10.5005/jp-journals-10009-1176

REVIEW ARTICLE

Ultrasonic Diagnosis of Fetal Bone and Small Parts

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ABSTRACT

The prenatal diagnosis of fetal bone and small parts is a challenging task to the variable disorders and large number of possible diagnosis. Fetal limb anomalies may be congenital or acquired *in utero*. The former occur as anomalies either systemically or, in some limbs, due to hereditary or sporadic impairment in the formation or development of bone, cartilage or soft tissue. Acquired anomalies are caused by mechanical factor of an amniotic band or oligohydramnios. Both types present functional and cosmetic abnormalities, and skeletal dysplasia in particular includes lethal diseases, which makes prenatal diagnosis in such cases highly important, both medically and societally. Diagnostic imaging for prenatal diagnosis is accomplished by ultrasound, MRI and CT scan, and chromosomal and genetic diagnosis is also performed as needed. We focus on skeletal dysplasia to review prenatal diagnosis of fetal bone and small part anomalies by noninvasive ultrasound. For the authors as perinatologists, this is the imaging modality of choice.

Keywords: Fetus, Skeletal dysplasia, Small part abnormality, Ultrasound, Prenatal diagnosis.

INTRODUCTION

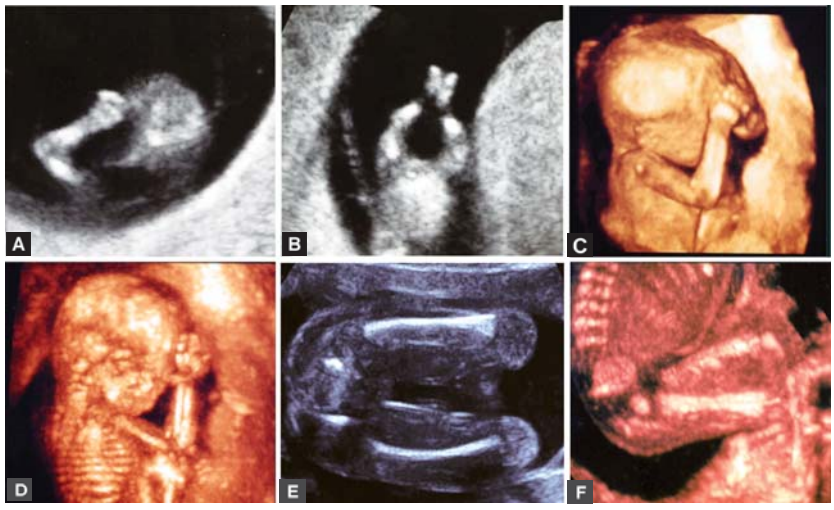
Ultrasonography is the imaging modality of choice for pregnancy evaluation due to its relatively low cost, real-time capability, high resolution, safety, and operator comfort and experience. Two-dimensional ultrasonography has been used conventionally for pregnancy evaluation, and three-dimensional/four-dimensional ultrasonography is increasingly available and also has been used successfully for detection of fetal structural anomalies, including those of the central nervous system, scalp, face, thorax, internal organs and limbs.[1] Screening ultrasonography reportedly did not reduce perinatal morbidity or mortality when compared with selective use of ultrasonography based on clinician judgment, and detection of major anomalies by ultrasound examination did not alter outcomes.[2] However, the role of ultrasonography includes screening for congenital abnormalities and diagnosis and management of obstetric pathology, such as re-evaluation of dating, growth restrictions and placenta previa. In cases of positive findings, patients and their families should be counseled, medical and social services should be available, and patients should be referred for appropriate postnatal radiological and hereditary examinations. At present, all pregnant women in Japan receive ultrasonic examination.

Anomalies of the limbs occur in 0.2 to 0.3% of all fetal structural anomalies, and approximately 60% are discovered in prenatal diagnosis.[3] Anomalies of the limbs may be congenital or acquired with the former occurring as anomalies either systemically or, in some limbs, due to hereditary or sporadic impairment in the formation or development of bone, cartilage, or soft tissue; acquired anomalies are caused mechanically by an amniotic band or oligohydramnios. Congenital anomalies include a number of different diseases, such as bone dysplasia accompanied by chromosomal or genetic abnormalities, or dysostosis accompanying maternal diabetes or other obstetric complications. Particularly in the case of bone dysplasia, lethal diseases included in classification of skeletal dysplasia make prenatal diagnosis highly important. Prenatal discovery of any limb anomalies also provides a clue for discovery of other potential anomalies in these findings.

OBSERVATION OF FETAL LIMBS AND SMALL PARTS

Diagnostic Time Frame

The presence of fetal limbs is discernable on ultrasonic examination from approximately 10th week of gestation, and skeletons, including hands and feet, are observable from week 14.[4,5] Major limb defects and malformations of the hands and feet are thus diagnosable in the fetus from the 2nd trimester, when amniotic fluid is relatively copious (Figs 1A to F).[6] Diagnosis is confirmed by subsequent amniocentesis, particularly for chromosomal abnormalities accompanied by developmental anomalies, where limb malformation or other complications are characteristic. However, there are two cautionary pitfalls in early diagnosis of skeletal dysplasia, despite the improved performance of current diagnostic ultrasonography equipment.



