

# Clinical and ultrasonographic hints for prenatal diagnosis and management of the lethal skeletal dysplasias: a review of the current literature

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## Abstract

**Introduction:** Skeletal dysplasias are a large, heterogeneous group of conditions with different prognosis for every individual disease entity that involves the formation and growth of bone. Prenatal diagnosis of skeletal dysplasias is a diagnostic challenge for obstetricians. Overall high detection rates can be achieved by detailed ultrasonographic examination of the fetuses suspected to have any skeletal dysplasia. Differentiation of lethal skeletal dysplasias from non-lethal ones is extremely important for parent counseling. As diagnostic accuracy of a specific diagnosis is not always possible, prediction of prognosis is of importance for obstetric management of affected couples. External examinations of the neonate with postnatal photographs and radiographs, autopsy in lethal cases, and sparing the tissue specimens for possible molecular genetic, biochemical, enzymatic and pathological testing studies are extremely important for making an accurate diagnosis. In this review, articles have been extracted from "PubMed" and "Cochrane Database" using "prenatal diagnosis of skeletal dysplasia" word group, dated between 1993 and 2011. The prominent features of specific disease entities to facilitate clinicians' decision-making process about prognosis when they encounter a fetus suspected to have a skeletal dysplasia have been summarized in this review.

**Keywords:** Skeletal dysplasia, Lethal, Prenatal diagnosis, Management

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## Introduction

Prenatal ultrasonography of suspected skeletal dysplasias necessitates systematic imaging and evaluation of the long bones, thorax, hands and feet, skull, spine, and pelvis. Detailed postnatal examination of the neonate is precisely required for accurate diagnosis and determination of the recurrence risk for subsequent pregnancies of the couples [1, 2]. Autosomal dominant, autosomal recessive, X-linked, genomic imprinting errors, somatic mosaicism mutations and teratogen exposure are causative factors for skeletal dysplasias [3, 4]. The genetic defects related to skeletal dysplasias have been identified for approximately 160 of the 350 well-recognized disorders [5]. Substantial progress about prenatal diagnosis of skeletal dysplasias has made molecular genetic confirmation by invasive prenatal diagnosis for at-risk families besides ultrasound and postmortem findings [6]. The overall birth prevalence of skeletal dysplasias and lethal skeletal dysplasias is

estimated to be 2.4 per 10,000 and 0.95 to 1.5 per 10,000 births, respectively. Skeletal dysplasias are responsible for approximately 9 perinatal deaths per 1000 births.

A femur length below the 5th centile for gestation presents a significant diagnostic dilemma for a clinician. Inaccurate dating, a normal variant in constitutionally small fetuses, skeletal dysplasias and chromosomal abnormalities should be kept in mind of clinicians when encountered with a short femur [3, 7, 8].

The thanatophoric dysplasia (29%), osteogenesis imperfecta type 2 (14%), and achondrogenesis (9%) are three most common lethal skeletal dysplasias. Association of skeletal dysplasias with abnormalities in other organ systems is also possible. It is crucial for a clinician to determine whether a skeletal dysplasia is lethal or non-lethal. The presence or absence, length, shape (curvature) and fractures of bones are variables that can be visualized

well at  $\geq 14$  weeks of gestation by ultrasonography for evaluation of suspicion for a skeletal dysplasia.

## Materials & Methods

The evidence acquisition of this review has been prepared with evaluating the articles extracted from a “PubMed” and “Cochrane Database” search using “prenatal diagnosis of skeletal dysplasia” word group between 1993 and 2011. Good quality designed prospective, retrospective, meta-analysis and review articles have been selected with respect to their contributions to prenatal diagnosis of skeletal dysplasias. Furthermore, detailed information for prenatal diagnostic prominent features of lethal skeletal dysplasias has also been designed and presented in a table format in this review.

## Clinically and ultrasonographically useful hints to diagnose common fetal skeletal dysplasias

Increased compressibility of the calvarium by the ultrasound probe is the most reliable sonographic sign of a lethal skeletal dysplasia with decreased mineralization suggesting osteogenesis imperfecta type II, achondrogenesis, or hypophosphatasia. Thoracic circumference/abdominal circumference ratio  $< 0.6$  to  $0.79$ , ribs that encircle less than 70 percent of the thoracic circumference at the level of the four-chamber cardiac view, narrowed anteroposterior (AP) diameter on sagittal ultrasonographic view, concave or bell-shaped contour of the thorax on coronal view, femoral length/abdominal circumference  $< 0.16$  are useful prenatal diagnostic ultrasonographic features that suggest pulmonary hypoplasia.

