measurement provides the first clue that bone formation or growth is abnormal. Even in patients with established dating criteria, a FL < 2 SD of the mean is not necessarily diagnostic for a skeletal dysplasia. The differential diagnosis of a short femur includes a normal physiologic variation, intrauterine growth restriction, a focal shortening of one femur and an abnormal karyotype. However, when the femur length is [3] 5 mm below 2 SD of the mean, a significant skeletal dysplasia is almost certain[4].

If the femur length is between 2 SD of the mean and 5 mm below 2 SD, interval growth of the FL can be evaluated. During the 2nd trimester the femur length normally increases 2.5 mm/week. The time of onset and degree to which FL growth is inhibited is specific for each skeletal dysplasia. For example, a fetus with heterozygous achondroplasia may have an abnormal FL between 21 and 27 weeks' menstrual age; the femur length of fetuses with osteogenesis imperfecta type II is already abnormal at 15 weeks' menstrual age[5].

BODY PROPORTIONALITY

As the fetus grows and develops, there is an inherent proportionality between all of the body parts. Hence, a comparison of femur length with another independently growing body part can help to confirm the diagnosis of a skeletal dysplasia.

FL/Head Circumference (HC)

An FL/HC ratio < 3 SD below the mean suggests a skeletal dysplasia[6].

FL/Abdominal Circumference (AC)

The FL/AC ratio is normally between 0.20 and 0.247. A ratio < 0.16 is diagnostic for a skeletal dysplasia8,9. However, this cut-off should only be utilized in patients with a suspected skeletal dysplasia. In the normal population an FL/AC ratio < 0.16 would have a high false positive rate for the detection of a severe skeletal dysplasia.

FL/Foot

In a normal fetus the FL and foot are generally of equivalent length. The growth of the foot is not affected by severe skeletal dysplasias10. Hence, with a severe skeletal dysplasia, the FL/foot ratio is decreased to < 0.8711(Fig. 1).

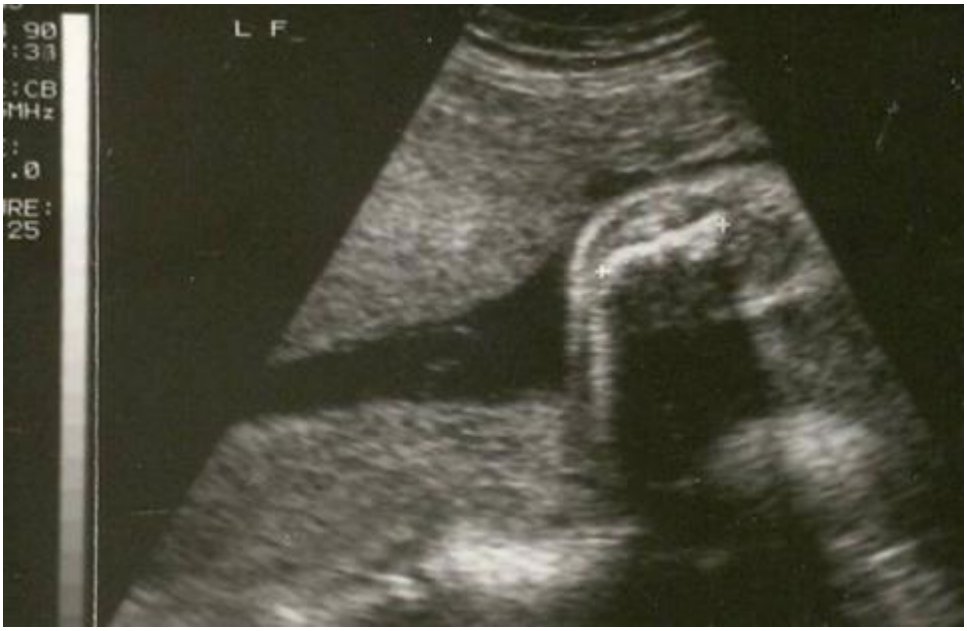

Figure 1a. Abnormal FL (2.6 cm) to foot (4.7 cm) ratio: 55%. Click for larger image.

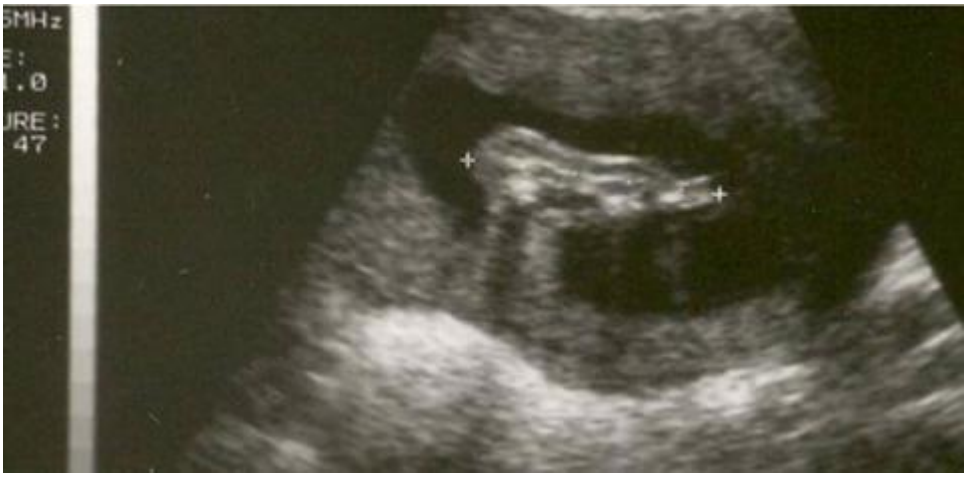

Figure 1b. Abnormal FL (2.6 cm) to foot (4.7 cm) ratio: 55%. Click for larger image.

