СЛУЧАЙ ИЗ ПРАКТИКИ

PRENATAL US- AND MR-DIAGNOSTICS OF TWIN PREGNANCY WITH REGRESSIVE COMPLETE HYDATIDIFORM MOLE AND A COEXISTING LIVE FETUS

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Purpose. A hydatidiform mole belongs to trophoblastic tumors and represents an abnormal pregnancy with embryonic development pathology due to genetic abnormalities. The coexistence of a complete hydatidiform mole and a normally developing fetus is a very rare pathology (1:20.000 – 1:250.000) that presents significant challenges in determining obstetric management due to high risks of complications for both fetus and mother.

Materials and methods. The article describes a clinical case of unique example of intrauterine verification of coexistence of a complete hydatidiform mole and a normally developing fetus using ultrasound (US) and magnetic resonance imaging (MRI), with a favorable outcome for fetus and mother. The full range of radiological prenatal diagnostic methods, biochemical markers, morphological, immunohistochemical and genetic technologies for diagnosis verification is demonstrated.

Results and Discussion. The presented clinical observation demonstrates that the coexistence of a hydatidiform mole and a normally developing fetus, although carrying high risks of complications, has a chance of a favorable outcome. Comprehensive examination allows for rational systematic monitoring, differential diagnosis and evidence-based prognosis of the outcome of such pregnancy.

Conclusion. This observation shows that timely radiological and laboratory diagnosis, systematic monitoring, enable predicting a favorable outcome and making the correct decision regarding the preservation of the pregnancy.

Keywords: twin pregnancy, hydatidiform mole, ultrasound, magnetic resonance imaging, prenatal diagnosis.

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ПРЕНАТАЛЬНАЯ УЗ- И МР-ДИАГНОСТИКА ДВОЙНИ С РЕГРЕССИРУЮЩИМ ПОЛНЫМ ПУЗЫРНЫМ ЗАНОСОМ И СОСУЩЕСТВУЮЩИМ ЖИВЫМ ПЛОДОМ

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Цель исследования. Полный пузырный занос относится к трофобластическим опухолям и представляет собой аномальную беременность с патологией эмбрионального развития из-за генетических отклонений. Сосуществование полного пузырного заноса и нормально развивающегося плода является очень редкой патологией (1:20.000 – 1:250.000), которая создает значительные трудности в выборе тактики ведения беременности из-за высокого риска возникновения осложнений как для плода, так и для матери.

Материалы и методы. В статье представлен клинический случай, демонстрирующий внутриутробную верификацию сосуществования полного пузырного заноса и нормально развивающегося плода с помощью ультразвукового исследования (УЗИ) и магнитно-резонансной томографии (МРТ) с благоприятным исходом для плода и матери. Продемонстрирован полный спектр методов пренатальной лучевой диагностики, биохимических маркеров, морфологических, иммуногистохимических и генетических технологий для верификации диагноза.

Результаты и обсуждение. Представленное клиническое наблюдение показывает, что сосуществование полного пузырного заноса и нормально развивающегося плода, хоть и сопряжено с высоким риском осложнений, имеет шансы на благоприятный исход. Комплексное обследование позволяет проводить дифференциальную диагностику и прогнозирование исхода такой беременности.

Заключение. Наблюдение показывает, что своевременная лучевая и лабораторная диагностика, систематический мониторинг позволяют прогнозировать благоприятный исход и принимать правильное решение относительно ведения беременности.

Ключевые слова: беременность двойней, полный пузырный занос, УЗИ, магнитно-резонансная томография, пренатальная диагностика.

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Introduction.

A hydatidiform mole (HM) belongs to trophoblastic tumors (TT) and represents an abnormal pregnancy with embryonic development pathology due to genetic abnormalities. In combination with a normal diploid fetus, a hydatidiform mole can be a result of placental mosaicism, where the fetus has a normal chromosomal set while the placenta is polyploid. Cases have been described where only half of the placenta represents a tetraploid hydatidiform mole, while the remaining part is normal. One possible explanation for this is discordant monochorionic twin gestation (normal/tetraploid). In this case, the abnormal fetus stops developing very early and is not visualized [1, 2]. The frequency of twin pregnancies with a complete hydatidiform mole in one fetal sac and normal development of the other fetus is 1:20.000 – 1:250.000. Most of these cases are dizygotic dichorionic twins. Only one case of a monozygotic monochorionic twin with a similar abnormality has been described. In cases of a complete hydatidiform mole in combination with a normally developing fetus, with moderate obstetric risks and the consent of the pregnant woman, prolongation of pregnancy is possible [1, 3, 4].

