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Prenatal Diagnosis, Management and Outcomes of Skeletal Dysplasia

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Abstract

Objective: To evaluate prenatal ultrasound findings of Skeletal Dysplasia (SD) and examine the contribution of radiological, histological and genetic exams.

Methods: Retrospective study including all cases of SD managed in a tertiary maternity center between 1996 and 2010.

Results: Eight cases of SD were diagnosed (1.4/10,000 births) by ultrasonography (USE). Three (38%) cases of SD were discovered in the first trimester, and five in the second trimester. We found short femurs in all cases. Anomalies consisted of the thickness of the femoral diaphysis, broad epiphysis, short and squat long bones, costal fractures, thinned coasts, anomalies of the profile and vertebrae, and a short and narrow thorax. Associated anomalies consisted of ventriculomegaly, hygroma, hydramnios, and thick nuchal fold. We found mutations of the FGFR3 gene in achondroplasia, of the Delta 8/7 sterol isomerase in a case of chondrodysplasia punctata and deletion of the DTSDT gene in a case of IB achondrogenesis.

USE diagnosed the type of SD in 6 cases. Five patients underwent termination, and 3 were delivered by cesarean section.

Skeletal radiography or fetal autopsy confirmed the bone anomalies and the type of SD. Final diagnoses included 4 cases of osteogenesis imperfecta, 2 cases of achondroplasia,1 case of IB achondrogenesis and 1 case of punctata chondrodysplasia.

Conclusion: USE allowed the prenatal diagnosis of SD since the first trimester and, in most cases, identified the type of SD. Skeletal radiography, genetic testing, or fetal autopsy in cases of termination confirmed the diagnosis and type of SD.

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Keywords: Skeletal dysplasia; Achondroplasia; Osteogenesis imperfecta; Ultrasound exam; Genetic testing; Skeletal radiography; Short long bones

Introduction

Skeletal Dysplasias (SDs) are rare congenital conditions that can be classified into 23 types [1]. Their frequency varies between 1 in 30,000 and 1 in 10, 000 deliveries [2]. Achondroplasia is the most frequent form of dwarfism, which results in short limbs, and is caused by mutations in the FGFR3 gene [3].

SD can be diagnosed prenatally by 2D ultrasonography [4]. Short limbs are usually found, particularly short femurs, below the third percentile in the second or third trimester of pregnancy [5]. Short limbs are often associated with skeletal abnormalities, such as a small chest or cephalic abnormalities [5]. In some cases, the diagnosis can be made more precisely by three-dimensional ultrasonography or helicoidal computed tomography during the third trimester [6,7]. However, in some cases, ultrasound exams are not effective in determining the precise type of skeletal dysplasia. Molecular diagnosis has been used to identify the mutations in the genes involved [3,8]. Skeletal radiography, or fetal autopsy in cases of termination, will allow for the diagnosis of the type of skeletal dysplasia. There are few published studies regarding SD, and they are often limited to a small number of cases given that these pathologies are rare.

The diagnosis of skeletal dysplasia is not always made in the first trimester of pregnancy, as guidelines of the first ultrasound exam include the measurement of the crown-rump length and the nuchal translucency, which mainly screens for Down syndrome. The measurement of the limbs during this ultrasound is not obligatory. The time of prenatal diagnosis of SD varies between 10 and 35 weeks [9],

and sometimes, the diagnosis is only made postnatally. There are few studies on the diagnosis of SD by early ultrasound.

SD is well described in cases of fetal autopsy following termination or fetal death. However, there are few data concerning the prenatal diagnosis of skeletal dysplasia and the outcomes of these pregnancies.

We aimed to evaluate prenatal ultrasound findings in our maternal-fetal medicine unit to examine the diagnosis of skeletal dysplasia and the contribution of radiological, histological and genetic exams in the management of SD as well as the fetal and maternal outcomes.

Materials and Methods

We reviewed all cases of skeletal dysplasia diagnosed in utero and managed in our maternal-fetal medicine unit between 1 January 1996 and 31 December 2010.

All patients' charts were analyzed anonymously; an anonymous number was assigned to each chart in agreement with ethical guidelines.

