

Skeletal Dysplasia

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ABSTRACT

The word dysplasia originates from the ancient Greek words *dys* (anomalous) and *plasia* (formation). Skeletal dysplasia (SD) is a heterogeneous group of congenital anomalies characterized by abnormalities in the development of bone and cartilage tissues. These diseases may present either in the form of isolated findings or a phenotypic manifestation of a chromosomal aberration or a genetic disorder. Prenatal diagnosis is mainly on the ultrasonographic appearance, which is usually achieved during the second trimester of pregnancy. Two-dimensional ultrasonography may detect the majority of SD, however, difficulties in the diagnosis as well as the differential diagnosis are frequently arising. In such cases, further evaluation is needed by the use of additional imaging modalities or by invasive procedures, in order to detect an underlying chromosomal abnormality or a single gene disorder. Accurate diagnosis is crucial in order to establish successful genetic counseling as well as appropriate case management. This approach includes the use of three-dimensional ultrasonography and three-dimensional computed tomography; whereas fetal magnetic resonance imaging is less important. These new imaging modalities have an important role in the prenatal multidisciplinary approach of the diagnosis of SD. Despite the indisputable progress that has been achieved during the last few years, in some cases, the antenatal detection of SD delays and is feasible only at the late second or even third trimester. Thus, important ethical and medical issues arise in the antenatal management and counseling of these pregnancies, particularly in the case of lethal SD.

Keywords: Skeletal dysplasias, Prenatal diagnosis, Ultrasonography, 3D ultrasound, 3D computed tomography, Fetal MRI.

INTRODUCTION

The word *dysplasia* originates from the ancient Greek words *dys* (anomalous) and *plasia* (formation). Skeletal dysplasia (SD) is a heterogeneous group of congenital anomalies characterized by abnormalities in the development of the bone and cartilage tissues.¹ This results in mark disproportion of the long bones, the spine and the fetal head in relation to the trunk. The incidence of SD is estimated as 2 to 5/10,000 live births. Prior to the introduction of ultrasound within the routine obstetrical practice, the diagnosis of skeletal anomalies was not possible antenatally. However, despite the progress in imaging techniques and genetics, the correct prenatal diagnosis remains a challenge.² This is mainly due to the rarity of the disease, the high number of different SD, the phenotypic variability of each syndrome,

the overlapping features and the imaging variation that is related to the gestational age during the examination.

Prenatal diagnosis of SD requires a detailed ultrasonographic examination by a fetal medicine specialist. The classification of SDs is based on the clinical, the radiological and finally the postmortem examination. The "International Nosology and Classification of Constitutional Disorders of Bone, 2002 (last revised version)" has identified 300 different SDs, of which only half of them can be recognized antenatally. The current classification is presented in Table 1.^{3,4}

Lethal dysplasia and achondrogenesis are responsible for 62% of the deaths due to skeletal anomalies. Lethal dysplasias are summarized in Table 2.^{2,3} From the affected fetuses, 44% die during the early neonatal period and 13% intrauterine. The neonatal deaths are mainly due to pulmonary hypoplasia and

Table 1: Classification of common skeletal dysplasia

SD group	Abnormality	Diseases and syndromes
Osteochondrodysplasias	Abnormal bone and cartilage development	Osteogenesis imperfecta, achondroplasia, hypochondroplasia, thanatophoric dysplasia, achondrogenesis
Dysostosis	Isolated dysplasia of a bone or a group of bones	Craniofacial dysostosis (Crouzon syndrome), craniosynostosis, amelia, polydactyly, syndactyly, brachydactyly, Poland syndrome
Idiopathic osteolysis	Multifocal osteolysis	
Related to genetic syndromes	<ul style="list-style-type: none"> • Aneuploidy • <i>de novo</i> or inherited mutations 	
Related to metabolic syndromes	Bone demineralization due to congenital deficiency of alkaline phosphatase	Hypophosphatemia

Table 2: Lethal skeletal dysplasias

- Achondrogenesis
- Thanatophoric dysplasia
- Short-rib polydactyly syndromes (types I, II and III)
- Fibrochondrogenesis
- Atelosteogenesis
- Homozygous achondroplasia
- Osteogenesis imperfecta, perinatal type
- Hypophosphatasia

the methods used for assessment of lung hypoplasia are summarized in Table 3. This accounts for 0.9% of all perinatal deaths.

