REVIEW ARTICLE

Fetal Skeletal System

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ABSTRACT

The prevalence of skeletal dysplasias is between 1 and 2000, and 1 and 4000 live births. While here are over 200 skeletal dysplasias approximately four disorders comprise 70% of the total: Achondroplasia, thanatophoric dysplasia, osteogenesis imperfecta, and achondrogenesis. The appropriate identification of lethal skeletal dysplasia is important not only for current pregnancy management, but also for genetic counseling concerning future pregnancies. Detection of skeletal dysplasias is usually possible by prenatal ultrasound, an accurate specific diagnosis is possible by radiologic, pathologic and molecular genetic examination. A total body ultrasound approach should include assessment of the following: Limbs, long bones and extremities, bone mineralization, any joint contractures, joint dislocations, fetal calvarium, spine and thorax.

Keywords: Fetus, Short bones, Skeletal dysplasia.

INTRODUCTION

The prevalence of skeletal dysplasias is between 1 and 2000 and 1 and 4000 live births.[1] While here are over 200 skeletal dysplasias, approximately 4 disorders comprise 70% of the total: achondroplasia, thanatophoric dysplasia, osteogenesis imperfecta, and achondrogenesis[2] (Fig. 1).

The appropriate identification of lethal skeletal dysplasia is important not only for current pregnancy management but also for genetic counseling concerning future pregnancies. (Table 1) provides the genetic inheritance for a few of the more common skeletal dysplasia.

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 neonate is undertaken.

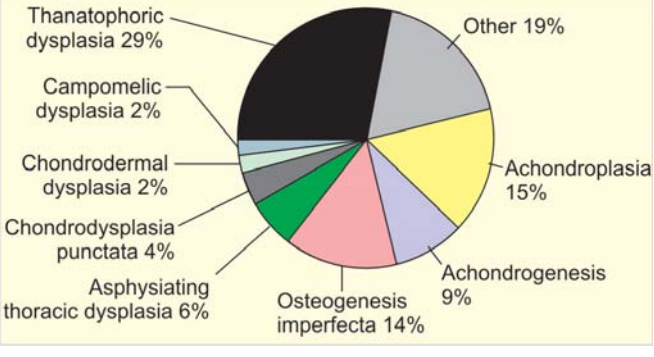

Fig. 1: Showing percentage distribution of various skeletal dysplasias

Diagnostic Approach

- When to suspect
- Targeted scan for diagnosis following suspicion.

When to Suspect?

Femur Length

Accurate dating and biometric measurements should be established in any scan.[5-9]

The measurement of the femur length (FL) is a 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 5 mm below 2 SD of the mean, a significant skeletal dysplasia is almost certain.[10]

Table 1: Inheritance of skeletal dysplasia[4]

Usually lethal dysplasia	*Mode of inheritance*
Achondrogenesis	AR
Short-rib polydactyly	AR
Osteogenesis imperfecta	AD*, AR
Congenital hypophosphatasia	AR
Usually non-lethal dysplasia	
Camptomelic dysplasia	AR
Achondroplasia	AD
Diastrophic dysplasia	AR
Asphyxiating thoracic dysplasia	AR

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.[11]

Ratios Suggesting Skeletal Dysplasia

FL/Head Circumference (HC)

An FL/HC ratio < 3 SD below the mean suggests a skeletal dysplasia.[12]

FL/Abdominal Circumference (AC)

The FL/AC ratio is normally between 0.20 and 0.24.[13] A ratio < 0.16 is diagnostic for a skeletal dysplasia.[14,15]

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 dysplasias.[16]

Hence, with a severe skeletal dysplasia, the FL/foot ratio is decreased to < 0.8711.

Chest Circumference/AC

The chest circumference is measured perpendicular to the fetal spine at the level of 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.[17,18]

Chest Circumference/HC

The normal chest circumference/HC ratio (+ 2 SD) is 0.80 (+ 0.12). This ratio is also not gestational age dependent.[17]

Targeted scan for diagnosis following suspicion:

Accurate Specific Diagnosis

Detection of skeletal dysplasias is usually possible by prenatal ultrasound, an accurate specific diagnosis is more difficult.

1. Radiologic
2. Pathologic
3. Molecular genetic examination.[19]

A total-body ultrasound approach should include assessment of the following:

- Limbs: long bones and extremities
- Bone mineralization
- Any joint contractures and joint dislocations
- Fetal head: calvarium, central nervous system CNS
- Spine and thorax.[20]

Assessment of the Affected Bone

All long bones should be measured in all extremities. A detailed examination of each bone is necessary to exclude the absence or hypoplasia of individual bones (e.g., fibula or scapula).

The bone shape may also provide important clues. The degree of long bone curvature should be examined. At present, there is no objective means for this assessment, only by experience can an operator discern the boundary between normality and abnormality.

Bone curvature suggests osteogenesis imperfecta, camptomelic dysplasia, and hypophosphatasia whereas telephone receiver shape suggests thanatophoric dysplasia and a dumb-bell appearance of the long bones is typical of metatropic dysplasia (Fig. 2).

The mineralization of bones can also be assessed by its echogenicity, hypomineralization occurs in hypophosphatasia, achondrogenesis, and osteogenesis imperfecta (Fig. 3).

Calvarial mineralization: The degree of mineralization is best appreciated on the transthalamic axial view, also in the case of hypomineralization, minor pressure exerted with the transducer can produce deformation of the skull, which is very soft. An important hint to enable recognition of the presence of calvarial hypomineralization is the appearance of the brain. If the