We noted the general characteristics of the pregnant women (e.g., age, previous medical and obstetrical history, height) and the data contributing to the prenatal diagnosis, which included the level 1 and 2 ultrasound findings, the radiological exam, amniocentesis, the report of the multidisciplinary center of prenatal diagnosis of Orleans, the results of the helicoidal computed tomography and the pregnancy outcomes. We reported the results of the fetal autopsy in cases of termination, and we reported the results of skeletal radiography and genetic exams when they were performed. In cases of delivery, the mode of delivery and the results of the neonatal exam are reported. Data were recorded and analyzed using Microsoft Excel 2007. The means and standard deviations were calculated.

Results

Eight cases of skeletal dysplasia were diagnosed prenatally between 1 January 1996 and 31 December 2010 in the department of maternal-fetal medicine of the regional hospital center of Orleans. The hospital is a tertiary care maternity center that performs approximately 4300 deliveries per year and has a multidisciplinary center of prenatal diagnosis.

The prevalence of SD was 8 cases among 58000 births, which is 1.4 cases of SD per 10000 births.

The mean age of the women was 32 ± 5 years.

Six patients were of French geographic origin and 2 were of Southern European origin. The mean height of the pregnant women was 1.55 ± 0.16 m (below the average height of French women, which is 1.62 ± 0.04 m).

Seven patients were multiparous, and one patient was nulliparous. One patient was achondroplastic (height 1.30 m) and delivered two achondroplastic fetuses. Maternal serum screening for Down syndrome was performed in two of the 8 cases and did not indicate that the patients were at increased risk. Nuchal translucency was measured in 6 of the 8 cases and was increased in 2 cases (25%). There was one case of cystic hygroma. The mean fetal age at diagnosis of SD was 17 ± 5 weeks of gestation. Three cases of SD (38%) were diagnosed in the first trimester (11-13 weeks of gestation), 3 cases of SD were not diagnosed in the first trimester and 2 patients did not undergo a first-trimester ultrasound exam. Five cases of SD were diagnosed in the second trimester of pregnancy. All patients had an additive level 2 ultrasound exam performed by a referent physician at the multidisciplinary center of prenatal diagnosis at our hospital.

Ultrasound findings

We found biometric and morphological abnormalities of the long bones and of the skeleton (Tables 1 and 2).

Biometric anomalies: A short femur was observed in all cases (8/8). All segments of the upper and lower limbs were variously involved. Short femurs, tibiae, fibulas, humeri, and radii were observed (Figure 1)

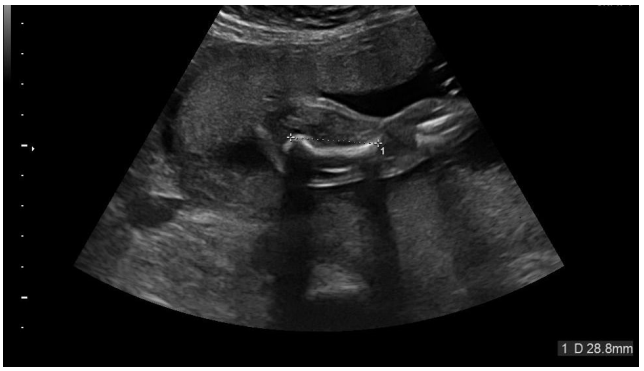

Figure 1: Ultrasound exam of the femur at 22 weeks of gestation.

Morphological abnormalities consisted of angled aspects of the femurs (shaped like a V, Figure 2) and fractures, which are often observed in cases of osteogenesis imperfecta. Other aspects were also observed: thickened femoral diaphysis, broad epiphysis in the cup, short and squat long bones, costal fractures, hail moniliform coasts, vertebral anomalies, flattened nasal bridge and frontal bossing (Figure 3 Profile of achondroplastic fetus), and a short and narrow thorax.

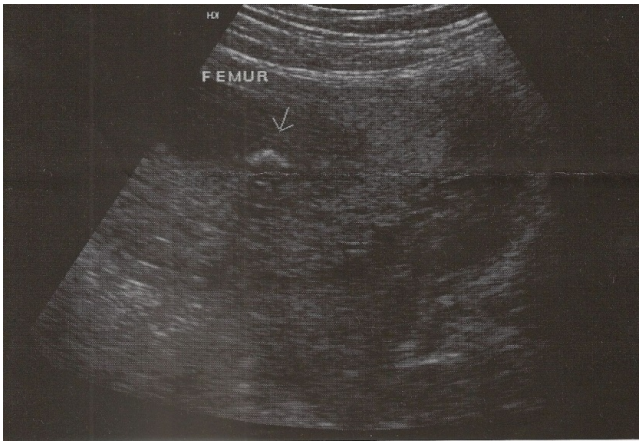

Figure 2: Shaped as a V.