Chest Circumference/AC

The chest circumference is measured perpendicular to the fetal spine at the level of the 4-chamber view (Fig. 2). In order to ensure an appropriate cross-section, only one rib should be imaged on either side of the chest. The normal thoracic/AC ratio (+ 2 SD) is 0.89 + 0.06. This ratio does not vary with gestational age[11,12].

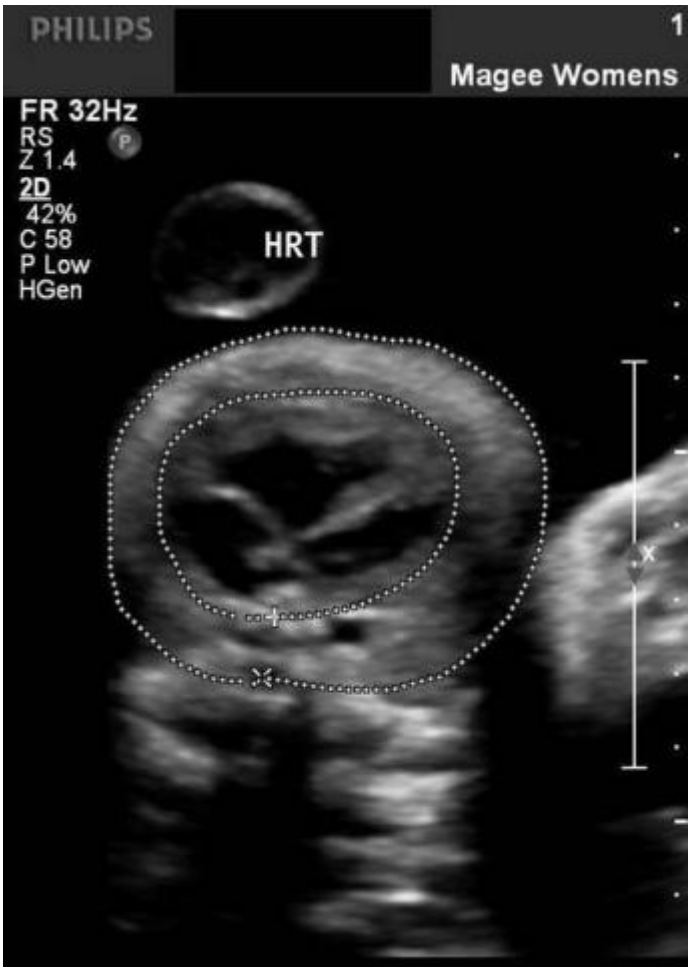

Figure 2. Thanatophoric dysplasia. Chest circumference < 2 SD. The normal sized heart takes up an inordinate amount of space within the chest. Click for larger image.

Chest Circumference/HC

The normal chest circumference/HC ratio (+ 2 SD) is 0.80 (+ 0.12). This ratio is also not gestational age dependent[11].

CHEST APPEARANCE

Normally, the 4th rib extends two-thirds around the thorax (Fig. 3). In lethal skeletal dysplasias the chest cavity is characteristically narrowed. Hence, the heart fills the chest cavity. On a sagittal view the marked narrowing of the chest results in the abdomen appearing protuberant (Fig. 4).

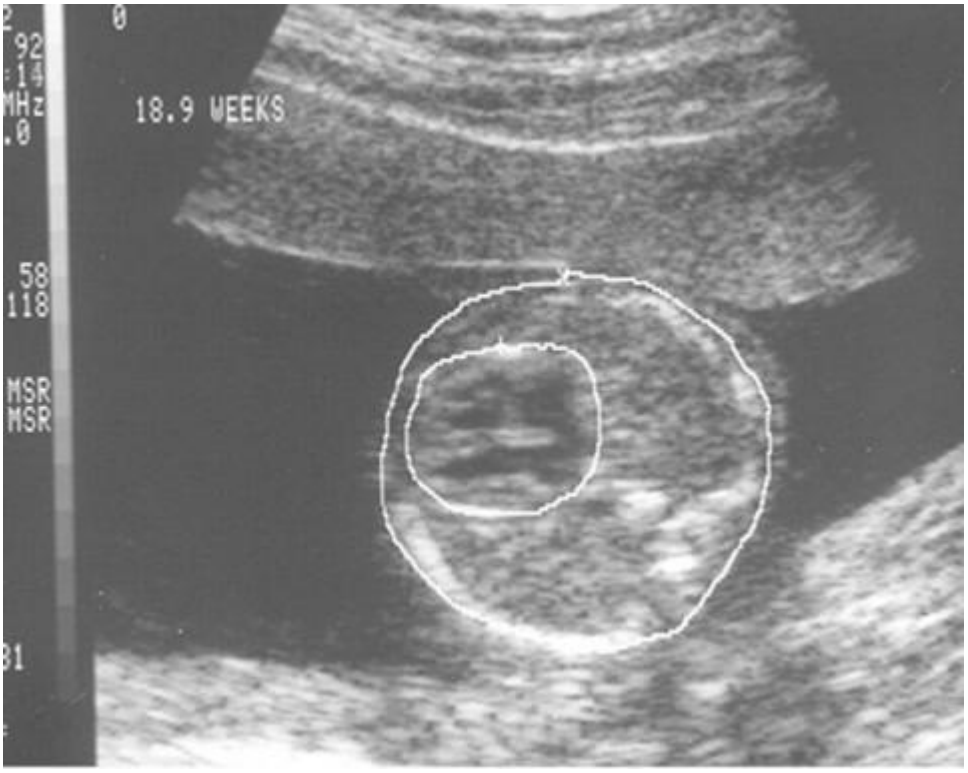

Figure 3. Normal chest circumference. Click for larger image.