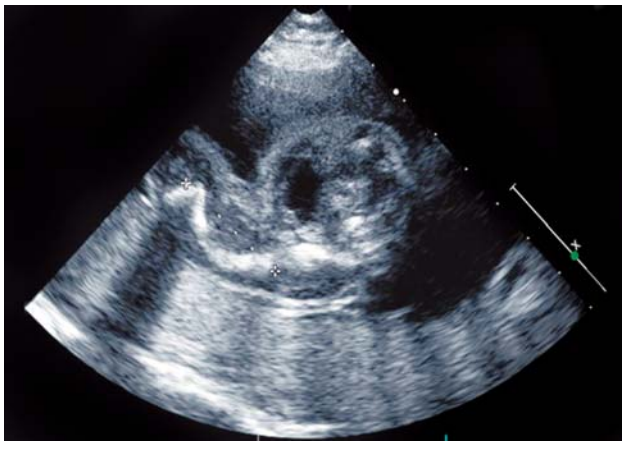

Fig. 2: Abnormal bone curvature in a case of osteogenesis imperfecta type 2

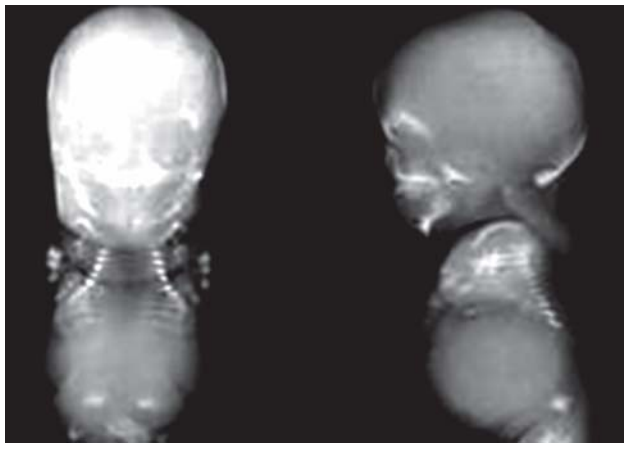

Fig. 3: Poorly mineralized spine seen in a case of achondrogenesis type 2

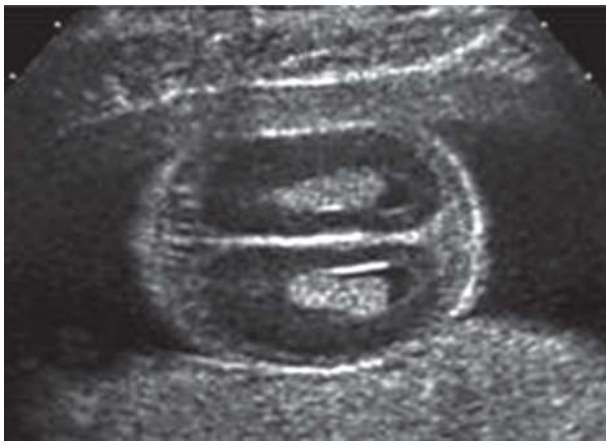

Fig. 4: Demineralization of the skull in a case of osteogenesis imperfecta. The lateral ventricle and choroid plexus in the near field are well seen due to lack of normal mineralization of the calvarium. Normally reverberation artifact from the calvarium would obscure these structures

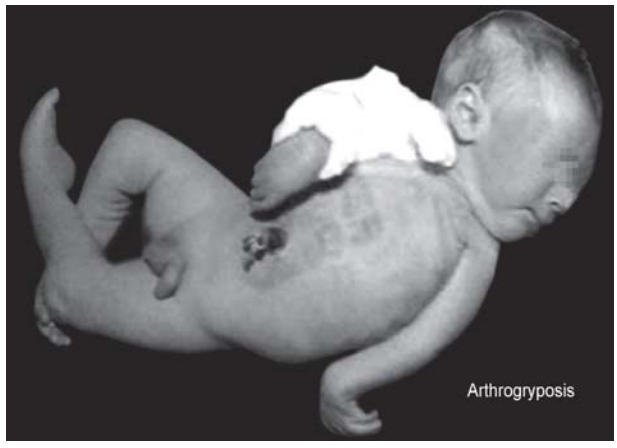

Fig. 7: Newborn with arthrogryposis multiplex congenita. Note the rigidity in the limbs and the straight fingers

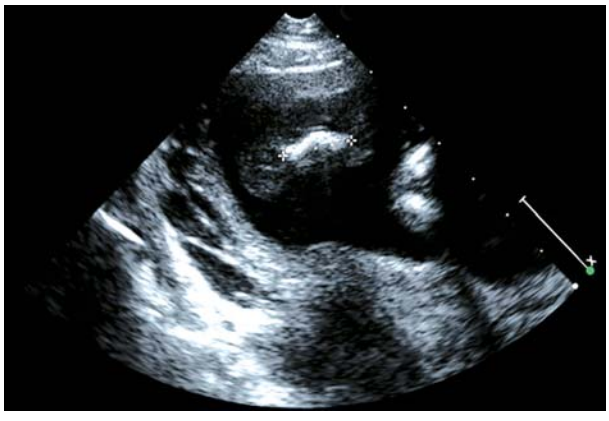

Fig. 5: Fractures and angulation in a pregnancy diagnosed at 14 weeks highly suggestive of osteogenesis imperfecta type 2

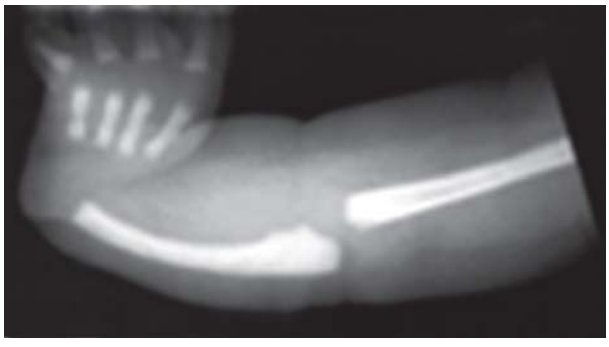

Fig. 6: Absent radius with clubbed hand classically seen in thrombocytopenia absent radius syndrome

ossification of calvarium is deficient then the ultrasound waves are less absorbed by it and display the details of the CNS much better (Fig. 4).

Approach to Hypomineralization

Additional features → Micromelia + fractures → Osteogenesis imperfecta type II (Fig. 5).

Additional features → Micromelia → Hypophosphatasia

Additional features → Micromelia + thoracic hypoplasia → Achondrogenesis (Fig. 3).

Additional features → Micromelia + congenital heart disease + polydactyly → Short-rib polydactyly syndrome.

Detection of aplasia or hypoplasia of certain bones can also provide diagnostic information (Fig. 6). Detection of short clavicles may be the initial sign of cleidocranial dysplasia and camptomelic dysplasia is characterized by hypoplastic scapula.

Joint contractures: The display of the fetal body at low magnification is the best way to recognize possible joint contractures. Alternatively, when an advanced gestational age makes this approach impossible, separate sagittal view of the upper and lower limbs should be sought. When affected by pathologic contractures, the lower limbs often appear hyperextended and with crossed legs (scissors-like) due to the fact that the femoral extensor muscles (quadriceps) are stronger than flexors (biceps). The reverse occurs for upper limbs, where flexor muscles (biceps) are stronger than extensors (triceps): This is why, in the case of contractures, the upper limbs often appear flexed with the clenched hands lying on the thorax (Fig. 7).

Finally, the possibility of fractures should be considered (Fig. 5). They can be detected in conditions like osteogenesis imperfecta and hypophosphatasia. The fractures may be extremely subtle or may lead to angulation and separation of the segments of the affected bone. The ultrasound recognition of a fracture is straight forward in some cases, but can prove difficult and tricky in others, especially early in gestation.

2nd trimester—osteogenesis imperfecta type 2.

3rd trimester—osteogenesis imperfect type 3.

Increased nuchal translucency or cystic hygroma may be the initial manifestation of a variety of skeletal dysplasias during the first trimester and early second trimester.

Assessment of the Severity and the Type of Limb Shortening[21-23]

Comparisons with other segments should be made to establish, if the limb shortening is predominantly rhizomelic, mesomelic,

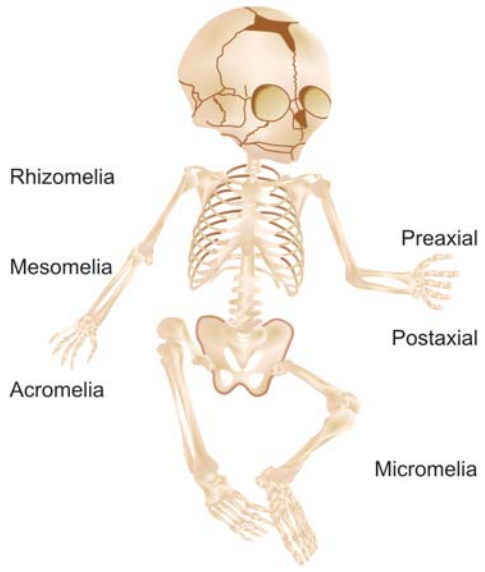

Fig. 8: Shortening of the extremities can involve the entire limb (micromelia), the proximal segment (rhizomelia), the intermediate segment (mesomelia) or the distal segment acromelia

or involves all segments. When limb shortening is identified, it can be characterized as involving the entire limb (micromelia), the proximal segment (femur/humerus) (rhizomelia), the intermediate segment (tibia and fibula/ulna and radius) (mesomelia), or the distal segment (foot/hand) (acromelia) (Fig. 8).