There was one case each of ventriculomegaly, hygroma, hydramnios and a thick nuchal translucency of 3 mm (Tables 1 and 2).

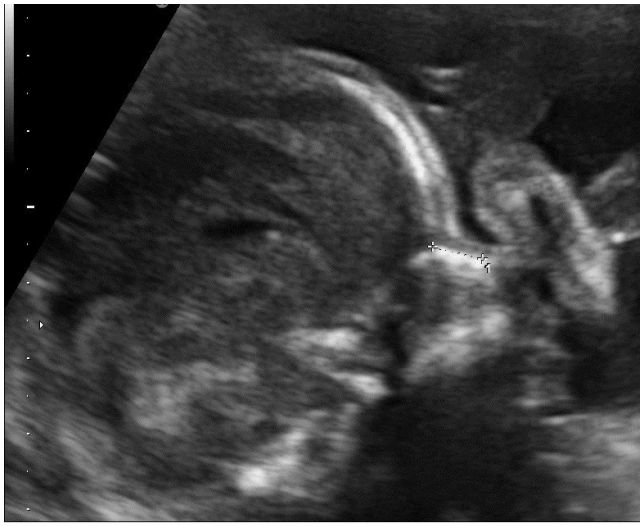

Figure 3: Profile of achondroplastic fetus.

N=8	MBT	WG for NT/CRL	NT/CRL	WG at diagnosis	Findings of the first ultrasound exam
1 oi	1/7000	12	Normal	23	Short femur, doubt on costal fractures
2 oi	Note done	12	0,9/59	22	Curved femurs <3rd p, aspect in adduction of the 2 thighs, thickened femoral diaphysis with irregular contours and angulations (fractures?), incurvation of the tibiae
3 oi		14	1,7/84	14	Short femurs: 9 to 10 mm, arc forms in the circumflex accent, squat and short humeri, malposition of the hands and the feet, ventriculomegaly of 13 mm, a narrow thorax
4 oi		13	3	13	The measure of femur 4.6 mm <3rd percentile, 3 short limbs in the wrong position
5 ap	1/10000	12+5	1,87/73	23	Short femur of 38,75 mm <10th percentile
6 ap				27	Frayed aspect of the long bones, head circumference >97th percentile, femurs <3rd percentile, hydramnios
7 CPD				22	Femur <3rd percentile: 29,5 mm, abnormal aspect of the vertebrae. Impossibility of placing the rachis in continuity, moniliform aspect of certain coasts, short and squat femur, tibiae and fibula
8 IB ach		12		12	Cystic hygroma, short upper and lower limbs, angulation of the rachis, generalized subcutaneous edema

Table 1: First ultrasound findings for skeletal dysplasia.

Following the level 1 ultrasound exam, a second exam was performed by a level 2 ultrasonographer (Table 2).

In 3 cases, the first ultrasonography exam was performed by a level 2 echographic.

The level 2 ultrasound exams confirmed short long bones and highlighted the following anomalies of the skull and face: brachycephaly, anomalies of the profile, saddle nose, and ventricular dilation. This exam demonstrated the morphological anomalies more precisely than the level 1 exam.

n=8	Weeks of gestation diagnosis (WG)	Findings of the first ultrasound exam	Level 2 ultrasound exam
1 oi	23	The short femur, coastal fractures suspected	Brachycephaly, short femurs <3rd P, humeri at 6th p, squat and short long bones with broad epiphysis in cups and angulations
2 oi	22	Curved femurs <3rd p, aspect in adduction of the 2 thighs, thickened femoral diaphysis with irregular	Femur <3rd p, upper limbs <3rd percentile, thickened femoral diaphysis, curved and short tibia, and fibulas
3 oi	14	Short femurs: 9 to 10 mm, arc forms in circumflex accent, squat and short humeri, malposition of the hands and the feet, ventriculomegaly of 13 mm, a narrow thorax	Idem first exam
4 oi	13	The measure of femur 4.6 mm <3rd percentile, 3 short limbs in the wrong position,	-
5 ap	23	Short femur 38,75 mm <10th percentile	Femur <<< 3rd P at 32 weeks, the evocative profile of achondroplasia, short and frayed long bones and fractures of the upper extremity of the femurs, radius and cubitus, and fibulas