Figs 1A to F: Normal findings of fetal limbs and bones: (A) Upper limbs at 14 weeks gestational age, (B) lower limbs at 14 weeks gestational age, (C) upper limbs at 18 weeks gestational age using 3D surface mode, (D) upper limbs at 18 weeks gestational age using 3D skeletal mode, (E) femur at 24 weeks gestational age, (F) femur at 24 weeks gestational age using 3D skeletal mode

The first is the possibility of missed diagnosis due to the embryologic characteristics of bone itself, when early confirming diagnosis of lethal skeletal dysplasia is attempted on the basis of tubular bone morphology and measurements. For example, in some cases of achondrogenesis, thanatophoric dysplasia, short-rib-polydactyly syndrome, and all of osteogenesis imperfecta and fetal hypophosphatasia, death results from respiratory failure caused by thorax hypoplasia, and accurate assessment of the prognosis requires an evaluation of the individual morphology and growth of rib and other tubular bone, and balance of them. But ossification of tubular bone begins roughly in 24th week of gestation, and prior to this point in time, conditions such as achondroplasia cannot be diagnosed.[7] Saunders et al also studied eight cases of skeletal dysplasia, and based on their contrary diagnoses of one case of campomelic dwarfism and three cases of osteogenesis imperfecta respectively, they suggest a risk of overdiagnosis in the 2nd trimester.[8] Confirming diagnosis of lethal skeletal dysplasia at an early stage should be treated with care.

The second pitfall in diagnosing skeletal dysplasia is a discrepancy that exists between the timing of prenatal diagnosis and correct diagnosis rates without regard to the lethality of the disease concerned. This limitation exists even if detailed, time-series observation is performed, and suggested causes are inter-individual differences, embryological characteristics of the disease and heterogeneity of skeletal dysplasia.[9]

Ultrasonography of Fetal Bones

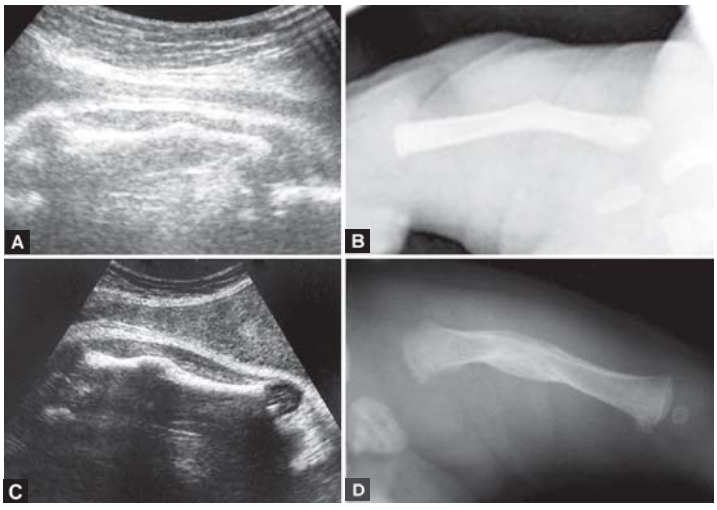
The advantages of ultrasound useful for fetal observation are capability for real-time observation and lower invasiveness than conventional observational methods. At the same time, the large difference in acoustic impedance between bone and the surrounding soft tissue means that 50% or of the ultrasonic power is reflected, and signal is also attenuated within bone and thus does not reach deeper regions. These phenomena impede the use of ultrasound to depict bone images completely, and bone is depicted primarily by reflected waves at its surface and represents a reflected image rendered complex by multiple reflection as well as acoustic shadow and other artifacts.

Fetal tubular bone develops early in the fetal period. Endochondral ossification first proceeds along longitudinal axes, and the diaphysis and metaphysis are formed in primary ossification proceeding from intramembranous ossification along transverse axes. An epiphyseal ossification center appears next at each end, and an epiphysis is formed as a secondary ossification. As a result, ultrasonography of the fetal femur and other fetal tubular bones depicts only those diaphyses and metaphyses where ossification has proceeded, and structures, such as the greater trochanter and femoral condyle appear only as hypoechoic, round regions, and when observing or measuring tubular bone morphology, only the ossified areas of the former are discerned in observations (Figs 2A to D).[10]

When observing fetal bone, echo gain is adjusted to depict the femoral head cartilage with no echo, and the zoom function is used to display on the monitor a large image of the fetal bones under observation. When the entire ossified diaphysis is observed, the ultrasonic beam is positioned perpendicular to the tubular bone and, when the epiphysis is observed, the beam is angled. The operator should also be aware that the image of the fetal bone actually depicted differs, depending on the angle of incidence between the ultrasonic beam and the tubular bone.

SKELETAL DYSPLASIA

Skeletal dysplasia is a hereditary or sporadic disease, which causes abnormalities in the growth and development process of bone and cartilage, leading to systematic abnormalities in the entire skeletal morphology and structure. There has been substantial progress in identification of the molecular defects responsible for the osteochondrodysplasias, and the genetic



Figs 2A to D: Abnormal findings of fetal bones: (A and B) Bowed femur in the case of campomelic dysplasia, (C and D) fractured femur in the case of osteogenesis imperfecta type IV. Fracture and reossification affect the sonographic penetration, and the deformity is observed in radiograph

defects have been identified for approximately 160 of 350 well-recognized disorders.[12] Inherited skeletal dysplasia can be caused by an autosomal dominant, autosomal recessive or X-linked disorder, and some disorders that result from imprinting errors, somatic mosaicism and teratogen exposure.[11-15]

Because skeletal dysplasia is a general term for a number of diseases which include various anomalies, precise estimation of the incidence is difficult, but the incidence is 1.1 to 9.5 in 10,000 births with thanatophoric dysplasia being most frequent, followed in order by achondroplasia, achondrogenesis, osteogenesis imperfecta type II.[16-18] The names of diseases included in skeletal dysplasia had long been confused with the same disease sometimes called by different names or different diseases given similar names. Consequently, since the first international classification performed in 1977, numerous revisions have led to the recent release of a newly revised version in 2006.[11] This version classifies a total of 372 diseases into 37 groups and is notable for presenting the underlying gene causing each disease as currently known. Despite the fact that treatment of skeletal dysplasia involves pediatricians, orthopedists, obstetricians and radiologists, in Japan the disease has not been discussed outside the Journal of Orthopaedic Science, and truly widespread familiarity is therefore lacking. Specialties and academic societies should now work in earnest to unify and use this terminology.[19]