Osteochondrodysplasia

Skeletal dysplasias are traditionally classified in terms of which portions of the limbs are shortened: Rhizomelia indicates shortening of the proximal limbs, such as the femur and the humerus. Mesomelia indicates shortening of the middle portion of the limb, such as the forearm or lower leg bones. Acromelia is shortening of the hand and foot bones. Micromelia means severe shortening of all portions of a limb, but the term is also used to indicate shortening of a limb without a specific reference of the particular portion that is shortened.

The osteochondrodysplasias most commonly assessed by ultrasound are:

- Thanatophoric dysplasia
- Osteogenesis imperfecta
- Achondroplasia
- Achondrogenesis
- Campomelic dysplasia
- Spondylothoracic dysplasia
- Atelosteogenesis
- Others.

Skeletal dysplasias have a variety of phenotypic expressions. Not every case can be assigned a specific diagnosis, and other entities may mimic skeletal dysplasias, including dysmorphic syndromes and IUGR. The most common skeletal dysplasias have the most accurate diagnosis by ultrasound (US), and the less common ones are less likely to have a specific diagnosis made at US.

The precise diagnosis is attempted by histopathological study, assessing the characteristics of endochondral ossification line or ideally by DNA assessment identifying mutations responsible of the anatomic alteration.

Thanatophoric Dysplasia

This is the most common lethal dysplasia (1:4,000-15,000 births). It is characterized by severe rhizomelic micromelia⁵ (affecting all portions of a limb) with bowing (Figs 1 and 2). The bones are well mineralized and there are no fractures in long bones. The thorax is bell shaped, and the ribs are shortened. There is usually macrocrania, frontal bossing and a depressed nasal bridge.

The name is derived from the Greek word thanatophoras, meaning death bearing, because of the uniformly lethal outcome of this dysplasia in the perinatal period, mainly due to pulmonary hypoplasia secondary to thoracic hypoplasia. There are two types. Type I is characterized by curved femurs (telephone receiver configuration) and has sporadic inheritance. Type II accounts for 15% of the cases, presents with femurs of normal configuration and the skull presents a markedly cloverleaf configuration, with a trilobed appearance in the coronal view.

Osteogenesis Imperfecta

This is a heterogeneous group of genetic disorders characterized by severe bone fragility, blue scleras⁶ and prenatal growth deficiency (Figs 3 and 4).

Table 3: Assessment of pulmonary hypoplasia

Chest biometry

- Chest circumference < 5th percentile
- Chest circumference/abdominal circumference
- Chest area-heart area/chest area < 5th percentile
- Chest/trunk length ratio < 0.32

Nimrod 1986, Chitkara 1987, Songster 1989
Johnson 1987, Vintzileos 1989, Ohlsson 1992, Yoshimura 1996
Vintzileos 1989, Ramus 1998
Ishikawa 2003

Lung biometry

- Lung area < 5th percentile
- Chest diameter < 5th percentile
- Right lung area/thoracic area ratio < 0.11
- FL/AC < 0.16

Maeda 1993, Yoshimura 1996
Laudy 2000
Nakata 2003
Rahemtullah 1997, Ramus 1998

Doppler assessment of the pulmonary arteries

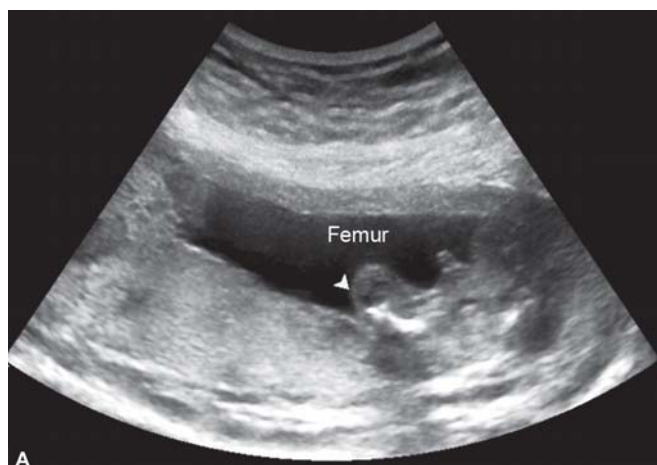
Mitchell 1998, Laudy 2002, Fuke 2003

Doppler assessment of the tracheal fluid

Kalache 1998

Assessment of the lung volume by 3D-US

Ruano 2004a; Bahmaie 2000; Chang 2003; D'Arcy 1996
Kalache 2003, Laudy 1998, Lee 1996, Osada 2002, Pohls 1998
Ruano 2004b, Sabogal 2004