6 ap	27	Frayed aspect of long bones, head circumference >97th percentile, femurs <3rd percentile, hydramnios	Idem first exam
7 CPD	22	Femur <3rd p: 29,5 mm, abnormal aspect of the vertebrae impossibility of putting the rachis in continuity, moniliform aspect of certain coasts, short and squat femur, tibiae and fibula	-
8 IB ach	12	Cystic hygroma, short upper and lower limbs, angulation of the rachis, generalized subcutaneous edema	idem first exam
Weeks of Gestation=WG; Osteogenesis Imperfecta=OI; Achondroplasia=Ap; Chondrodysplasia Punctate=CPD; ChondrodyPlasia Ponctata=CDPL			

Table 2: Results of the level 2 ultrasound exam and comparison with the level 1 finding for skeletal dysplasia.

N=8	Karyotype	Parental decision	TOP Term (WG)	Delivery	Weight of the fetus/newborn (g)
1	46, XY	TOP	26		
2	No	conservation		Caesarean 39 WG	2470 g <2nd P
3	46, XY	TOP	17		175
4	46, XX	TOP	14		14
5	No	conservation		Caesarean 38 WG	2830
6	No	conservation		Caesarean 37 WG	2760
7	46, XX	TOP	27		885
8	46, XX	TOP	17		85

Table 3: Outcomes of skeletal dysplasia Achondrogenesis 1 B.

Outcomes of the pregnancies

Following the ultrasound exam, the diagnosis of skeletal dysplasia was suspected in all 8 cases. A karyotype by amniocentesis or trophoblast biopsy was proposed in all cases and accepted by 5 patients. The results were normal in these five cases (Table 3).

N°	Genetic	Bone radiographies pre/post-natal	Fetal autopsy/postnatal exam	Diagnosis
1		Osteogenesis imperfecta	Short upper and lower limbs, luxation of the hips and knees, curved aspect of the thighs and legs	osteogenesis imperfecta
2		Demineralization of the skull, diffuse osteopenia, multiple fractures of femur, clavicle, diaphysis, tibia, fibula, humerus, radius. Incurvation of the fibula, humeri and the 2 fronts of the arms. Thinned ribs	Born alive: luxation of the hips and knees, curved femurs, short long bones	osteogenesis imperfecta
3	De novo mutation or germinal mosaic genetic counseling	Major osteodysplasia of the bones of the 4 limbs, fractures of the coasts	the macerated fetus, short femurs, and curved humeri, heterogeneous, fractures of the coasts, ventriculomegaly	osteogenesis imperfecta
4		Curved and short long bones	Four short malformed limbs with angulations	osteogenesis imperfecta
5	FGFR3 gene mutation	No	Born alive, achondroplasia	Achondroplasia
6	FGFR3 gene mutation	No	Born alive, 44 cm tall <5th percentile, head circumference >95th p, respiratory distress, short limbs, right pneumothorax, and pneumomediastinum	Achondroplasia
7	mutation of Delta 8/7 sterol isomerase gene, dominant, bound to the X chromosome, maternal	Cartilaginous punctuation of the vertebrae, the bones of the hips, the coasts, the sternum, the larynx, the	Shorts upper and lower limbs, an abnormal reserve of cartilage with 50% without cell areas and zones of the mineral-bearing cartilaginous matrix,	Chondrodysplasia punctata (type CDPX2)

	transmission, genetic counseling	epiphyses of the long bones; Short and squat long bones		
8	homozygotic gene deletion of DTDST in delV340	Bones of the 4 limbs reduced to some irregular osseous cores in a wing of a butterfly, 2 small and deformed humeri and radii and ulnas, 2 very short femurs deformed in a cone. One bone in the 2 legs, five punctiform osseous formations of bones of hands and feet. The narrow thorax of 12 very short and enlarged coasts at their extremities, plane vertebrae	Hygroma of the neck, narrow, short and broad thorax, projecting abdomen, four short limbs with malpositions of the hands and the feet	1 B achondrogenesis

Table 4: Bone radiographic and fetal and maternal outcomes for skeletal dysplasia.

