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Fetal imaging in the skeletal dysplasias: overview and experience

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Abstract. The skeletal dysplasias (osteochondrodysplasias) comprise a heterogeneous group of disorders that are characterized by generalized abnormalities of skeletal growth and development. Of approximately 125 well-described skeletal dysplasias, about 50 are clinically apparent and identifiable at birth. The prevalence of these dysplasias in the newborn is quite frequent and has been estimated to be between 3–4.5 per 10,000, and the overall frequency of skeletal dysplasias among perinatal deaths to be about 9 per 1,000. Over the past 23 years we have acquired an enormous experience in the International Skeletal Dysplasia Registry with skeletal dysplasias diagnosable at birth or earlier. More and more cases referred to the registry over the past 2 years have been diagnosed as abnormal by ultrasound during the second trimester. The results of our evaluation of almost 400 fetuses and stillborn babies with reference to detailed prenatal history and postmortem evaluation including radiographs, chondro-osseous morphology and even some biochemical and molecular studies are presented. The most common disorders diagnosed were osteogenesis imperfecta (OI), thanatophoric dysplasia, campomelic dysplasia and achondrogenesis type II. Twenty-two types of neonatally diagnosable skeletal dysplasias are discussed together with potential fetal (second trimester) ultrasound findings, the number of fetal ultrasound cases referred to this registry, the number of total cases of that disorder sent to our registry, and the inheritance pattern of that skeletal dysplasia. This information should prove helpful in the evaluation of future cases ascertained by ultrasonography in the second trimester.

The skeletal dysplasias (osteochondrodysplasias) form a heterogeneous group of disorders characterized by generalized abnormalities of skeletal growth and development. Of approximately 125 well-described skeletal dysplasias, about 50 are clinically apparent and identifiable at birth [1]. The prevalence of these dysplasias in the newborn infant is quite significant and is estimated to be between 3–4.5 per 10,000 births. Furthermore, the overall frequency of "lethal" skeletal dysplasias among perinatal deaths is about 9 per 1,000.

Over the past 23 years we have acquired a vast experience in the International Skeletal Dysplasia Registry[1] with the skeletal dysplasias diagnosable at birth and even earlier. More and more cases referred to the Registry over the last 15 years have been diagnosed as abnormal by ultrasonography during the second trimester. This increasing usage of prenatal (second trimester) ultrasonography by both obstetricians and radiologists, together with image resolution improvement, has led to a greater rate of detection of abnormalities presumed to be skeletal dysplasias.

Most routine screening examinations have included measurements of the skull, abdomen and femur or femora. These long bones may be abnormal not only in size but also in shape and even in ultrasonic echo density. An abnormal screening ultrasound should result in a more intensive study (if the femoral measurements and/or dynamics are abnormal) progressing to a detailed examination that includes all the long bones: humeri, radii, and ulnae, as well as the tibiae (and fibulae if possible). A reexamination and reevaluation of the femora, and careful perusal of hands and feet, thorax size and shape (especially ribs and clavicles) and even the face and skull are mandatory to obtain as much information as possible for a specific diagnosis. In addition, non-skeletal abnormalities such as cardiac defects and kidney malformations may be helpful clues to the diagnosis of a specific skeletal dysplasia. Besides a specific diagnosis, which is often very difficult, a probable lethal condition can often be detected with this meticulous ex-

