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Ultrasound and MRI comprehensive approach in prenatal diagnosis of fetal osteochondrodysplasias. Cases series.

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Abstract

Aim: To present the systematic ultrasonographic assessment in fetal osteochondrodysplasias and to evaluate the fetal MRI intake, as a complementary exploration to US, in the prenatal diagnosis and perinatal prognosis of fetal nonlethal osteochondrodysplasias. **Material and methods:** In this tertiary multicentre study were included 37 cases diagnosed prenatally with various entities in the category of nonlethal fetal osteochondrodysplasias. The initial diagnosis was carried out by the routine or detailed ultrasound examination. Fetal MRI was accomplished for selected cases. **Results:** Nonlethal skeletal dysplasia was suspected and then diagnosed after 17 gestational weeks. The suspicion of osteochondrodysplasia as a reference diagnosis element has required systematic and thorough ultrasound examination. Fetal MRI is a valuable exploration, complementary to prenatal ultrasound bringing in very useful details for the diagnosis of osteochondrodysplasias. The global diagnosis of skeletal dysplasia depends to a great extent on the genetic or biochemical abnormality that causes them. **Conclusions:** US is always the fundamental screening exploration for fetal assessment in nonlethal osteochondrodysplasias. The details brought by the fetal MRI are useful, and the exploration is harmless for the fetus and the mother. Certain diagnosis cannot be accurate and complete without the contribution of genetics, maternal and fetal medicine, obstetrics or radiology.

Keywords: skeletal dysplasia, examination, complementary, systematic, complex

Introduction

Nonlethal fetal osteochondrodysplasias fall into the much more extensive group of skeletal dysplasias, and they are a very heterogeneous group of conditions concerning especially skeletal or musculoskeletal anomalies. This extensive group of conditions includes under various classifications about 456 pathological entities, distributed into 40 subgroups, according to molecular, biochemical or imaging criteria [1].

Phenotypically these disorders are characterized by the small size of individuals associated with different degrees of deformation of bone structures, deformities or joint, muscle or mixed dysfunction. Due to the extremely wide variability of clinical manifestations osteochondrodysplasias are conditions that are sometimes very dif-

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ficult to diagnose or to exactly classify, both prenatally and postnatally. Approximatively one hundred skeletal dysplasias have prenatal onset and other have clinically relevant onsets in the first two or three years of life [1,2].

Even if perinatal/maternal-fetal medicine, molecular genetics, or morphopathology progress is highly significant, accurate prenatal diagnosis of skeletal dysplasias remains a challenge for practitioners. Due to the high variability of these anomalies their exact incidence is difficult to quantify, being estimated at 1:5000 – 2.4:10000 live newborns [1,3].

A recent classification of these anomalies belongs to Offiah et al and Hall et al [4,5] The authors systematise skeletal dysplasias in osteodysplasias (bone abnormalities that result in the change of bone and bone mineral density), chondrodysplasias (phenotypical consequence of genetic abnormalities affecting the cartilage), and dysostoses (malformations of the bones or of certain bone groups resulting in the abnormal blastogenesis during the first 6 weeks of intrauterine life) [4,5].

Ultrasonography (US) is undoubtedly the fundamental examination tool for these entities, often bringing relevant information for the diagnosis, but due to the high variability of expression of US semiology, the contribution of complementary explorations for the accurate establishment of the prenatal diagnosis might be essential.

The aim of this study is to present the systematic ultrasonographic assessment in fetal osteochondrodysplasias and to evaluate the fetal MRI intake, as a complementary exploration to US, in the prenatal diagnosis and perinatal prognosis of fetal nonlethal osteochondrodysplasias.

Material and methods

This study was developed in six university tertiary centres over a period of five years between 2011 and 2016 (see affiliation of the authors). The study included 37 cases diagnosed prenatally with various entities in the category of nonlethal fetal osteochondrodysplasias. The pregnant patients' age ranged from 19 to 41 years. The initial diagnosis was carried out through the routine or detail US examination, both via 2D conventional technique and 3D, 4D or tomographic US imaging (TUI) using Voluson 730 Pro, Voluson E6, Voluson E8 Expert, ultrasound machines, equipped with RAB4-8L, RAB4-8D and RIC5-9-D ultrasound probes, GE Healthcare and Samsung H60 ultrasoud system equipped with CV1-8AD transducer, Samsung Medison.