Prenatal diagnosis of skeletal dysplasias is primarily based on distinguishing fetal ultrasound findings; in some cases magnetic resonance imaging, computed tomography, radiography, molecular analysis may be used to increase the accuracy of the probable diagnosis. Three-dimensional computed tomography (3D-CT) is a valuable diagnostic tool that improves diagnostic accuracy of the prenatal diagnosis of the skeletal dysplasias complementary to 2D and 3D ultrasonography at the expense of radiation exposure to the fetus [9, 10]. The lethal skeletal dysplasias typically have an earlier onset than the non-lethal group, thus lethal skeletal dysplasias are usually diagnosed earlier than non-lethal ones reflecting a worse prognosis as well. Parental counseling and decision-making regarding continuation of the current pregnancy, as well as possible options for prenatal diagnosis of future pregnancies makes diagnostic accuracy crucial [11].

## Systematic imaging of the long bones, thorax, hands and feet, skull, spine, and pelvis

### Long bones

The long bones in all of the extremities should be evaluated and recorded for presence, curvature, degree of mineralization, fractures, epiphyseal stippling and metaphyseal widening especially for fetuses with shortened limbs. The terms rhizomelia, mesomelia and micromelia define shortening of proximal, middle and whole segments of the limbs. While micromelia is a prominent feature of osteogenesis imperfecta and thanatophoric dysplasia, rhizomelic micromelia is a significant sign of achondroplasia and Ellis-van Creveld syndrome [12].

### Thorax

Abnormal rib size and configuration, absence or hypoplasia of the clavicles, absence of scapula are distinguishing prenatal ultrasonographic features of short rib polydactyly syndrome, cleidocranial dysplasia and camptomelic dysplasia, respectively. A chest circumference/abdominal circumference ratio less than the 5th percentile or less than  $0.60$ , a chest-trunk length ratio less than  $0.32$ , and a femoral length/abdominal circumference ratio less than  $0.16$  reveals thorax hypoplasia that is the main cause of neonatal death in many lethal skeletal dysplasias.

### Hands and feet

The hands and feet should be evaluated for pre-axial and post-axial polydactyly, syndactyly, clinodactyly and other deformities. Hitchhiker's thumb which is a prominent feature of diastrophic dysplasia, rocker-bottom feet, and clubbed feet or hands are abnormal postural deformities of the hands and feet. Radial ray abnormalities like radius aplasia or hypoplasia can cause clubbed hands.

### Skull

The shape, mineralization, and degree of ossification of the skull, interorbital distance for hyper- or hypotelorism, micrognathia, short upper lip, abnormally shaped ears, frontal bossing, cloverleaf skull, brachycephaly (anteroposterior shortening of the head), scapocephaly (lateral flattening of the head), and craniosynostoses (premature fusion of the sutures) are diagnostic prenatal ultrasonographic features that should be assessed for establishment of correct differential diagnosis of many skeletal dysplasias.

### Spine

The whole spine should be scanned on sagittal, coronal and axial views ultrasonographically. The curvature of the spine, mineralization of vertebral bodies and neural arches, and vertebral height should be evaluated. Platyspondyly defines flattened vertebral body shape and is also a prominent feature of thanatophoric dysplasia.

## Pelvis

The shape of the pelvis can be important in certain dysplasias and dysostoses; however, it is not always easy to evaluate fetal pelvis using two-dimensional ultrasonography.

Limb reduction defects can be due to amniotic band syndrome, exposure to a teratogen, or vascular accident.

## Postnatal Evaluation

Most of the fetuses with a lethal skeletal dysplasia die in utero, are stillborn, die postnatally, or are delivered after termination of pregnancy. Although ultrasonographic identification rates of lethal skeletal dysplasias have been generally high at approximately 94–96%, an accurate prenatal diagnosis was made in only approximately 30–50% of cases [13–15]. Establishment of the correct diagnosis of the skeletal dysplasia is extremely important for patient counseling about recurrence risk for future pregnancies. Postnatal comprehensive work-up with taking photos of the external view, postmortem whole-body radiographs, tissue biopsy specimens for chromosome analysis and preservation of fibroblasts for possible biochemical, enzymatic, or genetic studies of the neonate should be obtained for accuracy of the diagnosis.