Approach of Ultrasonographic Diagnosis

Ultrasonographic diagnosis of skeletal dysplasia includes methods of comparison by comprehensive checking for the morphological features of individual diseases in decreasing order of incidence, and methods of systematic narrowing to candidate diseases with algorithms for morphological diagnosis. As stated above, the current revision of the international classification classifies diseases by their gene of origin, which is rational from an etiologic perspective, but the greatest concern of perinatologists is to distinguish between lethal and nonlethal for prediction of prenatal outcomes. Thus, in this section, we refer prior reports and use the latter method for differential diagnosis of skeletal dysplasia.[20,21]

Step 1: Recognizing Skeletal Dysplasia

The first step in diagnosis of skeletal dysplasia is detection of short femur length on screening and determination of positive familial history (Fig. 3). One report establishes the cut-off for short femur length as the 95% confidence limit or –2.0 SD.[22] But in another report, the results from follow-up of 86 cases where femur length was –2.0 SD or lower in fetal screening during the second trimester showed skeletal dysplasia in only 11 cases; 28 cases were normal, 18 were fetal growth restriction (FGR), 16 were chromosomal anomaly, and 13 were anomalies other than skeletal dysplasia.[23] Likewise, comparison of 16 cases of femur length from –2.0 to 4.0 SD and 12 cases exceeding – 4.0 SD found that the former group included one case each of achondroplasia and chromosomal anomaly and 10 normal cases; the latter group included 10 cases of skeletal dysplasia; and the remaining two cases also had anomalies unknown in detail.[24] Because false-positives are increased if the cut-off line is set too low, these values are used at the outset in screening to include FGR and other limb anomalies, but for diagnosing skeletal dysplasia, adoption of a 99% confidence limit or –3.0 SD is effective. In Japan, nomograms for femur length use the standards set forth by the Japan Society of Ultrasonics in Medicine,[25] the rationale being that the largest determinant for femur length standards is race and Asians, including Japanese,

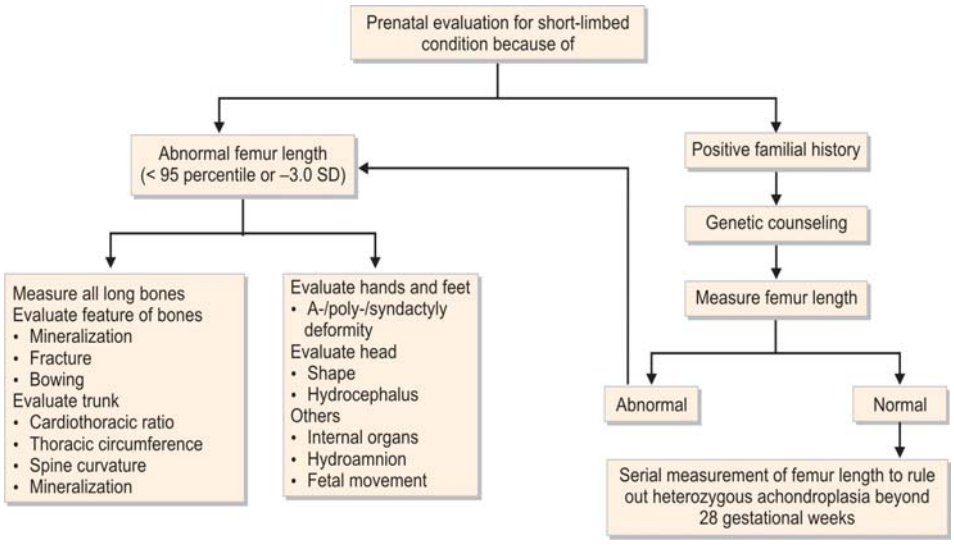


Fig. 3: First step for prenatal diagnosis of short-limbed condition

have a shorter femur length than Europeans and Americans.[26] Tubal bones other than the femur measured for length are the humerus, radius, and ulna in the upper limbs, and the tibia and fibula in the lower limbs. Because no Japanese data exist, reports from the EU and US are referenced.[27,28] Fractures, bowing, and hypomineralization are also evaluated. Fractures arise from osteogenesis imperfecta, in which repeated fracture and healing causes long-term deformation and shortening. Bowing is caused by thanatophoric dysplasia, campomelic dysplasia, achondrogenesis and hypophosphatasia, and a telephone receiver-like appearance is known frequently particularly in thanatophoric dysplasia. In single isolated fractures, discrimination from bowing may be necessary. Sonographic evaluation of mineralization is difficult. Useful signs of mineralization are an unusually prominent falx, absent or decreased visualization of the spine, decreased bone echogenicity and nonuniform or weak acoustic shadowing.[20, 29-31] The fetal head, spine, thorax, abdomen, hands and feet are also observed at such time. A great deal of information relating to diagnosis and prognosis can be obtained from the relationships of these measured values, and calculations should be made for femur length foot length ratio (normal = 1, <1 suggests skeletal dysplasia), chest circumference less than the 5th percentile for gestational age (< 5th percentile for gestational age suggests lung hypoplasia), and femur length—abdominal circumference ratio (< 0.16 suggests lung hypoplasia).[32-34]

Step 2: Classification by Relative Relationships of Limb Bone Length

The diseases of skeletal dysplasia can be classified into three groups according to the tubal bones in limbs that are relatively shortened: mesomelic (shortening of radius and ulna in upper limb and tibia and fibula in lower limb), rhizomelic (shortening of humerus in upper limb and femur in lower limb) and micromelic (shortening of all tubular bones in limbs).[20,21] (Fig. 4) These classifications are based on postnatal radiological findings, and there are also cases in which prenatal ultrasound provides no clarification, but cases are first classified into three groups, and narrowing to candidate diseases incorporates additional findings, specifically, morphology and epiphyseal findings for tubal bones, findings for nontubal bones, such as

