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FETO-FETAL TRANSFUSION SYNDROME: MODERN METHODS OF TREATMENT

(review article)

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✓ ***Resume***

The presented review discusses the problem of perinatal mortality associated with the development of feto-fetal transfusion syndrome in multiple monochorial pregnancies. Despite the great therapeutic advances achieved in recent years, feto-fetal transfusion syndrome leads to perinatal losses and a high incidence of newborns in 56-100% of observations of multiple monochorial pregnancy.

The article discusses the most modern approaches to the diagnosis of this complication, as well as current methods of treatment of pregnant women with diagnosed feto-fetal transfusion syndrome. For the correction of feto-fetal transfusion syndrome, fetoscopic laser coagulation of placental anastomoses, amniodeduction, selective reduction of one fetus from twins or termination of pregnancy are used. The review compares these treatments depending on the stage of feto-fetal transfusion syndrome and various factors affecting the choice of therapeutic tactics.

Keywords: multiple pregnancy, monochorial twins, feto-fetal transfusion syndrome, fetoscopic laser coagulation of placental anastomoses, serial amnioreduction, selective elimination.

FETO-FETAL TRANSFUSION SINDROMI: DAVOLASHNING ZAMONAVIY USULLARI

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✓ ***Rezyume***

Ushbu maqolada ko'p monoxorionik homiladorlikda feto-fetal transfuzion sindromining rivojlanishi bilan bog'liq perinatal o'lim muammosi muxokama qilinadi. So'nggi yillarda erishilgan katta terapevtik muvaffaqiyatlarga qaramay, feto-fetal transfuzion sindromi perinatal yo'qotishlarga va ko'p monoxorionik homiladorlik xolatlarining 56-100% da yangi tug'ilgan chaqaloqlarning yuqori kasallanishiga olib keladi.

Maqolada ushbu asoratni tashxislashning eng zamonaviy yondashuvlari, shuningdek, feto-fetal transfuzion sindromi tashxisi qo'yilgan homilador ayollarni davolashning dolzarb usullari muhokama qilinadi. Feto-fetal transfuzion sindromini tuzatish uchun platsenta anastomozlarining fetoskopik lazer koagulyatsiyasi, amnioreduksiya, egizaklardan bitta homilana tanlab qisqartirish yoki homiladorlikni to'xtatish qo'llaniladi. Ko'rib chiqishda ushbu davolash usullari feto-fetal transfuzion sindromi bosqichiga va terapevtik taktikani tanlashga ta'sir qiluvchi turli omillarga qarab taqqoslanadi.

Kalit so'zlar: ko'p homiladorlik, monoxorionik egizaklar, feto-fetal transfuzion sindromi, platsenta anastomozlarining fetoskopik lazer koagulyatsiyasi, ketma-ket amnioreduksiya, selektiv eliminatsiya.

ФЕТО-ФЕТАЛЬНЫЙ ТРАНСФУЗИОННЫЙ СИНДРОМ: СОВРЕМЕННЫЕ МЕТОДЫ ЛЕЧЕНИЯ (ОБЗОРНАЯ СТАТЬЯ)

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✓ ***Резюме***

В представленном обзоре обсуждается проблема перинатальной смертности, связанная с развитием фето-фетального трансфузионного синдрома при многоплодной монохориальной беременности. Несмотря на большие терапевтические успехи, достигнутые в последние года, фето-фетальный трансфузионный синдром приводит к перинатальным потерям и высокому уровню заболеваемости новорожденных в 56—100% наблюдений многоплодной монохориальной беременности.

В статье рассмотрены наиболее современные подходы к диагностике этого осложнения, а также актуальные методы лечения беременных с диагностированным фето-фетальным трансфузионным синдромом. Для коррекции фето-фетального трансфузионного синдрома применяются фетоскопическая лазерная коагуляция анастомозов плаценты, амниоредукция, селективная редукция одного плода из двойни или прерывание беременности. В обзоре сравниваются данные методы лечения в зависимости от стадии фето-фетального трансфузионного синдрома и различных факторов, влияющих на выбор терапевтической тактики.

Ключевые слова: многоплодная беременность, монохориальная двойня, фето-фетальный трансфузионный синдром, фетоскопическая лазерная коагуляция анастомозов плаценты, серийная амниоредукция, селективная элиминация.