Figs 1A and B: The femur and humerus are very short (micromelia)



Fig 2: Postnatal picture presenting the extremely short upper limb (micromelia) affecting all three portions in a fetus with thanatophoric dysplasia, after termination of pregnancy during the 17th gestational week

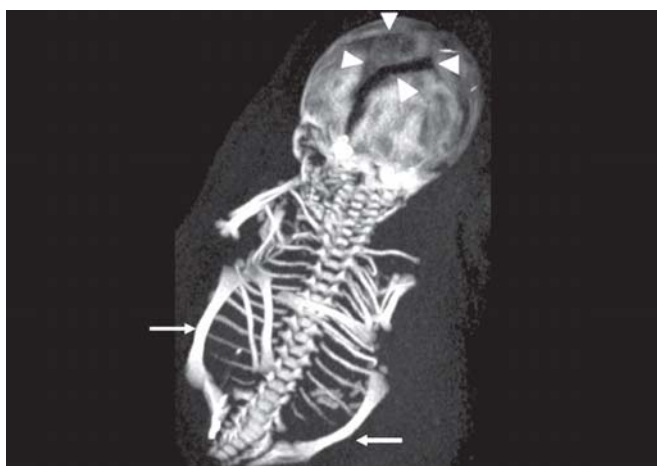


Fig 3: 3D-HCT of a fetus with osteogenesis imperfecta at 36 weeks
(By Cassart et al *Ultrasound Obstet Gynecol* 2007)⁶

They are classically divided in four types.¹ Type I is due to collagen deficiency and is inherited in an autosomal dominant fashion. Type II (Vrolich type) is the most severe form and the most frequently type diagnosed by antenatal ultrasonography. The inheritance follows the autosomal recessive pattern.

Osteogenesis imperfecta type II presents as a severe global osteochondrodysplasia affecting all segments (micromelic type). It is characterized by severe bone fragility, leading to abnormal ossification and multiple fractures and bone angulations.

Type II osteogenesis imperfecta is uniformly lethal, and the most frequent causes are respiratory failure due to pulmonary hypoplasia secondary to thoracic hypoplasia as a consequence of multiple rib fractures and cerebral hemorrhage.

Type III is inherited in autosomal dominant or recessive pattern and is characterized by abnormal collagen formation.

Types III and IV have a more favorable prognosis.

Achondroplasia

Osteochondrodysplasia is characterized by a rhizomelic (affecting humerus and femur) micromelia. Bone mineralization is normal and there are no long bone fractures (Fig. 6). Thoracic shape is normal. A macrocrania, frontal bossing and depressed nasal bridge can also be recognized. The trident hand (an increased interspace between the third and fourth digit) or the lack of widening of the lumbar canal can also be identified.

Prenatal detection is usually established at late second or third trimesters because in most cases osseous lengths are normal up to 25 or 26 weeks of gestation, and at this gestational age the growing pattern reaches a plateau (Fig. 5).

Homozygous achondroplasia is uniformly lethal. But the most frequent form, the heterozygous type, has good prognosis.

Achondrogenesis

This lethal SD appears every 40,000 births. It is inherited by an autosomal recessive way, so there is a 25% recurrence rate. It is characterized by bone hypoplasia, resulting in marked global limb shortening (severe micromelia) and is associated with severe pulmonary hypoplasia. Type I accounts for 20% of the cases while type II presents with normal shape of the skull (80%).⁸