Differential Diagnosis of Rhizomelia

- Achondroplasia
- Atelosteogenesis
- Chondrodysplasia punctata (rhizomelia type)
- Diastrophic dysplasia
- Thanatophoric dysplasia.

Approach to Rhizomelia

- Additional features→Frontal bossing ± mild macrocrania→ Achondroplasia.
- Additional features→Thoracic hypoplasia ± polydactyly/ renal anomalies→Asphyxiating thoracic dystrophy (Jeune syndrome).
- Additional features→Postural deformities + 'hitch-hiker's thumb' + micrognathia→Diastrophic dysplasia.

Differential Diagnosis of Mesomelia

- Acromelia
- Ellis-van Creveld syndrome.

Differential Diagnosis of Micromelia

- Achondrogenesis
- Atelosteogenesis
- Diastrophic dysplasia
- Dyssegmental dysplasia
- Fibrochondrogenesis
- Kniest dysplasia
- Osteogenesis imperfecta (type II)
- Short rib-polydactyly syndrome (types I and III).

Approach to Severe Micromelia

- Additional features→Thoracic hypoplasia ± cloverleaf skull →Thanatophoric dysplasia type II.
- Additional features→Ubiquitous fractures + hypomineralization→Osteogenesis imperfecta type II.
- Additional features→Thoracic hypoplasia ± hypomineralization→Achondrogenesis.
- Additional features→Severe ubiquitous hypomineralizationa→hypophosphatasia.
- Additional features→Thoracic hypoplasia + congenital heart disease + polydactyly ± hypomineralization→Short-rib polydactyly syndrome (s).

Abnormalities of Hands and Feet

Abnormalities of hands and feet are important clues to the type of skeletal dysplasia. Polydactly refers to the presence of more than five digits. It is classified as postaxial, if the extra digits are on the ulnar or fibular side and preaxial, if they are located on the radial or tibial side. Most commonly, the extra digit is a simple skin tag, difficult to see by ultrasound, but occasionally bone may be present too (Fig. 9).

Differential Diagnosis of Postaxial Polydactyly

- Asphyxiating thoracic dysplasia
- Chondroectodermal dysplasia (typical)
- Mesomelic dysplasia Werner syndrome type (associated with absence of thumbs)
- Otopalatodigital syndrome
- Short-rib polydactyly syndrome (type I, type III) (Fig. 10).

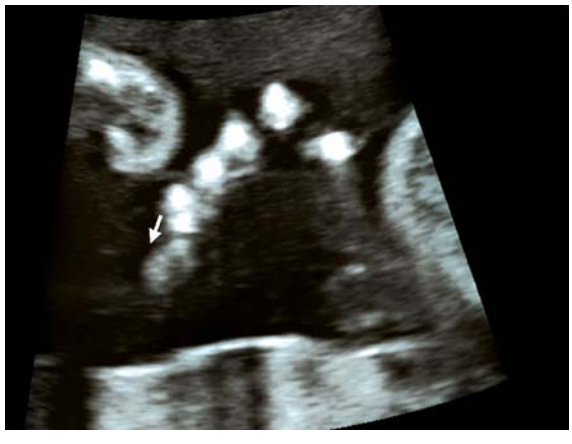

Fig. 9: Postaxial polydactyly on the ulnar side of hand

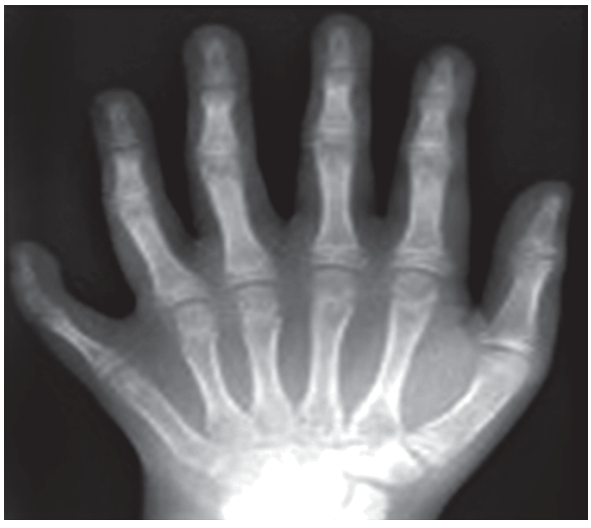

Fig. 10: Extra digits on the ulnar or fibular side are "postaxial" and "preaxial", if they are located on the radial or tibial side

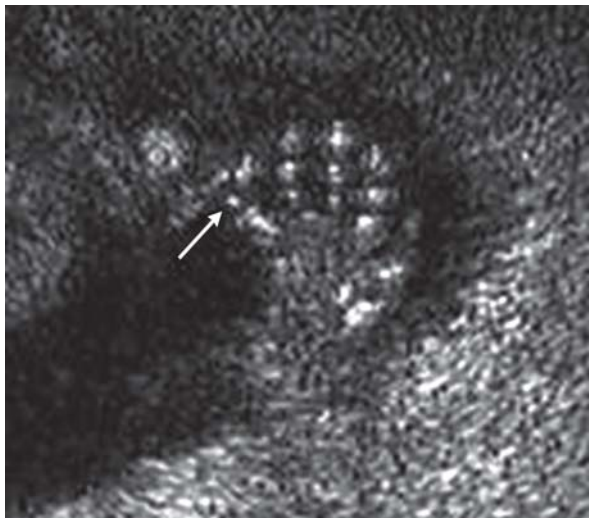

Fig. 12: Hypoplastic middle phalanx of little finger causing clinodactyly

Differential Diagnosis of Preaxial Polydactyly

- Carpenter syndrome
- Chondroectodermal dysplasia
- Short-rib polydactyly syndrome type II.

Approach to Polydactyly

- Additional features→Micromelia + Thoracic hypoplasia + Congenital heart disease → Short-rib polydactyly syndrome (s).
- Additional features→Congenital heart disease + Micrognathia + Multiple anomalies→Trisomy 13.
- Additional features→Thoracic hypoplasia + Renal anomalies →Asphyxiating thoracic dysplasia (Jeune syndrome).
- Additional features→Polycystic kidney + Cephalocele→ Meckel-Gruber syndrome.
- Additional features→Congenital heart disease + acromesomelia →Chondroectodermal dysplasia (Ellis-Van Creveld syndrome).

Differential diagnosis of Syndactly (Soft tissue or bony fusion of adjacent digits and is difficult to recognize in the less-severe forms) (Fig. 11).

- Apert syndrome
- Carpenter syndrome

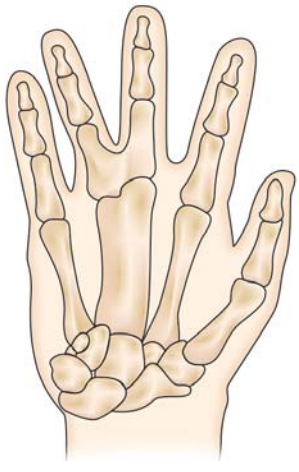

Fig. 11: Bony syndactyly

- Jarcho-Levin syndrome
- Mesomelic dysplasia Werner syndrome type
- Otopalatodigital syndrome
- Poland syndrome
- Roberts syndrome
- Thrombocytopenia – absent radius syndrome.