The systematic evaluation for the diagnosis of osteochondrodysplasias is detailed in Table I.

All pregnancies included in this study have been single pregnancies. All the patients were Caucasian. Combined screening, US and serological, in the first trimester of pregnancy was performed in all cases, without suggestive results of fetal chromosomal abnormalities.

Fetal MRI was performed in the cases in which targeted US or invasive prenatal explorations either did not bring additional data able to clarify the diagnosis or they raised more differential diagnosis issues. Fetal MRI was performed depending on the necessities, and the opportunity to have it done at a gestational age ranging from 17 weeks (+6 days) to 36 weeks (+6 days). We performed MRI on a high-field

Table I. Systematic ultrasound evaluation for the diagnosis of osteochondrodysplasias

Reference skeletal structures	Ultrasound assessment
Long bones	– systematic and very accurate measurement of long bones – qualitative assessment – degree of mineralisation – abnormal curvature – fractures – hypoplasia, absence, malformation – intersegmentary comparison – rhizomelia, mesomelia, acromelia, severe micromelia
Fetal skull	– frontal bossing – macrocephaly – micrognathia – cleft palate – hypertelorism, hypotelorism – cataract
Thorax	– chest biometry, overall morphology – assessment of pulmonary hypoplasia
Spine	– abnormal curvature, demineraliztion, fractures, platyspondyly
Pelvis	– size, overall shape
Hands and feet	– fingers – size, polydactyly, syndactyly – clinodactyly, equal toes, abnormal position – the trident sign
Clavicle	– abnormally shaped or small
Fetal motility*	– hypokinesia

* Systematically evaluated upon each examination as an indirect marker of skeletal abnormalities

and large bore scanner with high resolution images and super-fast acquisition sequences (Ingenia 3.0T, Philips Healthcare) using a body coil. The imaging algorithm included T1- and T2-weighted TSE (turbo spin echo) and BTFE (Balanced Turbo Field Echo) sequences with fat saturation (SPIR) in coronal and sagittal planes with 4 mm slice thickness.

The invasive prenatal diagnosis was done by amniocentesis for all cases. The birth of these fetuses investigated and diagnosed with nonlethal osteochondrodysplasias was carried out either in the clinics where they were evaluated for these abnormalities, or in centres where they were originally registered.

After birth, in the immediate neonatal stage, every newborn received full clinical examination, targeted radiological examination, echocardiography, cerebral, and abdominal US. The recommendation of postnatal monitoring for a period of 1-3 years was offered to all cases, in centres for medical genetics, paediatric surgery, and paediatrics departments, in order to detect associated abnormalities, possibly with later onset, or to correct or augment existing anomalies.

The parents' consent was obtained to publish, for medical research purposes, the postnatal pictures of the cases selected, in compliance with medical bioethics.

Results

The fetal osteochondrodysplasias diagnosed by US and then assessed by fetal MRI are described in Table II.

The representative images for fetal osteochondrodysplasias are illustrated in figures 1-5.