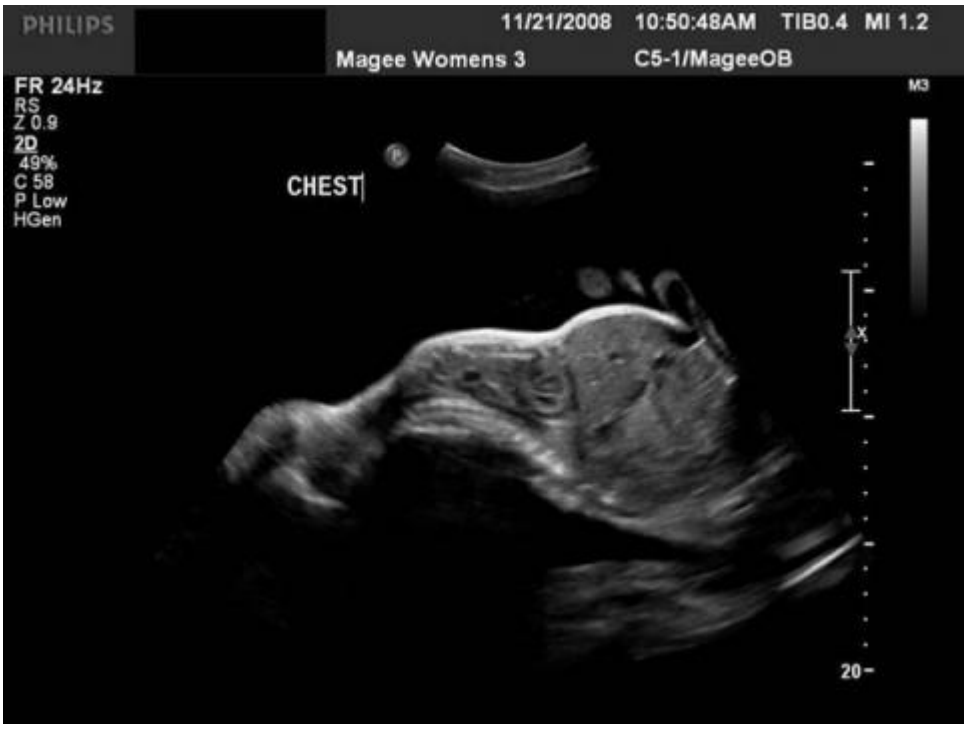

Figure 4. Thanatophoric dysplasia. Significant narrowing of the chest and protuberant abdomen. Click for larger image.

FETAL PROFILE

A sagittal view of the face can be used to diagnosis frontal bossing (Fig. 5), a depressed nasal bridge (Fig. 5) or micrognathia (Fig. 6). Fetuses with thanatophoric dysplasia or osteogenesis imperfecta will characteristically have frontal bossing. A cloverleaf skull (Fig. 7) may be detected with 14% of fetuses with thanatophoric dysplasia or fetuses with homozygous achondroplasia13. Three-dimensional imaging is particularly useful in evaluating facial dysmorphology[14].

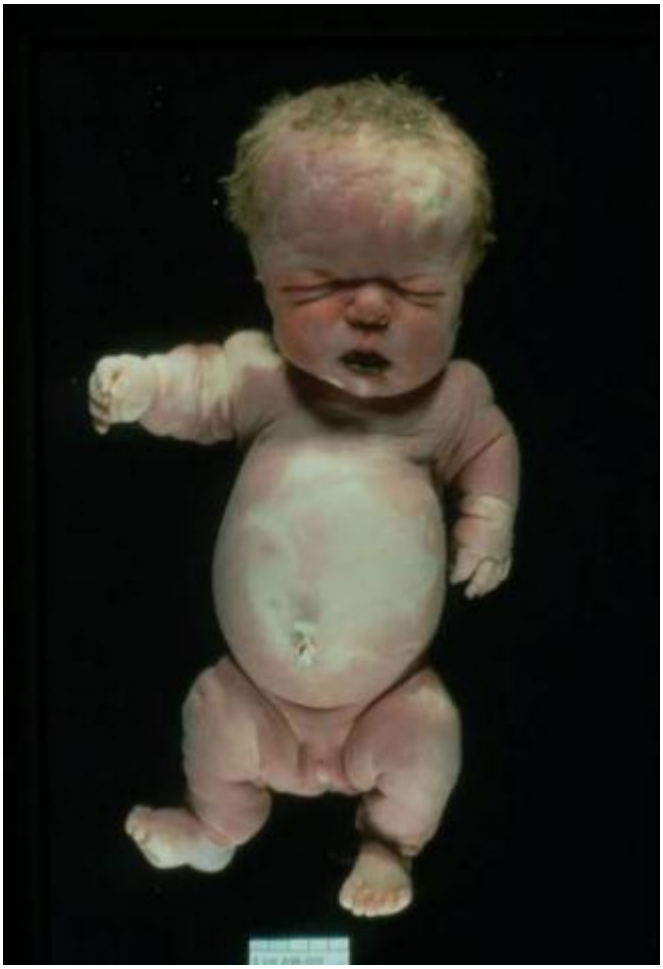

Figure 5. Thanatophoric dysplasia. Frontal bossing; depressed nasal bridge; narrowed chest; protuberant abdomen; shortened extremities; and redundant skin. Click for larger image.

