A case of atypical family form of imperfect osteogenesis (osteogenesis imperfecta)

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Abstract
This article presents an example of prenatal diagnosis of the IIA (lethal) form of imperfect osteogenesis during the second trimester screening examination. At the parents examination external signs of dysembryogenesis in the father are noticed. The further studying of the case allowed to draw the conclusions about the family form of imperfect osteogenesis when the father of a fetus had mild – IV – form of disease and in its baby the signs of more dangerous – II – type of the same disease were found.

Key words: imperfect osteogenesis, osteogenesis imperfecta, US examination, 3D, prenatal diagnosis

Introduction
Imperfect osteogenesis (IO) is clinically, biochemically, radiographically and genetically heterogeneous group of diseases caused by disorders of primary structure, formation and functions of type I procollagen, the major protein for normal skin and bone development (as a consequence of a mutation of genes COL1A1 and COL1A2 for alfa-1 and alfa-2 I type procollagen) [1]. It presents such manifestations as: osteopenia, bones fracture and blue scleras. The forms that occur during lifetime may also be accompanied by worsened hearing, disorders of teeth dentin covering, hypermobility of joints. Synonyms of the disease: osteogenesis imperfecta, Van der Hoeve syndrome, Eddowe syndrome, Lobstein disease, fragile bones disease, Vrolik disease.

Several hundreds of mutations are defined and most of the cases include dot mutations, and changes in natural base sequence; nevertheless, deletions and insertions also take place [1]. These mutations lead to the formation of pathological quantity (I type IO) of collagen or to the production of collagen in changed quality (IO of II, III and IV types) [3].

IO is a hereditary disease of connecting tissue which primarily affects bone, but such manifestations as visual complications, imperfect dentinogenesis, loss of hearing, weakness of joints, restrictive lungs disease and short stature confirm its systemic character [4].

IO may be a part of the following hereditary syndromes: IO, microcephaly and cataract; Brook’s syndrome – IO with innate joints contractures; Lewin’s IO.

The frequency of this disease is estimated to be between 1 : 25 000 [5] – 1 : 28 500 [6].

By ethiology, pathogenesis and clinical symptoms IO is divided into types and subtypes. Several classifications of the disease were proposed, the classification offered by Silence et al. (1979) being most popular [7]. The classification based on a phenotype was slightly changed. Primarily 4 phenotypes were numbered (I-IV), which included mutations of I type collagen gene (COL1A1 and COL1A2), but in some similar patients these mutations were not detected. The rest (3) phenotypes were added to this classification, one among which (type VII) is a result of cartilage-associated protein (CRTAP) gene mutation [8].

The research of recessive forms of IO among the black population of Southern Africa revealed both mutations of cartilage-associated protein (CRTAP) gene and proteoglycan gene (leucine proline-enriched proteoglycan 1 (LEPRE1) gene), each being connected to collagen hydroxylation [4].

Clinical symptoms of IO depend on the type of disease, age of the person at its manifestations, destruction degree of skeleton and other organs.

In type I of IO, which is autosomal dominant disease with a frequency of about 1 : 30000, bones hyperfragility, blue scleras and progressing deafness are noticed, but life expectancy is usual. Children are born with normal weight and length and multiple fractures are absent. It is sometimes possible during ultrasound examination in II and III trimesters to reveal separate long bones fractures. Displacement of the vertebrae and tubular bones curvature are rare complications. This type of IO is divided into A and B forms depending on the presence/absence of pathological dentinogenesis. Prenatal diagnosis becomes possible if DNA analysis is performed.
The case of atypical family form of imperfect osteogenesis diagnosis

Table 1. Classification of imperfect osteogenesis by Sillence (reviewed)

<table>
<thead>
<tr>
<th>Form</th>
<th>Type of inheritance</th>
<th>Frequency of fractures</th>
<th>Skeletal deformation</th>
<th>Imperfect dentinogenesis</th>
<th>Hearing disorders</th>
<th>Scleras</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>AD</td>
<td>+</td>
<td>/ +</td>
<td>–</td>
<td>+++</td>
<td>Dark blue</td>
<td>Mild</td>
</tr>
<tr>
<td>IB</td>
<td>AD</td>
<td>+</td>
<td>/ –</td>
<td>+</td>
<td>+</td>
<td>Dark blue</td>
<td>Mild</td>
</tr>
<tr>
<td>II</td>
<td>AD, AR</td>
<td>+++</td>
<td>+ / +</td>
<td>+ / –</td>
<td>+</td>
<td>Dark blue</td>
<td>Lethal</td>
</tr>
<tr>
<td>III</td>
<td>AD, AR</td>
<td>+++</td>
<td>+++</td>
<td>+ / –</td>
<td>+</td>
<td>White/blue</td>
<td>Severe</td>
</tr>
<tr>
<td>IVA</td>
<td>AD</td>
<td>+ / +</td>
<td>+ / +</td>
<td>–</td>
<td>+</td>
<td>White</td>
<td>Mild to average</td>
</tr>
<tr>
<td>IVB</td>
<td>AD</td>
<td>+ / +</td>
<td>+ / +</td>
<td>+</td>
<td>+</td>
<td>White</td>
<td>Mild to average</td>
</tr>
<tr>
<td>V</td>
<td>AD</td>
<td>+ / +</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>White</td>
<td>Average</td>
</tr>
<tr>
<td>VI</td>
<td>AR</td>
<td>+ / +</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>White/blue</td>
<td>Average</td>
</tr>
</tbody>
</table>

