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Case Report

Prenatal diagnosis and postmortem evaluation of osteogenesis imperfecta type III at 24th weeks of gestation

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Abstract

Present case demonstrates osteogenesis imperfecta type III, diagnosed by two dimensional sonography in a fetus at 24th weeks of gestation upon admission for second trimester ultrasound scan. Her first antenatal visit and ultrasound examination was performed at 15+5 weeks of gestation; normal growth and development of fetal morphometry was detected and no structural anomalies were observed. However, at 24th weeks of gestational age, we detected a fetus with bilateral femoral fractures and mild thoracal dysplasia. According to these features, the diagnosis was considered as osteogenesis imperfecta and medical legal abortion was performed after decision of family and taken informed consent. In post-mortem physical examination, moderate shortening of femur limbs and deformed ribs were detected. X-ray study of fetus confirmed the diagnosis of OI type III by demonstrating the bilateral femoral fractures, beaded ribs, normal bone mineralization of calvaria and upper extremities. Consequently, an early second trimester detailed ultrasound of the limb bones should be performed to all pregnant women with or without at risk for congenital skeletal abnormalities and prenatal diagnosis should be made before 24th weeks of gestation. This requires a participation of both sonologist and geneticist in a team in order to achieve a specific genetic diagnosis.

Key words:

Osteogenesis imperfecta type III; prenatal diagnosis; skeletal dysplasias; postnatal radiography.

Introduction

Osteogenesis Imperfecta (OI) is a heterogenous group of inherited connective-tissue disorders in which synthesis or structure of type 1 collagen, the major protein constituent of bone and many other connective tissues, is defective and causes osseous fragility and characterized by fragile, brittle and osteoporotic bones, blue sclerae, impaired hearing, defective dentition and hyperlaxibility of the joints [1,2]. The clinical phenotype is broad and ranges from a mild form in which there is a moderate increase in fracture frequency, to a severe form that is lethal in the perinatal period. Based on the pattern of inheritance, age at presentation, radiologic features, and natural history, Sillence et al. [3] described four types of osteogenesis imperfecta and current classification divides OI into four main groups [4], which provide the clinical framework for diagnosis. This classification recognizes two severe or lethal types (II and III) and two relatively mild forms (I and IV) [5]. The classification by Maroteaux et al. [6] also considers prognosis as an extension to the classification of Sillence et al. [3,4].

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Our aim while presenting this rare case was to focus on the attention to the gestational age when the skeletal abnormalities of osteogenesis imperfecta become evident and also to discuss the sonographic findings of all osteogenesis imperfecta types.

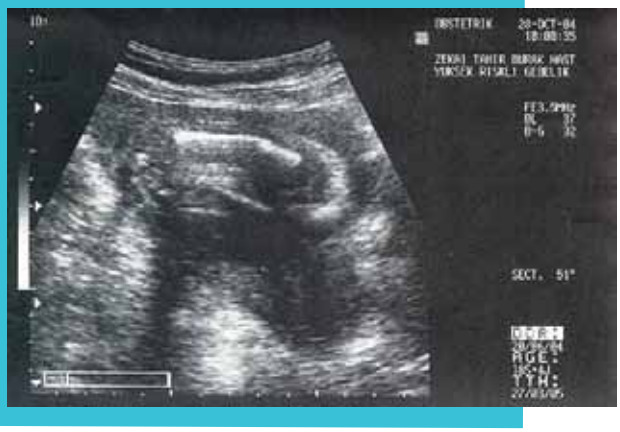
Case presentation

A 29 years old Turkish woman was admitted to our outpatient clinic for routine detailed second trimester ultrasound scan. She was at 24 weeks of gestation according to her last menstrual period. In her previous pregnancies; she gave birth to one healthy newborn and had a first trimester abortion with an unknown etiology. She and her husband were healthy and not relative. The family history of both the patient and her husband was negative for birth defects and congenital skeletal dysplasias. Her prior child was healthy and had no structural anomalies. Her first antenatal visit and ultrasound examination was performed in our antenatal unit at 15+5 weeks of gestation. At that time, normal growth and development of fetal morphometry was evaluated and no structural anomalies were detected.

In her second antenatal visit at 24th gestational week, a fetus with bilateral femoral fractures was detected and she was examined at our high pregnancy ultrasound unit by high resolution sonography (Five MHz convex probe, GE Medical Systems, Solingen, Germany). We observed a single live

breech presentation fetus with fetal measurements of 24 weeks gestation according to biparietal diameter and abdominal circumference. But femoral length is three weeks below the mean femoral length for gestational age. No other fractures of lower limbs and arm bones were seen other than bilateral femoral fracture (Figure 1). The hands were found to be normal. Normal face profile and skull bone mineralisation were observed. The trunk showed mild thoracal dysplasia and the spine was closed. The presence of isolated bilateral femoral fractures was a strong sign of osteogenesis imperfecta lethal type IIB or III. The sonographic findings and the fetal prognosis were discussed with the parents. Medical legal abortion was planned with decision of parents and the ethic committee of our hospital. 800 mcg misoprostol moistened with saline was applicated intravaginally every 6 hours, eleven hours later; a 480 gram female infant was terminated successfully.