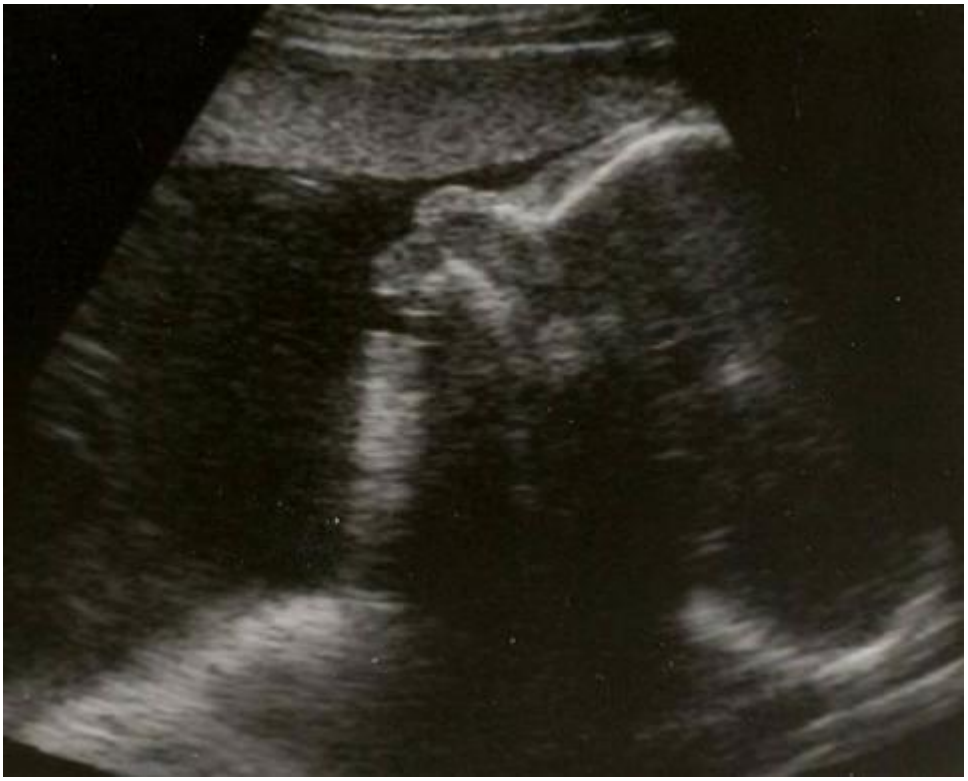

Figure 6. Micrognathia. Click for larger image.

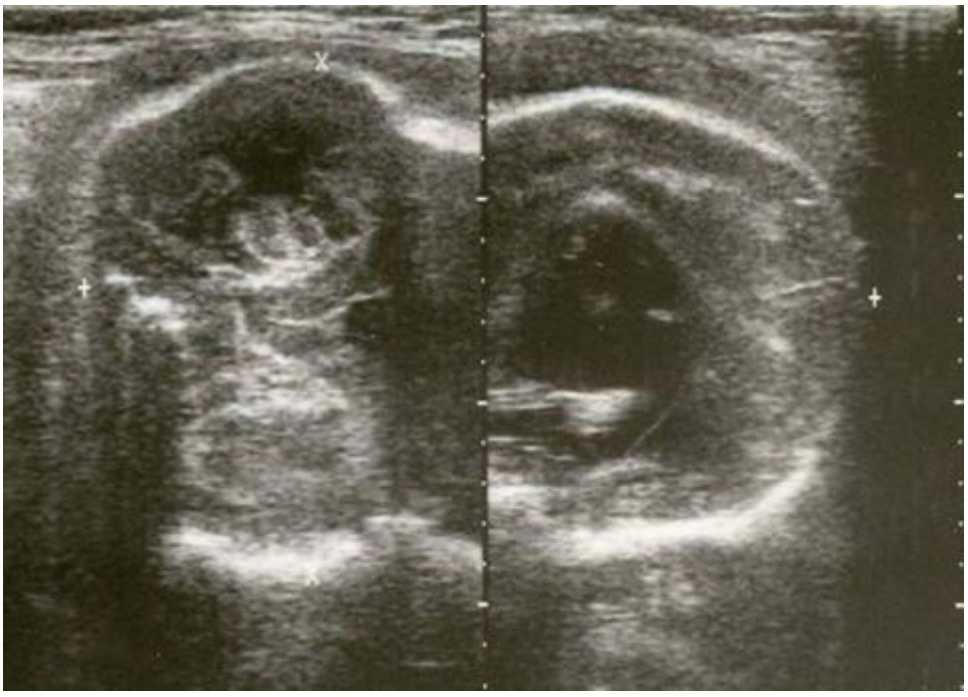

Figure 7. Cloverleaf skull of a 3rd trimester fetus. Click for larger image.

WHICH LONG BONES ARE AFFECTED?

Proximal long bone shortening (rhizomelia) is present in achondroplasia. With osteogenesis imperfecta type II and achondrogenesis there is a generalized shortening (micromelia) of all of the long bones.

LONG BONE APPEARANCE

Multiple long bone fractures occur with osteogenesis imperfecta type II. Bowed extremities are characteristic for camptomelic dysplasia, thanatophoric dysplasia, and osteogenesis imperfecta type II (Fig. 8).

