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Differential diagnosis of obstetric thrombotic microangiopathy: a review

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Thrombotic microangiopathy (TMA) is a clinical and morphological syndrome, which is based on damage of the endothelium. Clinically, TMA is characterized by a triad of symptoms: thrombocytopenia, microangiopathic hemolytic anemia, and target organ damage. In obstetric practice, TMA most often occurs with preeclampsia or HELLP syndrome, atypical HUS, thrombotic thrombocytopenic purpura (TTP). The review presents the basic differential criteria for the diagnosis of TMA during pregnancy and after childbirth, as well as the management of patients.

Keywords: pregnancy; preeclampsia; HELLP syndrome; thrombotic thrombocytopenic purpura; hemolytic-uremic syndrome, typical and atypical.

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Дифференциальная диагностика тромботической микроангиопатии в акушерстве: литературный обзор

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Тромботическая микроангиопатия (ТМА) представляет собой клинико-морфологический синдром, в основе которого лежит повреждение эндотелия сосудов микроциркуляторного русла. Клинически ТМА характеризуется триадой симптомов: тромбоцитопенией, микроангиопатической гемолитической анемией и поражением органов-мишеней. В акушерской практике ТМА чаще всего встречается при преэклампсии или HELLP-синдроме, атипичном гемолитико-уремическом синдроме, тромботической тромбоцитопенической пурпуре. В обзоре приведены опорные дифференциальные критерии диагностики ТМА при беременности и после родов, а также тактика ведения пациентов.

Ключевые слова: беременность; преэклампсия; HELLP-синдром; тромботическая тромбоцитопеническая пурпура; гемолитико-уремический синдром, типичный и атипичный.

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INTRODUCTION

Thrombotic microangiopathy (TMA) represents a clinical and morphological syndrome based on the damage to the endothelium of vessels of the microvasculature (MV). This condition is manifested by similar clinical symptoms and histological signs but mediated by various pathogenetic mechanisms. Endothelial damage results in thrombosis and inflammation of the vascular wall. TMA is morphologically manifested by the thickening of the walls of MV vessels, their edema and desquamation of endothelial cells from the basement membrane, deposition of hyaline deposits in the sub endothelial space, and formation of intravascular platelet thrombi with partial or complete occlusion of the vessels. Clinically, TMA is characterized by a triad of symptoms, namely, thrombocytopenia, microangiopathic hemolytic anemia (MAHA) (as a result of MV vascular occlusion), and target organ damage (as a result of ischemia due to vascular obstruction) [1].

Primary TMAs include thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (typical (tHUS) and atypical (aHUS)). In addition, preeclampsia and HELLP syndrome, autoimmune diseases (e.g., systemic lupus erythematosus, systemic scleroderma, and antiphospholipid syndrome), infections (human immunodeficiency virus and influenza, sepsis), malignant arterial hypertension, glomerulopathies, drug therapy (quinine, calcineurin inhibitors, and anticancer drugs), ionizing radiation, and organ transplantation can induce secondary TMA [2].

In obstetric practice, TMA is most often detected in preeclampsia or HELLP syndrome, aHUS, and TTP.

EPIDEMIOLOGY

The incidence of TMA is 1:25,000 in all pregnancies [3].

Preeclampsia has now become the most common cause of thrombocytopenia associated with signs of TMA at the end of trimester II or III of pregnancy. Preeclampsia complicates 2–8% of pregnancies. In the global structure of maternal mortality, the share of preeclampsia is 12–15%, and in developing countries, this figure is considerably higher and reaches 30% [4].

HELLP syndrome is the most common pregnancy-specific TMA condition, registered in 0.2–0.6% of pregnancies. The mortality in HELLP syndrome reaches 1–4%; the incidence is associated with complications such as pulmonary edema, acute kidney injury, disseminated intravascular coagulation, placental abruption, liver hemorrhage, respiratory distress syndrome in adults, stroke, or sepsis [5]. The incidence of TTP during pregnancy is 1 case per 100,000 of all pregnancies. Without the appropriate treatment of patients with TTP, the reported mortality rate is 90% [6].

aHUS is noted in 1 in 25,000 pregnancies; it occurs in 10–20% of all women for the first time during pregnancy. A total of 25–40% of women develop aHUS during their first pregnancy. Meanwhile, 80% of women with this disease develop postpartum aHUS [7].

The above statistics present the relevance of issues related to the timely diagnostics and proper treatment of patients with pregnancy-associated TMA. A timely diagnostics of TMA and promptly started treatment reduce the mortality rate by 10–20% [6–8].

ETIOPATHOGENESIS

Atypical hemolytic-uremic syndrome

aHUS is a rare genetic disease that develops as a result of dysregulation in the complement system. In aHUS, an uncontrolled activation of the alternative pathway of the complement system occurs. The regulation of the alternative pathway of the complement system is implemented by four proteins, namely, factors H and I, membrane cofactor protein, and thrombomodulin. Dysregulation can be caused by hereditary transmission of a heterozygous mutation of genes encoding regulatory complement proteins (H, I, and thrombomodulin) or membrane cofactor protein (CD46) and autoantibodies to factor H [8, 9].

