Diploma in Fetal Medicine & ISUOG Educational Series
The 18 - 23 weeks scan
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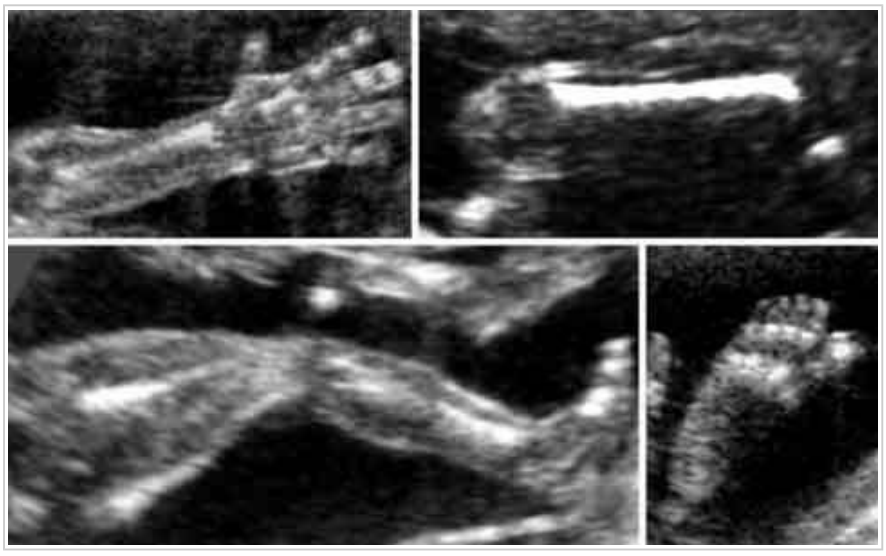
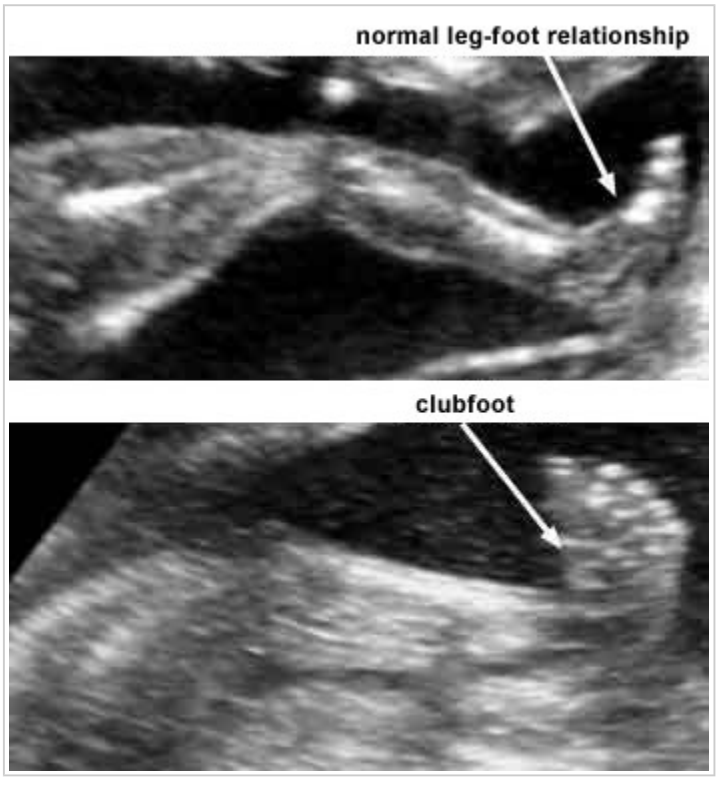
Chapter 9