Complications are possible in pregnancies associated with TT: bleeding (57%), hypertension, preeclampsia (21-32%), hyperthyroidism (15%), excessive vomiting (7%) and malignant gestational trophoblastic disease (37-46%). The outcomes of such pregnancies include live births (38-60%), preterm birth (28%-71.4%), termination of pregnancy due to complications (10-32%), intrauterine fetal demise or spontaneous abortion (18%), stillbirth (1%) and neonatal mortality (3.5%) [1, 3, 5, 6, 7].

Proper determination of perinatal management in the case of a hydatidiform mole requires considering multiple criteria based on current knowledge of the capabilities of prenatal radiological diagnosis, biochemical markers, morphological, immunohistochemical and genetic technologies for diagnosis verification. The described clinical case, verified by morphological, laboratory, genetic and immunohistochemical methods, as well as postnatal observation, demonstrates the possibilities of timely prenatal diagnosis in predicting a favorable outcome of pregnancy in a dichorionic twin with a complete hydatidiform mole that regresses by the end of pregnancy in one fetal sac and a normal second fetus.

Case Report.

Patient V., 28 years old, primigravida. No significant medical history. On ultrasound (US) at 13 weeks, a heterogeneous mass measuring 40 x 45 mm was identified adjacent to the chorion, protruding into the uterine cavity along the anterior uterine wall. Pregnancy biochemical markers (PAPP-A, β-hCG) in the first trimester were within reference values. On US at 20 weeks, the previously identified mass increased in size to 94 x 99 mm, with a thickness of 45 mm and a cystic structure. Color Doppler mapping revealed vascular structures predominantly in the basal parts of the mass. The mass was considered a possible trophoblastic tumor, specifically a hydatidiform mole.

On ultrasound at 23 and 34 weeks, a single fetus corresponding to the gestational age was identified in the uterine cavity. No developmental anomalies or markers of chromosomal abnormalities were detected. The placenta was located on the posterior uterine wall, had a normal structure and the umbilical cord showed central attachment. On the anterior uterine wall, predominantly to the left, a second placenta was located (previously described as a "heterogeneous formation adjacent to the chorion and protruding into the uterine cavity along the anterior uterine wall"). Its dimensions were 109 x 82 mm, with a thickness of 37 mm at 23 weeks and 26 mm at 34 weeks. The distance between the placental edges was 12 mm. No vascular anastomoses were detected. Throughout its volume, the second placenta contained multiple echolucent inclusions measuring 2-12 mm in diameter at 23 weeks and 2-4 mm (with less distinct contours) at 34 weeks of gestation. Color Doppler mapping showed fragmented blood flow, appearing as separate signals at 34 weeks (Fig. 1a). Considering the available data, a differential diagnosis was performed between placental mesenchymal dysplasia (possibly an accessory lobe) and trophoblastic tumors (hydatidiform mole in combination with a normally developing fetus in a twin pregnancy). hCG levels were monitored: by 27 weeks, they had increased to 420,000 mIU/mL, and by 34 weeks, there was a decrease to 185,000 mIU/mL. The pregnant woman received consultations from an oncologist and a geneticist and MRI of the pregnant woman's brain and thoracic cavity was performed, revealing no pathological formations. The pregnant woman decided not to undergo prenatal karyotyping and was oriented towards completing the pregnancy while discussing potential risks.

In order to clarify the changes in the placenta, an MRI was performed during the second and third trimesters of pregnancy. Fetal development corresponded to the gestational age and no developmental anomalies were detected. A mass was identified on the anterior

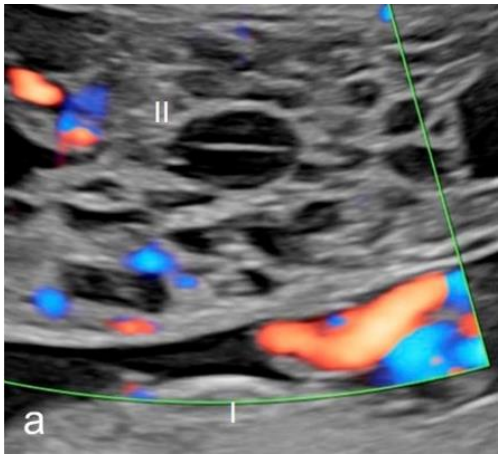


Fig. 1 a (Рис. 1 а)