Relevance

In recent years, the incidence of multiple pregnancies has increased worldwide from 1.6 to 35.40%. It is approximately 3% in the structure of birth and 14% in the structure of perinatal mortality, in connection with which multiple pregnancies are becoming an extremely urgent problem of modern obstetrics throughout the world. The increase in the frequency of multiple pregnancies is due to the widespread introduction into the practice of public health care of effective methods of treating patients with infertility, as well as the use of assisted reproductive technologies [2, 3, 12, 13, 21, 30, 39, 42].

Multiple pregnancies, especially after assisted reproductive technologies and in the presence of a complicated obstetric and gynecological history, are associated with a significant number of complications accompanying it from the early gestational period. This is what determines the increased level of antenatal and perinatal losses. The most significant of them are miscarriage at different times of gestation, premature birth, as well as an increase in the likelihood of preeclampsia, anemia, thrombosis, gestational diabetes mellitus, postpartum hemorrhage, the birth of children with low body weight, neurological complications and antenatal fetal death [21, 39]. Even with the modern development of medicine, perinatal mortality in multiple births is more than 6 times higher than in singleton pregnancy, the frequency of intrauterine fetal death is 4 times higher, and neonatal - 6 times [3, 15]. According to most researchers, the main cause of perinatal loss in multiple births is deep prematurity (and, accordingly, low birth weight and length), with prematurity ranking first among other causes [3, 25, 28, 39].

The next cause of perinatal morbidity and mortality in multiple births, as a rule, is placental insufficiency (delayed intrauterine development of fetuses) [31, 43]. Of particular importance is also the type of placentation, which is a factor that significantly affects perinatal morbidity and mortality. Approximately 80% of placentas in multiple pregnancies have a dichoral type, 20% - monochorial. The monochorial placenta is the only structure that in 90-95% of cases contains vascular anastomoses between the placental circulatory systems of two fetuses, which may be the basis of such

serious complications of multiple pregnancies as feto-fetal transfusion syndrome. According to most authors, feto-fetal transfusion syndrome is observed in the general structure of multiple births in 15–35% of pregnant women [14, 16, 22, 24].

Determination of feto-fetal transfusion syndrome

Feto-fetal transfusion syndrome, or Twin-to-Twin-Transfusion Syndrome, is a severe complication of multiple monochorial pregnancy associated with the presence of transplacental vascular communications and circulatory imbalance between the intraplacental vascular beds of twin fetuses [5]. In the presence of large vascular anomalies in the placenta between the fetuses' hemodynamic relations of fetus-donor and fetus-recipient with disproportion of circulating blood volumes are formed. Due to unbalanced blood transfusion, the donor fetus develops hypovolemia and anemia against the background of growth retardation. A critical decrease in the volume of circulating blood is accompanied by progressive oligouria and anuria, severe anhydrous, which prevents the normal maturation of lung tissue, and a high probability of antenatal fetal death [4]. In the recipient fetus, as a result of circulatory disproportion, the volume of circulating blood increases sharply, polycythemia develops, hypertrophic cardiomegaly is formed. Against the background of hemodynamic decompensation, congestive heart failure develops. Increased renal blood flow and increased urine production lead to an increase in the volume of amniotic fluid as a factor of increased risk of premature rupture of the fetal bladder and induction of premature birth [37].

Although anastomoses and, as a consequence, the discharge of blood between fetuses are present in all monochorial twins, feto-fetal transfusion syndrome usually develops only with diamniotic monochorial twins. This is likely due to the fact that monoamniotic pregnancies have more bidirectional superficial anastomoses than diamniotic [31].

The relevance of the problem of feto-fetal transfusion syndrome in modern medicine

Despite the great therapeutic advances achieved in recent years, feto-fetal transfusion syndrome is accompanied by high perinatal mortality and morbidity, the number of cases of which ranges from 56 to 100% and depends on the gestational term and severity of hemodynamic disorders [5, 13, 33]. The formation of vascular anastomoses in monochorial multiple births occurs in 85–100% of observations [4, 11]. According to L. Lewi et al. [18], feto-fetal blood transfusion syndrome is one of the most common causes of loss in monochorial pregnancies, especially up to 24 weeks of pregnancy. The development of feto-fetal transfusion syndrome before 26 weeks of gestation is associated with an extremely high risk of perinatal death [40]. In many observations, pregnancy ends in either miscarriage or premature birth due to polyhydramnion and sprain of the uterus or intrauterine fetal death associated with severe cardiovascular disorders. The prevalence of feto-fetal transfusion syndrome is 1 in 2000 pregnancies [39].