Thrombotic thrombocytopenic purpura

TTP is a systemic disease with microvascular thrombosis associated with the severe deficiency of a disintegrin and metalloproteinase with thrombospondin type 1 motif 13 (ADAMTS-13).

The pathogenesis of TTP is based on the formation of unusually large von Willebrand factor (vWF) multimers, which have a pronounced capability to fix on endothelial cells. As a result, conditions are created for generalized platelet aggregation on endothelial cells [9].

Preeclampsia and HELLP syndrome

Currently, the etiology and pathogenesis of HELLP syndrome are under investigation. The pathogenesis of HELLP syndrome is based on the damage to the endothelium of small vessels (capillaries and arterioles) and the development of microangiopathy. Endothelial dysfunction results in the disseminated deposition of microthrombi from agglutinated platelets [10].

Hypercoagulability in normal pregnancy. A secondary trigger is required to activate the clinical manifestations of TMA in patients with risk factors. One such trigger is pregnancy. A normal pregnancy is characterized by hypercoagulability, which is mediated by hormonal changes and protects the woman from blood loss during childbirth. In the first half of pregnancy, the levels of factor VIII and vWF increase, and the increase in vWF level continues throughout the pregnancy and returns to normal levels 6 weeks after childbirth. In addition, in healthy women, the ADAMTS-13 activity decreases in trimesters II and III of pregnancy. Its level is restored to normal values at the end of the postpartum period.

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The decrease in ADAMTS-13 during pregnancy is associated with the excessive consumption of vWF and the influence of estrogen [11, 12].

CLINICAL SIGNS

Clinical manifestations are the same in congenital and acquired forms of TTP. TTP is characterized by a pentad of symptoms, namely, thrombocytopenia, microangiopathic anemia, fever, kidney damage, and neurological symptoms. However, according to recent studies, the above pentad is noted in 5–40% of cases of all TTPs. In TTP, signs of brain damage are predominant. Neurological manifestations in TTP can be diverse and range from minor impairments of consciousness and behavior to sensorimotor disorders, seizures, coma, and aphasia. In TTP, abdominal pain, nausea, vomiting, diarrhea, hematuria, cardiac arrhythmias, and visual disorders can be registered. All these symptoms can be caused by a disorder of microcirculation in organs and tissues, including coronary vessels, retina, and vessels supplying the gastrointestinal tract. In the last several years, in a significant number of cases (5–10%), TTP manifested itself under the guise of acute pancreatitis. The development of a full-scale presentation of disseminated intravascular coagulation syndrome and severe renal, respiratory, and liver failure are atypical for TTP [12].

Thrombocytopenia and MAHA are also characteristic of aHUS but with predominant renal damage. Thus, in TTP, signs of brain damage predominate, whereas in HUS, the kidneys are mainly involved in the pathological process [13].

TTP during pregnancy most often occurs in trimesters II and III, and the development of aHUS clinical presentation is noted in the postpartum period [14].

According to retrospective studies by French doctors, patients with genetic mutations of the complement system during their second pregnancy are at the highest risk of clinical manifestations of pregnancy-associated aHUS [15].

By contrast, data on a cohort of 22 patients with aHUS during pregnancy were published in Spain, and 16 of them had aHUS during their first pregnancy [16].

According to Austrian retrospective studies, five out of seven pregnant women with aHUS were diagnosed with pregnancy-associated aHUS during their first pregnancy, accounting for 71.4% of all patients examined [17].

HELLP syndrome

In 69% of cases, HELLP syndrome occurs during pregnancy, more often in trimester III. HELLP syndrome can also develop within 48 h after delivery. Women with HELLP syndrome usually have additional symptoms, such as malaise, nausea/vomiting, pain in the abdominal right upper quadrant, or epigastric pain. HELLP syndrome was initially detected in the presence of preeclampsia, but 15–20% of HELLP syndrome cases occur without hypertension or proteinuria. Disseminated intravascular coagulation syndrome is a common finding in HELLP, especially in presence of postpartum hemorrhage, placental abruption, or fetal death [17, 18].

DIAGNOSTICS CRITERIA

The main laboratory criteria for TMA are consumption thrombocytopenia, which occurs due to platelet aggregation in the microvascular bed, and MAHA, which can be verified in the presence of schizocytes during microscopic examination of the peripheral blood film. In addition, the presence of TMA may be indirectly indicated by an increased level of lactate dehydrogenase (LDH), which occurs due to tissue ischemia and cell lysis [19].

Despite the variability of clinical presentations, the absolute criterion for the diagnosis of TTP is the pronounced deficiency in the activity of ADAMTS-13 protease. Rationally, the decrease in ADAMTS-13 must be assessed before the start of therapy given that its false positive activity can be noted after plasma transfusion. The diagnosis of TTP is also confirmed when ADAMTS-13 activity is restored after plasma infusion [20].

For TTP, the principal symptom is severe thrombocytopenia ($<30\times10^9$/l) or a decrease in platelets by more than 25% of the initial level; for aHUS, a more pronounced renal failure is a more characteristic sign with a serum creatinine of 1.7–2.3 mg/dl [21].