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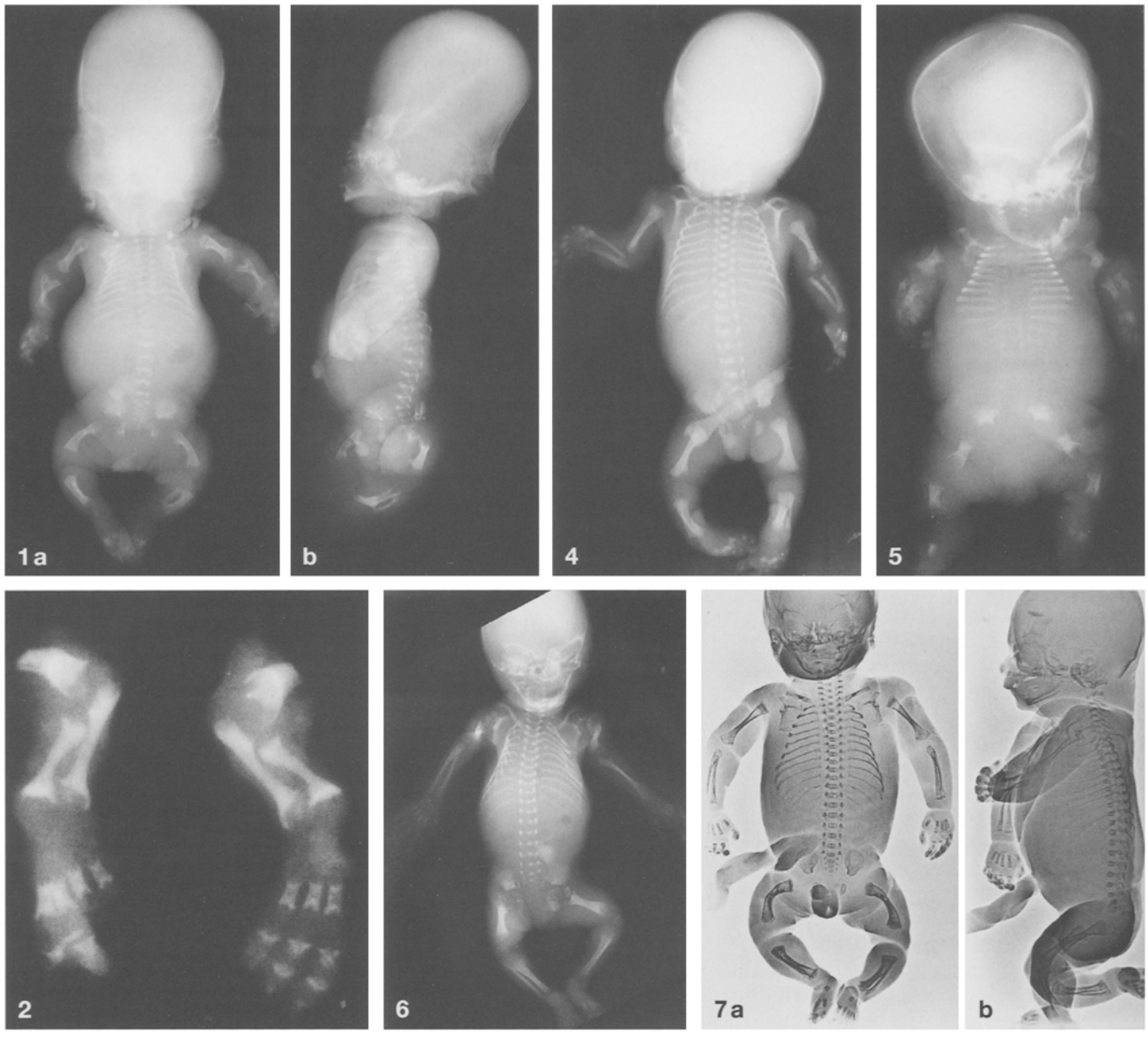

Fig. 1 a, b. Thanatophoric dysplasia with kleeblattschädel. Unknown gestational age fetus (probably second trimester) with micromelia, "French telephone receiver" femurs, platyspondyly, short ribs and a cloverleaf skull

Fig. 2. Metatropic dysplasia. Part of 19-week fetus (lower extremities) showing characteristic flared cupped metaphyses also involving the short tubular bones of the feet

Fig. 3. Asphyxiating thoracic dysplasia. Eighteen-week fetus in parts revealing short ribs, trident acetabulum, bent shortened femurs with metaphyseal flaring and shortened long bones