Clinodactly consists of deviation of finger(s) (Fig. 12). It may result from an abnormal middle fifth phalanx such as in brachymesophalangia.

Differential Diagnosis of Brachydactyly

- Mesomalic dysplasia
- Robinow syndrome
- Otopalatodigital syndrome
- Hitchhiker's thumb- Diastrophic dysplasia.

Approach to Ectrodactyly

- Additional features→Phocomelia + Cleft lip/palate→Roberts syndrome.
- Additional features→Aplasia radii + Micrognathia + Multiple anomalies→Trisomy 18 Anomalies.
- Additional features→Cleft lip/palate or malar hypoplasia →Ectrodactyly–Ectodermal dysplasia-clefting syndrome (EEC).
- Additional features→Micrognathia + External ear anomalies →Nager syndrome.
- Additional features→None→Split-hand–split foot syndrome.

Clubbing of the hand is very suggestive of radial ray anomalies. Radial ray anomalies range from abnormal thumbs (sometimes triphalangeal as in Holt-Oram syndrome) to hypoplasia or absence of the thumb and sometimes absence of the radius or even the radius and the hand. The three most likely

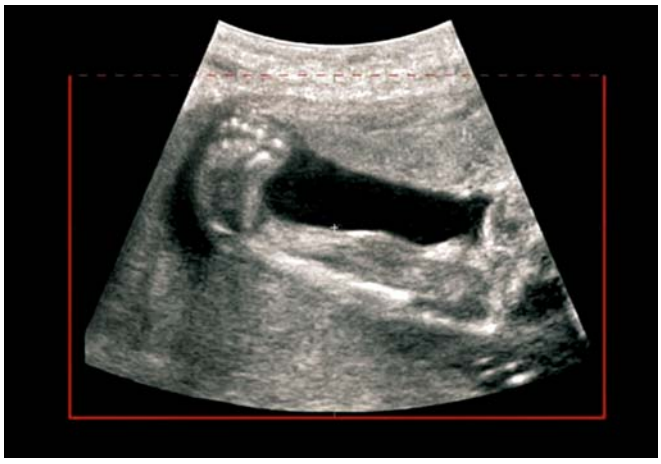

Fig. 13: Fetal club foot seen

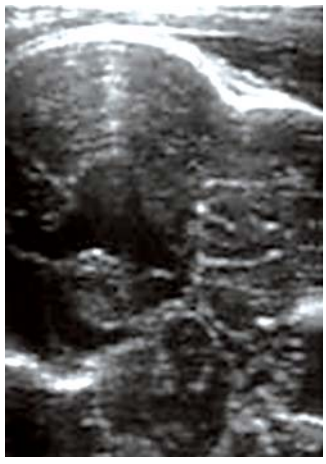

Fig. 14: Cloverleaf skull in a patient with thanatophoric dysplasia

diagnoses include Holt-Oram syndrome, thrombocytopenia-absent radius syndrome, and trisomy 18 (Fig. 6).

At the level of the feet, a rocker bottom foot (abnormal vertical position of the talus and calcaneus) or a clubfoot should also be sought. In clubfoot, the axis of the foot is no longer that of the lower leg. The foot is drawn up and bent inwards (*varus)*, and therefore, on the sagittal view of the leg, the sole is visible too (Fig. 13).

In the rarer equinus variant, the axis is same as that of the leg, but the foot is in fixed, abnormal hyperextension, with the sole facing backwards. In ulnar deviation of the hands, the hand appears abnormally and fixedly extrarotated on the ulnar side with overlapping fingers.

Differential Diagnosis of Club Foot

- Diastrophic dysplasia
- Kniest dysplasia
- Osteogenesis imperfecta
- Spondyloepiphyseal dysplasia congenita.

Abnormalities of Head and Face

Abnormalities of the head and face are also important in identifying the type of skeletal dysplasia. At the level of the head, deviations from the normal shape of the head should be observed. The classic axial transthalamic view is employed to detect possible deformations of the calvarial contour possibly due to early synostoses, such as in cloverleaf skull (thanatophoric dysplasia) (Fig. 14) although this anomaly is best displayed with a coronal approach, since the most significant deformation of the skull occurs below the transthalamic plane. These include brachycephaly, scaphocephaly and craniosynostoses.

Brachycephaly occurs in many acrocephalopolysyndactylies.

Scaphocephaly: It is characterized by an increased occipito-frontal diameter due to premature closure of the sagittal suture.

- Premature rupture of the membranes
- Growth restriction, *in utero* crowding
- Acromesomelic dysplasia.

Craniosynostoses result from premature fusions of the suture. The expanding brain deforms the adjacent bones resulting in specific anomalies. One of the common ones is the cloverleaf shape (or kleeblattschadel) that occurs in thanatophoric dysplasia type II. This is due to very premature closure of the lambdoid, coronal and sagittal sutures. The best view in which to appreciate the cloverleaf deformation is the coronal view of the head, since the parietal bones are the most severely affected. Other conditions with craniosynostosis are Carpenter syndrome, hypophosphatasia, acrodysostosis, trimethadione sequence, acrocephalosyndactyly, Antley Bixler syndrome, Apert syndrome and many others.

Acrocephaly or turricephaly is the presence of a pointed head (increased craniocaudal diameter) caused by premature closure of all sutures. Acrocephaly is typical of Apert syndrome.

Brachycephaly is characterized by a reduced occipitofrontal diameter caused by premature closure of the two coronal sutures.

Plagiocephaly, which is usually not detected *in utero*, denotes an asymmetric shape of the skull caused by unilateral premature closure of the coronal and lambdoid sutures.

Trigonocephaly indicates a triangular shape of the uppermost part of the skull, and is due to the closure of metopic suture (Fig. 15).

Frontal bossing is a deformity of the forehead that may not only be associated with achondroplasia and craniosynostosis but also may be due to increased intracranial size with large hydrocephalus. The diagnosis is often suspected in a section of the lips of the fetus (the section used to assess the presence of a cleft lip) and made or confirmed in a sagittal facial section. At the same time, a low nasal bridge may be present (Fig. 16).

A smaller jaw micrognathia should also be sought at this time of the examination. The assessment of the fetal facial