Figure 1.



Sonogram of the fetus showing femoral fracture, slightly thick and short femur.

In post mortem physical examination, moderate shortening of femur bones and deformed ribs were detected. Postnatal anteroposterior x-ray view of the fetus confirmed the diagnosis of osteogenesis imperfecta type III by demonstrating the slightly thick, low echogenicity of femurs and bilateral femoral fractures, beaded ribs, normal calvarial and body bone mineralization (Figure 2). Also unilateral new humerus fracture was observed and this finding thought to be caused due to trauma of the parturition passage. All these findings revealed us the diagnosis of osteogenesis imperfecte type III.

Discussion

Increasing use of high resolution ultrasonography has led to increasing ascertainment of skeletal dysplasias by the primary obstetrician prenatally. A specific diagnosis is important in counselling the family and in the decision for making process regarding management of the pregnancy. As a part of the fetal ultrasonographic examination, measurement of the head, abdomen and femur has become routine. In skeletal dysplasias, the femur and the other long bones may be ultrasonographically abnormal in their length, shape and mineralization. Examination of the hands and feet, cranium, spine and thorax may assist in refining the prenatal diagnosis of skeletal dysplasias in addition to absent or abnormal movement. Another important clue to the prenatal diagnosis of skeletal dysplasias is family history. However, most patients with a skeletal dysplasias represent sporadic cases [1,2,7-9].

The most common skeletal dysplasias are thanatophoric dysplasia, thanatophoric variant, achondrogenesis type II, osteogenesis imperfecta, campomelic dysplasia, chondrodysplasia punctata and hypophosphatasia. Although prenatal diagnosis of skeletal dysplasias can present a considerable diagnostic challenge, all these mentioned disorders can be detected between 15-24 weeks gestation However, increasing use of nuchal translucency (NT) scan during 11-14 weeks resulted in early detection or suspection of more skeletal dysplasias. The other few clustered cases are found in the early third trimester as a result of studies performed for gestational complications such as polyhydramnios, intrauterine growth retardation, premature labor, or intrauterine fetal death of affected fetuses [7-10].

Prenatal diagnosis of osteogenesis imperfecta was based on ultrasound findings of abnormal length and aspect of fetal limbs, for example; shortening, bowing, fractures, differences in length and shape between left and right, hypoechogenicity and diminished or absent acoustic shadowing. Other abnormalities of the fetal skeleton include rib fractures, hypoechogenicity of the skull and spine, clear visibility of the cerebral structures giving the cerebral ventricles almost the appearance of hydrocephalus (i.e., pseudohydrocephalus), and narrow chest [3-8].

OI type I is the most common variety with an incidence of 1:30000 live births and an autosomal dominant inheritance. It is characterized by osteoporosis and excessive bone fragility, distinctly blue sclera and presenile conductive hearing loss. Fractures generally occur after birth and lead to progressive deformity. Type IV is characterized by mild osteoporosis leading to skeletal fragility without other features of classic OI type I and IV are inherited in an autosomal dominant manner. Patients have variable ages of onset of fractures and show spontaneous improvement with adolescence. Their prognosis are much better than the prognosis of OI type II and III [3,5,7-9].

Type II is usually of autosomal recessive inheritance with sporadic instances representing fresh autosomal

dominant mutations. This form is always very severe and usually perinatally lethal due to lung hypoplasia. There are multiple fractures in utero and shortened long bones. The thorax is short but not narrow. OI type II occurs in approximately 1:55000 births and is subdivided into three groups as A, B and C based on radiologic criterion [6,11,12]. Type III, characteristically manifested in the newborn or young infant, leads to progressive skeletal deformity and death in childhood. Inheritance is autosomal recessive; however, clinical variability suggests genetic heterogenity. It occurs with an incidence of 1:70000 [6,7-9].