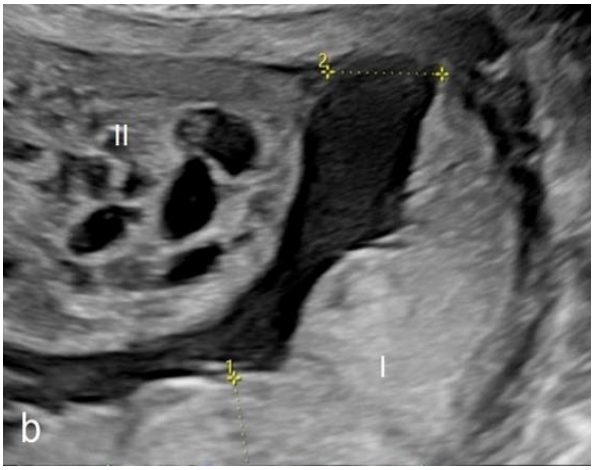


Fig. 1 b (Рис. 1 б)

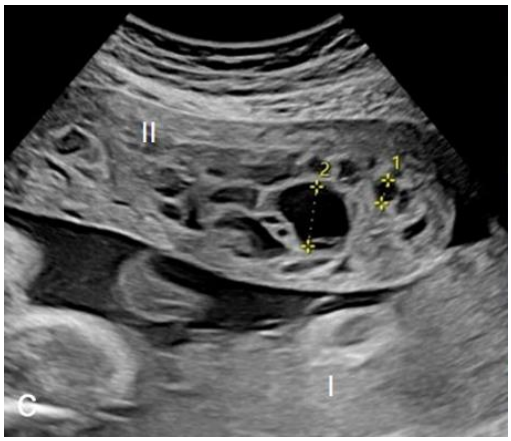


Fig. 1 c (Рис. 1 в)

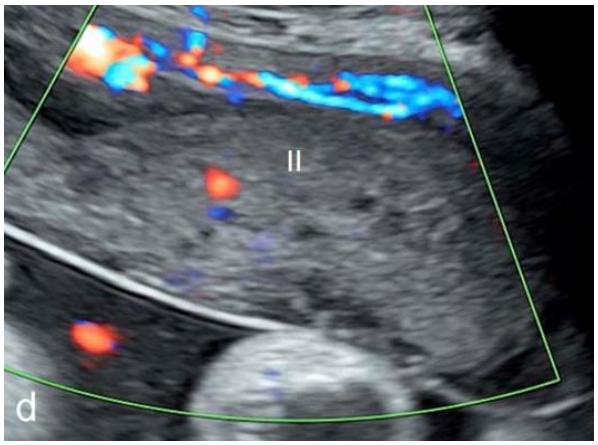


Fig. 1 d (Рис. 1 г)

Fig. 1.

a – US at 22 weeks 5 days, b, c – US at 26 weeks 5 days, d – US at 34 weeks 5 days. I – normal placenta, located on the back wall of the uterus. II – altered placenta located on the anterior wall of the uterus Measurements: 2 – interplacental distance (b), 1, 2 – diameters of cellular structure in the hydatidiform placenta (c). A significant decrease in the diameter and quantity of the cellular structure formation on the anterior wall of the uterus at 34 weeks of gestation is noted (d).

Рис. 1.

а – УЗИ на сроке беременности 22 недели и 5 дней; б, в – УЗИ на сроке беременности 26 недель и 5 дней; г – УЗИ на сроке беременности 34 недели и 5 дней. I – нормальная плацента, расположена на задней стенке матки. II – измененная плацента, расположена на передней стенке матки. Измерения: 2 – расстояние между плацентами (б), 1, 2 – диаметр кистозных включений в плаценте с пузырным заносом (в). Отмечается значительное уменьшение диаметра и количества эхонегативных включений в плаценте с пузырным заносом к 34 недели гестации (г).

uterine wall, resembling a placenta in shape, with a cellular structure containing multiple variable-sized and confluent lacunae filled with fluid component. It had a thickness of up to 48 mm at 23 weeks, decreasing to 45 mm by the 26th week of gestation, without signs of myometrial invasion (Fig. 2). The normal placenta was located on the posterior uterine wall with central umbilical cord attachment, consisting of three vessels (Fig. 2b). The MRI findings were consistent with the diagnosis of a hydatidiform mole with a coexisting viable fetus.

The course of pregnancy was complicated by the threat of preterm labor. At 35 weeks, labor began spontaneously, and a female infant weighing 2100g was delivered.