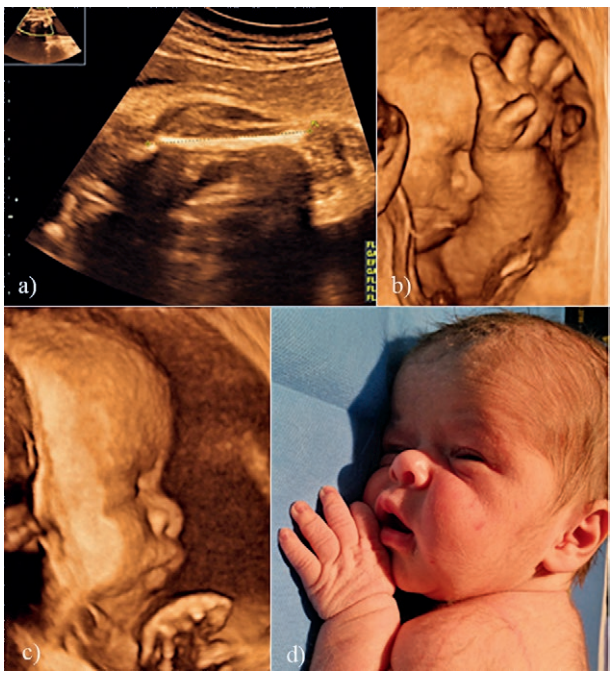

Fig 1. Achondroplasia in a fetus at 30 weeks (+5) of gestation: a) There is a marked shortening of the femur; b) 3D image demonstrates widening between second, third and fourth digits. Note the short fingers that appear the same length; c) 3D image shows fetal right profile. Note the obvious frontal bossing and the depressed nasal bridge; d) Postnatal image of the same fetus confirming the prenatal US findings – frontal bossing, depressed nasal bridge and fingers of equal length with a gap between the third and fourth digits (informed consent was obtained from the parents in order to publish for medical research purposes the picture of the neonate in compliance with medical bioethics).

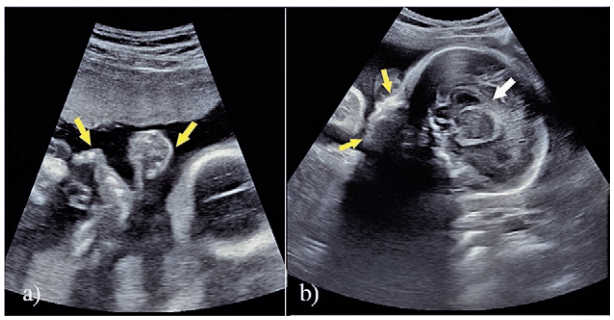

Fig 2. Arthrogryposis multiplex congenita in a fetus at 25 weeks (+3) of gestation: a) Image demonstrates upper extremity contractures of the elbow, wrist and fingers (arrows); b) Image demonstrates micrognathia and abnormal nose (yellow arrows). Note the partial absence of the corpus callosum (white arrow).

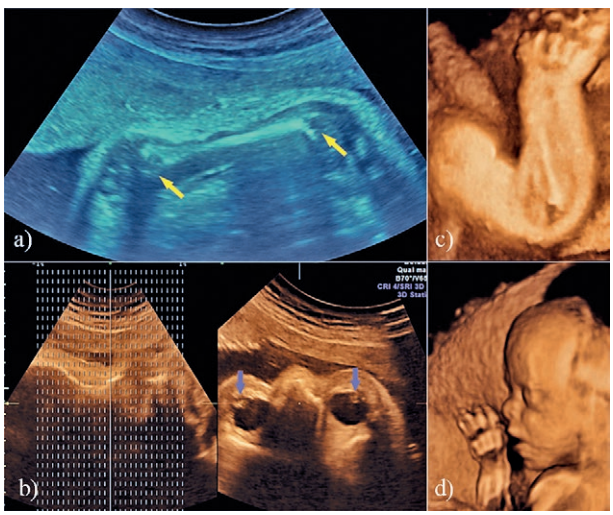

Fig 3. Chondrodysplasia punctata: a) A case at 33 weeks of gestation demonstrating calcific stippling in the proximal and distal humerus (arrows); b) TUI demonstrating bilateral cataract (arrows); c) 3D image demonstrating significant shortening of the rhizomelic portion of the upper limb; d) 3D image demonstrating flat nasal bridge and frontal bossing in chondrodysplasia punctata rhizomelic type in a 22 weeks (+5) fetus.