A – normal teeth, B – imperfect dentinogenesis; AD – autosomal dominant, AR – autosomal recessive (extremely rare)

Type II of IO is a lethal variant of the disease which is why the search for signs in this type is extremely important. This form of the disease occurs with a frequency of about 1:60000. It was considered to have autosomal recessive inheritance, but the absence of affected siblings in different series of investigations allowed to suppose a new mutations of dominant gene or not genetic ethiology of the disease. In this connection the empirical risk of recurrence is less than 25%; according to FMF data, frequency of recurrence is about 6%.

The majority of IO type II cases are accidental, caused by autosomal dominant mutations which arise de novo in primary reproductive cells of parents. For this reason the manifestations of this lethal type of IO are usually unseen and require very careful prenatal ultrasonographic screening for timely finding of corresponding pathological symptoms. At this form of the disease mutations lead to the synthesis of pathological procollagen chains that get bound to normal chains synthesized by the same cells and break their biological activity [9]. A strategy of mutant alleles neutralization is being elaborated [10].

The disease is characterized by early prenatal manifestations such as significant shortening and curvature of bones because of multiple fractures of long tubular bones and ribs, and weak mineralization of cranium bones.

Affected persons die prenatally or in early neonatal period because of respiratory failure and/or central nervous system injury. Multiple fractures are defined in the fetus; long bones shortened, wide and bent. A thorax is short and bell-shaped, with multiple fractured ribs. Cranium bones are not ossificated enough. Scleras are blue. Symmetric fetal growth retardation is often a case. Sillence et al. proposed to divide type II into three variants depending on radiological criteria. Short, wide and bent tubular bones, bead-like ribs are typical for the first (A) variant, for the second (B) – wide curved femurs and minimal or absent ribs fractures, for the third (C) – narrow femurs with fractures symptoms and bead-like ribs [6].

Type III of IO may have both autosomal dominant and autosomal recessive character of inheritance.

The scleras of the patient becomes less blue with age. Long bones are shortened and curved, multiple fractures are found out at birth in the majority of affected children. Cranium bones ossification is insufficient. The disease is characterized by gradual progression in long bones and spinal curvature that causes scoliosis and short stature.

Type IV of IO is autosomal dominant disease with different degree of symptoms expression. This type of IO belongs to the mildest form of the disease. Scleras are blue-colored in the newborn, but they become white with the years. Tubular bones are of normal length, but the femur may be curved a little. Patients with heavy manifestations may have long bones deformations because of fractures. According to the presence/absence of imperfect dentinogenesis type IV of the disease is divided into A- and B-form correspondingly.

Prenatal diagnosis of III and IV types may be carried out by chorion villi sampling and DNA analysis or by the confirmation of pathological production of collagen in fibroblasts culture (FMF).

As to the lethal form of the disease, there are a number of reports in the literature about prenatal ultrasound diagnosis of type II of IO. Sonographic symptoms of the pathology may be defined in parts of all bone system. Fractures, bending, shortening, local thickening because of callus formation, bow-shaped curvature and symptoms of demineralization may be found while examining of long tubular bones. These phenomena are usually more expressed in a femur, but may also occur in bones of the
arm. In rare cases the extremities are so shortened, that they cannot be measured. Cranium bones may be so thin, that the pressure of ultrasound transducer easily leads to their deformation. At severe forms of the disease the contours of a skull are wavy, cranium is easily compressed. Multiple ribs fractures result and cause formation of bell-shaped or narrow thorax. Echodensity of spine is rarely decreased. Fetus activity is lowered.

IO is rarely accompanied by other congenital defects, single cases of microcephaly, heart defects, anencephaly etc. are described [11]; there are some reports about the diagnosis of IO combined with other congenital defects in I trimester of pregnancy [12].

No doubt, IO is the most widespread genetic form of susceptibility to fractures. Depending on the age of disease manifestations, there may be difficulties with differential diagnosis of IO and some other genetic and non genetic causes of fractures [13].