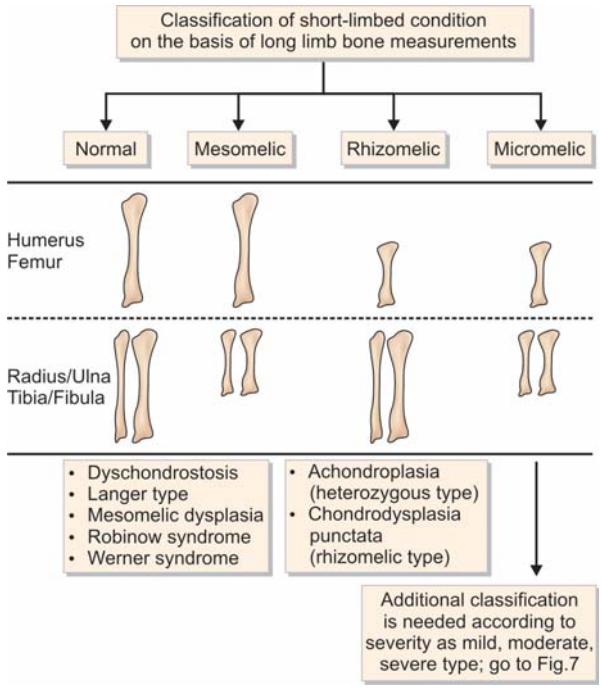


Fig. 4: Second step for classification of short-limbed condition on the basis of long limb bone measurement

the skull and vertebrae, foot and hand, other soft tissue morphology and amniotic fluid findings.

Step 3: Diagnosis of Mesomelic Type

This type presents shortening of the radius and ulna in the upper limb, the tibia and fibula in the lower limb, normal size and morphology of the thoracic circumference, spine and head, and absence of polydactyly. In reality, however, there are often additional acromelic or rhizomelic anomalies and skeletal anomalies include sporadic instances of dysostosis. These findings are characteristic in, for example, Robinow syndrome and Werner syndrome, and in dyschondrostosis (Leri-Weill), Langer type (homozygous dyschondrostosis), and various subtypes of mesomelic dysplasia classified as mesomelic and rhizo-mesomelic dysplasia (Fig. 5). In these syndromes, Langer syndrome, Robinow syndrome and omodysplasia recessive type are an autosomal recessive, and others are hereditary autosomal dominant.[3,20,21]

Mesomelic syndromes are attended by variegated systemic anomalies and require medical management for problems of limb function and appearance, but many are nonlethal, and the question of ability to make prenatal diagnosis does not influence neonatal outcomes. The intelligence is also generally normal, but Robinow syndrome can result in mental retardation.[35] In contrast, acrofacial dysostosis syndrome type Rodriguez causes respiratory failure, heart failure and generally poor outcomes.[36]

Step 4: Diagnosis of Rhizomelic Type

This type presents shortening of the humerus in the upper limb, the femur in the lower limb, and comparatively frequent instances of rhizomelic type are achondroplasia and chondrodysplasia punctata rhizomelic type (Fig. 5).

Achondroplasia

The incidence of this disease is 0.32 per 10,000 births, making this the most common nonlethal skeletal dysplasia.[16] The cause of this disease is a mutation in the FGFR3 (fibroblast growth factor receptor 3) gene with autosomal dominant inheritance. In primary ossification of tubal bones, overactivation of FGFR3 suppresses endochondral ossification, which affects longitudinal growth, but transverse intramembranous ossification is normal, and tubal bones are consequently shortened. Nearly all achondroplasia is heterozygous and presents normal mental and sexual development with generally normal life span, but 25% of neonates born to affected individuals have homozygous achondroplasia with femur length in the 3rd or lower percentile from early in the second trimester, and present a thanatophoric dysplasia-like phenotype; consequently, thoracic constriction causes poor outcomes.[37-39]

Sonographic findings in fetuses with heterozygous achondroplasia reveal shortened proximal tubal bones with normal mineralization and no fractures at 21 to 27 gestational weeks; a large scalp; and characteristic features of frontal bossing and depressed nasal bridge; short, trident hand and normal amniotic fluid index. Particularly in this type, the appearance of these findings is late onset, and reliable ultrasonographic diagnosis is performed in the third trimester[40] (Figs 6A to C).

Chondrodysplasia Punctata Group, Rhizomelic Type

The incidence of the chondrodysplasia punctata group is 0.09 per 10,000 births, and three of 11 diseases included in this group present rhizomelia.[16,19] Rhizomelic chondrodysplasia punctata with autosomal recessive inheritance is due to alterations in perioxisomal metabolism; whereas, X-linked dominant type is a result of mutations in the delta 8 sterol isomerase enzyme, resulting in abnormal cholesterol biosynthesis.[41,42] These are lethal diseases with severe mental retardation, spastic tetraplegia and thermoregulatory instability.[43] Findings can include craniofacial dysmorphism (a flat face with a small "saddle" nose and lymph edema), ocular abnormalities, cutaneous

