Sirenomelia with urethral atresia, corresponding megacystis and bilateral hydronephrosis, diagnosed in the first trimester of pregnancy after assisted reproductive technologies

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Abstract

We present a case of ultrasound diagnosis (USD) and fetoscopic confirmation of mermaid syndrome (sirenomelia) at 12 weeks GA after assisted reproductive technologies (ART) with intracytoplasmic sperm injection (ICSI) due to primary infertility. Sirenomelia sequence is a rare and lethal anomaly characterized by fusion, rotation, hypotrophy or atrophy of the lower limbs and severe urogenital abnormalities (usually associated with the absence of bladder and agenesis or dysgenesis of kidneys) leading to oligohydramnios in the second half of pregnancy. Our case is not typical considering the presence of urethral atresia, megacystis and bilateral hydronephrosis. In fact, there are no such cases presented in world medical literature. Usually the main task of first trimester screening at 11+0 – 13+6 weeks is the assessment of the individual chromosomal abnormalities risk. Using OSCAR (One Stop Clinic for Assessment of Risk of fetal anomalies) methodology, last years we also placed high emphasis on simultaneous accurate examination of fetus anatomy in first trimester and on evaluation of the possible late obstetrical complications risk. Our case demonstrates that even such rare lethal anomalies may be diagnosed with a high degree of confidence in the first trimester of pregnancy. Our experience as well as world medical literature allowed us to conclude that USD performed during combined screening examination in the first trimester is the best method for mermaid diagnosis.

Key words: sirenomelia, mermaid syndrome, megacystis, prenatal diagnosis, first trimester, screening, OSCAR, fetoscopy, infertility treatment, ART, ICSI

Introduction

The name “sirenomelia” (“mermaid syndrome”) originates from physical similarity of affected fetus to mythical creatures – mermaids – magic women with lower part of the body in the form of fish tail when fusion of the lower limbs and partial or full fusion of the feet (fig. 1a, b) take place.

Frequency of this anomaly according to different authors ranges from 1:24,000 up to 1:100,000 live birth [32, 44, 46, 48, 49, 50, 56]. Nevertheless, these data can be deceptive, considering similarity of this defect to so-called caudal dysplasia or regression. Controversy exists in the literature regarding whether sirenomelia occurs as a separate entity or the extreme form of caudal regression syndrome [15, 42, 49, 53, 54, 56]. However, the presence of two umbilical arteries, non-lethal renal anomalies, non-fused lower limbs, abdominal wall defects and also anomalies of tracheoesophageal tree, nervous tube and heart allows differentiating caudal regression syndrome and sirenomelia. Besides, caudal regression syndrome shows continuous association with maternal diabetes mellitus [20, 25, 33, 43, 56, 63], and also with multiple pregnancy [2, 3, 8, 16, 34, 39, 47, 56, 63]. A case of combination of mermaid syndrome and amniotic band was observed. Association with assisted reproductive technologies, namely with application of ICSI (Intracytoplasmic Sperm Injection) was described [4].

Etiology of mermaid syndrome is still controversial. There are some theories, however, none of them are convincing enough [26, 50-52, 56, 61]. Assumptions come out that sirenomelia is a consequence of teratogenic factors, for example, sirenomelia has been obtained in animals after cadmium introduction in blood steam [23]. Experimentally this defect was achieved by irradiation of embryos caudal part [49], application of retinoic acid – acidic form of vitamin A [60], and cocaine abuse [45]. Some authors postulated that sirenomelia is only clinical manifestation of caudal regression syndrome because of abnormal development of fetal caudal mesoderm axis structures before fourth week of gestation that later spreads to different craniocaudal levels [26].
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It also leads to the absence of genitalia and kidneys agenesis if paramesonephral and mesonephral ducts are involved. If mesonephral ducts have developed enough, having reached ureters anlage, and have joined mesonephral blastema, kidneys can be developed. Sometimes mesonephral sites of mesoderm are damaged or underdeveloped, and in these cases hypoplastic or abnormal kidneys are being formed [5].