## Most common lethal skeletal dysplasias

### Thanatophoric Dysplasia

Thanatophoric dysplasia is one of the most common skeletal dysplasias with an estimated incidence of 0.2–0.5 per 10,000 births [16]. Severe micromelia with rhizomelic predominance, small thoracic circumference, macrocrania, normal trunk length, normal mineralization, no fractures, thickened and redundant skin folds, platyspondyly are prominent features of thanatophoric dysplasia (Figure 1). Type 1 (TD1) is the more common form of thanatophoric dysplasia. The R248C and Y373C mutations in the fibroblast growth factor receptor 3 (FGFR3) gene are frequently detected mutations of TD1. The typical “telephone receiver” shape of the curved femora, accompanied with frontal bossing and midfacial hypoplasia are distinguishing prenatal ultrasonographic features of TD1 (Figure 2). Type 2 (TD2) thanatophoric dysplasia is usually caused by the K650E mutation in the FGFR3 gene. The typically straight femora with flared metaphyses and most specific ultrasonographic feature of TD2, cloverleaf skull that results from premature craniosynostosis of the lambdoid and coronal sutures are key features for differential diagnosis from TD1. Polyhydramnios is present in approximately 50 percent of affected fetuses.

Spranger classified hypochondroplasia (HCH), achondroplasia (ACH), and thanatophoric dysplasias (TD-I and TD-II) as the same family of dysplasias within the group of pathologies caused by mutations causing ligand independent activation of FGFR3. This mutation



**Figure 1**

Coronal ultrasonographic image through the abdomen-chest demonstrating a *hypoplastic thorax* (white arrows) in thanatophoric dysplasia.



**Figure 2**

Ultrasonographic view of the *telephone receiver-shaped femur* (white arrow) in thanatophoric dysplasia.

results with generalized shortening of the long bones and abnormal differentiation of other bones according to the individual gene affected. All of the mutations related to FGFR3 are inherited in autosomal dominant pattern [17, 18]. Suspicion for skeletal dysplasia usually necessitates karyotype identification followed by molecular study for all exons implicated in the four most common skeletal dysplasias in FGFR3 gene based on the phenotype suggested. Molecular diagnosis is always indicated in cases of affected parents. Except rare germ line mosaicisms, affected offspring or positive molecular skeletal dysplasias in a previous pregnancy are caused by de novo mutations in FGFR3.

### Achondrogenesis

Achondrogenesis is the second most common lethal skeletal dysplasia, with a prevalence of 0.09 to 0.23 per

10,000 births that consists phenotypically and genetically diverse group of chondrodysplasias. Severe micromelia, small thoracic circumference, macrocrania, short trunk length, occasional fractures, decreased mineralization which is mostly marked in the vertebral bodies, ischium, and pubic bones are prominent features of achondrogenesis. Type 1 achondrogenesis (20% of cases) has autosomal recessive mode of inheritance. Decreased mineralization of the vertebral column, sacrum and pubic bones, calvarial demineralization are prominent features. Type 1A is caused by a mutation in the *TRIP11* gene (Golgi-microtubule-associated protein, 210-kDa, *GMAP210*) and type 1B is associated with a mutation in the *DTDST* gene (*SLC26A2* sulfate transporter). Type 2 achondrogenesis (80% of cases) is caused by a new dominant mutation in the *COL2A1* gene, which encodes type II collagen and is an autosomal dominant condition.

### Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a clinically and genetically heterogeneous group of collagen disorders. To date, wide variety of clinical and radiologic phenotypes, approximately 9, have been determined, and the OI type 2 (perinatally lethal), 8 and 9 are severely lethal. All types have been characterized by increased bone fragility. The overall prevalence of osteogenesis imperfecta is one in 28,500 live births [19]. The mutations that cause all types of OI, except OI type 3, are de novo autosomal dominant mutations [20]. It has been classified into four major subtypes based on genetic, radiographic, and clinical considerations. OI is caused by mutations in the genes that encode for type I procollagen (*COL1A1* and *COL1A2*). Severe micromelia, short trunk length, decreased mineralization, small thoracic circumference, normal cranial size, platyspondyly, micrognathia, multiple bone fractures, including multiple fractures within a single bone are prominent features of OI (Figure 3).

Irregularly long bones with multiple angulations and thickening due to innumerable fractures and repetitive callus formation that ensue within the demineralized bones. Multiple rib fractures result in a wavy ribs view on prenatal ultrasonography and also postnatal radiography characterized by concave thoracic contour at the lateral thorax (Figure 4). Demineralized cranium shows deformation upon mild pressure with the ultrasound transducer is commonly present (Figure 5). The diagnosis of OI may be made sonographically as early as 13 to 15 weeks of gestational age.

### Chondrodysplasia Punctata

Chondrodysplasia punctata or stippled epiphyses is etiologically a heterogeneous group of disorders that contain 11 skeletal dysplasias group some of which have been detected prenatally. This condition is related with



**Figure 3** Ultrasonographic image of the decreased bone mineralization and femur fracture (**white arrow**) in osteogenesis imperfecta.