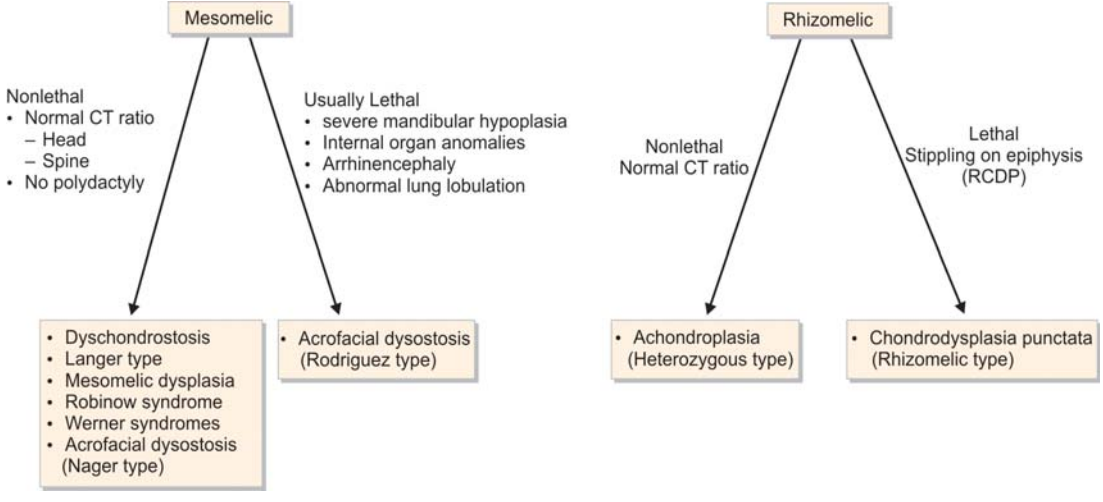
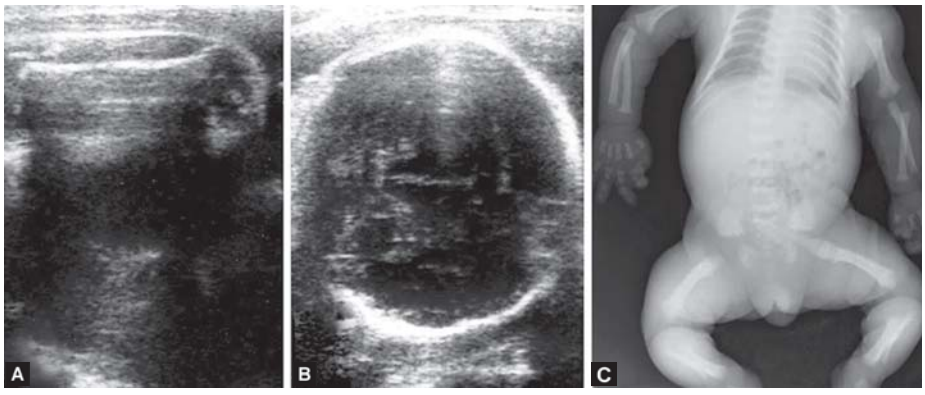


Fig. 5: Third (mesomelic type) and fourth (rhizomelic type) step for classification of short-limbed condition. CT – cardiothoracic



Figs 6A to C: Achondroplasia: (A) Mild shortening of femur with normal ossification, no fracture and no bowing, (B) mild enlargement of skull, (C) neonatal radiographs showed thick and mild bowed limb bones with normal ossification and no fracture, hypoplastic iliac wing and trochanteric cupping of femurs

abnormalities, asymmetric shortening of the limbs and joint contractures.[41,42] These include highly rhizomelic alteration of the limbs, markedly in the upper limbs. Epiphyses of tubal bones show characteristic punctate calcification reflecting calcific stippling and metaphyses show splaying.[44-46] Ascites and hydramnion have been reported.[47]

Step 5: Diagnosis of Micromelic Type

Diseases of this type present varied clinical outcomes and bone shapes, and are classified as mild, moderate (shortened and bowed) or severe based on findings for tubal bone length and curvature (Fig. 7). Particularly in disease classified as severe, thorax hypoplasia causes respiratory insufficiency and poor outcomes, and accurate prenatal diagnosis is needed.

Mild Micromelia

Representative diseases include those in the short-rib dysplasia group (asphyxiating thoracic dysplasia, chondroectodermal dysplasia) and diastrophic dysplasia in the sulphation disorder group.

Asphyxiating Thoracic Dysplasia (Jeune Syndrome)

The incidence of this disease is 0.12 per 10,000 births, and this is an often lethal skeletal dysplasia with neonatal asphyxia.[48] The disease has an autosomal dominant inheritence,[20] and sonographic findings can include proportionately shortened tubal bones, small thorax with a decreased cardiothoracic ratio, occasional polydactyly (30%) and hydramnion.[49-50]

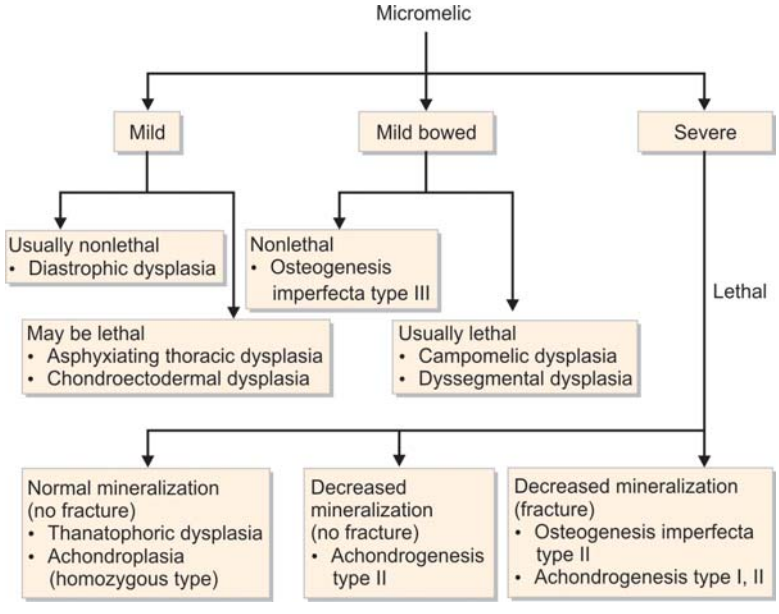


Fig. 7: Fifth (micromelic type) step for classification of short-limbed condition

Chondroectodermal Dysplasia (Ellis-van Creveld Syndrome)