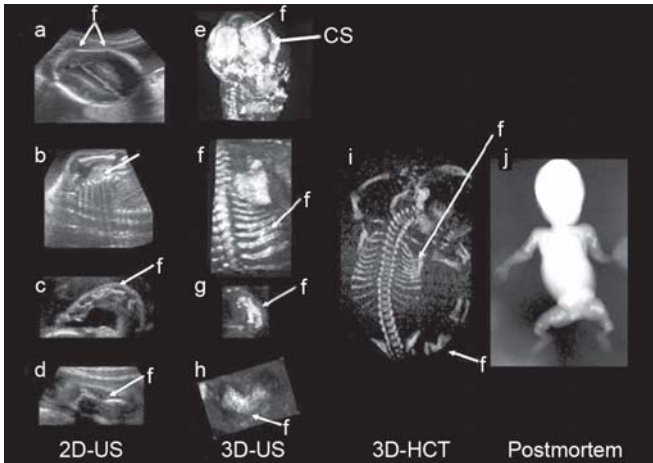


Fig. 4: Prenatal diagnosis of osteogenesis imperfecta at 33 weeks by 2D-US and 3D-US and three-dimensional computer tomography (3D-HCT) (a) 2D-US: transverse section of fetal head with a skull fracture (f) deformed due to the transducer pressure. (b) 2D-US: coronal section of fetal thorax showing irregular ribs (arrow); (c) 2D-US: sagittal section of the right arm showing a short and bowed arm (f); (d) 2D-US: sagittal section of fetal femur with a fracture (f); (e) 3D-US: 3D rendered bone mode image showing lateral view of fetal skull with a fracture (f), that could be differentiated from a normal coronal suture (CS) by the location and the deforming aspect depending on the transducer pressure; this was confirmed at postmodern examination; (f) 3D-US: rendered bone mode demonstrating posterior view of fetal thorax showing fractured and irregular ribs (f); (g) 3D-US: rendered bone mode image showing short and bowing radius and cubitus (f); (h) 3D-US: rendered bone mode image showing a fractured femur (f); (i) 3D-HCT: posterior view of entire fetus confirming fractures of ribs and femur (f) as well as decreased mineralization of the skull. (j) Postmortem radiological examination: confirming shortening, bowing and fracture of long bones. (By Ruano et al *Ultrasound Obstet Gynecol* 2004)



Fig. 5: Ultrasound image of fetal femur that appears to have normal configuration but is very short (< 5th percentile) (author's personal file)

Polyhydramnios is common, as is marked redundancy of the subcutaneous tissues (pseudohydrops) and generalized subcutaneous edema due to lymphatic ectasia. The outcome is fatal, although some cases of type II may survive for short periods in the neonatal period.

Campomelic Dysplasia

Campomelic dysplasia is a congenital disorder characterized by development of abnormal curvatures of long bones,

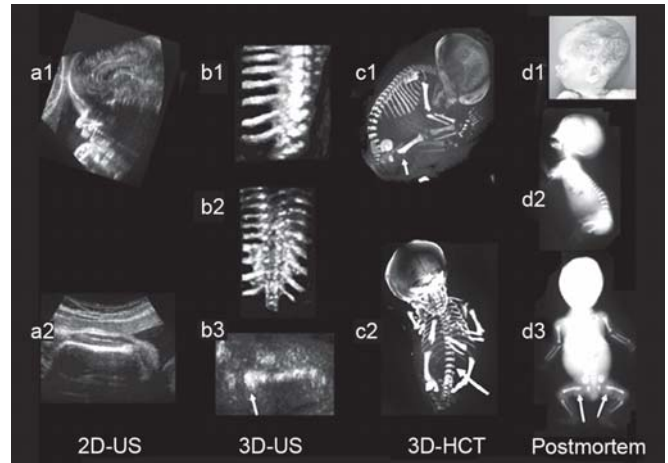


Fig. 6: Diagnosis of achondroplasia at 32 gestational weeks (a) 2D-US: (1) profile of fetal face showing frontal bossing, (2) the femur appears normal in shape but was short. (b) 3D-US: Rendered images of (1) the short ribs, (2) the dorsal spine, (3) the femur showing increased thickness of the femoral metaphysis, (c) 3D-HCT, (d) postmortem examination (By Ruano et al *Ultrasound Obstet Gynecol* 2004)



Fig. 7: Postnatal X-ray of a fetus diagnosed with campomelic dysplasia

particularly from lower extremities, such as femur and tibia (Fig. 7). The incidence is 1:1,50,000 births. Other sonographic features that are commonly present include bell-shaped narrow chest, eleven pairs of ribs and hypoplasia of the mid-thoracic vertebral bodies, fibula and scapula. Other findings include hydrocephalous, cleft lip, micrognathia, hydronephrosis and congenital heart anomalies.

