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MULTIPARAMETRIC ULTRASOUND DIAGNOSIS OF FETAL OSTEOCHONDRODYSPLASIAS AND PREDICTION OF POSTNATAL OUTCOMES

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ABOUT ARTICLE

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Abstract: The osteochondrodysplasias or skeletal dysplasias are a heterogenous group of over 350 distinct disorders of skeletogenesis. Many manifest in the prenatal period, making them amenable to ultrasound prenatal diagnosis. A retrospective analysis evaluated 1,500 cases referred to the International Skeletal Dysplasia Registry (ISDR) to determine the relative frequency of specific osteochondrodysplasias and correlation of ultrasound versus radiographic diagnoses for these disorders. Within the retrospective cohort of 1,500 cases, 85% of the referred cases represented well-defined skeletal dysplasias, and the other 15% of cases were a mixture of genetic syndromes and probable early-onset intrauterine growth restriction. The three most common prenatal-onset skeletal dysplasias were osteogenesis imperfecta type 2, thanatophoric dysplasia and achondrogenesis 2, accounting for almost 40% of the cases. In a prospective analysis of 500 cases using a standardized ultrasound approach to the evaluation of these disorders, the relative frequencies of osteogenesis imperfecta type 2, thanatophoric dysplasia and achondrogenesis 2 were similar to the retrospective analysis. This study details the relative frequencies of specific prenatal-onset osteochondrodysplasias, their heterogeneity of prenatal-onset skeletal disorders and provides a standardized prenatal ultrasound approach to these disorders which should aid in the prenatal diagnosis of fetuses suspected of manifesting skeletal dysplasias.

INTRODUCTION

The osteochondrodysplasias are a heterogenous group of over 350 disorders of skeletogenesis. They have been defined by employing a combination of clinical, radiographic, histopathologic, and molecular genetic criteria. These disorders can be inherited as autosomal dominant, autosomal recessive or X-linked disorders and teratogen exposure, maternal lupus and uniparental disomy can produce phenocopies of skeletal dysplasias. Mutations in the genes responsible for these disorders affect the patterning of the skeleton, joint morphogenesis, linear growth and the integrity of the articular surface. While the occurrence of each skeletal disorder is relatively rare, collectively they account for a significant number of newborns with genetic disorders, approximately 1 in 5000.

Both the appendicular and the axial skeletons undergo a programmed pattern of endochondral ossification, whereas the calvarium and portions of the clavicle and pubis ossify via membraneous ossification. Ossification occurs at relatively early human gestational ages: clavicle and mandible at 8 weeks; the appendicular skeleton, ileum and scapula by 12 weeks; and the metacarpals and metatarsals are ossified by 12–16 weeks. Secondary (epiphyseal) ossification centers can be seen by radiographs by 20 weeks gestation. Since bone is echodense by ultrasound, the fetal skeleton/bone is relatively well visualized by two-dimensional ultrasound in the second trimester of pregnancy. Ultrasound evaluation as a tool for identification of congenital abnormalities has become routine in many centers throughout the world. Thus, prenatal-onset skeletal dysplasias, especially the lethal disorders, are readily visualized and ideally should be diagnosed by prenatal ultrasound. The prognostic benefits of accurate diagnosis include determination of perinatal lethality, consideration for focused molecular analysis, prediction of neonatal complications, recurrence risk, and maternal management. The issue of mode of delivery in the skeletal dysplasias remains controversial, though knowing whether or not the disorder is associated with macrocephaly or other abnormalities may help influence obstetrical management.

Previously published series on the diagnostic accuracy of prenatal ultrasound for the osteochondrodysplasias have noted that about 40% of these disorders are correctly diagnosed in the prenatal period. Through the International Skeletal Dysplasia Registry, retrospective and prospective studies were performed to achieve the following goals: to reassess the diagnostic accuracy of prenatal ultrasound for the skeletal dysplasias, to determine the relative frequency of specific disorders, to determine which skeletal dysplasias had abnormal findings in the prenatal period and, ultimately, to determine if a standardized approach to evaluation of these fetuses could improve prenatal diagnostic accuracy. The International Skeletal Dysplasia Registry (ISDR) is a referral research registry focused on the study of osteochondrodysplasias and dysostoses. For each registered case the following information

is obtained; referring diagnosis, clinical information, radiographs and, in some cases, tissues for histologic, ultrastructural, biochemical and molecular analysis. The ISDR team analyses the clinical information, radiographs and histology to determine the diagnosis (authors, DK, DLR, WRW, and RSL). The database from 1990 to 2004 was searched for cases in which the propositus was a fetus or a neonate (<30 days of age). Only cases with the following features were utilized: propositus ascertained between 14 weeks gestation and one month neonatal age; at least one prenatal sonogram was performed during gestation and a referring diagnosis was based on sonographic findings; and postnatal radiographs and available histology were used for final diagnosis. Cases with incomplete information, or inadequate radiographs were excluded from further analysis. In this 14-year time period 1,500 cases were identified for review among the approximately 7700 cases referred during that time period.

Each case was classified by radiographic diagnosis and histology when available. Histology was used for diagnosis when radiographs were not interpretable due to disruption of the fetal skeleton, or if the radiographic findings suggestive a novel pattern of abnormalities. Diseases or diagnosis categories followed the nosology established by the International Nosology Committee. For this analysis, disorders were also grouped into the following categories; osteogenesis imperfecta types 2, thanatophoric dysplasia, achondrogenesis type 2, campomelic dysplasia, short-rib polydactyly syndromes, other specific skeletal dysplasias, unclassified skeletal dysplasias, genetic syndromes, and normal. The classification “normal” was used if the radiographs failed to show any specific skeletal abnormalities. Each case was placed into the above listed categories to determine their relative frequency using the total number of cases for the time period. In addition, for each case and category, the radiographic diagnosis was compared to the referring ultrasound diagnosis to determine percent correlation for ultrasound versus radiographic diagnosis. From the period 1996–2006 the International Skeletal Dysplasia Registry (ISDR) analyzed prenatal-onset skeletal dysplasias by reviewing consecutively referred ultrasound images in 500 cases (14–38 weeks gestation). Each referred case (real-time ultrasound or hard-copy ultrasound images) were reviewed or performed by one of the authors (DK). Analysis and documentation of real-time ultrasound included the following parameters found to be important for diagnosis: appearance, shape and size of the cranium, measurements of the mandible and clavicles, measurements of all long bones, chest circumference and abdominal circumference. Other parameters that were evaluated that aided in differentiating these disorders included the shape of the scapula, vertebral bodies and ribs, the mineralization and shape of the long bones, the appearance of the metaphyseal ends of the bones, presence of facial dysmorphism, evaluation of the hands and feet (absent or extra digits), and presence or absence of the calcaneus and distal femur epiphyses in the late

second and third trimester, as well as other congenital anomalies, posturing of the distal extremities and neck and amniotic fluid volume.

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