Fig. 4. Diastrophic dysplasia. Twenty-two-week fetus with clubbed feet, hypoplastic metacarpals and phalanges of hands (and feet), and hitch-hiker thumbs (hypoplastic metacarpals)

Fig. 5. Achondrogenesis II. Twenty-three-week fetus revealing absent vertebral body ossification, short, wide long bones with metaphyseal cupping, short ribs and cupped acetabulae

Fig. 6. Rhizomelic chondrodysplasia punctata. Twenty/twenty-two-week fetus showing marked rhizomelic shortening with stippling in the epiphyseal areas

Fig. 7 a, b. Kyphomelic dysplasia. Twenty-three-week fetal xerograms showing short, bent femurs and tibiae with metaphyseal widening and irregularity

Fig. 8. Osteogenesis imperfecta type II. Twenty-week fetus showing poorly ossified skull, short, wide long bones, beaded ribs, and accordion femurs

amination. When a previous family history of a specific (or even non-specific) skeletal dysplasia is recorded, especially if it is a disorder that may affect the fetus as early as the second trimester, then obviously this more meticulous examination should be performed and even repeated in the case of any equivocal results to produce the greatest certainty of diagnosing an abnormal, affected fetus. If a specific diagnosis of a previously affected sibling has been made, then one can look carefully for certain areas of involvement with the aim of making the diagnosis of affection in the fetus during the second trimester. The importance of *second trimester diagnosis* is that the family cannot only be counseled as to recurrence risks and prognosis but also, if the condition is a lethal one, can be given the opportunity to consider therapeutic abortion.

Materials and methods

We originally studied 226 fetuses and stillborns referred to the International Skeletal Dysplasia Registry in the years 1974 to 1990 [2]. In addition, I have recently partially upgraded the January 1991 to June 1993 material. This study includes all the cases with abnormal second trimester ultrasonography. All the patients concerned were referred to us as cases of a suspected skeletal dysplasia during pregnancy. The material sent to us also included postmortem radiographs, some whole fetuses for postmortem analysis; chondromorphologic material (growth plates), electron microscopic material, fibroblast culture material and tissue for biochemical analysis (such as the evaluation of collagen type I and II defects).

Results

In the early period (1974–1990), 46 % of the cases were ascertained by routine ultrasound or ultrasound for maternal complications (104 cases of a total 226), most of which were second trimester ultrasound examinations. More recently (1991–June 1993) 96 cases of probable skeletal dysplasias, both lethal and non-lethal, presenting either as abortant fetuses or stillborns and referred to the Registry, of a total of 162 cases (almost 60 %) had abnormal second trimester ultrasound examinations. This shows a remarkable increase of ultrasound-diagnosed cases over the most recent period.

The series included 22 fetuses that were ascertained by a positive family history for a previously affected sibling or cousin. Eighteen had the same diagnosis as their family member. Four of these patients did not have a skeletal dysplasia. In two situations where possible autosomal dominant parental transmission was suspected, one skeletal dysplasia and one apparently normal infant were discovered.

In about 75 % of the 226 fetuses and stillborns, we were able to diagnose a specific skeletal dysplasia from combinations of radiographs, chondro-osseous morphology and other material. The most common disorders diagnosed in this series included OI (18 %) (mostly OI type II), thanatophoric dysplasia (14 %), campomelic dysplasia (6 %), and achondrogenesis type II (5 %). All the other specific diagnosable skeletal dysplasias made up 29 % of the 226 cases. In 15 cases (7 %) a skeletal dysplasia was obviously present but a specific diagnosis could not be made. We prefer to index these cases as lethal or non-lethal unclassifiable skeletal dysplasias. In this series 16 % of the cases had a dysmorphic syndrome which did not appear to represent a skeletal dysplasia. Finally a group of 15 patients (7 %) did not appear to have any form of skeletal dysplasia or dysmorphology present. The apparent abnormality in this group of cases could have been in reality just short limbs or perhaps misdating of the pregnancy. We feel, however, that it is most likely that at least some of these cases represent fetuses with intrauterine growth deficiency, as was recently suggested [3–5].