Although the karyotypic sex ratio is approximately M2:F13, the vast majority show a female phenotype with ambiguous genitalia.

Almost all result in neonatal or infant death due to respiratory complications secondary to tracheobronchomalacia.

Spondylothoracic Dysplasia

The spondylothoracic dysplasia is actually a group of disorders characterized by delayed ossification and deformity of the spine and ribs. The prognosis is variable with some lethal forms and other types that can reach the adult life. It is important to establish the differential diagnosis with other osteochondro-

dysplasias, such as asphyxiating thoracic dysplasia (Jeune thoracic dystrophy), short-rib polydactyly syndrome.

Atelosteogenesis

Also known as spondylo-humero-femoral dysplasia. It is characterized by a “bent” tibia showing a “boomerang” configuration and the absence of fibula with shortened long bones.

Chondrodysplasia Punctata

This is a rhizomelic dysplasia. It is lethal during the neonatal or early childhood period and carries severe mental retardation. The occurrence is 1:10,00,000 births and is inherited in autosomal recessive fashion. The ultrasonographic findings include the punctuated ossification of the diaphysis and micromelia (Fig. 8).

Other Osteochondrodysplasias

In occasions, long bones have a normal appearance but are shortened. The differential diagnosis among some conditions, such as an authentic osteochondrodysplasia, a normal variant or an IUGR must be considered.

One must follow-up bone growing pattern. Standard obstetrical management is not altered. In the newborn period and during infancy, the growing process must be strictly controlled.

Reductional Defects

This is a heterogeneous group of diseases, characterized by the absence of any portion of a limb (Fig. 9). The term amputation



Fig. 9: Postnatal picture of a fetus with amelia

has been substituted because in the vast majority of cases the defect is due to a development alteration.

It includes:

- Terminal defects
- Phocomelias
- Proximal focal femoral deficiency
- Split-hand and split-foot syndromes.

They are often (50% of cases) isolated defects and usually affect only one extremity. 25% may affect more than one limb, and 25% may be associated with other structural defects or are features of a genetic syndrome (Figs 10A and B). The outcome depends on the degree of compromise and the possibility of a correct postnatal orthopedic surgical repair.

Terminal Defects

Usually, it affects the upper extremities in 75%, and they are more frequent left sided. They may be associated with other structural defects as features of a genetic syndrome. In occasions they are secondary to constriction bands due to early amnion rupture sequence. They can also be found in association with facial defects (microretrognathia) as part of genetic syndromes.

Phocomelias

The name is derived from the “seal” aspect of fetuses. The terminal and middle portion of the limbs are aplastic or hypoplastic, and feet and hands are directly articulated to the ankle or shoulder.

Phocomelia is seen in many genetic syndromes and conditions, such as Holt-Oram syndrome, thrombocytopenia absent radius (TAR) syndrome and Robert’s syndrome (characterized by midface and limb anomalies; which are usually severe with microcephalia and growth restriction).

Proximal Femoral Focal Deficiency (PFFD)

It is a rare anomaly varying in severity from a marginally short femur to a complete absence of femur in severe cases. It may be a unilateral defect (usually right sided) or bilateral in 10 to 15% of cases. PFFD is almost always an isolated occurrence except for associated ipsilateral fibular hemimelia (sporadic) or ulnar hemimelia (genetic).