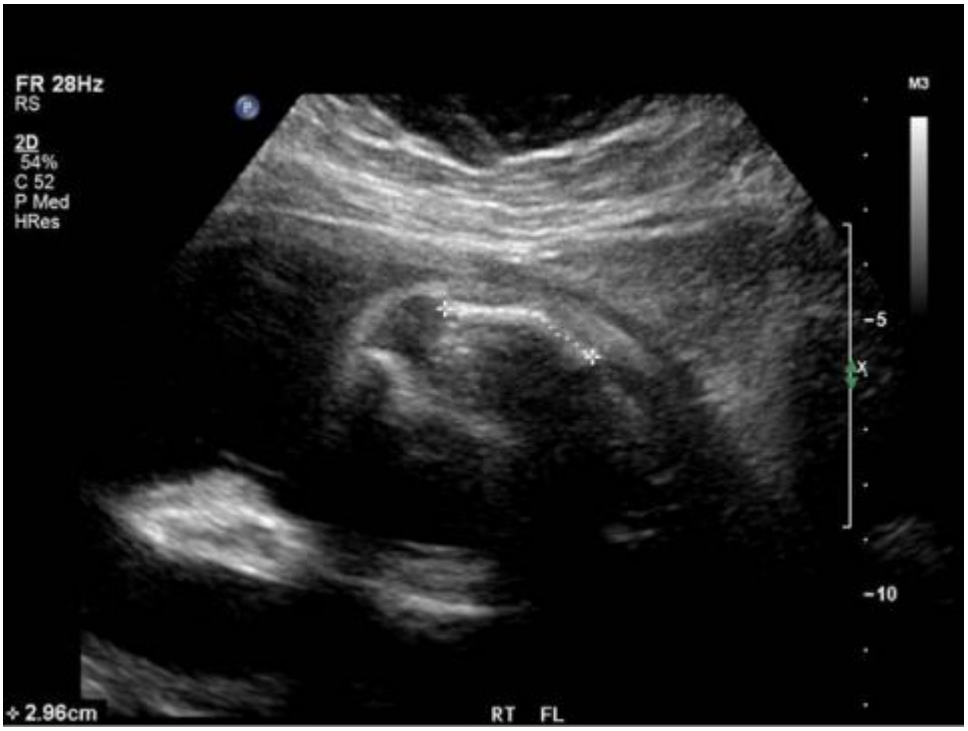

Figure 8. Camptomelic dysplasia. Bowed femur length. Click for larger image.

FETAL SPINE

While it is difficult to appreciate sonographically, widening of the intervetebral spaces and flattening of the spine (platyspondyly) occurs with achondroplasia and thanatophoric dyplasia[15].

BONE MINERALIZATION

Acoustic shadowing is normally present from the edges of the calvarium, as well as from the long bones. In skeletal dysplasias associated with hypomineralization, acoustic shadowing is not present. Flattening of the skull with compression by the ultrasound transducer is an indication of the hypomineralization associated with osteogenesis imperfecta type II. Hypomineralization of the spine is characteristic of achondrogenesis type II.

HANDS AND FEET

Whenever a skeletal dysplasia is suspected, the hands and feet should be carefully evaluated. Pre-axial (thumb side) or post-axial (5th finger side) polydactyly may occur. The extra digit could be a skin tag or contain bone. When the fist is clenched, post-axial polydactyly may not be detectable. Both hands should be evaluated when extended. A three-dimensional sweep is helpful when attempting to accurately evaluate the hands and/or feet[16] (Fig. 9). While neither diagnostic nor specific, clubbed feet (Fig. 10) have been reported with osteogenesis imperfecta and diastrophic dysplasia.

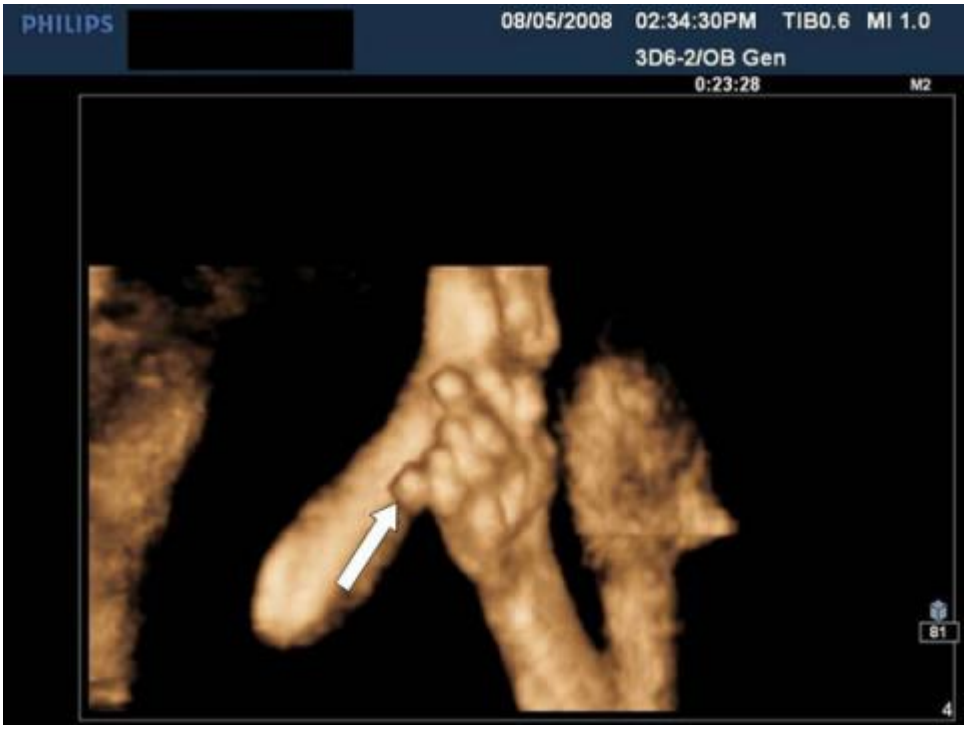

Figure 9. Post-axial polydactyl (arrow). Click for larger image.