Discussion

Let us now look more closely at specific skeletal dysplasias that appear in our series (or may appear as a potential diagnosis). At the top is the family or group that each belongs to according to the most recent nomenclature [6]. Below this is the present accepted name for the skeletal dysplasia. In the column on the left are listed the specific ultrasound findings to look for in a possible affected fetus during the second trimester. On the right are the number of fetal second trimester ultrasound cases ascertained in our registry series through June 1993, then the total number of cases of that disorder in our registry dating back to 1970, and finally, the inheritance pattern for that disorder.

Group *Skeletal dysplasia*	
Ultrasound (US) findings (Fig.)	Fetal ultrasound (US) cases, second trimester Total number of cases in the registry Inheritance
Achondroplasia group *Thanatophoric dysplasia*	
US findings Large (or cloverleaf) skull Very short long bones Curved (or straight) femurs flat, small vertebral bodies Small hands and feet Small and narrow thorax (Fig. 1 a, b)	US cases – 42* Total Registry – 221 Inheritance – autosomal dominant (AD)
Achondroplasia group *Achondroplasia*	
US findings Short long bones especially short femora and humeri Flat vertebral bodies Large skull	Homozygous US cases* – 7 Total Registry – 11 Inheritance – AD

* 27 of the 42 cases ascertained since January 1991

* We believe that heterozygous achondroplasia cannot be clearly ascertained until the growth falls off in the third trimester [7]

Achondrogenesis (I) group
Achondrogenesis types IA and IB

US findings	US cases – 8
Very short (fractured-beaded) ribs	
Very short long bones	Total Registry – 42
Distended, enlarged abdomen	
Deficient, absent vertebral body ossification	Inheritance – autosomal recessive (AR)

Spondylodysplastic group
*Thanatophoric variants**

US findings	US cases** – 12
Same as thanatophoric dysplasia (without cloverleaf skull)	Total registry – 42
	Inheritance – sporadic, probably AD

* Also known as platyspondylic lethal skeletal dysplasia, various types
** Seven US cases in the past $2^1/_2$ years

Metatropic dysplasia group
Fibrochondrogenesis

US findings	US cases – 3
Very short, broad long bones (ectopic calcification)	
Short ribs	Total Registry – 5
small thorax	
Omphalocele	Inheritance – AR

Metatropic dysplasia group
Schneckenbecken dysplasia

US findings	US cases – 7
Very short long bones	
Short ribs	Total Registry – 10
Small thorax	
Small poorly ossified vertebrae posteriorly	Inheritance – AR

Metatropic dysplasia group
Metatropic dysplasia

US findings*	US cases – 1
Long trunk/spine	
Very flat dense vertebrae	Total Registry – 26
Small, narrow thorax (rib shortening)	
Short dumbbell-shaped long bones	Inheritance – AD
(Fig. 2)	

* Only severely affected phenotype

Short rib (polydactyly) dysplasia group
Short rib polydactyly types 1–4

US findings	US cases – 11
Very narrow thorax	
Short long bones	Total Registry – 67
Normal vertebral bodies	
Polydactyly (if present)	Inheritance – AR

Short rib (polydactyly) dysplasia group
Asphyxiating thoracic dysplasia

US findings	US cases – 3
Short ribs	
Narrow chest	Total Registry – 27
(no polydactyly)	
Normal spine	Inheritance – AR
(renal dysplasia, cysts)	
(Fig. 3)	

Short rib (polydactyly) dysplasia group
Ellis-Van Creveld (chondroectodermal dysplasia)

US findings	US Cases – 1
Mesomelic shortened long bones	
Polydactyly (hands and feet)	Total Registry – 23
Short ribs	
(femoral bowing)	Inheritance – AR
Cardiac defect	