During the morphological examination of the placenta, the presence of two placentas was confirmed. The umbilical cord originated from a morphologically normal placenta measuring 12x19 cm and weighing 450 g. The second placenta, measuring 14x20 cm and weighing 780

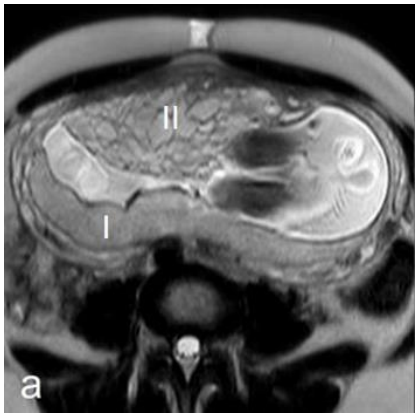
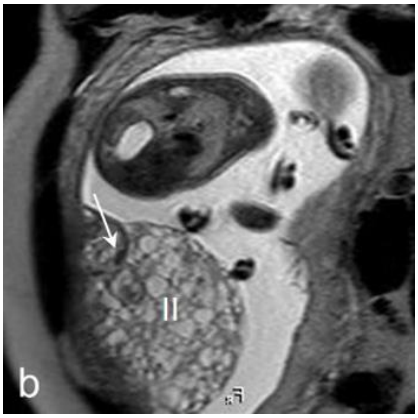


Fig. 2 a (Рис. 2 а)



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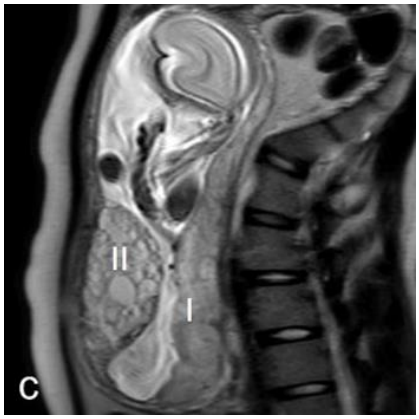

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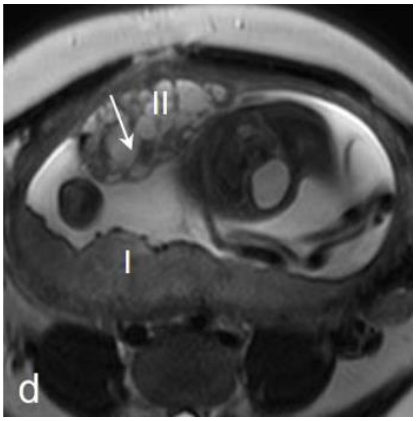

Fig. 2 d (Рис. 2 г)

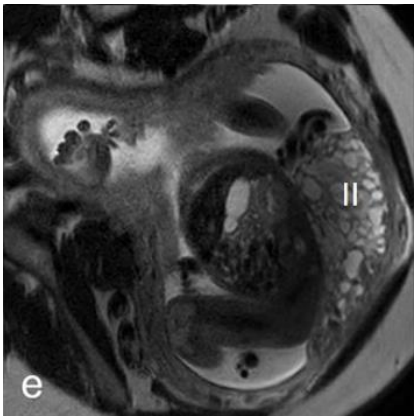

Fig. 2 e (Рис. 2 д)

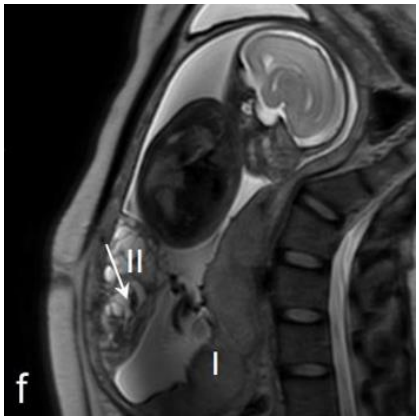

Fig. 2 f (Рис. 2 е)

Fig. 2. MRI at 23 weeks (top row) and 26 weeks (bottom row), a,d – axial, b,e – frontal, c,f – sagittal section (relative to the pregnant woman).

T2-SSH images revealed normal placenta on the posterior wall with central attachment of the umbilical cord (I), a cellular structure formation on the anterior wall of the uterus (II) with inclusions of sharply hypointense signal corresponding to hemorrhagic content of individual cells (arrows). In the uterine cavity there is a normally developed live fetus. Regression of the size of the pathologically altered placenta is noted.

Рис. 2. МРТ на сроке беременности 23 недели (верхний ряд), на 26 неделе (нижний ряд). а, г – аксиальная плоскость; б, д – фронтальная плоскость; в, е – сагиттальная плоскость (относительно беременной женщины).