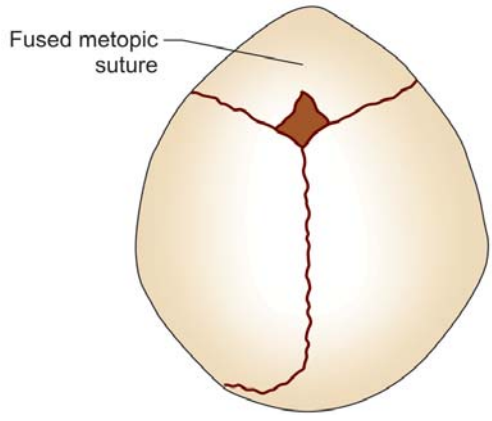

Fig. 15: Trigonocephaly

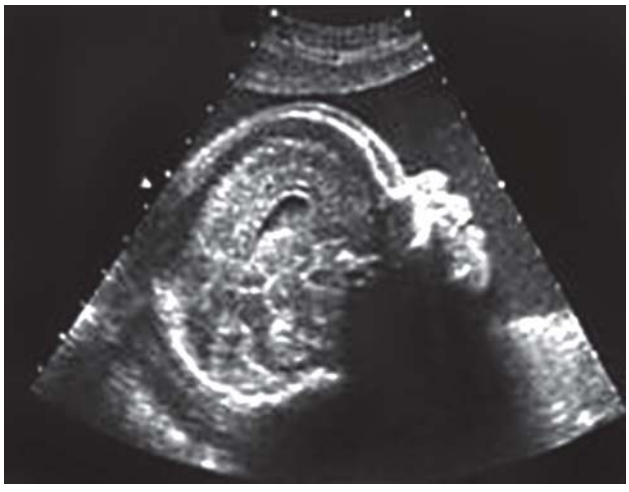

Fig. 16: Frontal bossing in sagittal scan in a fetus with achondroplasia

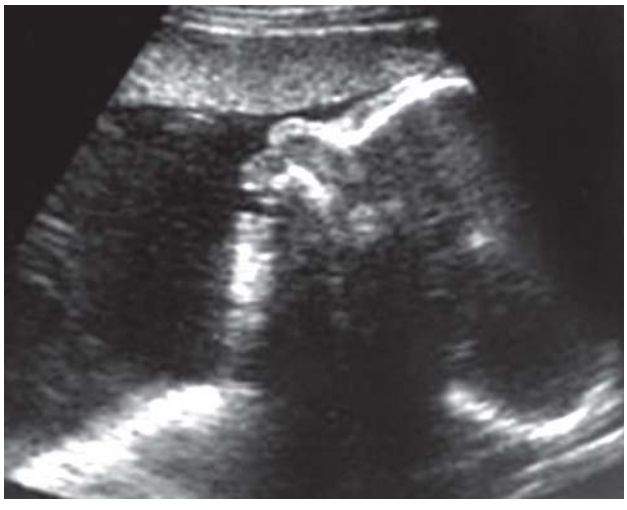

Fig. 17: Micrognathia

profile, performed on the midsagittal view, is needed to detect micrognathia (Fig. 17).

Approach to Short Limbs with Micrognathia

- Additional features→Micromelia + Hypomineralization + thoracic hypoplasia→Achondrogenesis.
- Additional features→Bowed tibias and femurs + Hypoplastic scapula→Campomelic dysplasia.
- Additional features→Rhizomelia + Joint contractures + Hitch hikers thumb→Diastrophic dysplasia.
- Additional features→Ubiquitous joint contractures + Hydrops→Fetal akinesia deformation sequence.

While looking at the head, note the distance between the eyes. A decreased distance (hypotelorism) or increased distance (hypertelorism) may be present in skeletal dysplasia.

Other associated findings in the face may be cleft palate and cataract.

Abnormalities of Thorax

Assessment of Spine and Thorax

The spine is electively evaluated using the midsagittal view, possibly performed with an anterior spine, in order to assess the vertebral bodies and the cutaneous contour, taking care to reduce the pressure on the transducer to leave some amniotic fluid between the proximal uterine wall and spine, which greatly enhances the acoustic window. This sagittal view allows display of neural tube defects as well as possible fusions of vertebral bodies. It also allows the suspicion of scoliosis to be raised, if the axis of the spine cannot be displayed from head to breech on a single plane; if this is suspected, a coronal view of the spine allows one to evaluate the degree of scoliosis[24] (Fig. 18). Hemivertebra have also been diagnosed *in utero*.

Also, the midsagittal view of the spine allows one to identify possible focal or general mineralization defects of the vertebrae. Parasagittal views at the level of the outer thoracic walls are used to display, on 2D ultrasound, gross mineralization or developmental anomalies of the ribs, as well as fractures (Fig. 19). To exclude thoracic hypoplasia, the dimensions of the thorax should be assessed on the 4-chamber and on the midsagittal view (Fig. 20).

At the level of the chest, look for abnormal rib size resulting in a chest that is too marrow (Fig. 21). Thoracic dimensions can be assessed by measuring the thoracic circumference at the level of four chamber view of the heart. It is ideal to refer to charts showing relationship between gestational age and thoracic circumference (Fig. 22).[25,26]

This is a typical finding of most of the lethal skeletal dysplasia. These conditions are not lethal because the bones are abnormal, but the ribs are too short and, thus prevent the normal growth of the lungs. The resulting pulmonary hypoplasia is lethal.

Differential Diagnosis of Short Ribs

- Achondrogenesis
- Asphyxiating thoracic dysplasia (Jeune syndrome)
- Atelosteogenesis
- Camptomelic dysplasia
- Chondroectodermal dysplasia (Ellis-van Creveld syndrome)

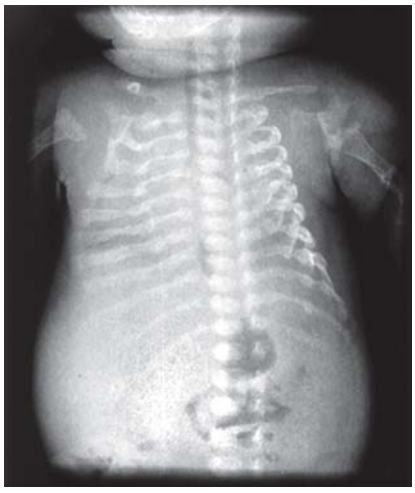

Fig. 18: Fractured fetal ribs with beaded appearance seen in a case of osteogenesis imperfecta type 2

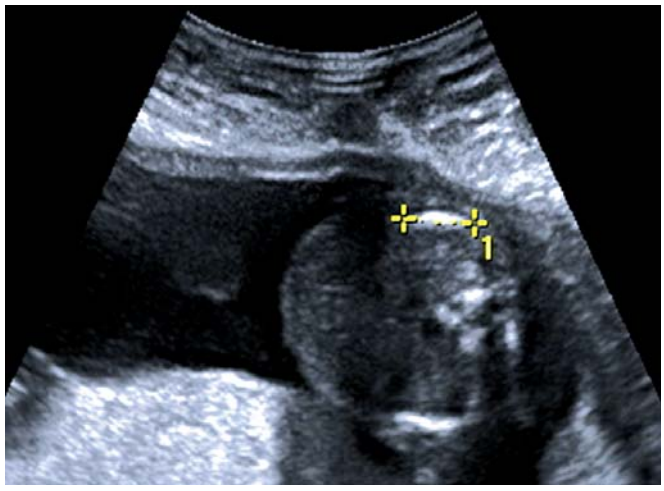

Fig. 21: Figure showing short ribs leading to a narrow thorax

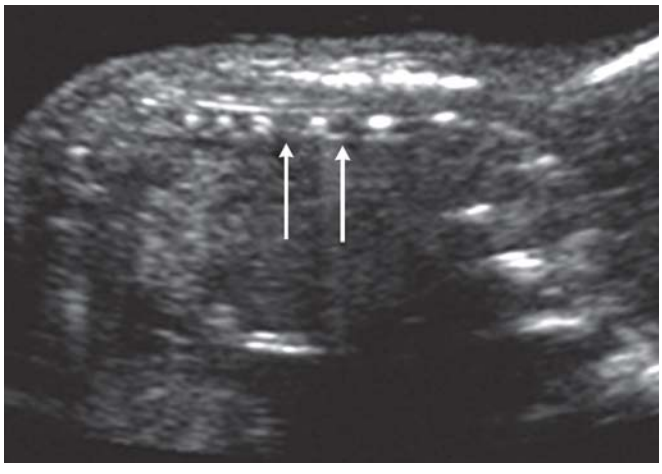

Fig. 19: Ossification and segmentation defects of spine seen at 14 weeks of gestation