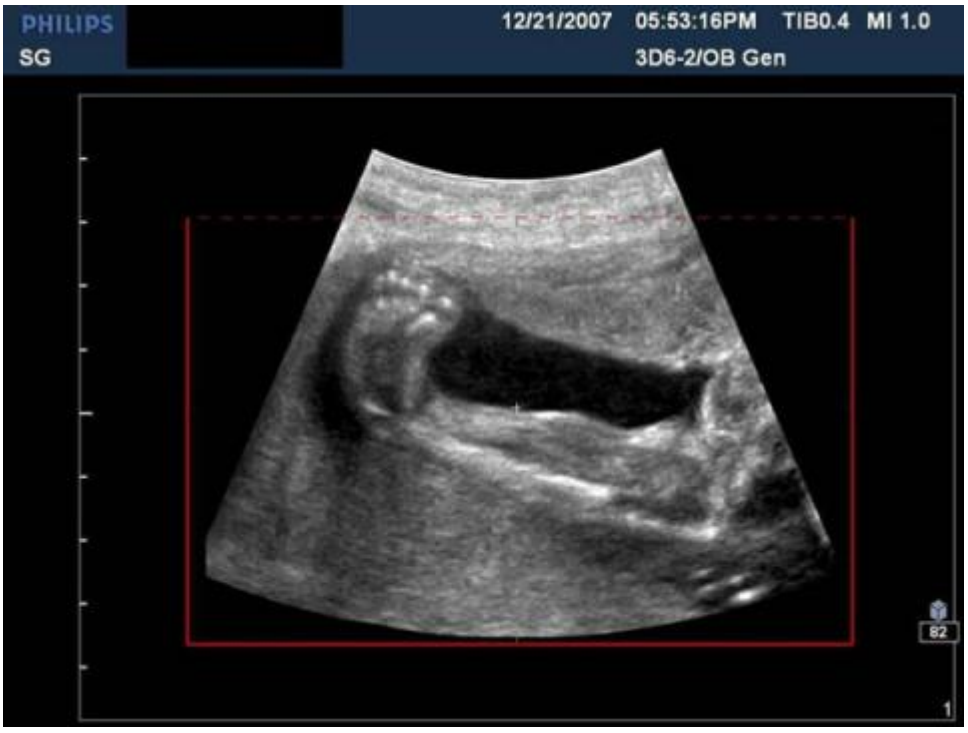

Figure 10. Clubbed foot. Click for larger image.

POLYHYDRAMNIOS

Polyhydramnios may be present in approximately 50% of fetuses with thanatophoric dysplasia and 25% of fetuses with achondroplasia[17]. Other skeletal dysplasias are associated with a much lower prevalence of polyhydramnios[18,19].

NON-IMMUNE HYDROPS (FIG. 11)

Chest compression has been hypothesized as the reason for the higher frequency of non-immune hydrops with short-rib polydactyly[18] and achondrogenesis[19]. What differentiates those fetuses with a specific skeletal dysplasia that have non-immune hydrops from those who do not have non-immune hydrops has not yet been determined.

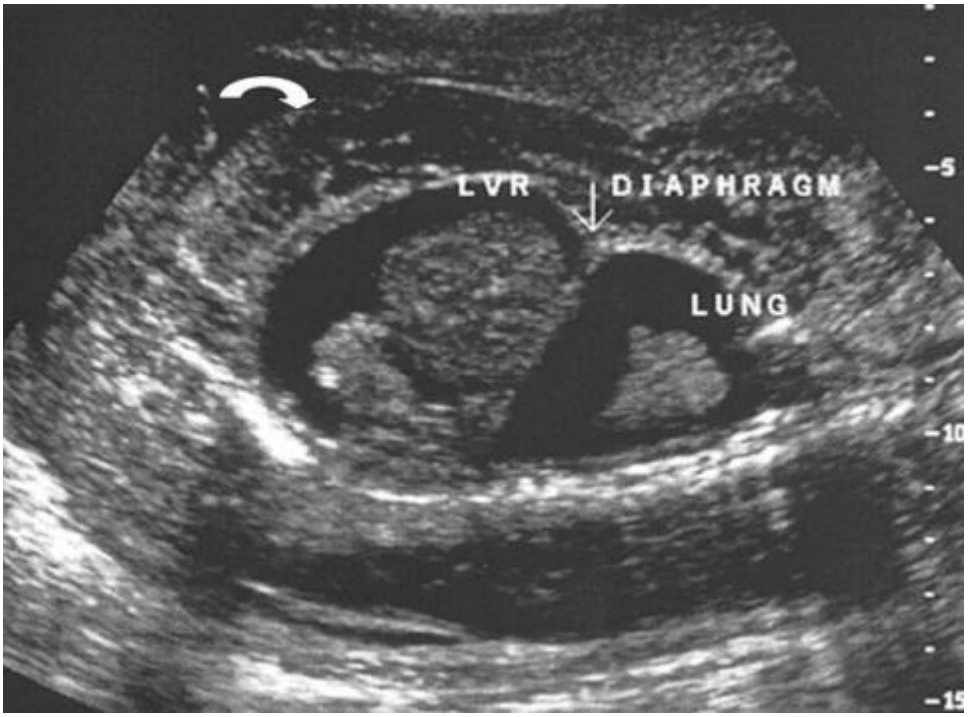

Figure 11. Non-immune hydrops; pleural effusion; ascites; anasarca (curved arrow). Click for larger image.

SPECIFIC SKELETAL DYSPLASIAS

Thanatophoric Dysplasia (Fig. 5)

Thanatophoric dysplasia is the most common lethal skeletal dysplasia with an incidence of 1 in 4000 to 1 in 30,000[1,20,21]. Mutations in gene 3 fibroblast growth factor result in thanatophoric dysplasia. This growth factor is also present in the central nervous system. Those infants with thanatophoric dysplasia who survive the neonatal period consequently have profound mental handicaps[22]. Molecular diagnostic methods permit the prenatal diagnosis of thanatophoric dysplasia through chorionic villus sampling or amniocentesis[23].