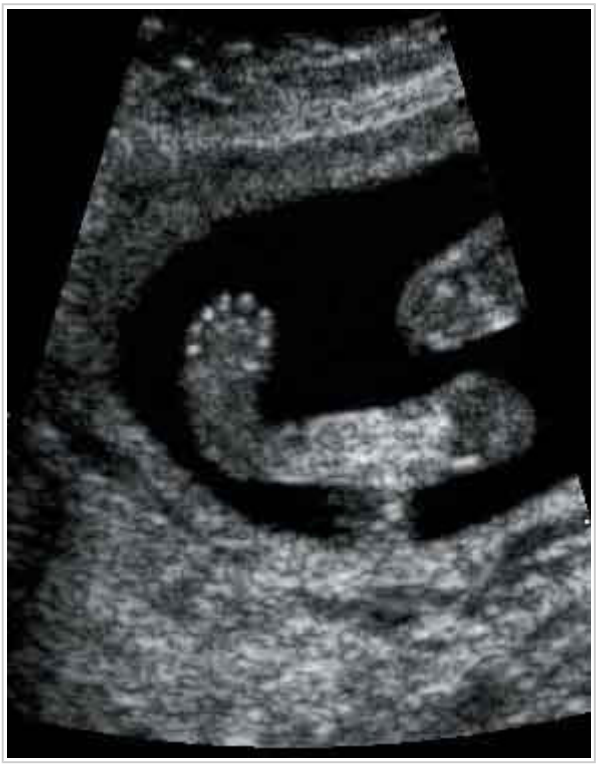
Skeleton

NORMAL SONOGRAPHIC ANATOMY

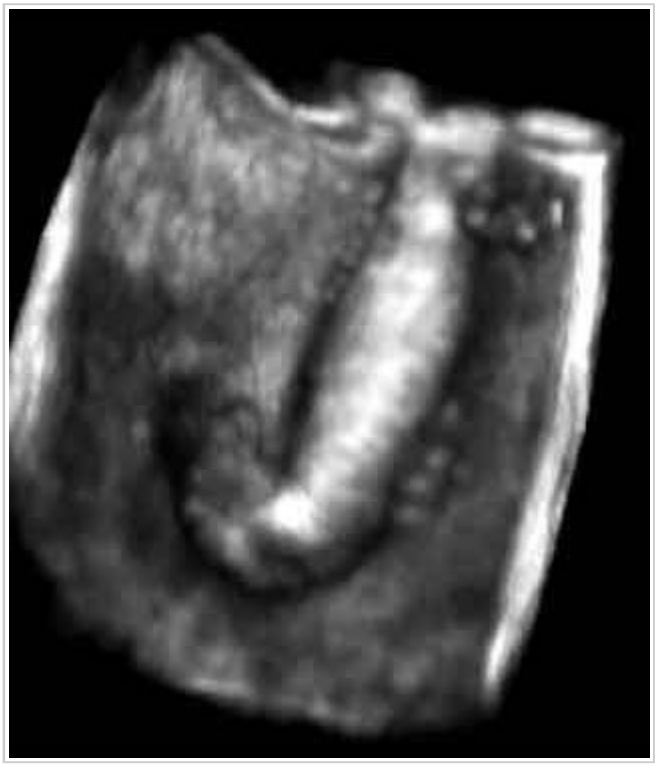
Limb buds are first seen by ultrasound at about the 8th week of gestation; the femur and humerus are seen from 9 weeks, the tibia/fibula and radius/ulna from 10 weeks and the digits of the hands and the feet from 11 weeks. All long bones are consistently seen from 11 weeks. Body movements (wiggling) are seen at 9 weeks and, by 11 weeks, limbs move about readily. The lengths of the humerus, radius/ulna, femur and tibia/fibula are similar and increase linearly with gestation. At the 18–23-week scan, the three segments of each extremity should be visualized, but it is only necessary to measure the length of one femur. The relationship of leg and foot should also be assessed to rule out clubfoot.







Clubfoot - 2D Ultrasound



Clubfoot - 3D Ultrasound (rendering mode)

SKELETAL ANOMALIES

Prevalence

Skeletal dysplasia is found in about 1 per 4000 births; about 25% of affected fetuses are stillborn and about 30% die in the neonatal period.

Classification

The existing nomenclature for skeletal dysplasias is complicated. Some disorders are referred to by eponyms (such as Ellis–Van Creveld syndrome), by Greek terms describing a salient feature of the disease (diastrophic or twisted, metatrophic or changeable) or by a term related to the presumed pathogenesis of the disease (such as osteogenesis imperfecta). The fundamental problem with any classification of skeletal dysplasias is that the pathogenesis of these diseases is largely unknown and, therefore, the current system relies on purely descriptive findings of either clinical or radiological nature. According to the International Nomenclature for Skeletal Dysplasias, the diseases are subdivided into three different groups:

(1) Osteochondrodysplasias (abnormalities of cartilage and / or bone growth and development);

(2) Disorganized development of cartilaginous and fibrous components of the skeleton; and

(3) Idiopathic osteolyses.

Approach to prenatal diagnosis

There is a wide range of rare skeletal dyplasias, each with a specific recurrence risk, dysmorphic expression, and implications for neonatal survival and quality of life. Our knowledge of the in utero expression of these syndromes is based on a few case reports and, therefore, in attempting to perform prenatal diagnosis of individual conditions in at-risk families, extrapolation of findings from the perinatal period is often necessary. The incidental discovery of a skeletal dysplasia on routine ultrasound screening, in a pregnancy not known to be at risk of a specific syndrome, necessitates a systematic examination to arrive at the correct diagnosis. All limbs must be evaluated as to their length, shape, mineralization and movement, and associated abnormalities in other systems, particularly the head, thorax and spine, should be sought.

Assessment of long bones

Shortening of the extremities can involve the entire limb (micromelia, such as achondrogenesis, short-rib polydactyly syndrome, diastrophic dysplasia osteogenesis imperfecta type II), the proximal segment (rhizomelia, such as achondroplasia), the intermediate segment (mesomelia, such as mesomelic dysplasia) or the distal segment (acromelia, such as Ellis–Van Creveld syndrome). The diagnosis of rhizomelia or mesomelia requires comparison of the dimensions of the bones of the leg and forearm with those of the thigh and arm. The femur, however, is abnormally short even in mesomelic dwarfism and, therefore, in our routine fetal abnormality screening, we tend to confine limb measurements to that of the femur. When dealing with pregnancies at risk for a skeletal dysplasia, both segments of all limbs are measured.

The severe limb reductions associated with osteogenesis imperfecta type II, achondrogenesis and thanatophoric, diastrophic, and chondroectodermal dysplasias can be detected by a single measurement of the femur length at 16–18 weeks of gestation. In the case of achondroplasia, however, the diagnosis may not become obvious until 22–24 weeks and, therefore, serial measurements are necessary; homozygous achondroplasia, which is usually lethal, manifests in abnormally short limbs earlier than the heterozygous form.

A minor degree of lateral curvature of the femur is commonly seen in normal fetuses. Pronounced bowing, however, is observed in association with campomelic dysplasia, thanatophoric dwarfism, autosomal dominant osteogenesis imperfecta, achondrogenesis and hypophosphatasia. In the latter, fractures and callus formation may also be detected. Reduced echogenicity of bones, suggestive of hypomineralization, is seen in such disorders as hypophosphatasia, osteogenesis imperfecta and achondrogenesis. The virtual absence of ossification of the spine, characteristic of achondrogenesis, may lead to the erroneous diagnosis of complete spinal agenesis. Similarly, the pronounced clarity with which the cerebral ventricles are imaged, as a result of the poorly mineralized globular cranium in cases of hypophosphatasia, may result in the misdiagnosis of hydrocephalus. Care must be exercised, however, because lesser degrees of hypomineralization may not be detectable.

Isolated limb reduction deformities, such as amelia (complete absence of extremities), acheiria (absence of the hand), phocomelia (seal limb) or aplasia–hypoplasia of the radius or ulna, are often inherited as part of a genetic syndrome (Holt–Oram syndrome, Fanconi pancytopenia, thrombocytopenia with absent radii syndrome) and are readily diagnosible by ultrasonography in an at-risk fetus. Other causes of focal limb loss include the amniotic band syndrome, thalidomide exposure and caudal regression syndrome.