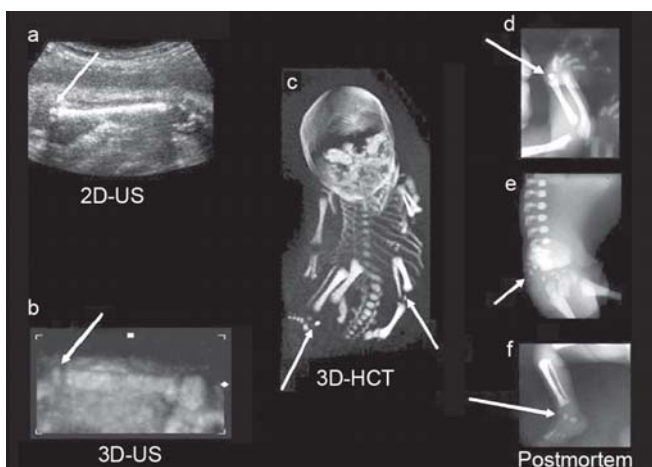
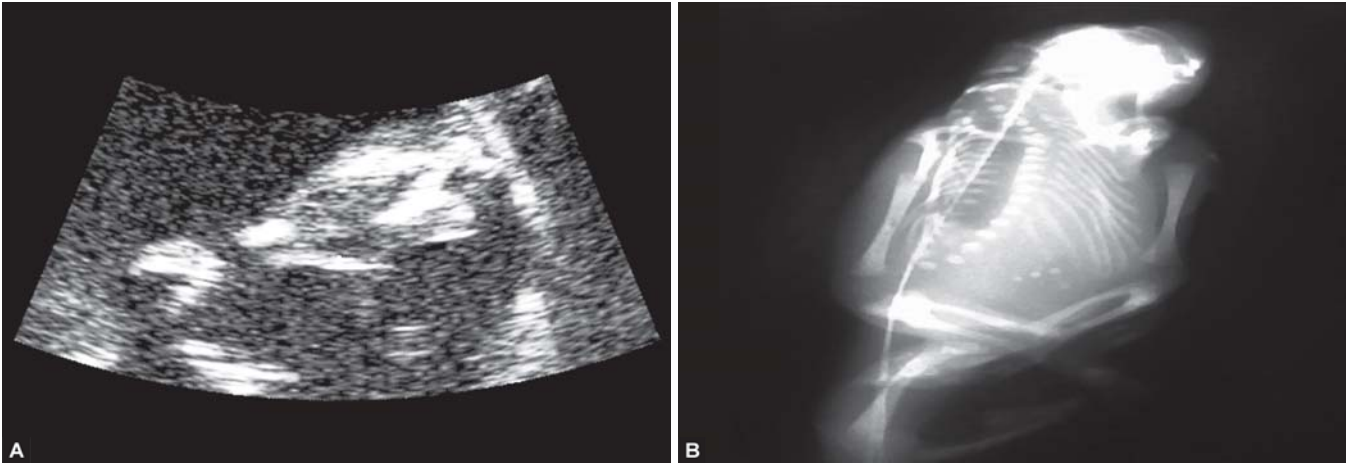


Fig. 8: Prenatal diagnosis of chondrodysplasia punctata by 2D-US and 3D-US and 3D-HCT (a) 2D-US: sagittal section of fetal femur showing epiphyseal calcifications of long bones (arrow); (b) 3D-US: rendered bone mode image of fetal femur demonstrating epiphyseal calcifications of long bones (arrow); (c) 3D-HCT: frontal view of the entire fetal skeleton showing epiphyseal calcifications of long bones (arrows); (d) postmortem radiological examination of fetal arms confirming epiphyseal calcifications of radius (arrow); (e) postmortem radiological examination of fetal spine revealing calcifications of vertebral bodies (arrow). (f) Postmortem radiological examination of fetal legs confirming epiphyseal calcifications of long bones (arrow) (By Ruano et al *Ultrasound Obstet Gynecol* 2004)⁷



Figs 10A and B: Ultrasound and postnatal images of Sirenomelia

Split-Hand and Split-Foot Syndrome (SHFM)

SHFM is a limb malformation involving the central rays of the autopod (the distal division of the limb, such as hands or feet) and presenting with syndactyly, median clefts of the hands and feet, and aplasia and/or hypoplasia of the phalanges, metacarpals and metatarsals.

The two typical manifestations are:

- The isolated typical case, affecting all four limbs in a “V” configuration and showing a familiar presentation
- The atypical isolated case, affecting only one extremity (usually the upper limbs) in a “U” configuration.

SHFM may be associated with other structural defects as in the cleft hand and absent tibia syndrome or absent cubitus syndrome. It may also be associated with the ectrodactyly-ectrodermal dysplasia-cleft (EEC) syndrome.

Hand and Foot Malpositions

Malpositioned Hands

May be:

- Cubitals: Rare, isolated
- Radials: Usually associated with an absent or hypoplastic thumb, radial aplasia or hypoplasia, genetic syndromes, chromosome anomalies (T18), hematological disorder (Fanconi pancytopenia), cardiac disorders (Holt-Oram syndrome) or scoliosis.

