THROMBOCYTOPENIA IN PREGNANT WOMEN

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ТРОМБОЦИТОПЕНІЯ У ВАГІТНИХ ЖІНОК

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Акушерсько-гінекологічна лікарня Інфланська, Варшава, Польща[1], Дитяча клініка легеневих захворювань та Ревматологія, Університетська дитяча лікарня Любліна, Польща[2], Університетська лікарня Брайтон і Сассекс, NHS Trust, Великобританія[3], кафедра гінекології, Медичний університет Любліна, Польща[4], Ліверпульська жіноча NHS Foundation Trust, Великобританія[5], завідувач кафедри акушерства та перинатології, Люблінський медичний університет, Польща[6]

Тромбоцитопенія є другим після анемії за поширеністю гематологічним розладом у вагітних. Тромбоцитопенія характеризується зменшенням кількості тромбоцитів в одиниці об'єму крові нижче 150 тисяч. Перебіг захворювання часто є безсимптомним. Однак можуть виникати симптоми, що приводять до небезпечних для життя ускладнень вагітності або загострення супутніх захворювань під час вагітності. У близько 75% випадків, пов'язаних з тромбоцитопенією вагітних жінок, виникає, так звана гестаційна випадкова тромбоцитопенія (ГІТ), патомеханізм якої зазвичай складний і пов'язаний з перебігом вагітності. Решта 20% випадків пов'язані з прееклампсією та HELLP синдромом. Первинна імунна тромбоцитопенія становить 3-4%. Інші типи тромбоцитопенії у вагітних складають 1-2% (вроджені, пов'язані з інфекцією, пов'язані впливом медикаментозних засобів, пов'язані зі злоякісними захворюваннями крові). В роботі викладено основні аспекти впливу тромбоцитопенії на перебіг вагітності, які зустрічаються в сучасній літературі. Крім того, описано діагностику та етіологію захворювання, принципи терапевтичного лікування.
Ключові слова: вагітність, тромбоцитопенія, діагностика, лікування.

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Thrombocytopenia is the second most commonly occurring haematological disorder in pregnant women after anaemia. It is usually characterized by a drop in platelet count below 150 G/L. Its course is mild and asymptomatic, although it may predispose to the occurrence of symptoms leading to life-threatening complications of pregnancy or exacerbation of the comorbid disease in pregnancy. In about 75% of cases associated with thrombocytopenia in pregnant women there is so-called gestational incidental thrombocytopenia (GIT), the pathomechanism of which is usually complex and associated with the course of pregnancy. The subsequent 20% of cases are associated with pre-eclampsia and HELLP syndrome. Primary immune thrombocytopenia accounts for 3-4%. Other types of thrombocytopenia in pregnant women constitute 1-2% (congenital, infection-related, drug-related, related with neoplastic diseases of the blood). The paper presents the influence of thrombocytopenia on the course of pregnancy in the light of literature. It also explains diagnostics and etiology, and takes into account the principles of therapeutic treatment.
Key words: pregnancy, thrombocytopenia, diagnostic procedures, treatment.

Introduction

Thrombocytopenia is the second most commonly occurring haematological disorder in pregnant women after anaemia. It is defined as a platelet count (PLT) below 150x10^3 / uL, which can lead to acquired purpura. According to various sources, it concerns about 6.6% -11.6% of women in the final period of pregnancy [1,2,3]. It should be noted that even in physiological pregnancy, there may be a reduction in platelets count by approximately 10% [3,4,5]. Depending on the number of platelets, we can distinguish low (PLT 100-150x10^3 / uL), medium (PLT 50-100x10^3 / uL) or high thrombocytopenia (PLT <50x10^3 / uL) [4].