Evaluation of hands and feet

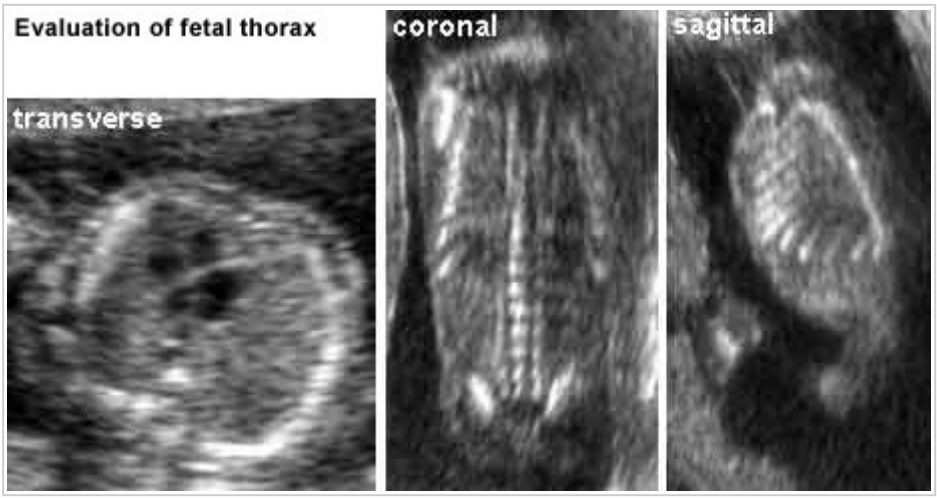
Fetal fingers and toes can be seen, and, with meticulous examination, abnormalities of numbers, shape, movement and attitudes can be recognized. Several skeletal dysplasias feature alterations of the hands and feet. Polydactyly refers to the presence of more than five digits. It is classified as postaxial if the extra digits are on the ulnar or fibular side and preaxial if they are located on the radial or tibial side. Syndactyly refers to soft tissue or bony fusion of adjacent digits. Clinodactyly consists of deviation of a finger(s). Disproportion between hands and feet and the other parts of the extremity may also be a sign of a skeletal dysplasia.

Examination of fetal movements

Maternal perception of fetal movements is usually decreased in fetuses with skeletal dysplasias, such as achondrogenesis and thanatophoric dysplasia. Ultrasonography can aid in the diagnosis of conditions characterized by limitation of flexion or extension of the limbs, such as arthrogryposis and multiple pterygium syndrome.

Evaluation of thoracic dimensions

Several skeletal dysplasias are associated with a small thorax, and chest restriction leads to pulmonary hypoplasia, which is the common cause of death in these conditions. The appropriateness of thoracic dimensions can be assessed by measuring the thoracic circumference at the level of the four-chamber view of the heart and examining the thoracic-to-abdominal circumference ratio, the thoracic-to-head circumference ratio, or the thoracic-to-cardiac circumference ratio.



Skeletal dysplasias associated with a long narrow thorax include asphyxiating thoracic dysplasia (Jeune), chondroectodermal dysplasia (Ellis–Van Creveld), campomelic dysplasia, Jarcho–Levin syndrome, achondrogenesis and hypophosphatasia. Dysplasias with a short thorax include osteogenesis imperfecta (type II), Kniest's dysplasia (metatrophic dysplasia type II) and Pena–Shokeir syndrome. Hypoplastic thorax is found in short-rib polydactyly syndrome (type I, type II), thanatophoric dysplasia, cerebrocostomandibular syndrome, cleidocranial dysostosis syndrome, homozygous achondroplasia, Melnick–Needles syndrome (osteodysplasty), fibrochondrogenesis and otopalatodigital syndrome type II.

Evaluation of the fetal head

Several skeletal dysplasias are associated with defects of membranous ossification and, therefore, affect skull bones. The face should also be examined for the diagnosis of hypertelorism, micrognathia, short upper lip, and abnormalities of the ears.

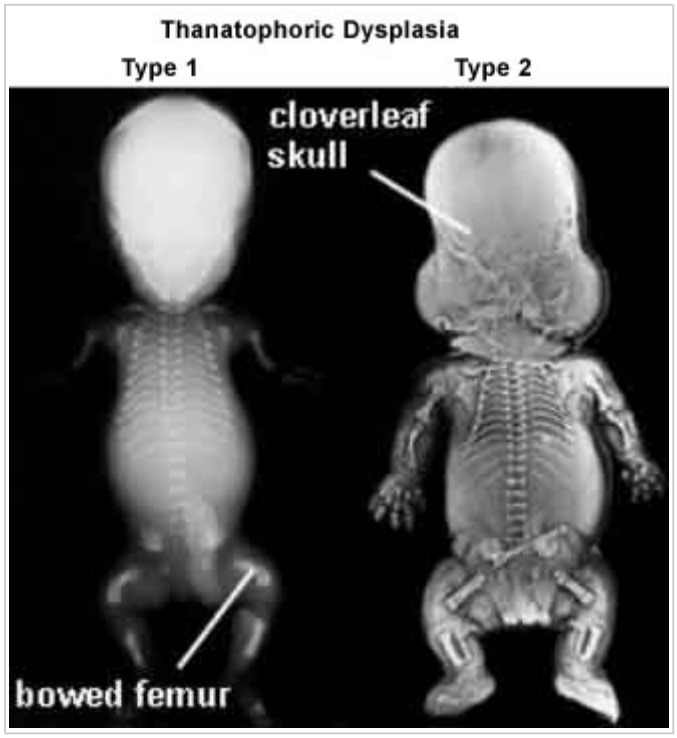
Diagnostic tests complementary to sonography