Table II. Prenatal diagnosis of fetal osteochondrodysplasias in the cases serie

Types of OCD	N	GA	MRI (N)	US and MRI signs Other diagnostic features Outcome
Achondroplasia	15 (40.5)			
• heterozygous achondroplasia	14 (37.8)	18-26	9	Rhisomelic limb shortening with femur lenght < the 3rd percentile, frontal bossing, depressed nasal bridge, equal fingers, progressive macrocephaly with increase of skull circumference > the 95th percentile, trident hand, polyhydramnios (AFI>24 cm). 3D/ 4D US – details on the face and limbs. MRI confirmed rhisomelia, frontal bossing, the absence of pulmonary hypoplasia and essential for the confirmation of the diagnosis, the narrowing of the foramen magnum.
• homozygous achondroplasia	1 (2.7)	15+5		Invasive prenatal diagnosis by amniocentesis. Termination of pregnancy.
Congenital spondyloepiphyseal dysplasia	1 (2.7)	27-32	–	Long bones (arms, legs) < the 5th percentile, flat facies, delayed ossification of spine and knee. US diagnosis is a challenge. Certain postnatal diagnosis by molecular genetics (COL2A1 mutations).
Chondrodysplasia punctata	3 (8.1)	18-28	1	Rhizomelia, proximal humerus punctate calcifications, proximal and distal femoral calcifications, calcaneus calcifications, frontal bossing, micrognatia, cataract, coronal clefts of the vertebrae, scoliosis, microcephaly, polydactyly. MRI – useful for vertebral anomalies and complications of microcephaly. US- the standard for diagnosis.
Dystrophic dysplasia	2 (5.4)	22-25	1	Shortened limbs, clubfeet, joint contractures, hitchhiker thumbs, scoliosis. 3D/4D US useful in facial, spine, and fetal mobility evaluation. Invasive prenatal diagnosis – amniocentesis and molecular genetics. Fetal MRI provides a reasonable assessment of the spine, hip, and shoulder joints.
Ellis van Creveld Syndrome – chondroectodermal dysplasia	3 (8.1)	13-26	1	↑ NT, polydactily, mesomelic limb shortening, long narrow thorax, atrial septal defect. Tests of molecular genetics confirmed the diagnosis. MRI confirmed mesomelic limb shortening and small chest with small ribs.
Arhrogryposis multiplex congenita (AMC)*	9 (24.3)	18 -31	7	Hypokinesia and akinesia, generalized contracture, talipes equinovarus uni/ bilaterally, deformities through flexion and extension of fetal limbs, detected by US in the second and third trimesters, family history. MRI – additional data regarding the intracranial and spinal pathology, possibly responsible for fetal hypokinesia and the assessment of muscular mass. In the mode cine sequence fetal MRI, fetal movement can be assessed.
Osteogenesis imperfecta*	1 (2.7)	35+4	–	Severe deforming type III. Frontal bossing, kyphoscoliosis, multiple short and bowed bones. Certain postnatal diagnosis by molecular genetics (mutation COL1A1).
Craniosynostosis*	2 (5.4)	23-33	1	Abnormal fetal skull by coronal or sagittal craniosynostosis, midfacial hypoplasia, hypertelorism, frontal bossing and proptosis. 3D/ 4D US contribute to the assessment of the fetal face and limbs. MRI – details on the CNS, involvement of cranial sutures, facial dysmorphism, syndactyly hands and feet.
Mesomelic dysplasia*	1 (2.7)	34+6	–	Microcephaly, mesomelia, frontal bossing, mandibular hypoplasia, hypertelorism. ↑ NT, assessed retrospectively. Retrospective postnatal diagnosis by multidisciplinary reassessment. Molecular genetics (ROR-2) and retrospective US assessment suggested classification as Robinow Syndrome.

OCD – osteochondrodysplasias, N – number of cases (%), GA – gestational age (weeks+days), AFI – amniotic fluid index, NT – nuchal translucency. * Entities not classically attributable to nonlethal osteochondrodysplasias, but due to the high phenotypical variability, they can take some features of pathology that could be associated with these representative categories.

