Prenatal diagnosis of the thanatophoric dysplasia type 1

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Abstract
This paper describes a case of one of the most often lethal skeletal dysplasia, thanatophoric dysplasia. The patient at the admission to the hospital presented uterine contractions, abdominal pain, and polyhydramnios. Ultrasound examination showed a shortening length of fetal long bones. A small thoracic circumference on the level of four-chamber view, narrow, bell-shaped chest, shorter ribs with a normal trunk length, and normal mineralization of bones were also seen. The assessment of fetal face revealed signs of facial dysmorphia. The midface hypoplasia, concave nasal bridge, short nasal skillet and frontal bossing were noted. The assessment of fetal extremities showed the opposing setting of the hallux, medial position of the feet, abnormal bending of long bones. The patient underwent a several amnioreductions due to severe polyhydramnios and karyotyping that revealed a normal female karyotype. At 32 weeks of gestation spontaneously preterm rupture of the membrane appeared. Four days later the patient delivered spontaneously and the female newborn weighing 2775 g was born. The neonate presented sign of respiratory failure. The X-ray examination confirmed prenatally observed abnormalities of the skeletal system. Genetic testing revealed a mutation in the newborn FGFR3 gene locus 4p16.3 encoding fibroblast growth factor receptor-3. The prenatal suspicion of thanatophoric dysplasia type 1 was confirmed. The neonate died 7 days after delivery due to pulmonary hypoplasia.

Key words: skeletal dysplasia, ultrasound diagnosis, pregnancy

Introduction
Skeletal dysplasias begins to manifest in the early stages of fetal development. They can be due external causes (eg. teratogen exposure, maternal autoimmune disorders, etc.) or internal causes (single gene disorders with autosomal dominant, recessive, or X-linked modes of inheritance: imprinting errors, chromosomal abnormalities [1]. The overall prevalence of skeletal dysplasias is estimated to be 2.4 per 10 000 birth [2, 3]. The prevalence during pregnancy appears to be higher than 7.5 per 10 000 ultrasound screen pregnancy [4]. The prevalence of lethal skeletal dysplasia ranges from 0.95 to 1.5 per 10 000 live births [2, 3, 5]. Thanatoforic dysplasia, osteogenesis imperfecta Type 2 and achondrogenesis are three most common lethal dysplasias. The overall frequency of perinatal deaths due to skeletal dysplasia is approximately 9 per 1000 birth with 23% stillborn and additional 32% who do not survive beyond the first week of life [3, 6].

Prenatal diagnosis of skeletal dysplasias is based upon fetal ultrasounds diagnosis, magnetic resonance imaging (MRI), computer tomography (CT), Xray scan and molecular analysis. It is often a challenging and very difficult process. The most challenging diagnoses are the skeletal dysplasias with variable phenotypic expression, which are not always lethal.

Case report
35 years old multipara was admitted to the hospital at 22 week’s gestation at risk of preterm delivery, presenting abdominal pain and polyhydramnios (AFI – 40 cm). The gestational age was confirmed by the last menstrual period and ultrasound in the first trimester. On ultrasound polyhydramnios and femur length was diagnosed. Moreover, the remaining long bones were measured and slightly shortening of them was noticed. The transverse scan through fetal chest revealed shorter ribs and a narrow fetal thorax. Reduction 2000 ml of amniotic fluid was performed. The AFI was reduced up to 24 cm. The abdominal pain and respiratory disorders disappeared. The skeletal dysplasia was suspected.

After two weeks the patient was readmitted to the hospital at 24 week’s gestation because of reappearance of abdominal pain, contractions due to polyhydramnios and a high blood pressure. Ultrasound examination showed significantly shortened length of fetal long bones reaching up to 3-4 weeks of difference and amniotic fluid index over 37 cm. Under sonographic guidance amnioreduction with karyotyping was performed. The Doppler examination and 24-hours blood pressure Holter was performed. On ultrasound a small thoracic circumference on the level of four-chamber view, narrow, bell-shaped chest, shorter ribs with a normal trunk length, and nor-
mal mineralization of bones were seen. The assessment of fetal face revealed signs of facial dysmorphia.

The midface hypoplasia, concave nasal bridge, short nasal skull and frontal bossing was noted. The assessment of fetal extremities showed the opposing setting of the hallux, medial position of the feet, abnormal bending of long bones. A few days later polyhydramnios and contractions were observed again. Amnioreduction No 3 was performed. The genetic testing revealed a normal female karyotype (46,XX). Additionally, the TORCH infections were excluded as well. Within the next 10 days the next amnioreduction of 2640 ml was performed. The patient was on tocolysis and Verapamil $3 \times 40$ mg/d was ordered. The re-admission to hospital was at 30 weeks of gestation. During this stay at the hospital two further amnioreduction were performed due to an increasing polyhydramnios.

Ultrasound screening showed a shortening of fetal long bones as well as in proximal as in the distal parts. So, the micromelic shortening of the long bones was confirmed. At 32 weeks of gestation spontaneously preterm rupture of the membrane was appeared. Four days later the patient delivered spontaneously and the female newborn weighting 2775 g, Apgar score 3,1,4 was born. The neonate presented sign of respiratory failure and an infant was treated with a respirator and 100% oxygen was used. The X-ray examination confirmed prenatally observed abnormalities of the skeletal system. Genetic testing revealed a mutation in the newborn FGFR3 gene locus 4p16.3 encoding fibroblast growth factor receptor-3. The diagnosis of thanatophoric dysplasia type 1 was confirmed. The neonate died 7 days after delivery due to pulmonary hypoplasia.