Atelosteogenesis/diastropic dysplasia group
*Atelosteogenesis types 1 and 2**

US findings	US cases – 5
Absent, hypoplastic (tapered) humeri	
Short femurs	Total Registry – 28
Cleft vertebrae	
Twisted fingers	Inheritance (except type 2) – AR
(boomerang-shaped tibiae)	
(omphalocele)	

* Includes Boomerang dysplasia

Atelosteogenesis/diastropic dysplasia group
Diastrophic dysplasia

US findings	US cases – 3
Short long bones	
small hitchhiker thumb	Total Registry – 46
severe clubbed feet	Inheritance AR
(Fig. 4)	

Kniest/Stickler dysplasia group
Dyssegmental dysplasia (Silverman-Handmaker and Rolland-Desbuquois types)

US findings	US cases – 2
Bizarre vertebral ossification	
Large, tiny, and absent vertebrae	Total Registry – 18
(very short dumbbell long bones)	
(encephalocele)	Inheritance – AR

Kniest/Stickler dysplasia group
Kniest dysplasia

US findings	US cases – 0
Probably not significantly affected in second trimester, except for slightly short long bones	Total Registry – 59
	Inheritance – AD

Spondyloepiphyseal dysplasia congenita group
*Achondrogenesis II/hypochondrogenesis**

US findings	US cases – 18**
Short ribs	

Very short to moderately short long bones	Total Registry – 93
Absent to deficient vertebral body ossification	
Small thorax	Inheritance – AD
(Fig. 5)	

* Type II collagenopathy
** 7 Ultrasound cases in past $2^1/_2$ years

Spondyloepiphyseal dysplasia congenita group
Spondyloepiphyseal dysplasia congenita

US findings	US cases – 9
Short long bones	
Flat, hypoplastic vertebrae	Total Registry – 82
Small thorax	Inheritance – AD

Dysostosis multiplex group
Mucolipidosis II

US findings	US cases* – 4
Short long bones	Total Registry – 8
	(3 in one family)
	Inheritance – AR

* Diagnosis made biochemically, but ultrasound may be helpful

Chondrodysplasia punctata group
Rhizomelic chondrodysplasia punctata

US findings	US cases – 5
Disproportionately short femurs (and humeri)	
Slightly short other long bones	Total Registry – 14
(Fig. 6)	Inheritance – AR

Bent bone dypslasia group
Campomelic dysplasia

US findings	US cases – 10
Disproportionately long bent femora	
Short bent tibiae	Total Registry – 43
Milder, similar changes in upper extremities	
Sex reversal (XY phenotypic females)	Inheritance – AR

Bent bone dysplasia group
*Kyphomelic dysplasia**

US findings	US cases – 17
Short bent femora	
Short long bones (short ribs and thorax)	Total Registry – 23
(Fig. 7 a, b)	Inheritance – AR

* Including Stuve-Wiedemann dysplasia

Dysplasias with decreased bone density
Osteogenesis imperfecta [8]*

US findings	US cases – 33*
Decreased skull echoes	
Short ribs, beaded ribs	Total Registry – 151
Bent short long bones, often wide very short femora	Inheritance – AD
Decreased bone echoes	
(Fig. 8)	

* Almost all these cases were ascertained in the last $2^1/_2$ years

Dysplasias with defective mineralization
*Hypophosphatasia**

US findings	US cases – 7
Absent (for few) skull echoes	
Prominent falx cerebri	Total Registry – 29
Scattered marked absence of bone echoes	Inheritance – AR
Short bent long bones (with fractures)	

* Both perinatal and infantile forms

The 22 skeletal dysplasias listed here constitute the most common entities diagnosed in this series and also potential diagnoses that have to be considered when the suspicion of a skeletal dysplasia is investigated by second trimester ultrasound [9]. Hopefully the findings in this series and the information given will be helpful in the evaluation of such a problem case. It is very important that all potentially helpful material be collected in such cases and, if necessary, that such cases be referred to a specialized group such as the International Skeletal Dysplasia Registry together with all records.

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