Features of pregnancy management complicated by feto-fetal transfusion syndrome. Diagnostics.

As shown by studies [14, 15], observation of patients with spontaneous multiple pregnancies is carried out according to an algorithm based on the determination of choriality, i.e. the number of chorions (placenta). Early diagnosis of the number of chorions and amnions allows you to anticipate possible complications and conduct timely prevention in order to reduce the number of adverse outcomes associated with monochorial pregnancy. The optimal time for determining choriality with ultrasound is 11-14 weeks, since after 15 weeks of pregnancy, the diagnostic capabilities decrease [21, 30]. According to the practical recommendations of ISUOG (The International Society of Ultrasound in Obstetrics & Gynecology), choriality should be determined between the 11th week and the 13th week of 6 days of pregnancy, the guidelines should be the thickness of the membrane at the site of attachment of the amniotic membrane to the placenta and the identification of a T-sign or λ-trait (lambda trait), as well as the identification of the number of placental masses visualized during ultrasound examination [13]. If it is impossible to unambiguously determine the type of choriality, pregnancy is recommended to be conducted as monochorial until the opposite is confirmed [27]. Starting from the 16th week of pregnancy, an ultrasound examination is indicated every 2 weeks. It is necessary to assess the maximum and minimum pockets of amniotic fluid, the size of the bladder in

fruits and the dynamics of their growth. Collar edema in monochorial twins is not so much a sign of chromosomal abnormalities in fetuses as an early prognostic sign of the development of severe feto-fetal blood transfusion syndrome. Weekly ultrasound is indicated for suspected formation of feto-fetal transfusion syndrome, the first sign of which will be an imbalance of amniotic fluid. Starting from the 20th week of pregnancy, the maximum systolic velocity in the middle cerebral artery of the fetus should be evaluated as a screening for anemia-polycythemia syndrome [13, 21, 26, 32].

When confirming the diagnosis of feto-fetal transfusion syndrome, the performance of dopplerometry and cervicometry allows you to clarify the stage and decide on the choice of adequate therapeutic interventions. Ultrasound signs indicating a high risk of developing feto-fetal transfusion syndrome include discordance of the values of the thickness of the collar space, the presence of pathological blood flow in the venous duct in combination with a difference in fetal size of more than 25% [26].

The stage of feto-fetal transfusion syndrome is determined in accordance with the classification of R. Quintero and co-authors [33, 34]:

Stage I: the recipient's polyhydramnion in combination with the donor's oligo/anhydramnion; the bladder of the donor fetus is determined;

Stage II: the donor's bladder is not visualized with a 60-minute ultrasound, the state of blood flow in the umbilical cord artery and/or venous duct is uncritical;

Stage III: critical hemodynamic disturbance according to dopplerometry (absence or reverse diastolic blood flow in the umbilical cord artery, reverse blood flow in the venous duct or pulsating in the umbilical cord vein) in the donor fetus and/or recipient fetus;

Stage IV: dropsy in the recipient fetus;

Stage V: Death of one or both fetuses.

Despite the fact that the stages proposed by R. Quintero and co-authors do not always accurately predict the outcome of pregnancy or the chronological evolution of feto-fetal transfusion syndrome, they are the main classification system for feto-fetal transfusion syndrome [13].

Monochorial multiple pregnancy, predisposed to the risk of placenta-associated vascular complications, requires more frequent monitoring, and in the period of 32-34 weeks of pregnancy, it is necessary to develop tactics for further management of such patients or choose a method of delivery in order to prevent fetal death [21].