**Discussion**

Prenatal screening and diagnosis of skeletal abnormalities are primarily performed in the second trimester. The ultrasound evaluation of bones includes the assessment of length, shape (curvature), mineralization,
and a presence of fractures what can be observed after 14 weeks of gestation [7]. The femur bone is routinely measured beginning from the first trimester when screening for Down syndrome is performed. The next measurement must be performed during the next screening between 18 and 22 week’s gestation. The short femur is defined as below 5th percentile or below two standard deviations from the mean value for gestational age. The shortened femur length may be constitutional, may be a marker of aneuploidy, or may be also a part of intrauterine growth restriction (IUGR) and skeletal abnormalities. IUGR may be a result of maternal diseases (such as an arterial hypertension), due to vascular and placental factors, chromosomal abnormalities or teratogens exposure. Usually IUGR is associated with small abdominal circumference, abnormal placental morphology, abnormal Doppler parameters, such as an increased resistance to the blood flow in the umbilical arteries, uterine arteries and/or signs of blood flow redistribution in the middle cerebral artery [8]. In presented case all Doppler parameters were within a normal range as well as 24 hours ambulatory blood pressure monitoring. So, a placental source of growth abnormalities might be excluded [8, 9].

Krakov at al. suggested that, the following fetal ultrasound parameters must be visualized and plotted against normative values when a fetus manifest signs of skeletal dysplasia: fetal cranium (biparietal diameter, occipital-frontal diameter, and head circumference), abdominal circumference, mandible, clavicle, scapula, chest circumference, and all fetal long bones. Comparison of the relative length of all the long bones and against normative values will determine whether there is primarily rhizomelia, mesomelia, or that both segments are involved [1]. The most predictive ultrasound findings of skeletal dysplasias that are associated with relative brachydactyly and equinovarus. The long bones length more than 3D below the mean are a strong parameters of a skeletal dysplasia, especially if the head circumference is greater than the 75th centile [1]. Most skeletal dysplasias with prenatal-onset show a relative disproportion of the skeletal measurements when compared with those of the cranium. Finally, the close attention should be paid to the shape and mineralization pattern of the fetal calvarium and other fetal bones (searching for any signs of poor or ectopic mineralization). Determining the elements of the skeleton that are abnormal, coupled with the findings of mineralization and shape of the bones can aid in diagnosis. Appropriate consultation with a geneticist or genetic counselor is recommended to assess the constellation of abnormalities and determine the most likely differential diagnoses. Prognosis and natural history can then be discussed using the most likely diagnoses as the basis for discussion [1].

From the clinical point of view the most important is a prediction of lethality in skeletal dysplasias. It can be done thanks to multiple sonographic parameters among them the most crucial is a small chest circumference associated with the pulmonary hypoplasia. The most suggestive findings for pulmonary hypoplasia are: thoracic circumference < 5 percentile at the level of four-chamber heart view, thoracic/abdominal circumference ratio < 0.6 to 0.79 [13-16], short thoracic length (from the neck to the diaphragm), markedly narrow anteroposterior (AP) diameter, bell-shaped contour of the thorax, and femur length/abdominal circumference < 0.16 [17], short ribs that encircle less than 70% of thoracic circumference at the level of the four-chamber view [18]. According to presented case, micromelic shortening of fetal long bones and bonded bones were observed. Additionally, the narrow, bell-shaped thorax, with short ribs and a prominent abdomen was noticed as a sign of lethality. Shram at al. pointed that one of the most characteristic parameters of thanatophoric dysplasia (TD) type 1 is the narrow thorax, with short ribs and a prominent abdomen [19]. It has been also mentioned that the head circumference is large in half of cases, with the nasal bridge de-
pressed, and in some (mainly in type 2) there is craniosynostosis (‘cloverleaf skull’). Some fetuses with TD have hydrocephaly. In the third trimester, polyhydramnios is common. Growth in FL is slowing down with advancing gestation, leading to steadily decreasing Z-scores with advancing age [19].

On the prenatally diagnosed skeletal abnormalities the diagnosis of TD type 1 was made. This is one of the most common lethal skeletal dysplasia diagnosed prenatally. Type 1 TD is caused by R248C and Y373C mutation in the fibroblast growth factor receptor 3 gen (FGFR3). The typical appearance of TD1 includes the “telephone receiver” shape of femur [20, 21] along with frontal bossing and midface hypoplasia but no cloverleaf skull deformity. However, not all fetuses present the typical bone shape appearance. According to Thomas et al polyhydramnios is present in approximately 50% of affected fetuses [22]. The observed polyhydramnios was the main reason of hospital admission in presented case. There are also other technics that may improve the diagnosis such as: three-dimensional ultrasound (3D-USG), magnetic resonance imaging (MRI), or postpartum radiography or computer tomography.

Summarizing, skeletal dysplasia are large heterogenous group of conditions involving formation and growth of the bones. Lethal skeletal dysplasia are characterized by a sever micromelia and a small chest, what inhibits lung development and leads to a pulmonary hypoplasia. Prenatal diagnosis is based mainly on fetal ultrasound findings, genetics testing, and may be supported by 3D ultrasound, MRI, as well as postpartum radiography or computer tomography.

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References