На T2-SSH последовательности по задней стенке матки – нормальная плацента с центральным прикреплением пуповины (I), по передней стенке матки выявлено образование ячеистой структуры (II) с геморрагическими включениями (стрелки). В полости матки визуализируется один живой плод. Отмечается уменьшение размеров патологически измененной плаценты с увеличением срока гестации.

g, was located close to the first one and consisted of tissue with multiple small vesicular formations. There were no vascular anastomoses between the placentas (Fig. 3a). Microscopic examination of the "normal" placenta showed predominant intermediate and immature villous fields, as well as terminal fields with fully blood-filled capillaries. Compensatory reactions were well expressed in terms of vascular and cellular types. Focal hemorrhages in the intervillous space and small deposits of fibrinoid were observed (Fig. 3b). The "altered" placenta exhibited features characteristic of antenatal fetal demise: villous necrosis, including necrosis and desquamation of the covering epithelium, collapse of the intervillous space with parallel orientation of the villi, multiple fibrinoid deposits, and small foci of calcification at the sites of fibrinoid deposits (Fig. 3c). However, amidst these findings, there were large-caliber villi showing pronounced hydropic degeneration of the stroma, with the formation of cavities in some areas (Fig. 3d). The trophoblast covering the villi was destroyed in multiple areas, while in a few preserved areas, there was proliferation and nuclear atypia ranging from mild to moderate. The basal membrane showed widespread necrosis and focal hemorrhages (Fig. 3e).

Cytogenetic diagnosis of the placenta was unsuccessful. FISH (fluorescence in situ hybridization) analysis was performed using probes for chromosomes 21 and the sex chromosomes (Fig. 4). The FISH analysis result was normal in the "normal" placenta (Fig. 4a) and ineffective due to DNA degradation in the cells of the altered placenta (Fig. 4b).

Immunohistochemical examination of the "altered" placenta was performed (Fig. 4c, d). The proliferative activity index (the percentage of cells expressing Ki-67 antibodies) in trophoblast cells ranged from 15% to 30%, and the expression index of p53 antibodies was 65%. The level of expression indicated moderate proliferative activity [8, 9]. The expression of p53 antibodies led to the conclusion that a complete molar pregnancy was more likely in one of the fetuses from a dichorionic twin pregnancy [10].

Thus, it was concluded that the "altered" placenta represents a complete molar pregnancy. One month after delivery, the hCG level in the patient was within the normal range. The newborn has been rehabilitated and is growing and developing normally during the first year.

Discussion.

Complete hydatidiform mole is associated with a high risk of preeclampsia, bilateral ovarian cysts, persistent gestational trophoblastic disease, hyperthyroidism (up to thyrotoxic crisis), development of acute respiratory failure associated with pulmonary embolization of mole fragments. Therefore, in the case of twin pregnancy with a combination of a normal fetus and a complete mole in the second fetus, the choice is always difficult. [1, 3, 11]. To determine the appropriate management approach for a specific pregnancy, it is essential to establish an accurate diagnosis. Differential diagnosis is performed with: 1) partial hydatidiform mole and developing fetus; 2) mesenchymal dysplasia of the placenta (MDP); 3) other placental abnormalities (intraplacental hematomas, chorionangiomas, limited placental mosaicism). In the case of partial hydatidiform mole, most fetuses show multiple developmental abnormalities, anomalies in the karyotype, and fetal growth restriction. The placenta may be enlarged and have varying numbers of hypoechoic areas of different sizes. In partial hydatidiform mole, the ratio of the transverse to anteroposterior size of the gestational sac is more than 1.5 (with a test sensitivity of 87%) [12]. In MDP, Beckwith-Wiedemann syndrome is possible in addition to chromosomal and structural developmental abnormalities in 21-30% of fetuses. [5].

MDP is characterized by the presence of placentomegaly with multiple large cysts, overdeveloped vasculature, without atypical trophoblastic proliferation and areas of hemorrhage in altered sections of the placenta characteristic of HM [13, 14]. One of the tasks of MRI is to exclude invasion of the altered placenta into the myometrium and to exclude hemorrhagic complications [15]. Both MRI and US are informative methods in the differential diagnosis of placental involvement variants.

In MDP, multiple cystic cavities occupy the entire area of the placenta or part of it. Unlike partial hydatidiform mole, they are visualized as separate rounded echonegative structures with smooth distinct contours, smooth inner surfaces on US, with less pronounced cystic and fluid components and smoother contours on MRI. The architecture of the placental vascular network is not disrupted. Visualization of dilated vessels of the stem villi is possible [5, 16, 17]. However, the precise nature of placental changes can only be determined morphologically [4, 5].