Modern approaches to the treatment of feto-fetal transfusion syndrome

In no other specialty does the clinical situation change with such rapidity as in obstetrics, when the tactics of managing patients can instantly become the opposite. For the treatment of feto-fetal transfusion syndrome, fetoscopic laser coagulation of placental anastomoses, amnioreduction, selective reduction of one fetus from twins or termination of pregnancy are used. The most effective method of treating this syndrome currently remains fetoscopic laser coagulation of anastomoses, in which the cause of transfusion is eliminated. Another method of treatment - amniocentesis - removes only a consequence of the disease. Factors affecting the choice of tactics are the degree of equipment of the medical institution, the experience of the staff, the duration of pregnancy, the stage of feto-fetal transfusion syndrome, the length of the cervix, as well as the technical capabilities that limit the conduct of fetoscopy (localization of the placenta, places of attachment of the umbilical cord and features of the mother's anatomy) [6, 13, 21, 27, 29, 38]. According to most authors, with expectant tactics, perinatal mortality in feto-fetal transfusion syndrome reaches 95% and according to their point of view, such tactics are not a rational approach to the treatment of this pathology in modern obstetrics [9, 10, 26]. Despite this, at present, in many obstetric centers around the world, stage I according to Quintero is conducted conservatively. But it should be borne in mind that if conservative management is chosen, then symptoms such as an increase in polyhydramnios, discomfort of the mother, shortening of the length of the cervix should be considered as criteria signaling the need to switch to treatment with fetoscopic laser ablation [13].

Fetoscopic laser coagulation

In the process of studying the methods of treatment of feto-fetal transfusion syndrome by doctors of many countries of the world, the technique of surgical intervention underwent various

modifications. Initially, all vessels crossing the amniotic membrane were involved in the surgical process [7, 23]. Given that in this case the vessels that do not connect the circulation systems of both fruits and are not involved in the development of feto-fetal transfusion syndrome are also affected, R. Quintero and co-authors developed a method of selective laser coagulation. In this approach, only vessels connected to each other are coagulated, which may not be anatomically related to the amniotic septum [17, 33]. According to clinical recommendations for multiple pregnancies [27], there are differences in the technique of the operation, the intervention is performed with varying degrees of selectivity. The tactics of L. Salomon (from one end of the placenta to the other) are characterized by coagulation not only of anastomoses, but also of the placental equator between them; ideally, the placenta after ablation should become "dichorial", which can significantly reduce the risk of not only recurrence of feto-fetal transfusion syndrome, but also the occurrence of anemia-polycythemia syndrome [13, 27].

The outcomes of operations largely depend on the experience of operating doctors. Insufficient experience leads to the fact that anastomoses go unnoticed, and as a result, a relapse of feto-fetal transfusion syndrome develops before birth. So, according to E. Lopriore et al. [20], in 32% of cases, missed anastomoses were detected after laser coagulation. At the same time, in 44% this led to the development of anemia, polycythemia. At the International Training Center for Microinvasive Fetal Surgery (Prenatal International GmbH, Germany), the use of 1.0–1.2 mm optics and a reduction in trocar diameter from 3.8–4.3 mm (13 F, 11.27 mm2) to 2.3 mm (7F, 2.65 mm2) led to a significant improvement in neonatal outcomes. The survival rate after laser coagulation of at least one child increased from 94.9 to 100% and for two fetuses from 74.3 to 90% (n = 70) [41].

After intrauterine intervention, the patient is treated with treatment aimed at prolonging pregnancy in a hospital setting under the control of sonographic and laboratory parameters. The choice of drugs, dosage and duration of therapy are selected individually, according to existing protocols - micronized progesterone, hexoprenaline-selective β2-adrenomimetics, atosiban, anti-inflammatory drugs for topical use. The effectiveness of therapy is evaluated 14 days after the operation to normalize the amount of amniotic fluid, visualization of the bladder of the donor fetus. It is common practice to conduct an ultrasound examination once a week for the first 2 weeks after the therapy, followed by a decrease in the frequency of examinations to once every 2 weeks after the resolution of clinical symptoms [13, 27].

According to one of the studies, when comparing twins from pregnancies with intrauterine selective laser photocoagulation of vascular anastomoses of the placenta and without it, significant differences were revealed. The number of born donors who required blood transfusion on the first day of life in the group without selective laser photocoagulation of vascular anastomoses of the placenta was 33%, despite the fact that in the group with intrauterine correction this figure is much lower - 5%. Among newborn recipients, 1% of patients needed polycythemia correction by partial exchange transfusion surgery in the group with intrauterine selective laser photocoagulation of vascular anastomoses of the placenta, while in the group without intrauterine correction of feto-fetal transfusion syndrome - 24% [39, 40].