Genetic tests were performed in 3 of the 8 cases. A mutation of the FGFR3 gene was found in one case of achondroplasia, a mutation of the Delta 8/7 sterol isomerase gene was found in one case of dominant chondrodysplasia punctata linked to the X chromosome and a homozygotic deletion of the DTSDT gene in delV340 was found in one case of type IB achondrogenesis.

Ultrasound examination (USE) allowed the diagnosis of the type of SD in 6 of the 8 cases. The type of SD was not identified by USE in two cases: one case of IB achondrogenesis and one case of osteogenesis imperfecta.

With the patients' consent, fetal pathologies were presented and discussed in the multidisciplinary center of prenatal diagnosis. The diagnosis was confirmed and 5 out of 8 patients (62%) decided to terminate their pregnancies; 3 patients did not terminate their pregnancies and delivered by cesarean section.

Skeletal radiographs were performed after termination and confirmed the bone anomalies (Table 4).

A helicoidal CT was performed in one patient at 28 weeks of gestation and confirmed the diagnosis of achondroplasia.

In cases of TOP, a fetal autopsy confirmed the diagnosis in all cases. In cases of delivery, the diagnosis of SD was confirmed, and the SD type and prognosis were determined.

The final diagnoses included 4 cases of osteogenesis imperfecta, 2 cases of achondroplasia, 1 case of IB achondrogenesis and one case of punctata chondrodysplasia.

Prenatal USE diagnosed SD in the eight cases and determined its type in 6 cases. These diagnoses were confirmed by histological exam, postnatal exam, skeletal radiography and genetic analysis (Table 4). The type of SD was not diagnosed in one case of osteogenesis imperfecta and in one case of IB achondrogenesis.

Discussion

Although there was a low incidence of skeletal dysplasia in our population, prenatal ultrasound exams allowed for the diagnosis of SD in all cases. Short long bones were found in all cases.

The classic sign of SD was short femurs. There was also shortening of other long bones, such as the tibia, fibula, humerus, radius, and ulna. We found associated morphological abnormalities including curved, angled and squat long bones, suspected fractures in cases of osteogenesis imperfecta and frayed bones in cases of achondroplasia.

According to Schramm et al. [1], the diagnosis of skeletal dysplasia is possible in the majority of cases by 2D ultrasound exam and is improved by 3D USE [6,10,11].

In our study, the diagnosis of SD was made in the first trimester of pregnancy in three out of 8 cases. The classic sign was a short femur.

Konstantinidou et al. [9] also found that the diagnosis of SD is possible in the first trimester, although the majority of diagnoses were made in the second or third trimester [12].

Ultrasound diagnosis of SD is possible in the first trimester based on biometric criteria (short long bones) and morphological abnormalities of long bones, such as squat long bones with angulations, multiple fractures, V aspects and thickness of the diaphysis. Measurements of the femur and the humerus must be included in the first-trimester ultrasound in addition to nuchal translucency, and these results should be reported in percentiles.

In our study, the diagnosis of SD by first level ultrasonographers was confirmed in all cases by a level 2 ultrasound exam. However, the latter ultrasound permitted more precise examination and found fetal abnormalities of the profile (nasal ensellure), the skull, the vertebrae or the coastal grill. According to Cordone et al. [12], a level 2 ultrasound exam is more precise and confirms short long bones. In addition, it can also visualize macrocephaly, abnormalities of the profile and abnormalities of the hand, such as the three-pronged fork.

Level 1 ultrasound exam must be followed by a level 2 ultrasound exam in cases of skeletal dysplasia. A level 2 exam confirms the diagnosis and can visualize abnormalities of the profile, the skeleton, and the hands or the feet, which are more difficult to see in a level 1 exam. The exam of the entire skeleton is essential because it can find coast hails, fractures, narrow thorax, and vertebral anomalies that can be used to specify the type and the prognosis of SD.

In two cases, we found nuchal translucency anomalies (osteogenesis imperfecta and achondrogenesis IB).

Schonewolf Creulich et al. [13] found a thick nuchal translucency in osteogenesis imperfecta.

Associated anomalies, such as ventriculomegaly bound to the narrowness of the medullary channel, can be found with a thick nuchal translucency.

We proposed a karyotype test for all patients, and the results were normal in all cases. In cases in which there is suspicion of SD, it is necessary to eliminate chromosomal abnormalities. Molecular biology was performed in half of the cases and mutated genes were identified.