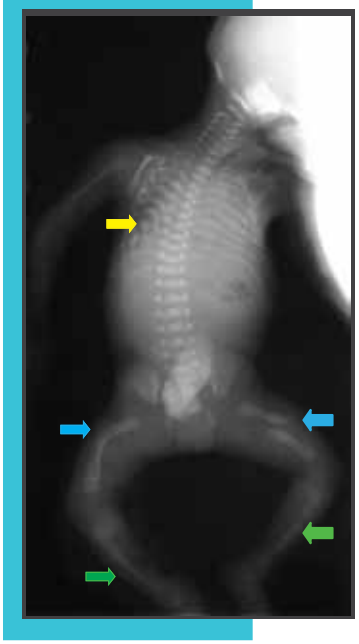
The sonographic features of OI type IIA, B, C are different depending on degree of bone shortening, bone echodensity and number of fractures. OI subtype IIA is the most severe form and the most common form of perinatally lethal OI, consisting of severe micromelia, innumerable fractures, short, broad crumpled femora, continuously beaded ribs and diffuse decreased bone density. OI subtype IIB only short, broad crumpled femora but normal ribs or ribs with incomplete beading, normal bone echo density and isolated fractures of long bones and subtype C by long, thin, inadequately modeled, rectangular long bones with multiple fractures and thin beaded ribs. The sonographic distinction between type IIB and IIC is quite subtle, but the type IIC has shortening of all limbs, unlike the isolated femoral shortening of type IIB [5,6,11-14].

Type III is a heterogenous subtype of type IIB. Sonographic differentiation of type IIB and III is quite diffucult. Type III may be differentiated by isolated limb fractures, but again has a poor prognosis [7-9,15,16]. Prenatal diagnosis of OI type III has been previously reported but only in limited number of cases [15-18]. OI type III is usually diagnosed at birth. In these reported cases of OI III, abnormalities of long bones were the only visible abnormality. Moderate shortening of long bones, which develops after 15 weeks' gestation, together with bowing and occasional fractures has been reported [15,17,18]. Our case confirms these findings by showing normal growth and development at 15 weeks of gestation. The only diagnostic clue and suspected finding on sonography was the isolated bilateral femoral fractures and mild thoracal dysplasia at 24 weeks of gestation.

It seems that prenatal diagnosis of OI type IIB, IIC and III needs a longer observation period because of their later onset. Fetuses with OI type III had normal measurements at 15 weeks, with femoral shortening and deformity only becoming apparent at 19 to 22 weeks [15,17,18]. Measurement of femur length should be a routine part of all scans after 11 weeks' gestation and is quick and easy to obtain. The finding of a short, deformed or fractured femur should thus prompt measurement and assessment of other long bones, skull and chest. Conversely, the finding of an abnormal chest or skull should prompt a detailed assessment of all fetal long bones. In the differential diagnosis of OI Type III, achondrogenesis types, hypophosphatasia and OI Type II must be considered. OI type III is rarely identified before 18 weeks gestation and confirmation of the diagnosis often requires serial ultrasounds to follow changes. However, OI type II, achondrogenesis types IA, IB and II, and autosomal recessive (severe infantile) hypophosphatasia can be identified at 14–16 weeks gestation [7-9,11-18]. In addition, their specific diagnosis can be determined by biochemical study of cultured cells or analysis of DNA from the fetus after the termination of pregnancy. Successful prenatal diagnosis of OI type by using cultured chorionic villi cells has been reported. Molecular biology and genetic studies offer new possibilities of prenatal diagnosis, but ultrasonography remains the first choice of investigation [1,2,19].

Based on reported prenatal sonographic findings and the case presented here, we can conclude that the main classical sonographic feature of OI type III include only bilateral isolated femoral fractures. Although the distinction between subtypes especially with OI IIB may be of limited value because all are lethal, they have different patterns of inheritance. The information of subtype may be helpful in the prediction of the occurence in subsequent pregnancies.

Figure 2.



Postmortem anteroposterior x-ray demostrating the beaded ribs (yellow arrow), bilateral femoral fractures (blue arrows), low echogenicity and abnormal posture of tibia and fibula (green arrows).

To mention again, increased NT thickness is associated with numerous fetal anomalies and genetic syndromes, including skeletal dysplasias in chromosomally normal

fetuses [7-10,20]. The combination of increased NT thickness and hypomineralization make some OI types easier to diagnose at 11–14 weeks of gestational age. Hypomineralization of skull may provide a clear visualization of intracranial structures, mimicking the sonographic appearance of increased NT thickness in some cases [10,20]. Therefore, the sonologist should pay attention to search other sonographic features of OI and measure all long bones. Although the mechanism of increased NT thickness is not fully understood in fetuses with OI, distorted and narrow thoracic cage due to rib fractures leading to mediastinal shifting and altered composition of extracellular matrix have been suggested as possible mechanisms [20]. Moreover, it has been demonstrated that the nuchal edema had disappeared when ultrasound was repeated at 16 weeks' gestation in a prenatally diagnosed case with OI type II at 13 weeks of gestational age [10].