With thanatophoric dysplasia the limbs are markedly shortened and the femurs have a "telephone receiver" appearance. There is macrocephaly. The chest is significantly narrowed due to the extremely short ribs. The abdomen is protuberant. There is a generalized redundancy in subcutaneous tissue. 3D surface imaging in the second and third trimester provides an excellent view of all of the external stigmata of thanatophoric dysplasia[24]. Polyhydramnios is a frequent 3rd trimester finding. Neonatal death from respiratory failure is the usual outcome for those fetuses that survive to term.

Two forms of thanatophoric dysplasias have been identified. Type I is characterized by short curved femurs. These fetuses rarely have a cloverleaf skull. Type II thanatophoric dysplasia is characterized by shortened, but straight femurs and is usually associated with a cloverleaf skull[25].

Camptomelic dysplasia must be considered in the differential diagnosis with thanatophoric dysplasia. Camptomelic dysplasia is characterized by shortened bowed lower extremities, hypoplastic fibulas and hypoplastic scapulas. Other features associated with camptomelic dysplasia include hypertelorism, cleft palate, ventriculomegaly and clubbed feet[26, 27]. Phenotypic female fetuses with camptomelic dysplasia may have a male karyotype. Fetal karyotyping may, therefore, be helpful in differentiating thanatophoric dysplasia from camptomelic dysplasia[28].

Osteogenesis Imperfecta

Mutation in the two genes that encode the chains of type I collagen results in the wide phenotypic expression of osteogenesis imperfecta[29]. Most cases of osteogenesis imperfecta are new mutations; autosomal recessive inheritance has also been described.

Osteogenesis imperfecta has been divided into 4 predominant types. Types I and IV have fractures, but survive; type II is lethal in utero, or during the early neonatal period. Because of its severity, type II osteogenesis imperfecta may be diagnosed in the 1st trimester[30].

Type II is further subdivided into subgroup A with short fractured long bones (Fig. 12) and fractured ribs (Fig. 13). Subgroup B has short fractured long bones without rib fractures. Subgroup C has thin and fractured long bones along with thin ribs[31].

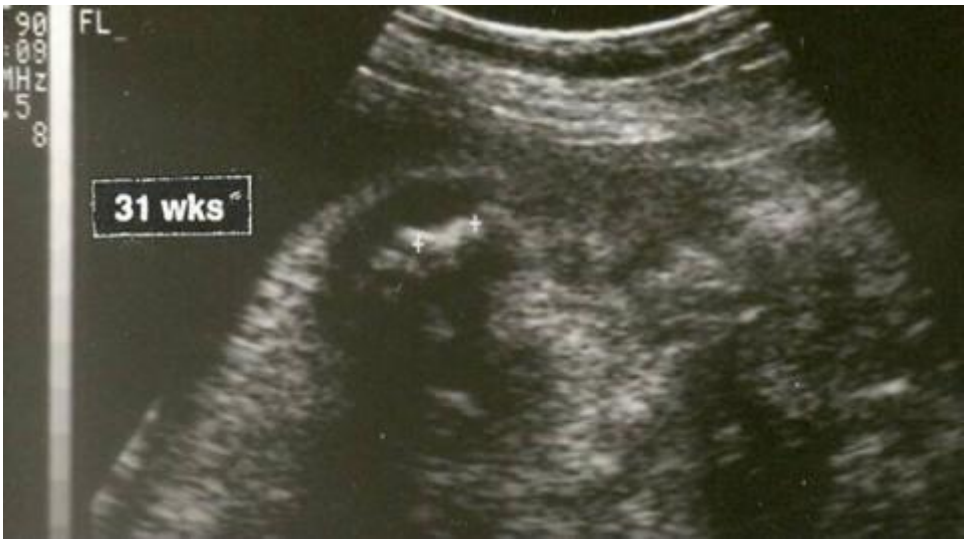

Figure 12. Osteogenesis type IIA. Shortened femur (8 mm) with multiple fractures. Click for larger image.