Discussions

Some of the entities discussed in this article, including arthrogryposis or craniosynostosis are not strictly defined as skeletal dysplasias, but they are presented in the study because of their rarity and due to the very high heterogeneity of this broad group of diseases [1]. The polymorphism of these anomalies and their many subtypes some-

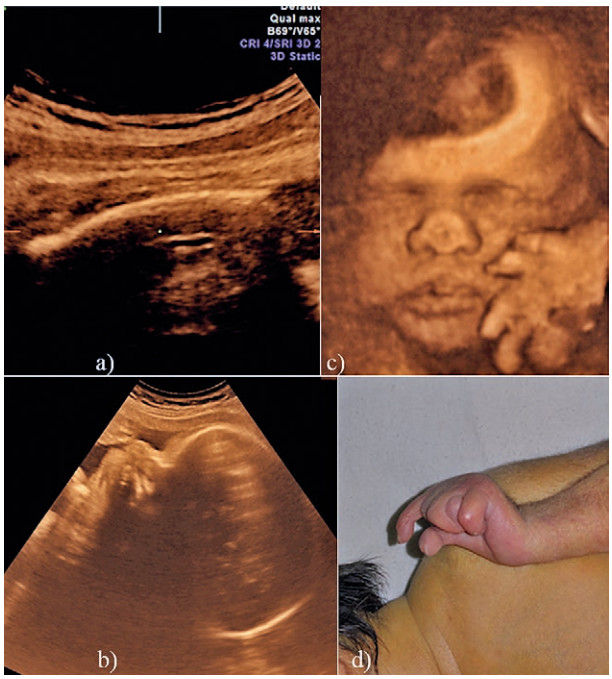

Fig 4. a) Osteogenesis imperfecta in a 35 weeks fetus – demonstrating bowed and irregular femur; b) Sagittal US shows frontal bossing and decreased skull echogenicity and compresibility in the same fetus; c) Diastrophic Dysplasia in a 34 weeks fetus. 3D image demonstrating abducted thumb and joint contractures of the hand (left hand is rotated – see the palmar face of te hand); d) Image of the neonate confirming joint contractures and abnormal position of the fingers (informed consent was obtained from the parents in order to publish for medical research purposes the picture of the neonate in compliance with medical bioethics).

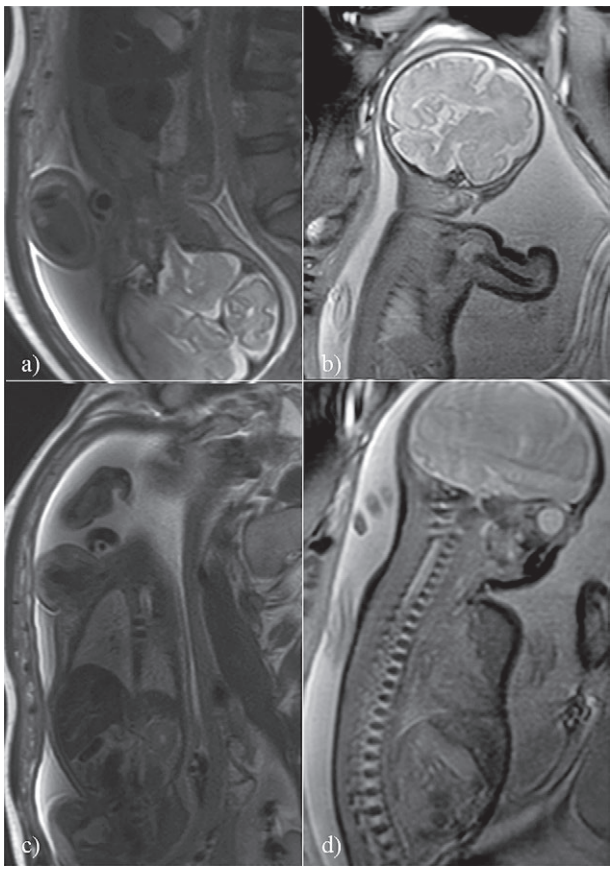

Fig 5. Fetal MRI: a) BTFE SPIR COR T2 – weighted sequence in a fetus with achondroplasia reveals narrowing of the foramen magnum; b) COR TSE T2 – weighted sequence in a fetus with osteogenesis imperfecta confirms rhizomelic bowed humerus; c) SAG TSE T2 – weighted sequence in a fetus with osteogenesis imperfecta confirms normal lung volume; d) COR TSE T2 – weighted sequence in a fetus with achondroplasia showing normal spine