There is a possibility to perform molecular-biological prenatal diagnosis but ultrasound examination remains examination of choice [2]. In addition, for laboratory prenatal diagnosis to be performed the case of such disease should be expected in family. Histomorphological (light-optical and electronic-microscopical) bones investigation allows more precise diagnose of IO type and the features of bone tissue ultrastructure explain the reason of its fragility [14].

Imperfect osteogenesis is a disease with a wide spectrum of clinical symptoms. Multiple fractures and intracranial hemorrhage may cause the death in antenatal, intra-, and neonatal periods. Nowadays the information concerning the prognosis of this disease diagnosed prenatally is limited due to the fact that pregnancy is usually terminated. The health of patients who survived varies extremely. Multiple fractures may be a reason for repeated operative treatment and may be accompanied by significant complications.

Type II of IO is a lethal form, types I and III are compatible with life, but patients may develop significant complications connected with multiple fractures and deformations. Type IV has the most favorable prognosis, fractures and deformations are rare.

The therapy of children, who were diagnosed by prenatal screening examination, begins prenatally. The management of labor should be performed with precise collaboration between paediatricians and gynecologists and should be defined by the expected degree of the disease anticipated on the basis of ultrasound examination.

Ultrasound examination in II trimester after 17-18 weeks is quite reliable method of prenatal diagnosis of lethal type II IO [18] though there are single reports about IO lethal forms diagnosis in 15 weeks and even in 13 weeks of pregnancy but in the case of additional congenital defects presence [19]. Unfortunately, reliable diagnosis of all IO forms by means of ultrasound exam remains impossible because mild forms of the disease do not give such changes that could be reliably revealed prenatally. In case of extremity fractures diagnosed prenatally, cesarean section should be performed. Indications for cesarean section is facilitated if breech presentation (that is often a case) is present [2].

The prognosis of type II IO is lethal, mainly due to lungs underdevelopment. As the majority of the cases of type II IO are the result of new autosomal dominant mutations, the recurrence frequency of such forms is reported to be as low as 6% [15]. The expected recurrence risk of rare autosomal recessive type II IO varies from 10% to 25% [16, 17]. Accordingly, considering the lethality of type II of the disease, in case of its prenatal diagnosis pregnancy termination in any time should be recommended.

Materials and methods

35-year old pregnant patient is admitted to the clinic of reproductive medicine “Nadiya” for the prenatal screening examination of her second natural pregnancy, second pregnant with the same partner with whom she had one healthy baby. Family history of this couple was unremarkable.

During the first trimester screening combined examination by OSCAR approach (One-Stop Clinic for Anomalies Risks assessment) in 12 weeks 2 days detailed explanations was given to the family concerning the sense and content of this examination; an informed consent was signed by; so-called first trimester biochemical markers of chromosomal anomalies PAPP-A (Pregnancy Associated Plasma Protein A) and free β-subunit of hCG (human Chorionic Gonadotropin) in patient’s blood were measured by laboratory analyzer “Kryptor” of German firm “B.R.A.H.M.S.”; detailed ultrasound examination on the expert class ultrasound scanner was performed according to all requirements of FMF (Fetal Medicine Foundation, UK) by FMF certificated operator. Personal risks of fetal chromosomal anomalies were calculated by special software ASTRAIA certificated by FMF for such calculations. Personal calculated risk of trisomy 21 was not increased – 1 : 6402.

No pathological signs were found during the first trimester ultrasound screening examination. Second trimester ultrasound screening examination was performed at 20 weeks of gestation.
Results and discussion

During routine screening ultrasound examination of 20 weeks of pregnancy the following pathological ultrasound signs were found: significant curvature and shortening of tubular bones of all extremities, typical for intrauterine bones fractures (fig. 1-4).

Fig. 1. 2D image of fractured bones of a shoulder and a forearm

Fig. 2. 2D image of fractured bones of a femur and a shin

Fig. 3. 3D image of fractured and bent arms (arrow)

Fig. 4. 3D image of fractured and bent arms and legs (arrows)

Fig. 5. 2D sagittal image of fractured ribs (arrows)

Fig. 6. 2D transversal image of fractured ribs

Multiple fractures of ribs on both sides (fig. 5, 6).

Fetus head was deformed because of insufficient cranium mineralization (fig. 7) and easily changed form when pressed by ultrasound transducer; we also fond the high prominent forehead, nose with visible but slightly
mineralized bones (fig. 8) and reduced size of the mandible (fig. 9).

Clear image of brain structures close to the transducer field was also a result of cranium hypomineralization (fig. 7).

No other fetal malformations or pathological features were found. A fetal measurements ratio was changed: cerebellum transverse diameter and head sizes in average corresponded to expected 20 weeks of gestation, the abdominal circumference – to 18 weeks, the length of bent, fractured and, thus, shortened tubular bones corresponded to 14-15 weeks of pregnancy (Table 2, 3).