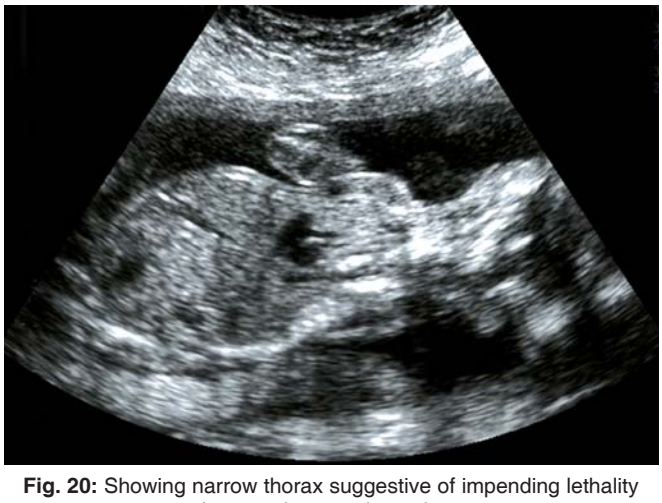

Fig. 20: Showing narrow thorax suggestive of impending lethality due to pulmonary hypoplasia

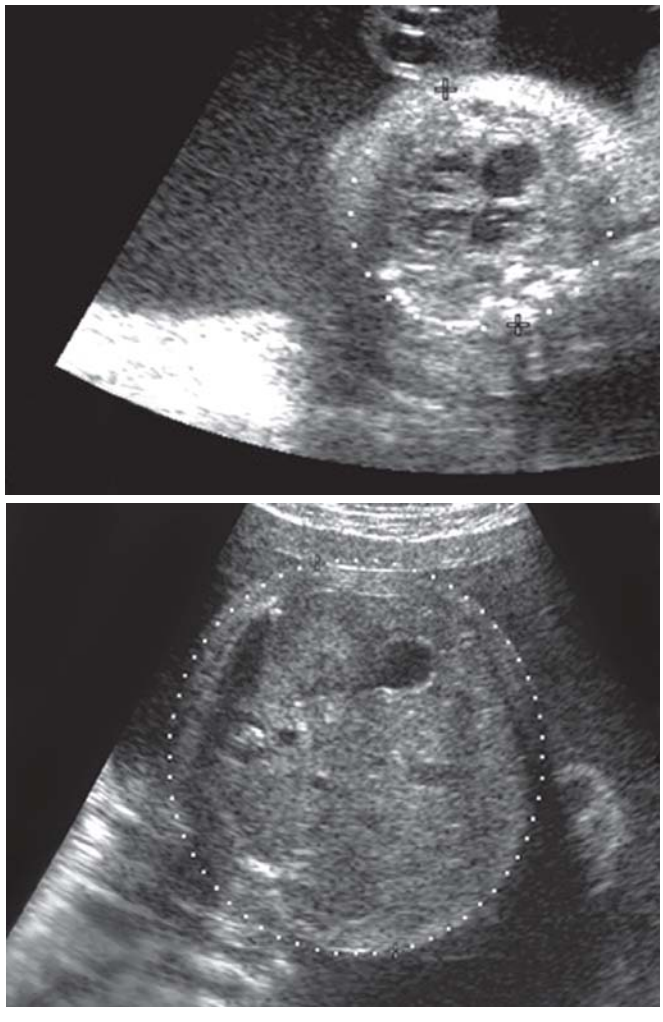

Fig. 22: Comparison of chest circumference with abdominal circumference in a case of thanatophoric dysplasia

- Cleidocranial dysostosis syndrome
- Fibrochondrogensis
- Hypophosphatasia
- Jarcho-Levin syndrome
- Kniest dysplasia
- Melnick-Needles syndrome (osteodysplasty)
- Metatropic dysplasia
- Osteogenesis imperfecta (type II)
- Otopalatodigital syndrome (type II)
- Pena-Shokeir syndrome
- Short-rib polydactyly syndrome (type I and II)
- Thanatophoric dysplasia.

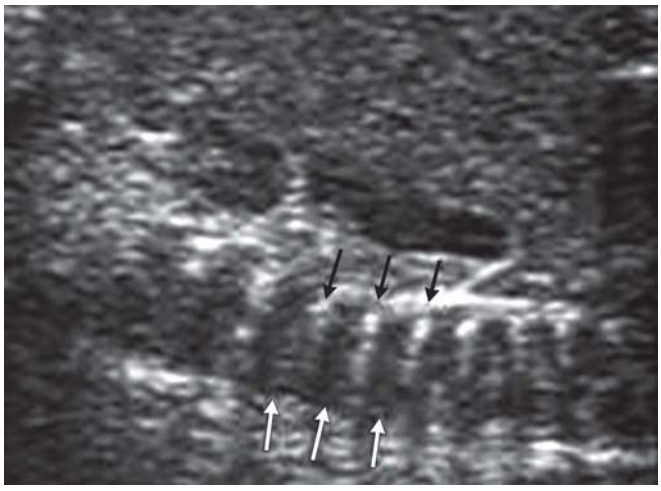

Fig. 23: Longitudinal scan of the spine in a fetus with thanatophoric dysplasia and platyspondyly. The intervertebral discs *(white arrows)* are greater in height than the vertebra *(black arrows)* which are flat

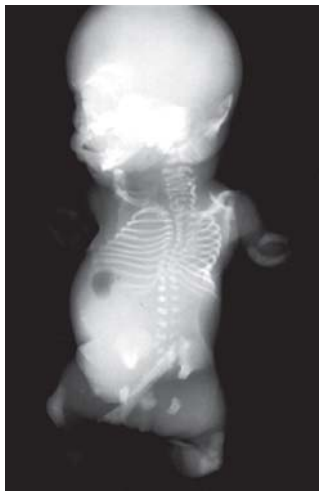

Fig. 24: Fetal spine showing scoliosis

Abnormalities of Spine

The most common spinal abnormality seen in skeletal dysplasias is platyspondyly, which consists of flattening of the vertebrae (Fig. 23). This sign is typical of thanatophoric dysplasia. Achondroplasia shows absence of normal widening of the lumbar spine. Achondrogenesis type I is characterized radio graphically by poor ossification of the spine (Fig. 24). Spondyloepiphyseal dysplasia shows multiple vertebral anomalies.[27]

Obstetric Management

Owing to the fact that most of the skeletal dysplasias diagnosed in the fetus are lethal, and if diagnosed within the legal time limit for termination of pregnancy (where this is allowed), most will result in termination. Furthermore, karyotyping should be performed only in the few cases in which a differential diagnosis with aneuploidies need be carried out, as in the case of diffuse joint contractures, which may be associated with trisomies 18 and 13 and neuroarthrogryposes. The perinatal management is also rather limited due to the fact that the non-lethal forms will need some respiratory assistance and physiokinesiotherapy in long-term.

After the Delivery

Despite all efforts to establish an accurate prenatal diagnosis, a careful study of the newborn is required in all instances. The evaluation should include a detailed physical examination performed by a geneticist or an individual with experience in the field of skeletal dysplasia and radiograms of the skeleton. The latter should include anterior, posterior, lateral and Towne's views of the skull and anteroposterior views of the spine and extremities with separate films of hands and feet. Examination of the skeletal radiographs permits precise diagnoses in the overwhelming majority of cases, since the classification of skeletal dysplasias is largely based on radiographic findings. In lethal skeletal dysplasias, histologic examination of the chondroosseous tissue should be included, as this information may help reach a specific diagnosis. Chromosomal studies should be included, as there is a specific group of constitutional bone disorders associated with cytogenetic abnormalities. Biochemical studies are helpful in rare instances. DNA restrictions and enzymatic activity assays should be considered in those cases in which the phenotype suggests a metabolic disorder such a mucopolysaccharidosis.