Malpositioned Feet

May be isolated (with a certain familiar predisposition) or associated with chromosome defects and skeletal dysplasias (Fig. 11).

Polydactyly

Prenatal detection is made by finding more than the normal number of digits in the fetal hand, foot or in both. It may be a unilateral or bilateral defect. Extra digits may consist solely of soft tissue elements or may contain bone.



Fig. 11: Malpositioned fetal foot. On the same image, the tibia, fibula and the sole of the foot can be assessed. Normally, in this view only the foot profile can be assessed and not the sole of the foot

- Preaxial polydactyly involves the radial aspect of the hand or foot
- Postaxial polydactyly involves the ulnar aspect of fetal hand or foot.

They may be isolated defects (showing dominant inheritance pattern) or may occur with a number of associations.

Hemivertebra

This term describes the abnormal curvature of the spine due to a failure in formation of vertebral bodies. Any segment of the spine may be involved, but the thoracolumbar is most frequent. Mild spinal curvature may be an isolated finding without any associated defect. However, associations with other structural abnormalities are common. Spinal curvature may be part of some genetic syndromes (Klippel-Feil), characterized by fusion of cervical vertebrae with short neck aspect.

Skeletal Akinesia Deformation Sequence

Deformative sequence is secondary to fetal akinesia due to intrauterine contractures of neurological, muscular, connective or skeletal origin.

The term arthrogryposis has been questioned from many authors.

Typical features include bilateral feet malposition, heel, knee and elbow deformities (in flexion or extension). The compromise is usually symmetric, affecting all the extremities. It may be found in association with polyhydramnios, thoracic hypoplasia, micrognathia and increased nuchal translucency (> 95th percentile). Some features may be present in other syndromes, such as multiple lethal arthrogryposis, multiple pterygium syndrome and Pena-Shokeir syndrome.

Ultrasonographic Examination of the Fetal Skeleton

The fetal limb buds start to be visible by ultrasound during the 8th gestational week. The femur and humerus are visible from the 9th gestational week, while the tibia, the fibula, the radius and the ulna become visible during the 10th gestational week. Fetal movements are observed initially during the 9th and 11th gestational weeks, and the fetal limb movements can be observed. All three parts of each limb should be visualized during the detailed second trimester ultrasound examination. If they are symmetrical, the length measurement of the femur and humerus is considered adequate.

Diagnostic Approach

Despite the progress in prenatal diagnosis of SDs, the precise diagnosis remains a difficult task. The international skeletal dysplasia's registry⁹ reports a diagnostic accuracy of 81.5%. This is considered above the average level reported by most of the fetal medicine units and it is possible attributed to the great experience of the center. The same center reports that the diagnosis of SDs is ideally placed between the 18th and 20th gestational week.

Increased nuchal translucency during the 1st trimester of pregnancy in fetuses with normal karyotype can be associated with serious SDs, such as achondrogenesis II, achondroplasia, lethal dysplasia, osteogenesis imperfecta, partial osteogenesis, osteochondrodysplasia blomstrand, body stalk anomaly and Jarcho-Levin syndrome. In most cases, apart from the increased nuchal translucency, the fetus presents with short limbs (< 5th percentile), and fetal movements are restricted. A significant percentage of the diagnosis of SDs happens during the third trimester of pregnancy, while the indication for the ultrasound

examination was different, usually a pathologic condition of pregnancy (i.e. polyhydramnios or short femur). It is worth mentioning that the ultrasound examination usually raises the suspicion of an SD. The main findings pointing to the diagnosis of SDs are the short limbs (mainly the femur) and the increased amniotic fluid volume. The main dilemma for the fetal medicine specialist is whether he/she is facing an SD or an IUGR fetus. This can be extremely difficult when the short limbs are observed for the first time during the third trimester of pregnancy.

The IUGR fetuses tend to present a normal morphology of the short limbs. In contrast, osteochondrodysplasias present also abnormalities of the limb figure. Another ultrasound marker that is helpful in the differential diagnosis process has been introduced by Prof Campbell,¹⁰ namely, the ratio of femur/lower limb. When this ratio is < 0.87 (< 5th percentile) a high level of suspicion of SD is raised.