times make their exact classification and diagnosis very difficult, requiring a broader and a more flexible approach. MRI has superior soft tissue contrast compared to the US. It also provides additional information about the stages of maturation of gray and white matter. In addition, it has several plans for reconstruction and a wide field of examination. Similarly to the US, MRI does not expose the patient nor the fetus to ionizing radiation and there is no clinical or experimental clue on possible adverse or teratogenic effects of the use of MRI during pregnancy [6,7].

Musculoskeletal abnormalities as a whole, but more specifically, limb abnormalities that characterize particularly nonlethal fetal osteochondrodysplasias, along with craniosynostosis and skeletal dysplasias specifically referred to, are indications for fetal MRI [8]. Fetal MRI is a valuable exploration, complementary to prenatal US. By the higher resolution and contrast, the ample field of examination and the ability to simultaneously explore both sides of the fetus, fetal MRI can sometimes be more accurate than US in fetal morphological assessment [8,9]. Prenatal diagnosis of skeletal dysplasia can sometimes be very difficult due to overlapping symptoms or to very subtle differences between different pathological subtypes and due to late onset of these conditions. The interdisciplinary approach of these entities both prenatally and postnatally is essential for perinatal prognosis.

Neonatal prognosis of non-lethal osteochondrodysplasias is also very variable. Newborns with abnormalities that interfere with the quality of life or malformations that require surgery or with signs of poor post-natal development are typically classified as having a degree of unfavourable prognostic [10].

Most newborns with heterozygous achondroplasia do not have serious perinatal complications, although there is

an increased risk of medullary compression by stenosis [11]. Secondary medullar compression by stenosis may occur in childhood or later [12,13]. Mild, isolated AMC may require only splints, physical therapy, or both. In more severe cases, surgery may be required to help mobilize joints [14]. In case of chondrodysplasia punctata, the long-term prognosis depends heavily on the biochemical anomaly that it determines, occasionally there may be a favourable diagnosis and a normal intellect in many cases [15]. The overall prognosis of skeletal dysplasias depends largely on the genetic or biochemical abnormality that causes them and the gravity of anomalies associated or caused by them.

Individuals with nonlethal osteochondrodysplasias can survive in some cases to adulthood and they are often able to have offspring [16-19]. The sometimes extremely different phenotypical expression for a certain abnormality suspected or diagnosed, the atypical evolution or events during the pregnancy or in the postnatal period, the lack of specific or targeted genetic tests for certain entities, as well as the multiple features and elements overlapping a certain group of diseases, make this exceptionally vast category a pathological complex extremely difficult to diagnose prenatally with precision [20-25].

Conclusions

The certain diagnosis of skeletal dysplasias is a challenge. US is always the fundamental screening exploration for fetal assessment in nonlethal osteochondrodysplasias. The full prenatal assessment of a fetus with a generic diagnosis of skeletal dysplasia is very difficult. The heterogeneity of US signs, the syndromic polymorphism, the highly diversified phenotypic expression, the very variable perinatal evolution and prognosis, make this group of conditions very difficult to assess prenatally in an accurate way. Fetal MRI has become a useful examination in maternal-fetal medicine, with very extensive indications and encouraging results in skeletal dysplasias. Fetal MRI is always complementary to the US. The details brought by the fetal MRI are useful, and the exploration is harmless for the fetus and the mother. The fetal imagining through conventional US or advanced techniques, alternatively completed with a fetal MRI must underlie the prenatal diagnosis of fetal osteochondrodysplasias. A certain diagnosis cannot be accurate and complete without the contribution of genetics, maternal and fetal medicine, obstetrics or radiology.

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Conflict of interest: none

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