In the case of hydatidiform mole, the normal placenta is often clearly separated from the affected placenta, as in our observation, while in the case of MDP, such clear demarcation is absent [18]. The detection of hemorrhagic content on MRI in individual cells of the affected placenta also supported the diagnosis of a mole [19]. The MRI was performed in our clinical case specifically for the differential di-

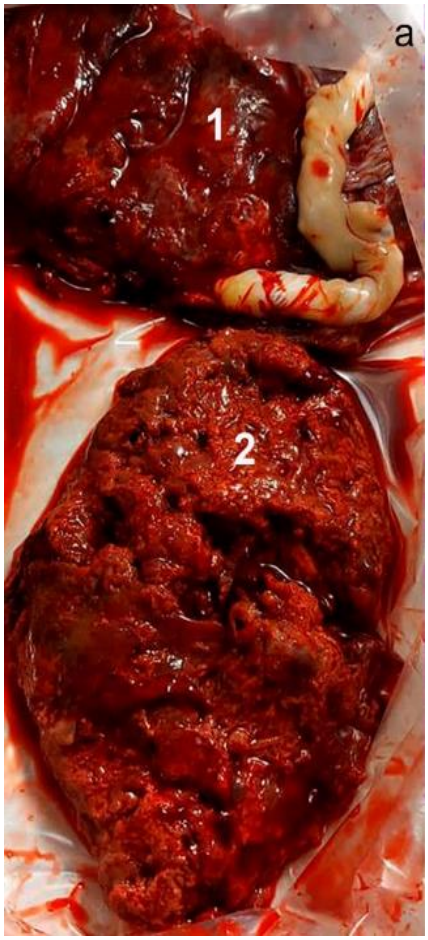

Fig. 3 a (Рис. 3 а)

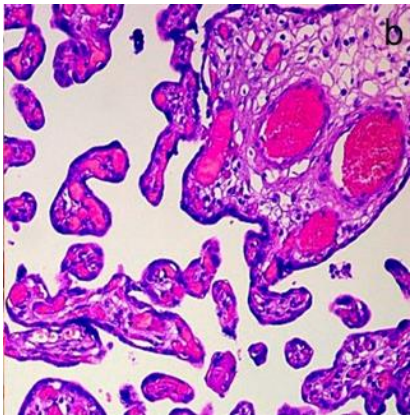

Fig. 3 b (Рис. 3 б)

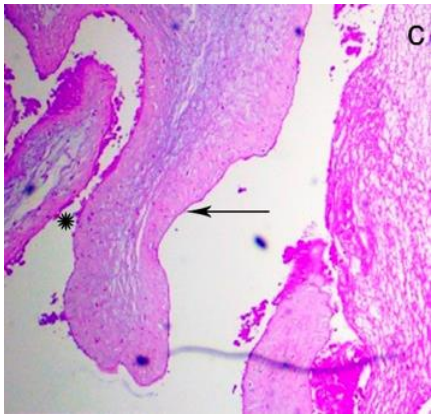

Fig. 3 c (Рис. 3 в)

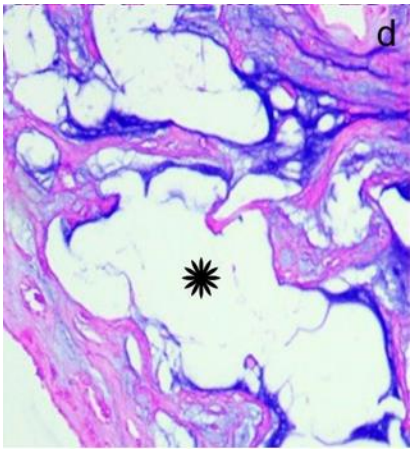

Fig. 3 d (Рис. 3 г)

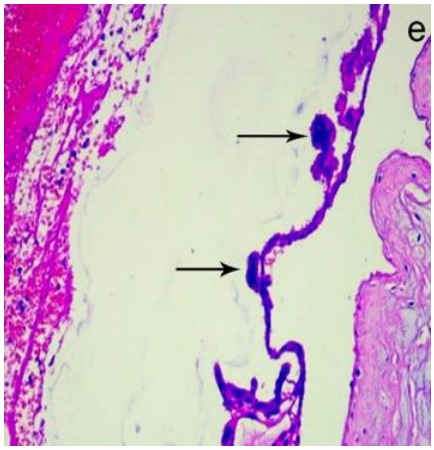

Fig. 3 e (Рис. 3 д)

Fig. 3.

a – Gross specimen: 1 – normal placenta, 2 – altered placenta (many small vesicular masses are seen in the altered placenta).

b – microscopy of normal placenta (the villi of the normal placenta are visible).

c, d, e – altered placenta.

c – the villi with necrosis, including necrosis and desquamation of the covering epithelium (arrow), collapse of the intervillous space (*) with parallel orientation of the villi.

d – large villi with marked stromal edema and cavity formation (*)).

e – villi with preserved trophoblast and its focal proliferation (arrow).