In summary, a reliable diagnosis of severe perinatal type of OI can be made by ultrasound examination during the second trimester, by identification of fractures of the long bones. Although seen rarely and accurate prenatal diagnosis is often difficult in the absence of a relevant family history, this lethal condition should be recognized when a sonography is performed to prevent unnecessary obstetric intervention. In families with a previously affected fetus, prenatal diagnosis by first trimester transvaginal ultrasound examination or chorionic villus sampling should be discussed. During second trimester ultrasound evaluation, osteogenesis imperfecta type III should be considered if a fetus has femur shortening, bowing or fractures, thorax deformity, ribs contraction and low echogenicity of lower limbs.

Conflict of interest statement

The authors declare no conflict of interest.

References

1. Byers PH. Etiology of osteogenesis imperfecta: an overview of biochemical and molecular genetic analyses. Connect Tissue Res 1995;31:257-9. Review.
2. Osteogenesis imperfecta. In: Royce PM, Steinmann B, eds. Connective tissue and its heritable disorders. Molecular, genetic and medical aspects, 2nd edition. New York: Wiley-Liss, 2002.
3. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 1979;16:101-16.
4. Sillence DO, Barlow KK, Garber AP, Hall JG, Rimoin DL. Osteogenesis imperfecta type II. Delineation of the phenotype with reference to heterogeneity. Am J Med Genet 1984;17:407-23.
5. Orioli IM, Castilla EE, Barbosa-Neto JG. The birth prevalence rate for the skeletal dysplasias. J Med Genet 1986;23:328-32.
6. Thompson EM, Young ID, Hall CM, Pembrey ME. Recurrence risks and prognosis in severe sporadic osteogenesis imperfecta. J Med Genet 1987;24:390-405.
7. Krakow D, Lachman RS, Rimoin DL. Guidelines for the prenatal diagnosis of fetal skeletal dysplasias. Genet Med 2009;11:127-33.
8. Schramm T, Gloning KP, Minderer S, Daumer-Haas C, Hörtnagel K, Nerlich A, et al. Prenatal sonographic diagnosis of skeletal dysplasias. Ultrasound Obstet Gynecol 2009;34:160-70.
9. Khalil A, Pajkrt E, Chitty LS. Early prenatal diagnosis of skeletal anomalies. Prenat Diagn 2011;31:115-24.
10. Viora E, Sciarrone A, Bastonero S, Errante G, Botta G, Franceschini PG, et al. Osteogenesis imperfecta associated with increased nuchal translucency as a first ultrasound sign: report of another case. Ultrasound Obstet Gynecol 2003;21:200-2.
11. Pfützenreuter N, Panzer F, Bastert G. Prenatal diagnosis of osteogenesis imperfecta congenita; a case report. Eur J Obstet Gynecol Reprod Biol 1990;34:189-94.
12. Munoz CM, Filly RA, Golbus MS. Osteogenesis imperfecta type II: prenatal diagnosis sonographic diagnosis. Radiology 1990;174:181-5.
13. Constantine G, Mccormack J, Mchugo J, Fowlie A. Prenatal diagnosis of severe osteogenesis imperfecta. Prenat Diagn 1991;11:103-10.
14. Bulas DI, Stern HJ, Rosenbaun KN, Fonda JA, Glass RB, Tifft C. Variable prenatal appearance of osteogenesis imperfecta. J Ultrasound Med 1994;13:419-27.
15. Robinson LP, Worthen NJ, Lachman RS, Adomian GE, Rimoin DL. Prenatal diagnosis of osteogenesis imperfecta type III. Prenat Diagn 1987;7:7-15.
16. Ulla M, Aiello H, Cobos MP, Orioli I, García-Mónaco R, Etchegaray A, et al. Prenatal diagnosis of skeletal dysplasias: contribution of three-dimensional computed tomography. Fetal Diagn Ther 2011;29:238-47.
17. Brons JTJ, van der Harten HJ, Wladimiroff JW, van Geijn HP, Dijkstra PF, Exalto N, et al. Prenatal ultrasonographic diagnosis of osteogenesis imperfecta. Am J Obstet Gynecol 1988;159:176-81.
18. Aylsworth AS, Seeds JW, Guilford WB, Burns CB, Washburn DB. Prenatal diagnosis of a severe deforming type of osteogenesis imperfecta. Am J Med Genet 1984;19:707-14.
19. DiMaio MS, Barth R, Koprivnikar KE, Sussman BL, Copel JA, Mahoney MJ, et al. First trimester prenatal diagnosis of osteogenesis imperfecta type II by DNA analysis and sonography. Prenat Diagn 1993;13:589-96.
20. Makrydimas G, Souka A, Skentou H, Lolis D, Nicolaides K. Osteogenesis imperfecta and other skeletal dysplasias presenting with increased nuchal translucency in the first trimester. Am J Med Genet 2001;98:117-20.