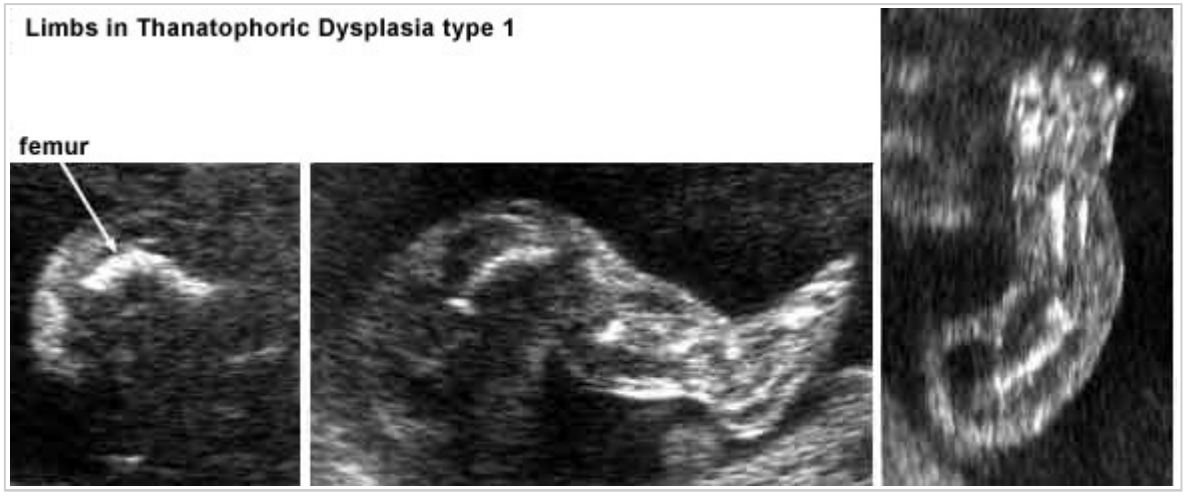
Prenatal or postnatal evaluation includes chromosomal studies, biochemical investigations (e.g. hypophosphatasia) and DNA analysis for an increasing number of the osteochondrodysplasias. Postnatally, examination of skeletal radiographs is of particular importance, since the classification of skeletal dysplasias is largely based upon radiographic findings.

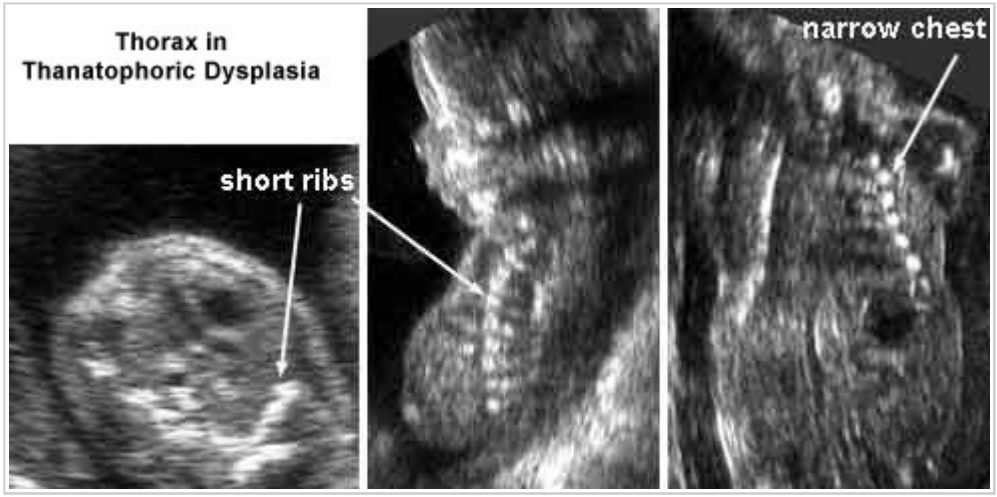
OSTEOCHONDRODYSPLASIAS

Thanatophoric dysplasia

This is the most common lethal skeletal dysplasia with a birth prevalence of about 1 in 10 000. The term derives from the Greek, meaning death-bearing and the characteristic features are severe shortening of the limbs, narrow thorax, normal trunk length and large head with prominent forehead. In type I, which is sporadic, the femurs are curved (telephone receiver) and in type II, which is autosomal recessive, the femurs are straight but the skull is cloverleaf-shaped.

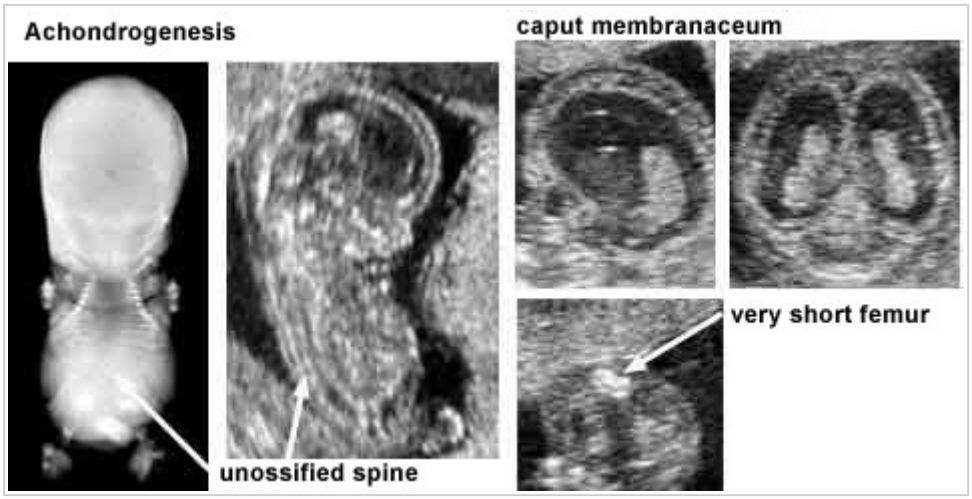






Achondrogenesis

This is a lethal skeletal dysplasia with a birth prevalence of about 1 in 40 000. The characteristic features are severe shortening of the limbs, narrow thorax, short trunk and large head. In achondrogenesis type I, which is autosomal recessive, there is poor mineralization of both the skull and vertebral bodies as well as rib fractures. In type II, which is sporadic (new autosomal dominant mutations), there is hypomineralization of the vertebral bodies but normal mineralization of the skull, and there are no rib fractures.