Рис. 3.

а – Макропрепарат: 1 – нормальная плацента, 2 – измененная плацента (отмечается множество везикулярных структур).

б – Микроскопия нормальной плаценты (отмечаются нормально сформированные ворсины).

в, г, д – Микроскопия измененной плаценты; с – ворсинки с участками некроза, включая десквамацию покровного эпителия (стрелка), коллапс межворсинчатого пространства (*) с параллельной ориентацией ворсинок.

г – Крупные ворсины с выраженным отеком стромы и формированием полостей (*).

д – Ворсины с сохраненным трофобластом и его очаговой пролиферацией (стрелка)

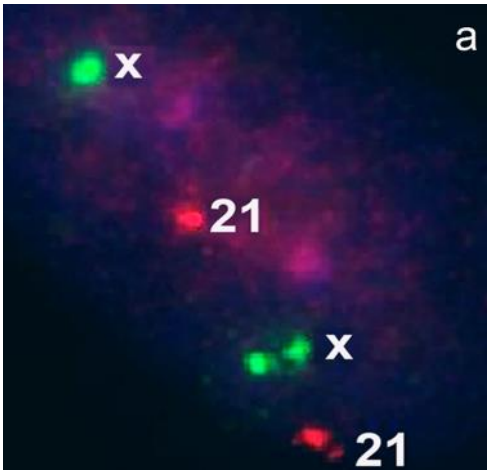

Fig. 4 a (Рис. 4 а)

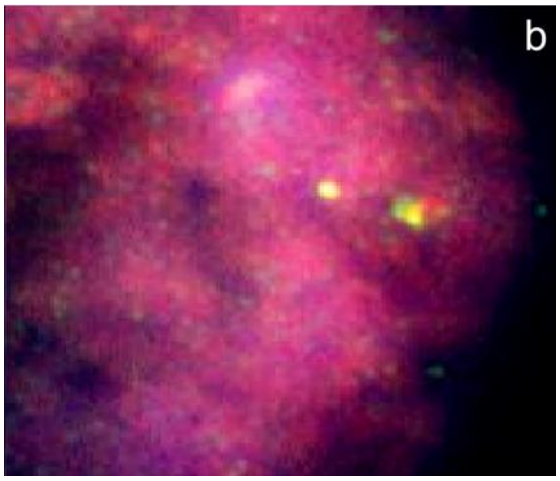

Fig. 4 b (Рис. 4 б)

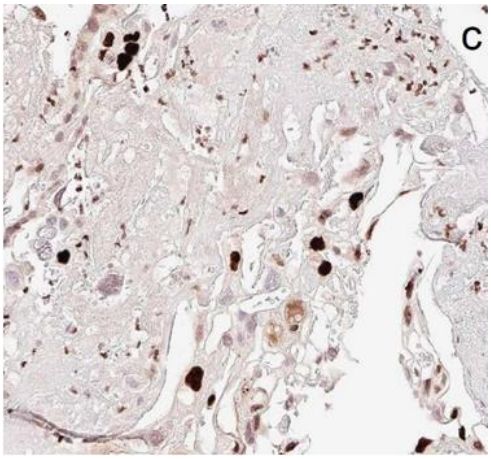

Fig. 4 c (Рис. 4 в)

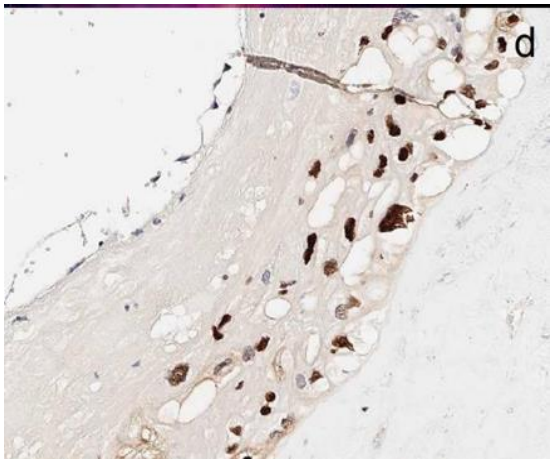

Fig. 4 d (Рис. 4 г)

Fig. 4.

a – material of placenta section with morphologically normal villi. FISH with DNA probes on the centromeric region of chromosome X (green signal), locus-specific probe on chromosome 21 (red signal). Magnification 1000x. b – material of placenta section with morphologically changed villi. DNA degradation is clearly visible. c – immunohistochemical study of the altered placenta with Ki-67. d – immunohistochemical study of the altered placenta with P-53.