In the publication of the Society for Maternal and Fetal Medicine on feto-fetal transfusion syndrome, it was noted that "fetoscopic laser coagulation of placental anastomoses is considered by most experts around the world to be the best approach to the treatment of stages II, III and IV of feto-fetal transfusion syndrome with a gestational age from the 16th to the 26th week" [8, 29, 33].

Amnioreduction

Despite the impressive advances in the use of laser coagulation, the current scientific literature has renewed interest in the use of serial amnioreductions in the early stages of feto-fetal transfusion syndrome. Serial amnioreduction consists in the repeated performance of transabdominal amniodenage in order to reduce the amount of amniotic fluid of the recipient fetus and prolong pregnancy. This is due to the fact that in stage I, a high incidence of no progression of the disease was noted, which revived interest in a more conservative method of treatment - amnioreduction [1, 27].

In addition, serial transabdominal amnioreduction is a second-line therapy in the absence of the possibility of performing selective laser photocoagulation in connection with a gestation period of more than 26 weeks, as well as in the recurrence of the syndrome after fetoscopic laser coagulation of

placental anastomoses and in the absence of a technical possibility to perform laser coagulation [13, 26, 27].

According to two controlled non-randomized trials that compared serial amniocentesis and selective laser photocoagulation of placental anastomoses, the survival rate of at least one fetus was 79% [35] and 83.1% [8]. A comparison of the data from these studies showed that survival in the amniodection group was 64.4% (78/121) compared to 81.5% (137/168) in the laser therapy group (p=0.001) [29]. Analysis of long-term outcomes of the development of the nervous system in newborn children after treatment of feto-fetal transfusion syndrome by amnioreduction showed that the incidence of cerebral palsy was 5.8-22.5%, psychomotor development delay - 7.5-22.5% [18, 19, 20, 41].

Other treatments for feto-fetal transfusion syndrome

The situation in monochorial pregnancy is significantly different from dichorial pregnancy, since intrauterine death of a fetus that is stunted in growth dramatically increases the risk of death, as well as the incidence of the second twin. If intrauterine fetal death in the second trimester after the 24th week of pregnancy cannot be avoided, and it is expected according to the results of Doppler sonography, the doctor faces a dilemma - to induce premature birth with a very dubious prognosis for both twins or to choose expectant tactics with a risk of 26% mortality and increased morbidity for a healthy twin. In some clinics, selective elimination of the fetus is performed by laser coagulation of the umbilical cord attachment site using bipolar forceps or radioablation of the umbilical vessels, which can lead to an improvement in the neonatal outcome for a healthy twin [6].

Selective elimination of the fetus (cardiac arrest) is recommended for use in the presence of anomalies in the development of one of the fetuses, a combination of feto-fetal transfusion syndrome with selective growth retardation of one of the fetuses with a discordance of more than 40% (up to 22 weeks of pregnancy), with stage IV feto-fetal transfusion in the absence of the technical possibility of performing laser coagulation. Umbilical cord occlusion is performed by coagulation of the vessels of one of the fetuses by fetoscopic or puncture access, using intrafetal laser or radiofrequency ablation. This means that one of the fruits is sacrificed in the hope of preventing the death of another fetus or the development of brain damage. In some rare cases, parents decide to terminate the entire pregnancy [13, 27, 36].

Currently, there is no single scientifically based point of view regarding the timing of planned delivery in feto-fetal transfusion syndrome without laser coagulation of placental anastomoses. According to different authors, this period varies from 32 to 37 weeks and in each case is chosen depending on the obstetric situation individually [1].

In any case of multiple monochorial pregnancy, the question of the choice of management tactics, the path and time of delivery should be approached with the utmost seriousness, paying attention to the slightest complications in the mother and fetuses [21].

Conclusion

Thus, multiple monochorial pregnancy is still one of the most complex and ambiguous pathologies in obstetrics and neonatology. Every day, doctors around the world make great efforts to understand the etiology and pathogenesis that cause the occurrence of feto-fetal transfusion syndrome in multiple pregnancies. Research is underway and new methods of diagnosis and treatment of feto-fetal transfusion syndrome are proposed. Currently, the development of medical technology, modern methods of prenatal diagnosis and the use of minimally invasive intrafetal methods for the correction of feto-fetal transfusion syndrome make it possible to preserve pregnancy, the life of the mother and both fetuses, to reduce the level of perinatal mortality worldwide.

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