**Figure 4** Irregular ribs due to healing fractures demonstrating wavy ribs (**white arrow**) in osteogenesis imperfecta.



**Figure 5** Decreased skull ossification prone to compressibility on ultrasonography, which allows visualization of the intracranial structures easily in a fetus with osteogenesis imperfecta. (**White arrows: compressions**)

peroxisomal dysfunction and low unconjugated estriol concentration can be seen on second trimester screening for Down syndrome. The enlarged epiphyses with characteristic stippling may be identified on ultrasound in the third trimester. Many small calcifications within the ossification centers of the cartilage, the ends of bones, and around the spine are characteristic. The mostly lethal type, the rhizomelic form (autosomal recessive), is characterized by a moderate rhizomelic shortening of the otherwise straight long bones consisting multiple premature calcifications within the epiphyses of the long bones or the calcaneus. Flat face, micrognathia, microcephaly, normal thorax size and severe mental retardation are other features of the disease.

### **Diastrophic Dysplasia**

Micromelic dwarfism, clubfoot, hand deformities (specifically abducted or hitchhiker's thumb), multiple flexion joint contractures, scoliosis, bones with crescent-shaped flattened epiphyses, a short and broad femoral neck, micrognathia, cleft palate and metaphyseal widening of the shortened tubular bones are characteristic features of this disease entity.

### **Short-rib polydactyly syndromes**

Short-rib polydactyly syndromes are a heterogeneous group of rare and lethal skeletal dysplasias with an autosomal recessive mode of inheritance.

They are subdivided into four groups:

- type I—Saldino-Noonan;
- type II—Majewski;
- type III—Verma-Naumoff;
- type IV—Beemer-Langer (which can occur without polydactyly)

Severe micromelia (present in 100% of cases), small thoracic circumference (present in 100% of cases), normal cranial size, normal bone mineralization, polydactyly, cardiac abnormalities, genitourinary abnormalities are prominent features of short-rib polydactyly dysplasias (Figure 6). Ellis-van Creveld syndrome and Jeune asphyxiating thoracic dystrophy are also short-rib polydactyly dysplasias with similar features except less severe micromelia and thoracic narrowing than the short-rib polydactyly syndromes, and are compatible with life (Figure 7).

### **Campomelic dysplasia or bent-limb dysplasia**

Campomelic dysplasia (CD) or bent-limb dysplasia is a rare autosomal-dominant condition caused by a new dominant mutation in the SOX9 gene (sex-determining protein homeobox 9 mapped to 17q24.3). In some cases, the identification of parental mosaicism greatly affects the recurrence risk, which is very difficult to define and molecular prenatal diagnosis in subsequent pregnancies is needed. However, the risk of recurrence should



**Figure 6**

Shortened ribs with accompanied with increased cardiothoracic ratio in short-rib polydactyly syndrome. (arrows and circle). (**White arrows:** shortened ribs; **circle:** heart)



**Figure 7**

Severe micromelia of the lower extremity (**white arrows**) of a fetus with hypophosphatasia congenita.

be considered to be as low as 1% for parents in whom a negative molecular test result is obtained from the affected offspring. Most cases (77%) are lethal because of respiratory insufficiency from laryngotracheomalacia accompanied with a mildly narrowed thorax. In particular, thanatophoric dysplasia, CD and osteogenesis imperfecta are responsible for about 70% of the prenatal cases of shortened and bowed femur. Hypoplastic scapula (present in 63% of cases), short femur and tibia that are ventrally bowed, hypoplastic or absent fibula, clubfoot, late ossification of midthoracic pedicles, dislocated hips, 11 rib pairs, facial abnormalities, including micrognathia and cleft palate (Robin sequence), congenital heart disease (present in 33% of cases), brain and renal abnormalities are other prenatal ultrasonographic features of campomelic dysplasia [21].

Clinically and ultrasonographically useful prominent

features of common fetal skeletal dysplasias are summarized in Table 1. Other lethal skeletal dysplasias include Boomerang dysplasia, de la Chapelle dysplasia, and Schneckbecken dysplasia are rare and difficult to diagnose accurately on prenatal ultrasound.

## Conclusion

It is likely that the integrated expertise of ultrasonographers, obstetricians, pediatricians and clinical geneticists will markedly improve the likelihood of accurate prenatal clinical diagnoses of skeletal dysplasias, and will facilitate comprehensive counseling of parents about the prognosis and decision-making for either the current and future pregnancies. External examinations of the neonate with post-natal photographs and radiographs, autopsy in lethal cases, and sparing the tissue specimens for possible molecular genetic, biochemical, enzymatic and pathological studies are extremely important for making an accurate diagnosis.