The incidence of this disease is 0.31 per 10,000 births in Finland, and this is usually a nonlethal skeletal dysplasia.[51] This disease has an autosomal dominant inheritance and manifests anomalies in all three germ layers during the development process.[20,52] Sonographic findings can include normal growth, shortened tubal bones, small thorax with a decreased cardiothoracic ratio, polydactyly, congenital heart defects (50-60%, e.g. atrial septal defect, ventricular septal defect, single atrium).[51,53] In chondroectodermal dysplasia, thoracic development is better than in asphyxiating thoracic dysplasia (Jeune Syndrome), and the incidence of congenital heart defects and polydactyly is higher.[49]

Diastrophic Dysplasia

The incidence of this disease is 0.17 per 10,000 births in Finland, and this is usually a nonlethal skeletal dysplasia with normal intellectual development.[54] The cause of this disease is a mutation in the DTDST (diastrophic dysplasia sulfate-transporter) gene, and due to its autosomal recessive inheritance, there is almost no experience in Asia.[55] Sonographic findings can include proportionally shortened tubal bones, joint contracture, abnormal supine curvature (kyphoscoliosis), distinctive hand and foot deformities (e.g. hitchhiker's thumb, clubfeet, varus) and cauliflower ear.

Mild Bowed Micromelia

Representative diseases include campomelic dysplasia, a bent bone dysplasia; dyssegmental dysplasia, a perlecan group disease; and osteogenesis imperfecta type III, a decreased bone dysplasia group disease.

Campomelic Dysplasia

The incidence of this disease is 0.05 per 10,000 births, and the disease is usually a lethal skeletal dysplasia with respiratory insufficiency in the neonatal period.[56] The disease has an autosomal dominant or sporadic inheritance.[57] Sonographic findings can include shortened tubal bones, bowed femurs and tibias, hypoplastic or absent fibulas, varus, hypoplastic scapula, small thorax with a decreased cardiothoracic ratio and hydramnion. Frequently, there are other anomalies, including microcephaly, hydrocephalus, cleft palate, micrognathia, congenital heart defects and hydronephrosis.[56-58]

Dyssegmental Dysplasia

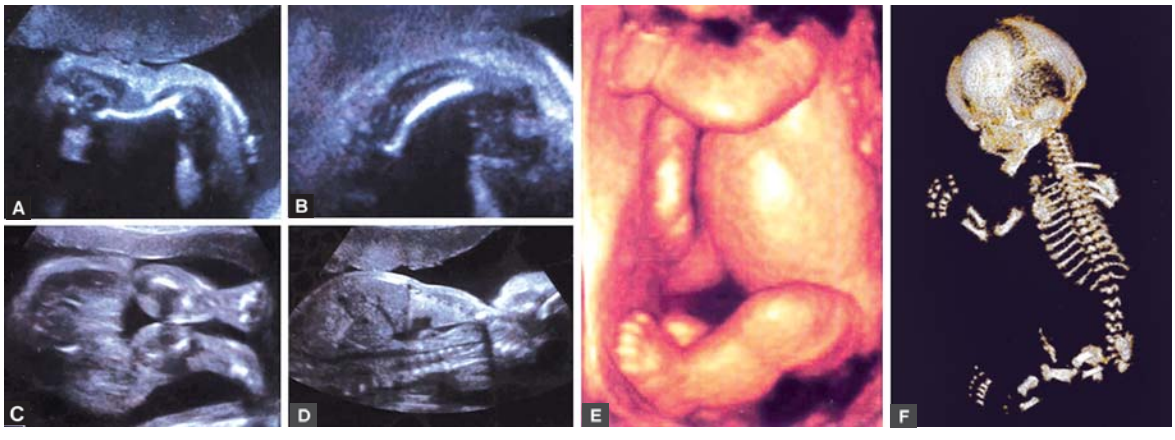
The incidence of this disease is very rare, and the disease is usually a lethal skeletal dysplasia with respiratory insufficiency in the neonatal period.[59] The disease has an autosomal recessive inheritance.[60] Sonographic findings can include shortened and sometimes bowed tubal bones. There is flaring of the distal metaphysis, which has a rounded contour and, in some instances, is three times as wide as the diaphysis. There is anterior bowing of the radius, ulna, tibia and fibula, and posterior bowing of the humerus and femur. The ribs are broad, short and cupped anteriorly.[61]

Severe Micromelia

Severe micromelia presents – 6.0 or lower, very short tubal bone, small thorax with a decreased cardiothoracic ratio and hydramnion, and is usually lethal. This comparatively frequent disease can be divided into three groups based on degree of ossification and fracture status.

Thanatophoric Dysplasia

The incidence of this disease is 0.69 per 10,000 births, and the disease is usually lethal skeletal dysplasia with respiratory insufficiency in the neonatal period.[16] Inheritance is generally autosomal dominant, and this condition is caused by mutations of the gene-encoding fibroblast growth factor receptor 3 (FGFR3).[62] Sonographic findings can include shortened tubal bones (which are bowed in type 1 and may be straight in type 2), hypoplastic narrow thorax with normal thorax length, platyspondyly (less severe in type 2 than in type 1), small pelvis, macrocrania, cloverleaf skull deformity (generally seen in type 2) and polyhydramnios (50-70%).[63-64] The neonates with valgus have a characteristic puppet-like posture (Figs 8A to F).