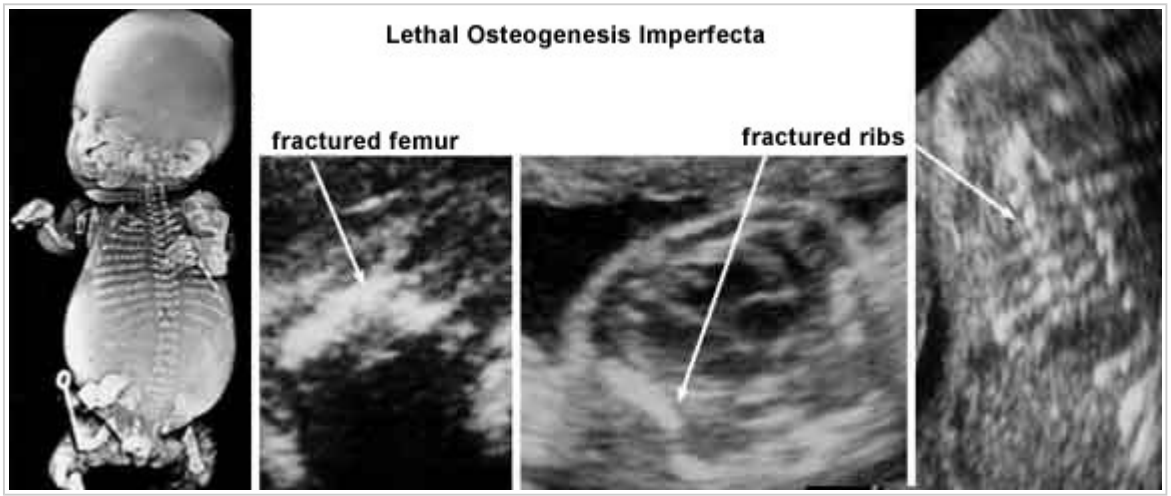


Osteogenesis imperfecta

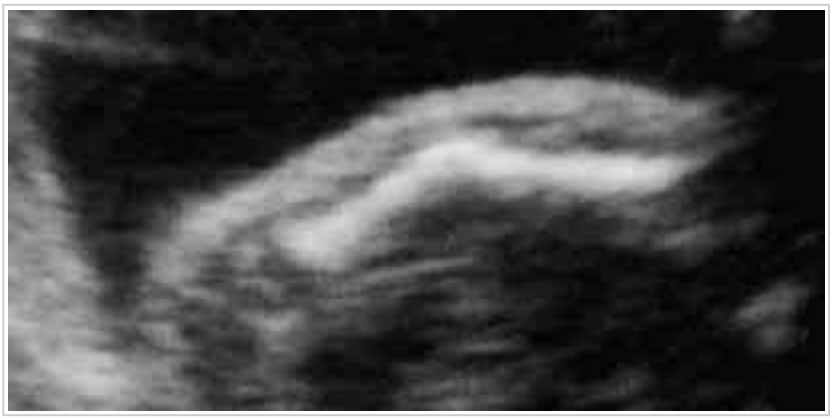
Osteogenesis imperfecta is a genetically heterogeneous group of disorders presenting with fragility of bones, blue sclerae, loose joints and growth deficiency. The underlying defect is a dominant negative mutation affecting COL1A1 or COL1A2 alleles, which encode the proA1(I) and proa2(I) chains of type I collagen, a protein of paramount importance for normal skin and bone development. The mutations result in the production of abnormal quantity (OI type I) or quality (types II, III and IV) of collagen.

There are four clinical subtypes. In type I, which is an autosomal dominant condition with a birth prevalence of about 1 in 30 000, affected individuals have fragile bones, blue sclerae and progressive deafness, but life expectancy is normal. Prenatal diagnosis is available by DNA analysis. Ultrasonography in the second and third trimesters may demonstrate fractures of long bones.

In type II, which is a lethal disorder with a birth prevalence of about 1 in 60 000, most cases represent new dominant mutations (recurrence is about 6%). The disorder is characterized by early prenatal onset of severe bone shortening and bowing due to multiple fractures affecting all long bones and ribs, and poor mineralization of the skull.



Type III is a progressively deforming condition characterized by multiple fractures, usually present at birth, resulting in scoliosis and very short stature. Bowing of the femur has been described in these cases in utero. Both autosomal dominant and recessive modes of inheritance have been reported.



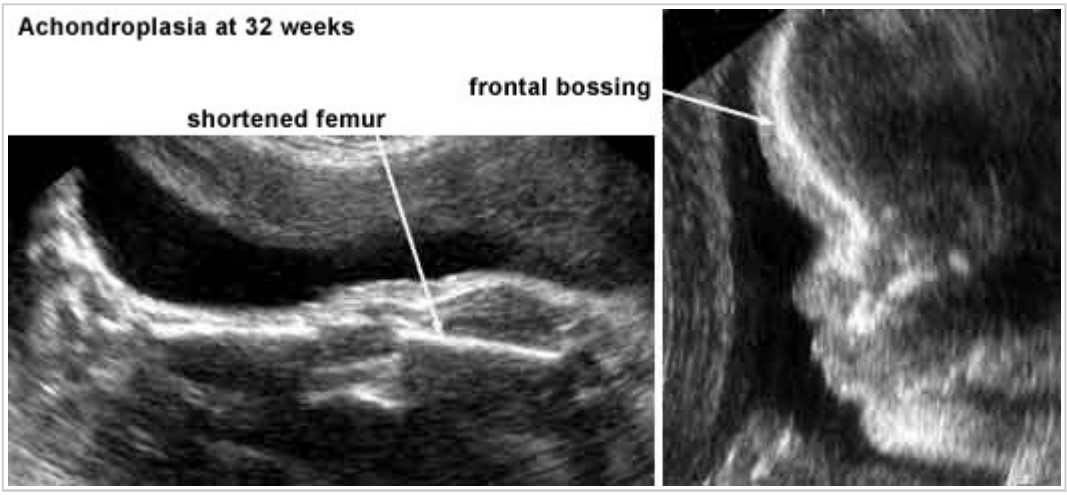
Type IV is an autosomal dominant condition with variable expressivity. Severely affected individuals may have deformities of the long bones due to fractures. Prenatal diagnosis of types III and IV can be made by chorion villous sampling and DNA analysis, or by demonstration of abnormal collagen production in cultured fibroblasts.