Three pathogenetic theories of sirenomelia are described: 1) the theory of pressure, 2) the theory of primary damage of caudal somites development that leads to the abnormal development of fetal lower part, 3) undernourishment of fetal caudal part. For understanding the pathogenesis vascular stealing phenomenon was proposed [53]. Sirenomelia can be caused by blastogenesis anomalies which interfere with blood supply to caudal parts of the fetus. The diverged vessel, being derivative of yolk artery, deviates from abdominal aorta of affected fetuses and works as a single big umbilical artery (right in most cases) – a vessel that returns blood through umbilical cord to placenta, i.e., in mermaid syndrome umbilical cord has only two vessels instead of three. This vessel “steals” blood from the structures located below its deviation, i.e. from the tissues of fetal caudal part. The abdominal aorta often happens to be smaller in cross section size in comparison to this vessel, and can have no sufficient branching itself. Because of vascular insufficiency and corresponding reduced blood supply to caudal part of the fetus marked anomalies of spinal cord, kidneys, gastrointestinal and urogenital tracts usually take place: absence of kidneys, kidneys dysgenesia, imperforated anus, adrenal ectopia, single umbilical artery [2, 10, 30, 36, 43, 46, 52, 54, 56]. Because of kidneys agenesis or dysgenesia of it is not possible to see them at all during ultrasound examination (USE) [13, 24, 26, 31, 46, 49, 53, 54, 56]. Reports have been presented about multicystic dysplastic kidneys associated with this pathology [24]. Bladder at sirenomelia usually is not defined at all. Marked oligohydramnios, usually caused by lethal kidneys anomalies, can limit an opportunity to detect other complex and dangerous structural anomalies. Oligohydramnios is also the reason of lungs hypoplasia and, accordingly, thorax hypoplasia and promotes dolichocephaly formation with so-called typical Potter face. Anomalies of kidneys, significant oligohydramnios and corresponding lungs hypoplasia account for sirenomelia lethality. Since the reason for defects formation is abnormal blood supply, a lot of associated anomalies can be observed, making two identical cases different. Beside anomalies described above one can observe: abdominal cysts, malposition of visceral organs – situs inversus, umbilical hernia, oesophageal atresia [30, 36, 43, 46, 51, 56]; absence of the upper extremities [8]; acardia and pentalogy of Cantrell [18, 46, 48, 56, 62]; anomalies of nervous tube organs – spina bifida, hydrocephalia, anencephalia, cyclopia, cebcephalia, holoprosencephalia, meningomyelocele [11, 27, 28, 36, 40, 44, 46, 47, 56]. There are also reports in medical literature about the presence of heart defects [54]. Possible facultative additional skeletal defects include: absence of sacrum, absence of the lower lumbar parts of spinal cord, segmental defects of distal parts of spinal cord. Cases of fixed view of lower extremities (only soft tissues fusion of lower extremities), single
lower extremity (bones fusion) and abnormal number of lower limbs are described [24, 49]. The single thick hip is described at bones fusion [13]. Feet can be absent, entirely or partially fused, can look like one foot, usually of changed configuration.

Although isolated cases of survival at not lethal visceral defects are described in the literature, first of all in cases of entirely formed extremities with only skin or soft-tissue fusion, combinations of limbs anomalies with anorectal defects, defects of urinary tracts, anomalies of pelvis and external genitals, have extremely poor prognosis and almost always lead to death or very significant disability [14, 32, 38, 52, 56]. Thus, in case of mermaid syndrome diagnosis before the fetus viability period termination of pregnancy is reasonable.

The best method of sirenomelia diagnosis during screening examinations is considered to be ultrasound diagnosis – bidimensional (2D) and three-dimensional (3D) modes, colour and power Doppler which is useful for searching of single umbilical artery, abnormal distal abdominal aorta and especially helps in case of oligohydramnios; in case of oligohydramnios magnetic resonance imaging (MRI) [1, 13, 17, 22, 24, 25, 29, 40-43, 49, 50, 54, 56, 57, 59] may also be very useful. Recently, owing to the increasing prevalence of combined screening examinations in 11+0-13+6 week’ gestation, it becomes clear that sirenomelia diagnosis in the end of the first trimester is more favourable in comparison to the second trimester because of sufficient amount of amniotic fluid which at this time much less depends on fetal urinary excretion [1, 7, 9, 22, 37, 46, 48, 58] and we also share this opinion. Joined femurs without their separate movements during ultrasound examination should suggest a possible lower limbs fusion. In the presence of oligohydramnios and bilateral kidneys agenesis, observation of fused fetal lower extremities is a key to antenatal diagnosis of mermaid syndrome. Besides at the moment there are no biochemical serum markers for antenatal sirenomelia diagnosis available.