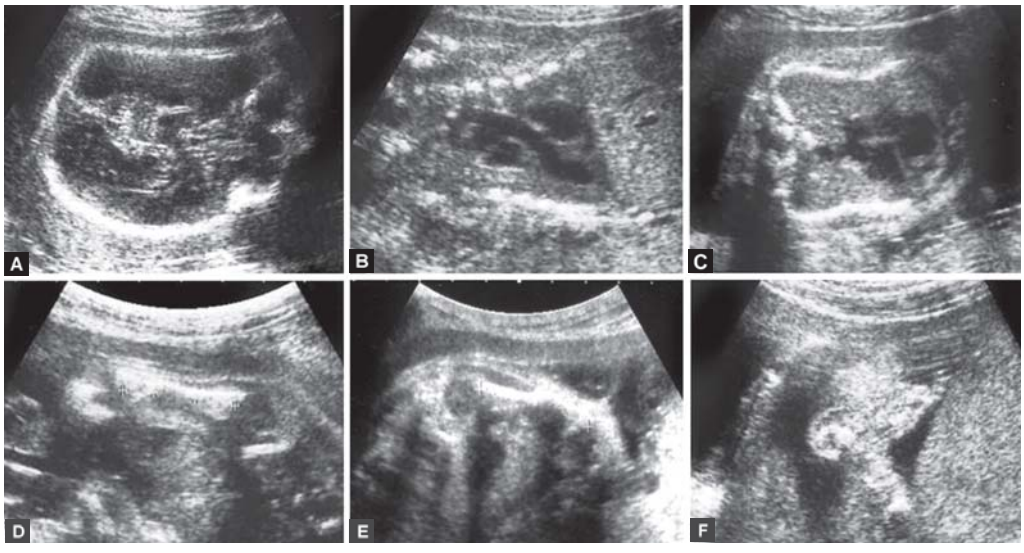
Figs 8A to F: Thanatophoric dysplasia: (A to C) Micromelic shortening of femur, humerus with mild angulation and lower limbs, (D) undersized thorax compared with the abdomen, (E and F) micromelic shortening of upper and lower limbs with normal ossification, no fracture and puppet posture in 3D ultrasound and 3D-CT scan

Osteogenesis Imperfecta Type II

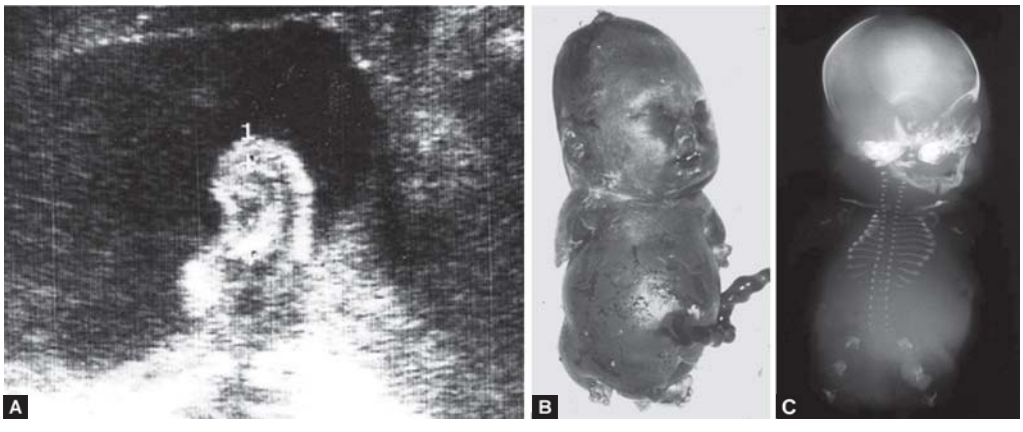
The incidence of this disease is 0.18 per 10,000 births, and the disease is a lethal skeletal dysplasia with respiratory insufficiency in the neonatal period.[16] Inheritance is generally autosomal recessive, and this condition included in the decreased bone density group is caused by collagen disorders. Sonographic findings can include shortened and fractured tubal bones with a 'crumpled' appearance, minimal acoustic shadowing bone, a poorly mineralized scalp easily deformed by probe pressure and hypoplastic small thorax with rib fracture. Other types of osteogenesis imperfecta show that type 1 is autosomal dominant and has fragile bones (but usually no fractures *in utero*). Type 3 is inherited as both autosomal recessive and dominant, and the bones are fragile but fractures occur late in pregnancy or after birth. Type 4 is the most mild and is autosomal dominant, and the long bones may bow but not fracture[65] (Figs 9A to F).

Achondrogenesis

The incidence of this disease is 0.23 per 10,000 births, and the disease is a lethal skeletal dysplasia with fetal death or respiratory insufficiency in the neonatal period.[16] Inheritance is autosomal recessive, and this condition is included in the collagen group (Type 2) and sulphation disorders group (type 1B). Sonographic findings can include severe micromelia and a short trunk with a large head, and there is poor ossification. There are two types in this condition: Type 1 with fractured and flared ribs, poorly ossified skull and iliac bones, and absent sacrum and pubic bones, and type 2 with no fractured ribs, variable ossified skull and iliac bones, and deficient sacrum and pubic bones. Frequently, there are other anomalies, including hydrocephalus, hydrops fetalis, cleft lip and palate, cystic hygroma, congenital heart and renal defects, and polyhydramnios[66] (Figs 10A to C).



Figs 9A to F: Osteogenesis imperfecta type II: (A) Macrocrania with unusual falx and demineralized skull easily deformed by the pressure of the US probe, (B and C) narrow thorax compared with the abdomen with fractured and deformed ribs, (D and E) severe micromelic shortening of angulated femur and fractured humerus, (F) abnormal foot like the locker-bottom



Figs 10A to C: Achondrogenesis: (A) Severe micromelic shortening of angulated femur with poor acoustic shadow (cursors), (B) severe micromelia in neonatal photograph, (C) severe micromelia, poorly mineralized spine and absent pubis in neonatal radiogram

Other Types

Dysostosis can cause a single morphological anomaly of bone or multiple anomalies in limited areas throughout the body, but the bone tissue itself is nearly normal, and the disease group is akin to bone malformation. Localized, digital anomalies include several diseases, such as adactyly or polydactyly and craniosynostosis (e.g. Crouzon disease, Apert syndrome). Previously, the disease was understood as a developmental anomaly caused by extrinsic factors, such as mechanical compression within the maternal body, maternal radiation exposure or drug administration (diphenylhydantoin, thalidomide, alcohol), but a succession of causal genes is now being identified.[67]