A mutation of the FGFR3 gene in achondroplasia was found using PCR-RFLP, and DNA sequencing of fetal blood uncovered a mutation in the Delta 8/7 isomerase gene in the case of chondrodysplasia punctata and a mutation of the DSDT gene in the case of achondrogenesis. Osteogenesis imperfecta is caused by autosomal dominant mutations in the genes for type I collagen; however, it also results from a recessive deficiency in cartilage-associated protein [14,15]. We did not distinguish between these mutations in our cases of osteogenesis imperfecta. Genetic counseling is essential in cases of prenatal diagnosis of SD.

In the majority of cases, we diagnosed the type of SD by 2D ultrasound examination. In 1 additional case, the familial and personal context (achondroplasia), molecular biology, and helicoidal computed tomography allowed us to identify the type of SD.

Some authors found that 3D USE is useful for identifying the type of SD [6]. Parilla et al. [16] made antenatal diagnoses of the type of SD in 65% of cases Ruano et al. [7]. have described the use of 3D ultrasonography in the third trimester and helicoidal computed tomography to identify the type of SD. We did not perform 3D USE in our study because the gestational ages were too early to produce quality images and also because 3D USE is not often performed for this indication.

The diagnosis of SD was confirmed in all cases after delivery or termination of the pregnancy by skeletal radiography, feto-pathological exam or genetic testing. As the prognoses of these cases of SD were severe, parental requests for pregnancy termination were accepted by the multidisciplinary center of prenatal diagnosis.

Osteogenesis imperfecta was the most frequent diagnosis, and many bone fractures were found. In half of these cases, we made the diagnosis in the first trimester. We did not perform genetic analysis. As described in Forlino et al. [14], the anomaly is caused by a deficiency in collagen I in its autosomal dominant form and a deficiency in cartilage-associated protein in its recessive form [15].

Achondroplasia (dwarfism with short limbs) represented the second leading cause of SD in our study and was caused by a mutation in the FGFR3 gene. Other authors found the same signs of short limbs with mutations in the FGFR3 gene in cases of achondroplasia [8,17-19]. Chitty et al. [5] confirmed the molecular diagnosis of achondroplasia using maternal plasma. Other types of SD found in our study were IB achondrogenesis and punctata chondrodysplasia.

Skeletal radiography [20], fetal autopsy in cases of termination and the molecular diagnosis of genetic mutations confirmed the diagnosis and the type of SD.

In our study, one-third of patients chose to continue their pregnancy to term and delivered by cesarean section. Parental information on fetal anomalies and prognosis must be complete, and the pediatric team must be involved. These fetuses should be delivered in departments with specialized pediatric teams, and some cases may require pulmonary, orthopedic and neurological specialists. Delivery by cesarean section is recommended due to bone fragility; macrocephaly and the possibility of fractures make vaginal delivery difficult.

In all cases of parental request for termination, the prognosis was poor, and the decision was accepted by the prenatal multidisciplinary team.

There are some limitations to this study. The number of cases of skeletal dysplasia studied is small. Because this anomaly is very rare, studies are often limited to a few cases. However, our study highlighted the ultrasound findings of SD and also included genetic, radiographic, and histological exams and the outcomes of the fetus and the pregnancy.

Conclusion

SD can be diagnosed prenatally by 2D ultrasound examination in the first trimester of pregnancy by measuring long bones, particularly the femur.

SD is characterized by short long bones. Morphological abnormalities, such as fractures and squat and short long bones are often found. Level 1 ultrasound examination allowed the diagnosis of all cases of SD in our study, although a level 2 ultrasound exam is necessary because it precisely examines the abnormalities of the entire skeleton, the profile and other associated anomalies, such as ventriculomegaly or hygroma. The type of SD can be determined in most cases by level 2 USE. The most frequent type of SD in our study was osteogenesis imperfecta, which was followed by achondroplasia. The karyotype was normal in all cases. In cases of SD, genetic mutations can be diagnosed by molecular analysis of the amniotic fluid or the fetal blood and can identify the type of SD.

Skeletal radiographs and helicoidal computed tomography can provide complementary information. In cases of termination, fetal autopsy with a histological exam is essential to confirm the diagnosis and the type of the anomaly.

In cases of the conservation of pregnancy, complete and multidisciplinary information must be provided to the parents regarding the complications and the prognosis of SD. Cesarean delivery is recommended in these cases, and genetic counseling is essential.

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