All these measurements are routinely performed by 2D ultrasound. So, is 2D ultrasound adequate? In the 21st century, it is reasonable to consider the input of 3D ultrasound. So, is 3D ultrasound contributing to a better and more accurate diagnosis of skeletal dysplasias? Can we compare the 2D vs 3D ultrasound diagnosis of SDs? As many authors have suggested, 2D ultrasound is the main tool for the identification of the dysplastic fetal bones. Commonly, the examiner identifies a significant shortening of the long bones. The diagnostic accuracy of 2D ultrasound in the prenatal examination of SDs has been studied by many authors and is presented in Table 4.

In a study by Krakow et al¹¹ regarding the use of 3D ultrasound imaging in the diagnosis of SDs, it has been reported that 2D US correctly achieved prenatal diagnosis while 3D US confirmed the diagnosis, provided detailed imaging and enhanced the genetic counseling. The authors scored the two diagnostic approaches accordingly (Table 5).

In a prospective study⁷ that examined the accuracy of prenatal diagnosis of SD by combining two-dimensional and three-dimensional ultrasound and intrauterine three-dimensional helical computer tomography (3D-HCT), correct diagnosis was achieved by 2D US in 66.7% of the cases. By combining the 3D-US and 3D-HCT, in all cases the reported sensitivity was 100%. In the diagnosis of thanatophoric dysplasia, Machado et al⁵ using 3D US were able to clearly demonstrate the severe frontal bossing and the deficient nasal bridge that characterizes this disease.

Table 4: Diagnostic accuracy of 2D-US in the diagnosis of skeletal dysplasias

Authors	Date	Cases	Correct diagnosis N
Hersh et al South Med J	1998	23	11 (48%)
Tretter et al Am J Med Genet	1998	27	13 (48%)
Gaffney et al Prenat Diagn	1998	35	11 (31%)
Doray et al Ann Genet	2000	47	28 (60%)
Parilla et al J Ultras Med	2003	31	20 (65%)

Table 5: 2D versus 3D imaging in the diagnosis of skeletal dysplasias

Ultrasound findings	Score	
	2D ultrasound	3D ultrasound
Rhizomelia	+	++
Mesomelia	+	++
Acromelia	+	++
Trident hands	+	++
Abnormal calcifications	+	++
Platyspondyly	+	+
Small thorax	+	+
Rib splaying (metaphyseal)	+	+
Frontal bossing	+	+++
Facial dysmorphisms	+	+++

2D US can identify the majority of SD, but the precise diagnosis is not always feasible.¹² The great advantage of 3D US is the lower cost, the absence of fetal irradiation and the better understanding of the disease for parents, helping them to appreciate the diagnosis.¹³ It provides detailed imaging, confirms the diagnosis, and the correct diagnosis is approached usually *in utero*. However, this approach is more dependent on the amniotic fluid volume and fetal position. The input of magnetic resonance imaging (MRI) has been evaluated by many authors in the diagnosis of SD, but the fetal movements pose many limitations in the routine use.¹⁴

In the third trimester, 3D-HCT can image the entire fetal skeleton. This provides the physician with impressive images. However, the 3D-HCT data alone are insufficient for diagnosis, and is indicated only when the ultrasonographic data are inconclusive.

On the other hand, the 3D-HCT although complementary, can identify a plethora of postmortem findings that 3D US can not. A potentially useful application of 3D-HCT originates from providing the physicians with the necessary training concerning the variety of findings that may be observed in SD. In conclusion, at present, 2D-US and 3D-US are the screening tools for the detection of SDs, and CT is a valuable complementary diagnostic tool.

Postnatal Assessment

The vast majority of fetuses with skeletal dysplasias either miscarry or die intrauterine or few hours after birth. It is crucial to perform an in-depth examination of the fetus in order to establish the precise diagnosis. The main indication for the postnatal assessment is regarding the counseling about the risk of recurrence that each couple needs to be aware of prior to a future pregnancy. This assessment should be carried out by a multidisciplinary team, including a neonatologist, a geneticist and a fetal medicine specialist.

The necessary exams that should be undertaken are:

- Thorough physical examination of the fetus
- X-ray of the skeleton
- Karyotypic analysis
- A microscopic examination of the bone tissue
- In individual cases, specialized exams, such as biochemical or enzyme analysis, DNA or cell cultures.

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