The specific diagnostic criteria for HELLP syndrome vary. Hemolysis is usually defined in cases of abnormal peripheral blood smear morphology suggesting MAHA (e.g., schistocytes), a total bilirubin level higher than 1.2 mg/dL, LDH level higher than 600 U/L, or haptoglobin level lower than the lower limit of the norm. The increased activity of liver enzymes aspartate transaminase (AST) and alanine transaminase (ALT) is more than two times higher than normal. A low platelet count is defined as a level of less than 100,000/μl. TMA is less probable in women without hemolysis, and they may have an alternative diagnosis such as acute fatty hepatosis of pregnancy [22].

In differential diagnostics, the results of direct Coombs test, an antiglobulin test performed to determine the presence of anti-erythrocyte antibodies on the erythrocyte membrane, are notably important. The presence of agglutination of autoantibodies to erythrocytes indicates the course of an autoimmune process. Thus, TMA due to the development of an autoimmune process is easier to diagnose with available results of the direct Coombs test (Table 1) [23].

TREATMENT

When TTP is suspected, plasma exchange is the primary choice of therapy. The expediency of plasma therapy consists of the elimination of autoantibodies to the ADAMTS-13 enzyme, vWF protease inhibitors in the acquired form of TTP, and replenishment of ADAMTS-13 in the case of a hereditary

Table 1. Differential diagnosis of obstetric thrombotic microangiopathy (TMA)

Nosology	Laboratory findings	Symptoms	Diagnosis	First line therapy
HELLP syndrome	MAHA, Coombs – negative reaction Platelets: <100,000/μl AST/ALT: >2 times Creatinine: >1.1 mg/dL	± epigastric or right hypochondrium pain, nausea, vomiting, headache, and vision disorders	Resolved within 48–72 hours after delivery	Labor
aHUS	MAHA, Coombs – negative reaction Platelets: <150,000/μl AST/ALT: limited data Creatinine: usually >2.0 mg/dL	± nausea, vomiting, abdominal pain, headache, altered mental status	Rule out other etiology	Eculizumab
tHUS	MAHA, Coombs – negative reaction Platelets: <150,000/μl AST/ALT: limited data Creatinine: usually >2.0 mg/dL	Bloody diarrhea ± fever, nausea, vomiting, abdominal pain	Stool culture for STEC-O157 Shiga toxin immunoassay or PCR	Supporting therapy
TTP	MAHA, Coombs – negative reaction Platelets: usually <30 000/μl AST/ALT: norm Creatinine: <1.1 mg/dL	± fever, confused mental state, altered mental status	ADAMTS-13 activity <10%	Plasma exchange

Note. MAHA — microangiopathic hemolytic anemia; aHUS — atypical hemolytic uremic syndrome; tHUS — typical hemolytic uremic syndrome; TTP — thrombotic thrombocytopenic purpura.

defect in the gene of this enzyme in Upshaw–Schulman syndrome. However, despite the timely treatment, the recurrence of clinical symptoms of TTP was registered in 36% of cases [24].

Y. Fujimura et al. analyzed 15 pregnancies with congenital TTP and reported 8 stillbirths or very early neonatal deaths, most of which were associated with childbirth in trimester II and early trimester III. However, most of the female patients included in this review did not receive plasma exchange therapy for their disease [25].

In a French review of the data of female patients with acquired TTP, the risk of stillbirth was 60% with a better prognosis for the fetus when TTP developed and was detected in trimester III [26].

In aHUS, eculizumab is the drug of choice, but due to its high cost, its use is unavailable in numerous countries; therefore, plasma exchange therapy is also prescribed, which is applied in aHUS to remove faulty protein regulators of the complement system [27]. The side effects of eculizumab include the risk of infections, especially meningococcal disease; thus, patients receiving this drug should be vaccinated against meningococcal disease [28].

In severe HELLP syndrome, delivery becomes the main method of treatment [29].

The results of randomized trials do not support the use of corticosteroids to reduce maternal hemorrhage or other diseases.

The diagnosis of TTP or aHUS should be considered in any woman who does not have clinical and laboratory improvement within 48–72 h postpartum or in women who experience clinical decompensation after childbirth [30, 31].

The risks of recurrence in subsequent pregnancies range from 5% to 94%, depending on several variables. The intake of low-dose aspirin (60–150 mg daily) during pregnancy does not significantly reduce the risk of preeclampsia, preterm birth, and fetal growth retardation in high-risk women. Treatment is started at a term of 12–16 weeks, but the effect may be noticeable when the therapy is started at the week 20th of pregnancy [31].

CONCLUSION

TMA is a life-threatening condition for pregnant women and the fetus and includes a number of etiologies, which cause difficulty in the diagnosis of this pathology. Differential diagnostics must be conducted in a timely manner, and correct diagnosis should be reached given that the approach to the treatment of this patient will depend on these actions. Thus, the patient's symptoms and laboratory data should be obtained. Currently, the diagnostics and treatment of TMA are still far from satisfactory. Thus, further research is necessary to reveal more accurate diagnostic criteria and develop effective methods of treatment.

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