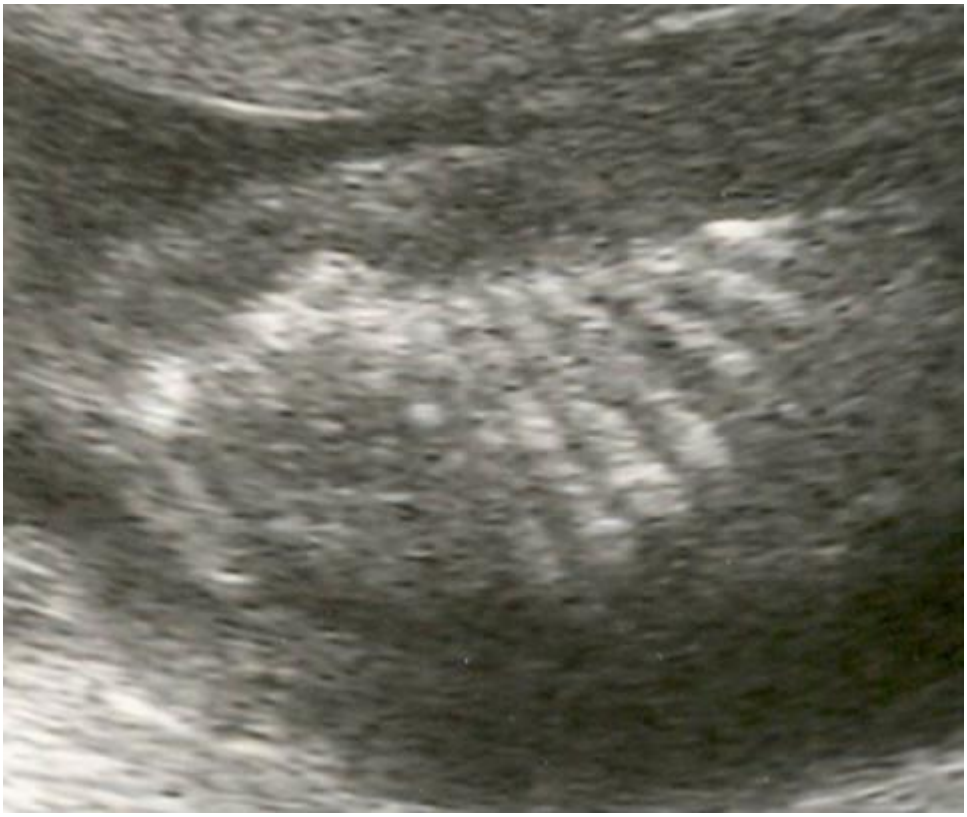

Figure 13. Osteogenesis type IIA. Stippled ribs, indicating multiple fractures. Click for larger image.

The absence of skull calcification permits enhanced visualization of the cerebral cortex nearest

to the transducer (Fig. 14). The lack of mineralization permits compression of the skull with the ultrasound transducer.

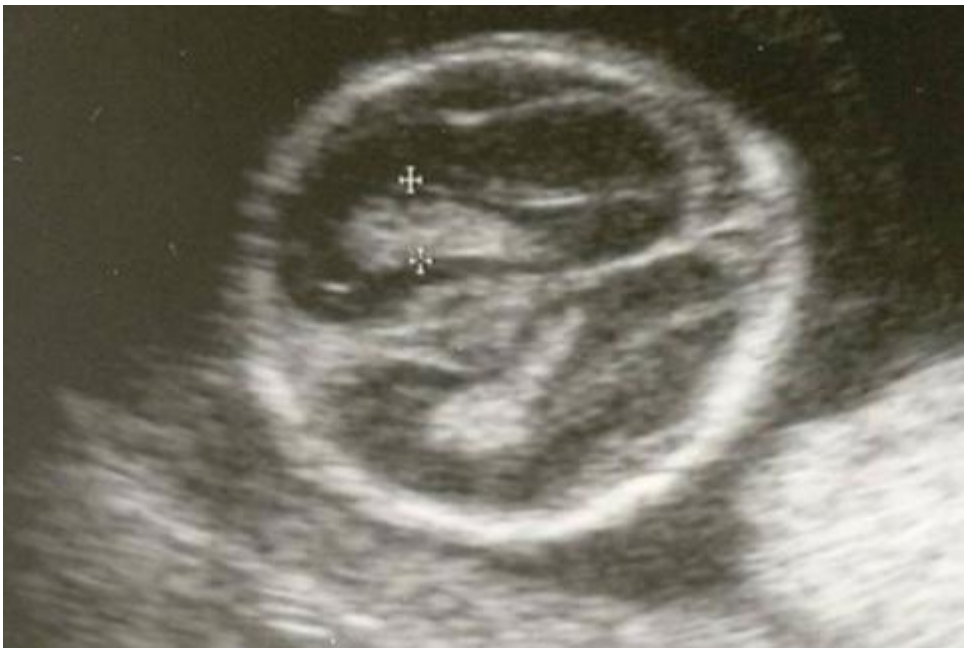

Figure 14. Osteogenesis Imperfecta Type IIA. The absence of skull calcification permits enhanced visualization in the near field. Click for larger image.

Third trimester polyhydramnios has been described.

A 2nd or 3rd trimester three-dimensional profile may help to distinguish the normal facies of osteogenesis imperfecta type IIA from the hypertelorism and broad base nose of short-rib polydactyly[32].

In some cases of osteogenesis imperfecta type II, there is significant bowing of the lower extremities rather than fractures. Type III OI may also have significant long bone bowing. However, osteogenesis imperfecta type III has normal bone mineralization and a normal chest circumference. In these specific cases osteogenesis imperfecta can mimic camptomelic dysplasia[26, 33].

Type III has variable expression; long bone shortening may only become apparent after 24 weeks' menstrual age.

Type IV is between types I and III in severity - most fractures occur before puberty. These individuals have short stature and an increased prevalence of kyphoscoliosis. Subgroups of type IV have been described. In 2006 two additional forms of osteogenesis imperfecta with AR inheritance were described[34].

Achondrogenesis

Severe micromelia and a narrow chest are also characteristic features of achondrogenesis. Defective cartilage formation results in poor ossification. Achondrogenesis is due to an autosomal dominant mutation[35].

Achondrogenesis type I has almost a complete lack of skull ossification. These fetuses have a short neck and trunk. Type IA has associated rib fractures, while fetuses with achondrogenesis type IB do not have rib fractures[36]. The inheritance pattern is autosomal recessive.

Achondrogenesis type II makes up 80% of cases[37]. It is characterized by a greater degree of calcification of the spine and pelvis than fetuses with type I. Fetuses with type II

achondrogenesis have normal skull ossification. Polyhydramnios and hydrops are common with type II achondrogenesis.

CONCLUSIONS

An evaluation of a fetus for a suspected skeletal dysplasia begins with the recognition of a significantly shortened femur length. The majority of lethal skeletal dysplasias will have markedly shortened long bones certainly by the 20 week ultrasound examination and sometimes even in the 1st trimester. The remainder of the extended fetal anatomic survey outlined above is performed primarily to determine the possibility of lethality. The sonographic parameters that have been discussed are able to predict lethality in between 92%8 and 100% of cases[38]. However, an accurate prenatal diagnosis is made only 48%[39] to 65%[22] of the time.

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