Hypophosphatasia

This lethal, autosomal recessive condition, with a birth prevalence of about 1 in 100 000, is characterized by severe shortening of the long bones, small thorax, hypomineralization of the skull and long bones. There is absence of liver and bone isoenzymes of alkaline phosphatase, and first-trimester diagnosis is made by measurement of alkaline phosphatase isoenzymes in chorion villous samples. The diagnosis can also be made by DNA studies.

Achondroplasia

This autosomal dominant syndrome has a birth prevalence of about 1 in 26 000, but the majority of cases represent new mutations. The characteristic features of heterozygous achondroplasia include short limbs, lumbar lordosis, short hands and fingers, macrocephaly with frontal bossing and depressed nasal bridge.



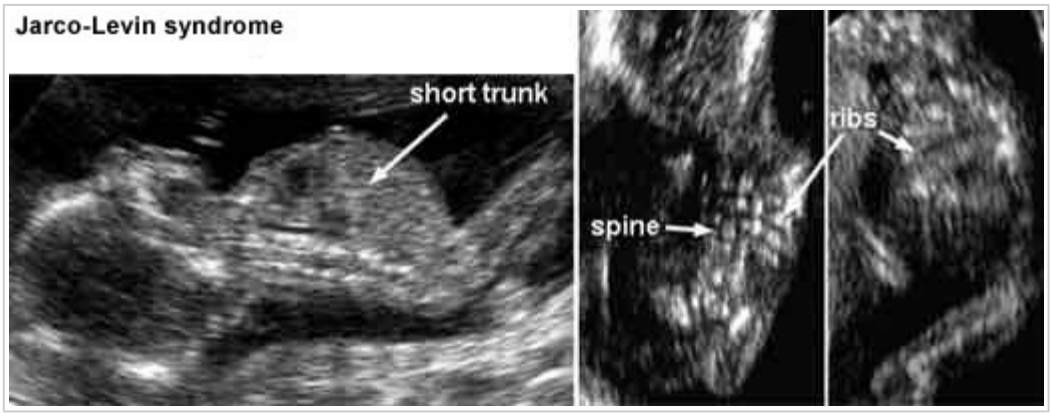
Intelligence and life expectancy are normal. Prenatally, limb shortening and typical facis usually become apparent only after 22 weeks of gestation. In the homozygous state, which is a lethal condition, short limbs are associated with a narrow thorax. Achondroplasia is due to a specific mutation within the fibroblast growth factor receptor type 3 gene (FGFR3) and can now be diagnosed by DNA analysis of fetal blood or amniotic fluid obtained in cases of suspicious sonographic findings. In cases where both parents have achondroplasia, there is a 25% chance that the fetus is affected by the lethal type and the diagnosis can be made by first-trimester chorion villous sampling.

Campomelic dysplasia

This lethal, autosomal recessive syndrome with a birth prevalence of 1 in 200 000 is characterized by shortening and bowing of the long bones of the legs, narrow chest, hypoplastic scapulae, and large calvarium with disproportionately small face. Some of the affected genetically male individuals show a female phenotype. Patients usually die in the neonatal period from pulmonary hypoplasia.

Jarcho–Levin syndrome

This is a heterogeneous disorder, characterized by vertebral and rib abnormalities (misalignment of the cervical spine and ribs). An autosomal recessive type is characterized by a constricted short thorax and respiratory death in infancy. Another autosomal recessive and an autosomal dominant type are associated with a short stature and are compatible with survival to adult life but with some degree of physical disability.



Asphyxiating thoracic dysplasia (Jeune syndrome)

This is an autosomal recessive condition with a birth prevalence of about 1 in 70 000. The characteristic features are narrow chest and rhizomelic limb shortening. There is a variable phenotypic expression and, consequently, the prognosis varies from neonatal death, due to pulmonary hypoplasia, to normal survival. Limb shortening is mild to moderate and this may not become apparent until after 24 weeks of gestation.

Chondroectodermal dysplasia (Ellis–Van Creveld syndrome)

This rare, autosomal recessive condition is characterized by acromelic and mesomelic shortness of limbs, postaxial polydactyly, small chest, ectodermal dysplasia, and congenital heart defects in more than 50% of cases.

Short limb polydactyly syndromes

This group of lethal disorders is characterized by short limbs, narrow thorax and postaxial polydactyly. Associated anomalies are frequently found, including congenital heart disease, polycystic kidneys, and intestinal atresia. Four different types have been recognized. Type I (Saldino–Noonan) has narrow metaphyses; type II (Majewski) has cleft lip and palate and disproportionally shortened tibiae; type III (Naumoff) has wide metaphyses with spurs; type IV (Beemer–Langer) is characterized by median cleft lip, small chest with extremely short ribs, protuberant abdomen with umbilical hernia and ambiguous genitalia in some 46,XY individuals.

Diastrophic dysplasia

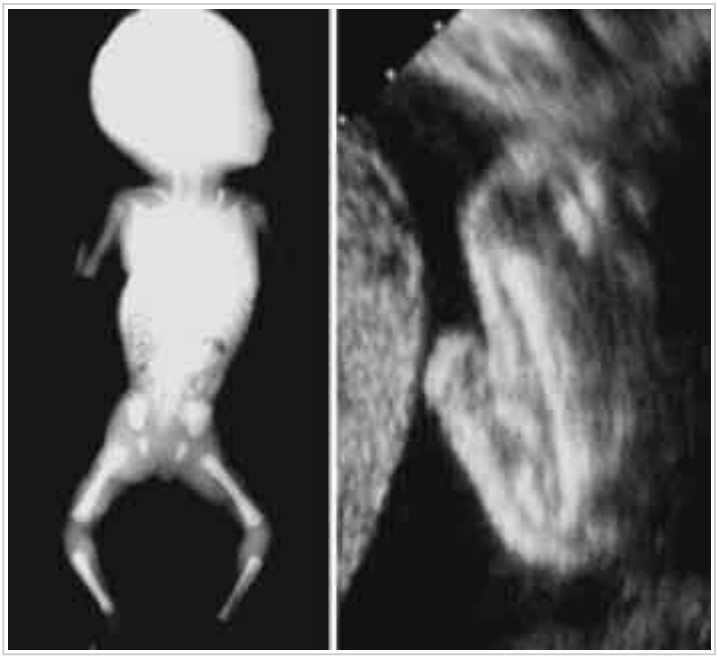
This autosomal recessive condition is characterized by severe shortening and bowing of all long bones, talipes equinovarus, hand deformities with abducted position of the thumbs ('hitchhiker thumb'), multiple joint flexion contractures and scoliosis. There is a wide spectrum in phenotypic expression and some cases may not be diagnosable in utero. This disease is not lethal and neurodevelopment is normal.