Brief Description of Common Clinical Fetal Skeletal Dysplasias

THANATOPHORIC DYSPLASIA

Definition

This condition is termed 'thanatophoric' (death-bringing) to emphasize its lethality. Two subtypes of thanatophoric dysplasia have been identified: type I, which is the most frequent, is characterized by curved femurs (Fig. 25) whereas type II is characterized by straight femurs and the classic cloverleaf skull.[28-30]

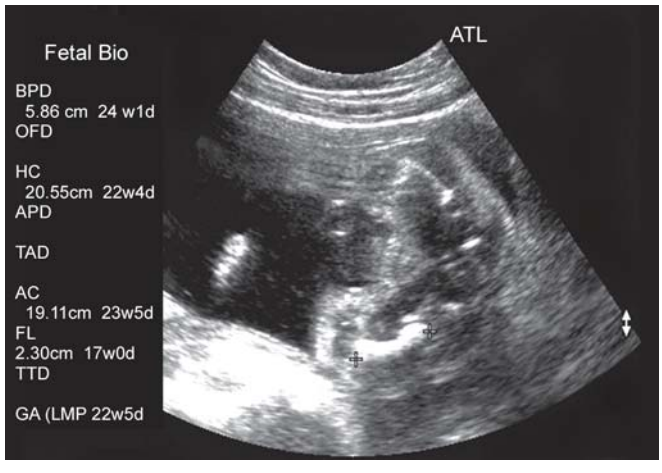

Fig. 25: Telephone femur with redundant soft tissue in a case of thanatophoric dwarfism

Ultrasound Diagnosis

Type I is characterized by bowed and extremely short femurs and humeri with metaphyseal cupping. This unusual aspect, also evident on ultrasound, has been noted as resembling the shape of a French telephone receiver. The ribs are very short and, on the midsagittal low-magnification view of the fetal trunk, a dip typical of severe thoracic hypoplasia can be seen at the level of thoracoabdominal junction. The head is large with frontal bossing and a low nasal bridge, no major synostoses are present in type I thanatophoric dysplasia. On the contrary, in type II, there is a classic cloverleaf skull, recognizable on a coronal view of the fetal head, which is due to synostosis of the lambdoid, coronal and sagittal sutures responsible for the temporal bossing. The femurs are short, although less so than in type I, and, above all, they tend to be straighter. Severe polyhydramnios is constantly associated.[31]

Etiology and Pathogenesis

An anomaly of the *FGFR3* gene has been found in both subtypes of this disorder. In particular, all cases showing a Lys650Glu substitution are type II and show straight femurs and cloverleaf skull. All other types of mutations found in the same gene have bowed femurs and no cloverleaf skull (type I). The latter subtype is resposible for 80% of cases. [32]

Outcome

Always lethal due to severe pulmonary hypoplasia.[33]

Inheritance Pattern and Recurrence Risk

Both types are due to *de novo* mutations. Therefore, the recurrence risk is very low.

Differential Diagnosis

This includes the other skeletal dysplasias characterized by micromelia and severe thoracic hypoplasia namely achondrogenesis, hypophosphatasia and osteogenesis imperfecta type II. With regard to type II thanatophoric dysplasia, the cloverleaf skull can also be present in very rare syndromes, such as Pfeiffer syndrome (different skeletal anomalies) and Crouzon syndrome (no limb shortening).[34]

OSTEOGENESIS IMPERFECTA (OI)

Incidence

Relatively frequent: 0.4/10 000 live births, 50% of which are accounted for by type II.

Ultrasound Diagnosis

Type II: Ubiquitous and diffuse fractures (Figs 26 and 27) thoracic hypoplasia, hypomineralization of the calvarium.

Type III: Late onset bowing of long bones and fractures. Types I and IV are not diagnosable in the fetus.[35]

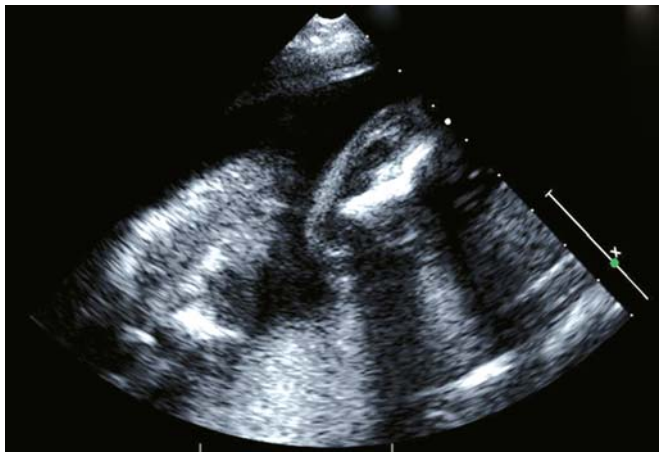

Fig. 26: Ultrasound images show bone fractures and deformities. Note the femoral irregularity and angulation

Index Case Microscopic Bone

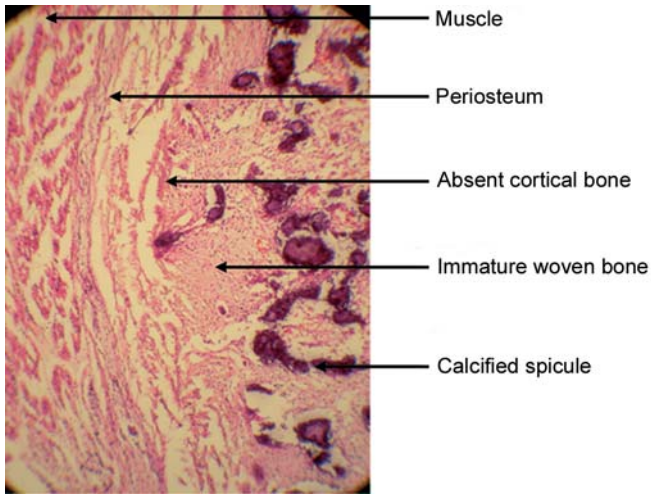

Fig. 27: Postmortem histopathology of the affected bone in a case of osteogenesis imperfecta

Outcome

Lethal in type II. Motor disability of various forms in type III. Recently, therapy with bisphosphonates and stem cell transplantation has given good results in the non-lethal forms.

Inheritance pattern and recurrence risk: Autosomal dominant inheritance pattern. However, all cases are due to *de novo* mutations, and therefore the recurrence risk is very low, although some authors have reported a 6% risk.

Differential Diagnosis

OI type II should be differentiated from other lethal skeletal dysplasias presenting with micromelia and calvarial hypomineralization, namely, achondrogenesis, and hypophosphatasia. In general, hypomineralization with clavicle sparing is a typical of hypophosphatasia. Micrognathia, present in achondrogenesis, is absent in hypophosphatasia while fractures are characteristic of OI type II.[36,37]

Prognosis, Survival and Quality of life

OI type II is invariably lethal. OI type III shows motor disability of variable severity (kyphosis and fractures) and worsening with age due to the extreme fragility of the bones. By adulthood, hearing loss (otosclerosis), a need for walking aids and dentition problems are extremely frequent. Types I and IV, which cannot be detected in the fetus, are associated with a better prognosis.