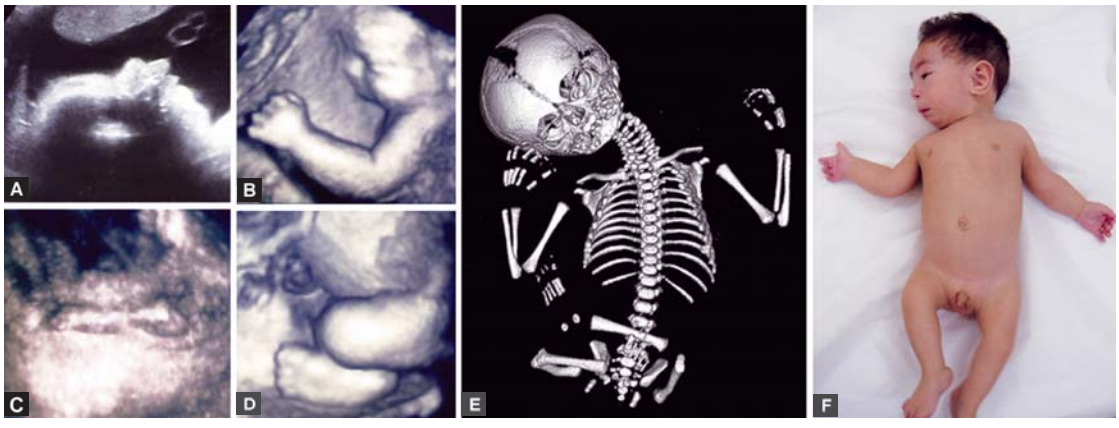
Femoral Hypoplasia-Unusual Face Syndrome

This is a very rare, nonlethal condition with normal intelligence, characterized by a variable degree of unilateral or bilateral femoral hypoplasia associated with facial clefting and other minor malformations. The association with maternal diabetes mellitus and a disruption of carbohydrate homeostasis are reported. Sonographic findings are short and bowed femurs (unilateral or bilateral), absence of fibulae dysplasia of the sacrum, short broad-tipped nose, long philtrum, thin upper lip, micrognathia and cleft palate, and other associated anomalies[68] (Figs 11A to F).

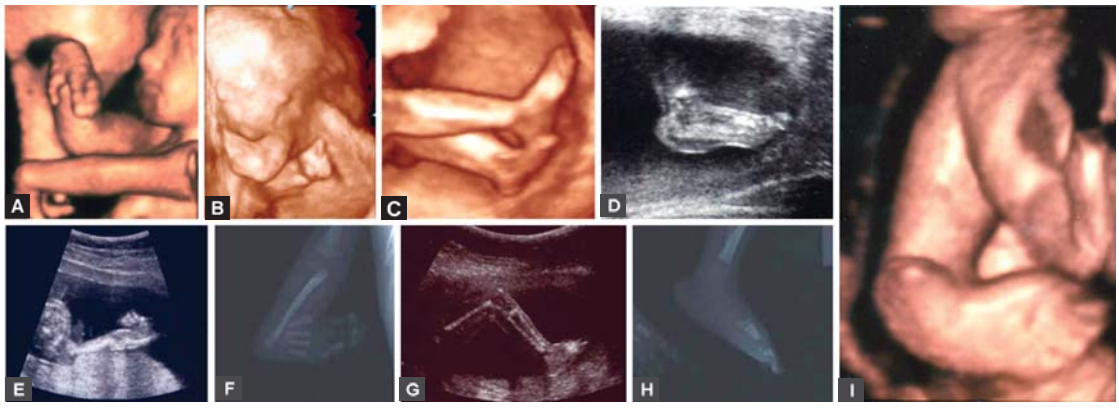
OTHER SMALL PART ABNORMALITIES

Chromosomal anomalies presenting skeletal abnormalities are trisomy 21 with slightly shortened humerus and femur, trisomy 18 with micrognathia, overlapping fingers, club foot and rocker bottom feet, and trisomy 13 with microcephaly, polydactyly and cleft palate.[69]

Most limb deficiencies with an overall incidence of 0.49 per 10,000 births are simple transverse reduction deficiencies of one forearm without associated anomalies. The remainder consist of multiple reduction deficiencies, such as VACTERL associations with additional anomalies of internal organs or craniofacial structures. Isolated extremity amputation can be due to amniotic band syndrome, exposure to a teratogen or vascular accident.[70] Other single or multiple small part abnormalities observed include congenital clubfoot/clubhand and talipes calcaneovalgus (Figs 12A to I).



Figs 11A to F: Dysostosis (femoral hypoplasia—unusual facies syndrome): (A) Micrognathia in sonographic sagittal view of face, (B) mild rhizomelic shortening of upper limb in 3D surface mode, (C) rhizomelic shortening of femur in 3D surface mode, (D) rhizomelic shortening of lower limbs in 3D surface mode, (E) shortening of femur and humerus, and absent of fibra in 3D-CT scan, (F) micrognathia and rhizomelic shortening of upper and lower limbs in neonatal photograph



Figs 12A to I: Other types of skeletal abnormalities: (A and B) Deformity of hands and fingers in the case of trisomy 18, (C and D) rocker-bottom foot in the case of trisomy18, (E and F) preaxial change of wrist joint with absent of radius in the case of VACTERL association, (G and H) absence of calcaneal bone in the case of VACTERL association, (I) sporadic varus foot

SUMMARY

The classification we present in this paper is intended as a starting point, and is based on the present understanding of skeletal dysplasia. Although not all the abnormalities and variants fit into groups, the categories are sufficiently broad to accommodate most cases. The radiologists, neonatologists and molecular biologists play a major role about the final diagnosis of skeletal dysplasia in our country, but the perinatologists and the representatives of other disciplines, including midwives, nurses and case workers, should provide important information necessary for establishing the correct diagnosis and supporting system.

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