Doppler data of blood flow in umbilical and uterine arteries were normal confirming good maternal-fetal circulation (fig. 10).

Table 2. Biometry table with fetal measurements

<table>
<thead>
<tr>
<th>Fetal Biometry</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Avg.</th>
<th>G.A.</th>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD</td>
<td>52.70</td>
<td>52.70 mm</td>
<td>21w0d ± 19d</td>
<td>81.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>175.00</td>
<td>175.00 mm</td>
<td>20w0d ± 10d</td>
<td>45.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>125.10</td>
<td>125.10 mm</td>
<td>18w1d ± 15d</td>
<td>0.26*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTA</td>
<td>1245.39 mm²</td>
<td>17w4d</td>
<td>0.87*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FL</td>
<td>15.60</td>
<td>17.30</td>
<td>18.20</td>
<td>17.03 mm</td>
<td>14w6d ± 10d</td>
<td>81.28</td>
</tr>
</tbody>
</table>

Figs. 7, 8, 9: Images of fetal ultrasound scans showing various anomalies and measurements.
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Table 3. Biometry table with fetus measurements

<table>
<thead>
<tr>
<th>Fetal long bones</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Avg.</th>
<th>G.A.</th>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUM</td>
<td>Jeanty</td>
<td>17.20</td>
<td>11.20</td>
<td>17.20 mm</td>
<td>14w6d ± 20d</td>
<td>0.01*</td>
</tr>
<tr>
<td>ULNA</td>
<td>Jeanty</td>
<td>13.70</td>
<td></td>
<td>13.70 mm</td>
<td>14w3d ± 22d</td>
<td>0.08*</td>
</tr>
<tr>
<td>TIB</td>
<td>Jeanty</td>
<td>12.50</td>
<td></td>
<td>11.85 mm</td>
<td>14w1d ± 21d</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fetal cranium</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Avg.</th>
<th>G.A.</th>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEREB</td>
<td>Hill</td>
<td>22.60</td>
<td>21.80</td>
<td>22.20 mm</td>
<td>20w6d ± 13d</td>
<td>92.07*</td>
</tr>
<tr>
<td>OOD</td>
<td>Jeanty</td>
<td>28.00</td>
<td></td>
<td>28.00 mm</td>
<td>18w1d ± 24d</td>
<td></td>
</tr>
<tr>
<td>IOD</td>
<td></td>
<td>9.50</td>
<td></td>
<td>9.50 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CM</td>
<td></td>
<td>3.50</td>
<td></td>
<td>3.50 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NF</td>
<td></td>
<td>1.80</td>
<td></td>
<td>1.80 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral Ventricle</td>
<td></td>
<td>5.20</td>
<td></td>
<td>5.20 mm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

On the basis of ultrasound signs we diagnosed the lethal form of osteogenesis imperfecta, type IIA, the family decided to terminate the pregnancy. Fetal karyotype, as it was anticipated, was normal male. Histopathological investigation confirmed the diagnosis.

The observation of the parents revealed some certain pathological features in the father and the general similarity of the father and the fetal features. After the review of childhood photos of the father and fetal photos after pregnancy termination a significant similarity of head structure was found (fig. 11-16).

As far as no increased susceptibility to fractures was noticed in father during his life, assumption was made about the presence of type IV mild form of IO in the father. Therefore, a case of prenatal diagnosis of IO in this family was considered to be an atypical family form because type IV of IO is usually a consequence of a dominant mutation.
Additional diagnostic tests of the father and also of the already born healthy child were recommended to the family. In case of family’s intention to have another pregnancy, DNA testing of all family members is desirable to compare findings with the future fetus during preimplantational or prenatal diagnosis.

Fig. 13. A postmortal fetus photo with multiple fractures of tubular bones

Fig. 14. The profile of baby’s father with significant similarity of features

Fig. 15. A full face of the baby’s father with similarity of features

Fig. 16. A postmortal photo of the fetus with multiple fractures of tubular bones

Conclusions

1) The presented case of timely diagnosed fetal form of type II A rare osteogenesis imperfecta is an example of systematic and successive approach to the first and second trimester prenatal screening examinations.

2) Diagnosis of such lethal malformations after 22 weeks of gestation according to Ukrainian current legislation, unfortunately, has no influence on perinatal mortality rate. Therefore this case once again reminds Ukrainian professional medical societies of necessity to open dialogue with politicians and legislators concerning the valid perinatological instructions improvement.

3) It is seems desirable and reasonable to perform all prenatal screening ultrasound examinations with both parents present: on the one hand, it sometimes helps in diagnostic process, on the other hand, in case of pathological findings the pregnant woman is psychologically supported by her partner.

References

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