Рис. 4.

а – Материал участка плаценты с морфологически нормальными ворсинами. Флуоресцентная гибридизация in situ (FISH) с зондами, специфичными центромерному району X хромосомы (зеленый сигнал), локус-специфичный зонд на 21 хромосому (красный сигнал). Увеличение 1000х. b – Материал участка плаценты с морфологически измененными ворсинами. Хорошо видна деградация ДНК. c – Иммуногистохимическое исследование измененной плаценты с Ki-67. d – Иммуногистохимическое исследование измененной плаценты с P-53.)

agnosis of hydatidiform mole and MDP, considering that the prognosis for pregnancy with MDP is more favorable [19]. Additionally, the inclusion of MRI in the prenatal diagnostic algorithm allowed for the reliable exclusion of invasive forms of GTN and confirmed the absence of fetal developmental anomalies.

Biochemical markers also play an important role in determining the management strategy when there is a suspicion of TT. In hydatidiform mole, the elevation of β-hCG is more pronounced than in MDP. If the β-hCG level exceeds 200,000 IU/L, there is an elevated PAPP-A (pregnancy-associated plasma protein-A) and decreased AFP (alpha-fetoprotein), it is ind icative of a mole [5, 18].

However, it is important to remember that not all TT is associated with high β-hCG levels. For example, placental site trophoblastic tumor and epithelioid trophoblastic tumor, as-

sociated with the proliferation of intermediate trophoblastic cells, are characterized by low β-hCG levels. And in the case of US with a complete hydatidiform mole, as well as in choriocarcinoma, abundant blood flow, neovascularization with arteriovenous shunts is observed [12].

A case of choriocarcinoma occurring 5 months after delivery and diagnosed with MDP (with a corresponding histological conclusion of the absence of trophoblastic disease) has been described. The authors concluded that there may be difficulties in histological examination and emphasized the need for postnatal monitoring with β-hCG control, which allows for timely diagnosis [20].

In the present clinical case, the β-hCG level did not exceed 420 mIU/mL (levels below 400 mIU/mL are a predictor of a favorable outcome for the fetus [5].

Thus, our clinical case confirms the justification of a conservative approach in the case of dynamic monitoring of the pregnant woman and the fetus using US and MRI, as well as monitoring of biochemical markers. A normal fetal karyotype also allows for a good outcome. 80% of fetuses with MDP have a normal female karyotype. Abnormal karyotypes include trisomy 13, X chromosome polysomy [20, 21]. In the case of partial hydatidiform mole, the fetus is triploid in 90% of cases, with corresponding manifestations [1, 11]. In the case of a complete hydatidiform mole in a single fetal sac in a dichorionic twin pregnancy, as in our observation, there is a higher chance of normal fetal development. This is also supported by the data from the review by [5], which analyzed 206 cases of complete hydatidiform mole in combination with a developing fetus in twins based on PubMed data for the period 1993-2016. A favorable outcome for the fetus was observed in 78 (37.9%) cases.

The effectiveness of immunohistochemical methods has been described by many authors [22, 23, 24]. In the diagnosis of TT, an expression of Ki67 in cytotrophoblast cells above 12.5% has a sensitivity of 90%, specificity of 93%, positive predictive value of 93.1%, and negative predictive value of 90.3% [8].

Conclusion.

Although rare, the occurrence of a twin pregnancy with a hydatidiform mole requires increased attention by obstetricians during prenatal care. The presented clinical observation demonstrates that the coexistence of a hydatidiform mole and a normally developing fetus, although carrying high risks of complications, has a chance of a favorable outcome. Comprehensive examination utilizing the full spectrum of radiological prenatal diagnostic methods, biochemical markers, morphological, immunohistochemical and genetic technologies for diagnosis verification allows for rational systematic monitoring, differential diagnosis and evidence-based prognosis of the outcome of such pregnancy.

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Conflict of interests.

The authors declare that there is no conflict of interest.

Research ethics.

The Ethics Committee of the ITC SB RAS approve the research on the topic "A perinatal observation of twin pregnancy with regressive complete hydatidiform mole and a coexisting live fetus: case report and literature review."

The work was carried out with the voluntary participation of patients and is not associated with the risk of harm to them.

Informed consent.

Informed consent was obtained from all individuals included in this study.

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