Recurrence Risk

OI type II shows an autosomal dominant inheritance pattern. However, all cases are due to *de novo* mutations, and therefore the recurrence risk is very low, although some authors have reported a 6% risk.

ACHONDROGENESIS

Outcome

Lethal.

Inheritance Pattern and Recurrence Risk

Autosomal recessive (25%). *De novo* mutations with autosomal dominant inheritance.

Subtypes of Achondrogenesis

Two main subtypes have been recognized differing in inheritance pattern (autosomal recessive for type I and autosomal dominant for type II) and in a few sonographic aspects. In type I, or Parenti-Fraccaro type, the ribs tend to be thin often with multiple fractures, and the cranium is disproportionately large due to marked edema of soft tissues. In fact, hydrops is frequently associated. Type II, or Langer–Saldino type, is characterized by virtual absence of ossification in the vertebral column, sacrum and pubic bones.

Etiology and Pathogenesis

A mutation in the *COL2A1* gene coding for collagen type II has been found in some cases of type II. Type 1B is associated with mutation in the gene for DTDST on the long arm of chromosome 5.

Ultrasound Diagnosis

The ultrasound diagnosis is based on the recognition of micromelia and thoracic hypoplasia, hypomineralization and micrognathia. In particular, the long bones appear barely visible and curved and the thorax extremely hyperplasic due to the underdeveloped ribs. The hypomineralization involves predominantly the spine, pelvis and calvarium. Severe micrognathia is also regularly associated. If the condition is recognized at 12 to 14 weeks of gestation, which is likely, hydrops and diffuse subcutaneous edema ('spaceman's suit') may also be seen.[38,39]

Differential Diagnosis

This includes all lethal conditions characterized by micromelia plus thoracic hypoplasia plus hypomineralization, such as lethal variant of osteogenesis imperfecta (type II), hypophosphatasia, and thanatophoric dysplasia. The constant occurrence of fractures in osteogenesis imperfecta type II, the lack of micrognathia in hypophosphatasia, and the only mild hypomineralization in thanatophoric dysplasia, which often also shows curved femurs, are the selective ultrasound findings that should contribute to reaching the correct final diagnosis.

SHORT-RIB POLYDACTYLY SYNDROMES (SRPS)

Ultrasound Diagnosis

Micromelia, thoracic hypoplasia with short ribs, polydactyly. In some cases, cardiac defects too. Regional hypomineralization, in some cases.

Outcome

Always lethal.

Inheritance Pattern and Recurrence Risk

Autosomal recessive: 25% recurrence risk.

Definition

The short-rib polydactyly syndromes (SRPS) comprise basically four subtypes (Saldino–Noonan, Majewsky, Verma–Naumoff, and Beemer–Langer). All are characterized by micromelia, thoracic hypoplasia with short ribs, and postaxial polydactyly. Some feature other anomalies, including median cleft lip, congenital heart disease (transposition of the great arteries) and renal dysplasia.

Etiology and Pathogenesis

The real incidence of these syndromes is not known, but they are very rare disorders. The genetic defect responsible for the SRPS is still unknown.

Ultrasound Diagnosis

The ultrasound diagnosis is based on the detection of severe micromelia, severe thoracic hypoplasia with short ribs, and postaxial polydactyly other anomalies that may be detected by ultrasound in the various types include: congenital heart disease, median cleft lip, polycystic kidney/renal dysplasia, and anophthalmia.

Differential Diagnosis

SRPS should be differentiated from the other lethal skeletal dysplasias presenting with micromelia and thoracic hypoplasia namely achondrogenesis, thanatophoric dysplasia, hypophosphatasia, and osteogenesis imperfecta type II. However, postaxial polydactytly is present in SRPS only, and, at the same time, hypomineralization is only rarely present in some subtypes of SRPS. Another condition to be distinguished from SRPS is chondroectodermal dysplasia (Ellis–Van Creveld syndrome), which also features thoracic hypoplasia and postaxial polydactytly, however, in the latter disorder, thoracic

hypoplasia is less pronounced and the limbs are less affected. The occurrence of median cleft lip identifies SRPS types II and IV (Majewsky and Beemer-Langer).

Recurrence Risk

All SRPS have an autosomal recessive inheritance pattern, which determines the 25% recurrence rate.

HYPOPHOSPHATASIA

Ultrasound Diagnosis

Micromelia, thoracic hypoplasia, severe hypomineralization (clavicles spared). Hydrops and subcutaneous edema if detected at 12 to 14 weeks.

Outcome

The forms detectable *in utero* are always lethal.

Inheritance Pattern and Recurrence Risk

Autosomal recessive: 25% recurrence risk.

ACHONDROPLASIA

Incidence

Relatively frequent: 1/10 000 live births.

Ultrasound Diagnosis

Rhizomelia, mild late-onset macrocrania, and low nasal bridge.

Outcome

Normal lifespan. No risk of mental retardation. Orthopedic and pulmonary long-term sequelae due to the relatively small thorax.

Inheritance Pattern and Recurrence Risk

Heterozygotic: due to a *de novo* mutation, with very low recurrence risk.

Autosomal dominant inheritance with high incidence, if one or both parents are affected (50% and 75% recurrence rates respectively).

Definition

There are two types of achondroplasia defined according to their inheritance pattern: homozygotic and heterozygotic. The former type, which is almost invariably lethal (severe pulmonary hypoplasia), is by far the rarer variant due to the fact that it occurs only if both parents are affected. The heterozygotic variant is the commoner one usually detected at birth and in some cases, *in utero*. Achondroplasia should short or borderline femur length and a tendency to macrocrania be detected in the 2nd trimester. However, in pregnancies at risk for achondroplasia, such as those in which one of the parents is affected, this search may be done on the chorionic villi, so that the diagnosis of achondroplasia can be confirmed or excluded.

Differential Diagnosis

The differential diagnosis should include the other conditions that are possibly characterized by a borderline or short femur. The first and the easiest to rule out is trisomy 21: a simple karyotype can serve this purpose. In addition, the same cells may be used to extract the DNA needed for the diagnosis of achondroplasia. The other most important condition to rule out is early-onset atypical fetal growth restriction (FGR), the onset of which may rarely be characterized by selective underdevelopment of the long bones. The other skeletal dysplasias that may enter in the differential diagnosis, due to the presence of moderate rhizomelia (at least in the 2nd trimester), are campomelic dysplasia, which is often characterized by micrognathia, and always by bowed bones, chondroectodermal dysplasia (*Ellis-Van Creveld Syndrome*), which is associated with significant thoracic hypoplasia, polydactyly, and cardiac defects.

Ultrasound Diagnosis

The ultrasound diagnosis is difficult, since the rhizomelia is of late-onset becoming evident only at 26 to 28 weeks of gestation. The femur and humerus are slightly–moderately shorter than normal showing biometry in the 1st to 5th centile range addition. The morphology of the affected long bones is normal, which makes the diagnosis even more difficult. In some cases, the involvement of the humerus is more severe than that of the femur. Additional criteria that, if present, may support the ultrasound diagnosis of achondroplasia are a tendency to macrocrania and a low nasal bridge.[11]

Etiology and Pathogenesis

The gene defect responsible for the disease has been identified in a *de novo* mutation of the gene for the fibroblast growth factor receptor (*FGFR3*), at chromosome 4p16.3. Ninety-seven percent of achodroplasic individuals show the same mutation, namely a guanine-to-adenine transition at nucleotide 1138 of the complementary DNA. This mutation prevents binding of FGF to its receptor, which in turn impairs bone growth.[3]

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