While performing differential diagnosis one should exclude Potter syndrome, Meckel-Gruber syndrome, kidneys dysplasia, variants of obstructive uropathy and severe intrauterine growth retardation syndrome that is extremely difficult to do in II or in III trimester because of severe oligohydramnios. Improvement of diagnostic ultrasound equipment quality and knowledge spreading among doctors about rare defects enable diagnosis of mermaid syndrome as early as I trimester of pregnancy. Table I presents 10 cases of mermaid syndrome diagnosed in the first trimester from 10 till 13 weeks found in the world medical literature (search was carried out via Internet by means of Google search system by Latin and Cyrillic letters; separate search among Polish, Ukrainian and Russian-speaking parts of Network did not give additional results).

Table 1. Cases of antenatal diagnosis of mermaid syndrome in I trimester

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<tr>
<th>Author</th>
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<tr>
<td>Carbillon L. et al.</td>
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<td>Monteagudo A. et al.</td>
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<td>Akhayir O. et al.</td>
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Occurrence and recurrence of mermaid syndrome is sporadic, fetus karyotype is usually unremarkable. This condition is considered to be much more often observed in monozygotic twins, 150 times more often than in singleton pregnancies [3, 46, 50, 56].

It is recommended to analyze chorion in the I trimester for fetus karyotyping, however one should remember that because of possible mosaicism chorion karyotype does not always corresponds to fetal karyotype. At the same time, besides chromosomal aberrations there are many other factors that can damage fetus development. Tissues obtained after pregnancy termination are often difficult to differentiate because of their damage. Thus, in most cases examination of removed fetus in first trimester is impossible. Even when any anomalies are detected at ultrasound examination, one cannot be confident whether these defects are isolated or are syndrome components. Starting from 11 weeks of gestation ultrasound diagnosis accuracy increases together with fetus growth but this accuracy considerably depends on quality of diagnostic equipment and doctor experience; and even under best conditions precise ultrasound diagnosis of, for example, facial dysmorphy or minor limbs defects in I trimester is challenging. Therefore, to search for additional possible diagnostic signs after some
defects sufficient for family decision of pregnancy termination being found at ultrasound examination, transcervical fetoscopy with subsequent cytogenetic analysis seems to be reasonable and necessary [64, 65].

In the article we present a case of ultrasound diagnosis of mermaid syndrome (sirenomelia) in a fetus with unremarkable karyotype at 12 weeks of gestation. Before pregnancy termination fetoscopy confirmation of diagnosis was performed by means of transcervical fetoscopy with subsequent cytogenetic analysis of fetus karyotype.

Material and methods

Affected fetus has been diagnosed during routine combined screening examination of I trimester by OSCAR method (One Stop Clinic for Assessment of Risk of fetal anomalies) in 31-year-old patient after primary infertility treatment. The woman had usual karyotype, her husband’s karyotype – 46,XY, inv. 9 (p21q22) (normal variant). Patients’ family history was unremarkable. Pregnancy was achieved after the first attempt of in vitro fertilisation (IVF) with intracytoplasmic sperm injection (ICSI). First trimester pregnancy course was unremarkable. At 12 weeks 2 days’ gestation during routine screening examination of I trimester by OSCAR method detailed transabdominal ultrasound examination was carried out on the expert class ultrasound scanner according to all Fetal Medicine Foundation (FMF) requirements by FMF accredited doctor.

Fetoscopy was performed by STORZ diagnostic microhysteroscope and without cervix dilatation. At the beginning of the procedure (at hysteroscope insertion into the uterine cavity) liquid speed was equal to 100 ml/min. After gestational sac was revealed chorion and amnion were cut by scissors. After hysteroscope insertion to the amnion speed of physiological solution infusion was decreased to 30-80 ml/min which allowed to scrutinize the fetus closely and to reduce fetus fluctuations by liquid flow.