In this review, we tried to summarize the clinical and ultrasonographic prominent findings of most common skeletal dysplasias to assist improving the diagnostic accuracy rates of clinicians. Furthermore, clinically and ultrasonographically useful hints to diagnose most common fetal lethal skeletal dysplasias have been summarized as a comprehensible table format.

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**Table 1** Clinical and ultrasonographical useful hints for the diagnosis of common fetal lethal skeletal dysplasias.

Diagnosis	Long bones	Thorax	Hands and feet	Skull	Spine	Trunk	Fracture	Bone mineralization	Gene mutations	Other
<b>Thanatophoric dysplasia</b>	Length 30-80% of the mean for GA; telephone-receiver femora	Hypoplastic; short ribs	Short	Frontal bossing, clover leaf skull	Platyspondyly	No	No	Decreased spine ossification	FGFR3* (AD)	Hydrocephaly; polyhydramnios
<b>Achondrogenesis</b>	Length < 30% of the mean for GA*	Narrow thorax; rib fractures	Short	Macrocrania	Squared iliac wings	Yes	Occasional	Partial or complete lack of ossification of calvarium, spine and ischial bones	COL2A1* Type 1: AR* Type 2: AD*	Hydrops; polyhydramnios
<b>Osteogenesis imperfecta</b>										
<b>type I (mild)</b>	Normal limb length,		Short	BPD ≤ 5th centile for GA*; thin skull; deformation after compression	Not specified	Yes	Few to 100	Decreased bone mineralization in late 3rd trimester	COL1A1*, COL1A2* (AD)*	Blue sclerae
<b>type II (lethal)</b>	Length 30-80% of the mean for GA*						Multiple	Markedly decreased bone mineralization		2A: dark blue 2B: light blue
<b>type III (severe)</b>	Progressive shortening: length 80-100% of the mean for GA*						Multiple	Decreased bone mineralization		Blue at birth, becoming normal with age
<b>Chondrodysplasia Punctata</b>	Rrhizomelic shortening of the otherwise straight long bones, multiple epiphyseal stippling	Normal	Not specified	Flat face, micrognathia, microcephaly	Not specified	Not specified	Not specified	Normal	(AR)*	Severe mental retardation

**Table 1**  
**—continued**

Diagnosis	Long bones	Thorax	Hands and feet	Skull	Spine	Trunk	Fracture	Bone mineralization	Gene mutations	Other
<b>Diastrophic Dysplasia</b>	Micromelic dwarfism, metaphyseal widening of the shortened tubular bones	Normal	Clubfeet, hitch-hiker's thumb	Micrognathia, cleft palate	Kyphosis	Not specified	Not specified	Decreased	DTDST* SLC26A2* (AR)*	DTDST* SLC26A2* (AR)*
<b>Short-rib polydactyly syndromes</b>	Severe micromelia	Small, short ribs	Small, short ribs	Normal	Not specified	Not specified	Not specified	Normal	(AR)*	Cardiac and genitourinary abnormalities
<b>Campomelic dysplasia</b>	Ventrally bowed short femur and tibia	Small	Clubfeet	Micrognathia, cleft palate	Not specified	Hypoplastic scapula	Not specified	Normal	SOX9*, (AD)*	Laryngotracheomalacia, cardiac, cerebral, renal abnormalities
<b>Fibrochondrogenesis</b>	Micromelia with metaphyseal flaring (dumbbell shape)	Small	Short	Normal size, demineralized, flat face	Platyspondyly, midline clefts	Not specified	Not specified	Decreased bone mineralization	(AR)*	Not specified
<b>Atelosteogenesis</b>	Severe micromelia, bowed long bones	Narrow, short ribs	Short	Flat face, facial clefts	Not specified	Not specified	Not specified	Decreased bone mineralization	Not specified	Not specified
<b>Hypophosphatasia congenita</b>	Severe micromelia	Narrow, short ribs	Short	Normal size, demineralized, compressible	Not specified	No	Occasional	Patchy or generalised demineralisation	TNSALP*, (AR)*	Not specified

\* **FGFR3**: Fibroblast growth factor receptor 3; **COL2A1**: collagen, type II, alpha 1; **AD**: Autosomal dominant; **AR**: Autosomal recessive; **DTDST (SLC26A2)**: diastrophic dysplasia sulfate transporter (solute carrier family 26 [sulfate transporter] member 2); **COL1A1**: collagen, type I, alpha 1; **COL1A2**: collagen, type I, alpha 2; **COL2A1**: collagen, type II, alpha 1; **SOX9**: sex-determining protein homeobox 9; **GA**: Gestational age