LIMB DEFICIENCY OR CONGENITAL AMPUTATIONS

Absence of an extremity or a segment of an extremity is referred to as 'limb deficiency' or 'congenital amputation'. The prevalence of limb reduction deformities is about 1 per 20 000 births. In about 50% of cases, there are simple transverse reduction deficiencies of one forearm or hand without associated anomalies. In the other 50% of cases, there are multiple reduction deficiencies and, in 25% of these, there are additional anomalies of the internal organs or craniofacial structures. In general, limb deficiency of the upper extremity is an isolated anomaly, whereas congenital amputation of the leg or bilateral amputations or reductions of all limbs are usually part of a genetic syndrome.

Isolated amputation of an extremity can be due to amniotic band syndrome, exposure to a teratogen or a vascular accident. There is an association between chorion villous sampling before 10 weeks of gestation and transverse limb

defects. Syndromes associated with limb deficiencies include the aglossia–adactylia syndrome (transverse amputations of the limbs ranging from absent digits to severe deficiencies of all four extremities, micrognathia, and vestigial tongue or ankylosis of the tongue to the hard palate, the floor of the mouth or the lips), and the Moebius sequence (facial anomalies attributed to paralysis of the 6th and 7th cranial nerves, leading to micrognathia and ptosis with upper limb defects, ranging from transverse amputations to absent digits). Both syndromes are sporadic.



Limb reduction defects associated with other anomalies include the CHILD syndrome (congenital hemidysplasia with ichthyosiform erythroderma and limb defects). This is characterized by strict demarcation of the skin lesions to one side of the mid-line and limb deficiencies, which are unilateral, varying from hypoplasia of phalanges to complete absence of an extremity. The condition is also associated with heart defects and unilateral hydronephrosis or renal agenesis.

In phocomelia, the extremities resemble those of a seal. Typically, the hands and feet are present (these may be normal or abnormal), but the intervening arms and legs are absent. Phocomelia can also be caused by exposure to thalidomide, but this is only of historical interest. Three syndromes must be considered in the differential diagnosis of phocomelia: Roberts syndrome (autosomal recessive disorder characterized by the association of tetraphocomelia and facial clefting defects or hypoplastic nasal alae), some varieties of thrombocytopenia with absent radius (TAR syndrome) and Grebe syndrome (autosomal recessive condition, described in the inbred Indian tribes of Brazil, characterized by marked hypomelia of upper and lower limbs, increasing in severity from proximal to distal segments – in contrast to Roberts syndrome, the lower limbs are more affected than the upper extremities).

Congenital short femur has been classified into five groups: type I, simple hypoplasia of the femur; type II, short femur with angulated shaft; type III, short femur with coxa vara (the most common); type IV, absent or defective proximal femur; and type V, absent or rudimentary femur. One or both femurs can be affected but the right femur is more frequently involved. Femoral hypoplasia–unusual facies syndrome, which is sporadic, consists of bilateral femoral hypoplasia and facial defects, including short nose with broad tip, long philtrum, micrognathia and cleft palate.

If the defect is unilateral, it may correspond to the femur–fibula–ulna or femur–tibia–radius complex. These two syndromes have different implications for genetic counselling; the former is non-familial, while the second has a strong genetic component.

SPILT HAND AND FOOT SYNDROME

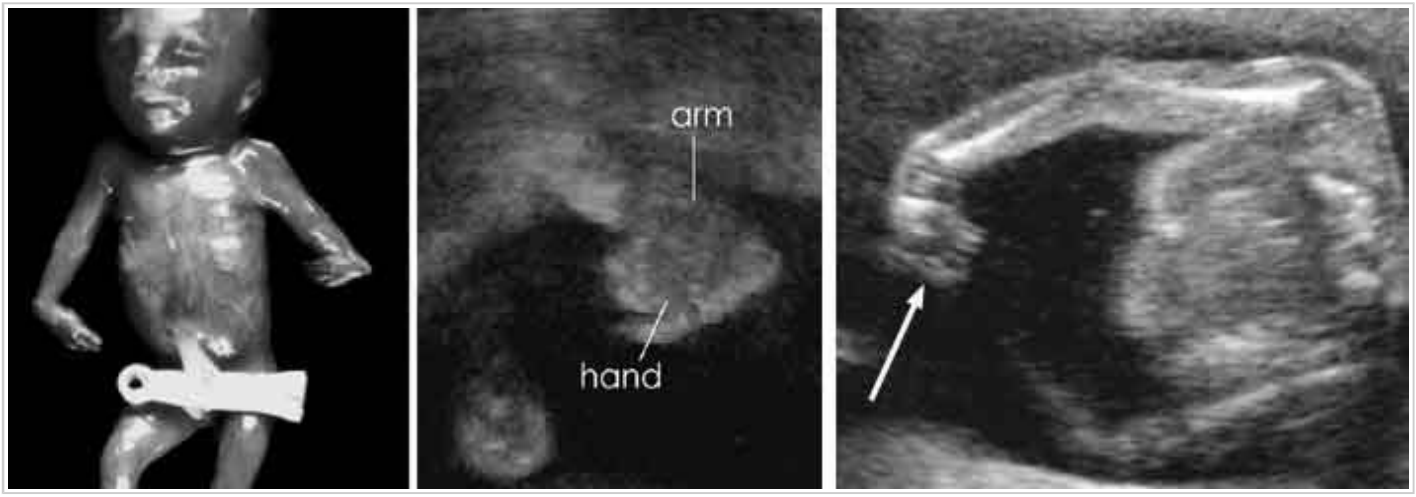
The term ‘split hand and foot’ syndrome refers to a group of disorders characterized by splitting of the hand and foot into two parts; other terms include lobster-claw deformity and ectrodactyly. The conditions are classified into typical and atypical varieties. The typical variety (found in 1 per 90 000 births and usually inherited with an autosomal dominant pattern) consists of absence of both the finger and the metacarpal bone, resulting in a deep V-shaped central defect that clearly divides the hand into an ulnar and a radial part. The atypical variety (found in 1 per 150