Pregnancy was terminated by curettage and aspiration through dilated cervical canal. The removed material was used for cytogenetic analysis of fetus karyotype.

Results and discussion

During ultrasound examination as a component of combined screening examination of I trimester OSCAR following symptoms have been found: reduced size of gestational sac (average size was equal to 50 mm, fig. 2), significantly increased size of the bladder (11 × 8 × 10 mm, fig. 3), marked bilateral hydronephrosis (fig. 4), single umbilical artery (power Doppler indicates single artery aside from bladder, fig. 5) and fused fetal lower extremities resembling fish tail (fig. 6). Any other visible defects were not found. Nuchal translucency was equal to 1.3 mm.
3D ultrasound examination was also performed to reconstruct the findings detected at 2D ultrasound and to ease the explanation of found anomaly to the parents (fig. 7a, b).

Taking into account fetus lethal anomaly and signs mentioned above, the parents were provided with all neces-
sary explanations and made the decision to terminate the pregnancy. After family sighed consent, transcervical fetoscopy was carried out before pregnancy termination and it confirmed the diagnosis of mermaid syndrome with fetus lower limbs being fused (fig. 8a, b) and single umbilical artery present (fig. 9). Other external defects were not found.

Fig. 9. Fetoscopic image of umbilical cord with two vessels instead of three; intact fetus head and hands are also evident.

Cytogenetic analysis result was: mos 46, XX [67 %]/-4n [33 %] – mosaic karyotype: normal female karyotype; near tetraploid karyotype (fig. 10).

Fig.10. Fetus karyotype

Now the patient is in her second pregnancy of about 20 weeks of gestation which was also achieved by means of ART and ICSI. Routine screening examination of I trimester by OSCAR method has been carried out in 12 weeks 3 days of gestation. Basing upon ultrasound examination, concentration of so-called biochemical markers of chromosomal anomalies of I trimester PAPP-A (Pregnancy Associated Plasma Protein A) and β-hCG (free subunit of human Chorionic Gonadotropin), measured in patient’s blood by means of Kryptor analyzer (B.R.A.H.M.S., Germany) and also personal patient data, patient risks of fetus chromosomal anomalies have been calculated by means of special ASTRAIA program, FMF approved for these calculations. Calculated personal risk of trisomy 21 was equal to 1:14945, i.e., which not increased. No pathological symptoms have been found during screening ultrasound examination of I trimester, therefore recommendations of routine screening examinations of II trimester and detailed ultrasound at 20-21 weeks of gestation for fetus anatomy assessment were given to the patient.

So, combination of ultrasound examination, fetoscopy and cytogenetic analysis enabled us to confirm initial diagnosis of mermaid syndrome, to draw a correct conclusion about population risk, to assess so-called further generation prognosis, to prevent considerable psychological traumas of family after sirenomelia diagnosis in II III trimester or even after childbirth and to help parents to make a decision about reasonability of repeated procedure of ART and ICSI.

Conclusions

1. Methodologically correctly carried out routine screening combined examination of I trimester (from 11 w. 0 days to 13 w. 6 days at CRL from 45 to 84 mm) by OSCAR method allows in 1-3 hours: to explain the purpose, sense and contents of this examination to the family; to receive family informed consent for examination; to assess patient’s personal risks of fetus chromosomal anomalies; to examine fetus anatomy; to give all necessary explanations to the family concerning the results of examination.

2. Ultrasound at this gestational age allows to solve many tasks and is informative enough even for diagnosis such so rare and complicated syndrome as mermaid syndrome.

3. Sirenomelia is easier to be diagnosed during screening examinations in I trimester (11+0-13+6), than in II trimester because of not so apparent oligohydramnios.

4. 3D ultrasound has no diagnostic advantages, however can sometimes be useful while explanations of found pathological symptoms are given to the parents.

5. Transcervical fetoscopy combined with ultrasound examination broadens diagnostic opportunities in I trimester, including the cases of lethal anomalies of the fetus.
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c[51x469]


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