000 births) is characterized by a much wider cleft formed by a defect of the metacarpals and the middle fingers; the cleft is U-shaped and wide, with only the thumb and small finger remaining.

Split hand and foot deformities can occur as isolated anomalies, but more commonly they are part of a more complex syndrome. Ectrodactyly–ectodermal dysplasia–cleft lip/palate syndrome (EEC syndrome), which is autosomal dominant, involves the four extremities with more severe deformities of the hands; the spectrum of ectodermal defects is wide, including dry skin, sparse hair, dental defects and defects of the tear duct. Other syndromes include split foot and triphalangeal thumb, split foot and hand and central polydactyly, Karsch–Neugebauer syndrome (split hand/foot with congenital nystagmus), acrorenal syndrome and mandibulofacial dysostosis (Fontaine syndrome).

CLUBHANDS

Clubhand deformities are classified into two main categories: radial and ulnar. Radial clubhand includes a wide spectrum of disorders that encompass absent thumb, thumb hypoplasia, thin first metacarpal and absent radius. Ulnar clubhand, which is less common, ranges from mild deviations of the hand on the ulnar side of the forearm to complete absence of the ulna. While radial clubhand is frequently syndromatic, ulnar clubhand is usually an isolated anomaly.



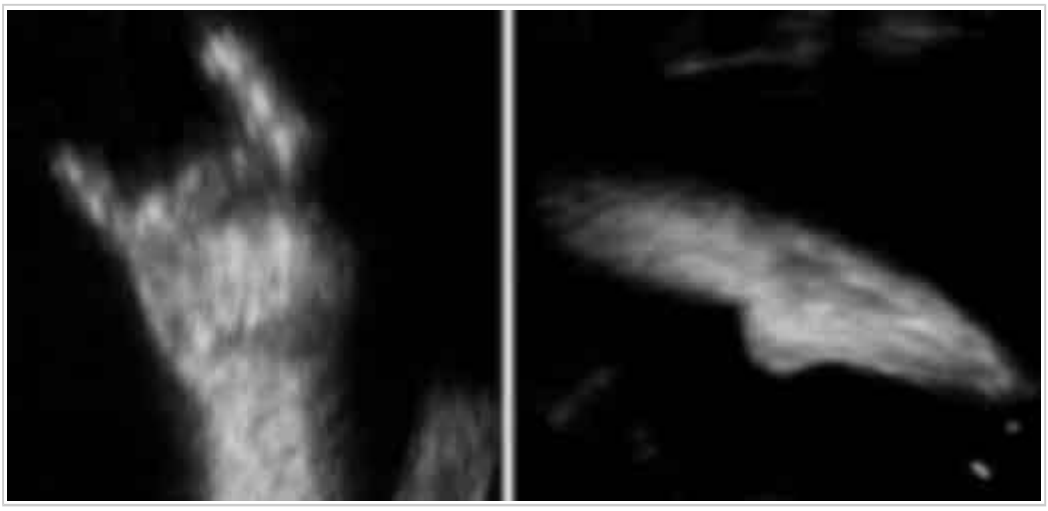
Clubhand deformities are often found in association with chromosomal abnormalities (such as trisomy 18), hematological abnormalities (such as Fanconi's pancytopenia, TAR syndrome and Aase syndrome), or genetic syndromes with cardiac defects (such as Holt–Oram syndrome, or the Lewis upper limb–cardiovascular syndrome). Radial clubhand is also associated with congenital scoliosis. The three syndromes that should be considered part of the differential diagnosis include the VATER association (vertebral segmentation, ventricular septal defect, anal atresia, tracheoesophageal fistula, radial and renal defects, and single umbilical artery), Goldenhar syndrome and the Klippel–Feil syndrome.

POLYDACTYLY

Polydactyly is the presence of an additional digit, which may range from a fleshy nubbin to a complete digit with controlled flexion and extension. Postaxial polydactyly (the most common form) occurs on the ulnar side of the hand and fibular side of the foot. Preaxial polydactyly is present on the radial side of the hand and the tibial side of the foot. The majority of conditions are isolated with an autosomal dominant mode of inheritance. Some of them are part of a syndrome, usually an autosomal recessive one. Preaxial polydactyly, especially triphalangeal thumb, is most likely to be part of a multisystem syndrome. Central polydactyly, which consists of an extra digit (usually hidden between the long and the ring finger), is often bilateral and is associated with other hand and foot malformations; it is inherited with an autosomal mode of inheritance.

FETAL AKINESIA DEFORMATION SEQUENCE (FADS)

This is a heterogeneous group of conditions with a birth prevalence of about 1 in 3000. Neurological, muscular, connective tissue, and skeletal abnormalities result in multiple joint contractures, including bilateral talipes and fixed flexion or extension deformities of the hips, knees, elbows and wrists.



This sequence includes congenital lethal arthrogryposis, multiple pterygium and Pena–Shokeir syndromes. The deformities are usually symmetric and, in most cases, all four limbs are involved. The severity of the deformities increases distally in the involved limb, with the hands and feet typically being the most severely affected. The condition is commonly associated with polyhydramnios (usually after 25 weeks), narrow chest, micrognathia and nuchal edema (or increased nuchal translucency at $10–13^{+6}$ weeks).