The mechanism of thrombocytopenia formation consists in the impaired production or excessive destruction of platelets. The causes of this phenomenon are seen in immunological diseases such as: collagenoses, immune thrombocytopenic purpura (ITP), antiphospholipid syndrome, thrombotic microangiopathies, thrombotic thrombocytopenic purpura, haemolytic-uremic syndrome (HUS). Thrombocytopenia may also result from the use of drugs, viral infections, bone marrow dysfunction (bone marrow aplasia), nutritional deficiencies, or disseminated intravascular coagulation syndrome (DIC) [6,7]. In addition, pregnant women are additionally exposed to thrombocytopenia due to only obstetric reasons. These include: pre-eclampsia (PEC), eclampsia (EC), in particular its most severe form – the HELLP syndrome [4,8]. Although thrombocytopenia in pregnant women usually has a mild course, it should be remembered that in some cases a significant decrease in PLT count may lead to dangerous bleeding. In immune thrombocytopenia, low levels of platelets in the foetus increase the risk of intracranial bleeding in the perinatal period. In addition, thrombocytopenia may be associated with pregnancy complications or a developing disease regardless of pregnancy. That is why it is so important to determine the cause of thrombocytopenia and to identify the risk it poses for both the mother and the child [1].

The most common form of this disease in pregnant women is GIT - gestational incidental thrombocytopenia, the incidence is estimated at 5%, which accounts for 75% of all diagnosed cases of thrombocytopenia during pregnancy [3,9]. Thrombocytopenia is a diagnosis of exclusion. Usually it is a low- medium thrombocytopenia with a platelet count above 70 x10^3/ uL without the symptoms of purpura and it does not occur before conceiving. The platelet count before and at the beginning of gestation usually falls within the normal range and after 1-12 weeks of its completion returns to normal values [10]. Its etiology is unknown. It is believed that incidental thrombocytopenia is secondary to accelerated platelet destruction and increased plasma volume associated with pregnancy and appears as a type of physiological thrombocytopenia. It develops usually in the second and third trimester of pregnancy. A low or medium reduction in the platelet count due to incidental thrombocytopenia is not associated with an increase in maternal, foetal or neonatal complications, indicating that these conditions do not require additional treatment except careful monitoring of platelet count [11,12].

However, immune thrombocytopenic purpura (ITP) may be the threat to the foetus, which affects over 4% of pregnant women [13,14]. It is a moderate-degree thrombocytopenia with a platelet count below 100x10^3 / uL before conceiving or at the beginning of gestation and a normal or increased megakaryocytes count in the bone marrow biopsy specimens [15]. During the diagnosis, there should be excluded other systemic diseases, splenomegaly or the use of drugs that may reduce the platelet count. Pregnancy does not worsen the course of ITP, but there may be adverse foetal and maternal consequences in some cases. Although rare, spontaneous bleeding is the main maternal risk especially when the platelet count falls below 20x10^3 / uL [16]. Antiplatelet antibodies (mainly IgG antibodies, less frequently IgM) lead to accelerated platelet destruction, thus shortening their survival rate. Maternal IgG antibodies can pass through the placenta and bind to foetal blood cells leading to the development of thrombocytopenia. This is manifested by the appearance of bruises, petechie, bleeding from the gastrointestinal tract, as well as intracranial hemorrhage in the neonatal period. Congenital thrombocytopenia in the course of maternal ITP occurs in about 50% of newborns, and in 12-15% of newborns the platelet count is below 50x10^3 / uL [16,17]. Serious haemorrhagic complications are found in 3% of newborns, and in less than 1% of cases, intracranial bleeding occurs. Even if the mother's platelet count stabilizes, the risk of having a baby with thrombocytopenia is approximately 30% [2]. Medium-severe thrombocytopenia can cause greater morbidity for both mothers and newborns, and the method of diagnosis, treatment or termination of complicated pregnancy is still the subject of disputes [2,7].

For the explanation of the cause of thrombocytopenia, it is very important to take medical history, to make physical examination and select appropriate laboratory tests. Based on the medical history, it should be determined whether:

1) thrombocytopenia occurred prior to conception
2) thrombocytopenia occurred in the present pregnancy and in which trimester
3) thrombocytopenia occurred in a child from the previous pregnancy
4) there is a positive obstetrical history (miscarriage, delivery of a dead foetus caused by haemorrhage to the central nervous system),
5) the offspring develops properly and there are no delays in psychomotor development, cerebral palsy, epilepsy,
6) thrombocytopenia is an isolated or comorbid symptom [18,19].

Thrombocytopenia may be a symptom of serious diseases complicating the pregnancy itself, such as: induced hypertension, pregnancy with oedema and protenuism, DIC, thrombotic microangiopathies (thromboembolic syndrome),

thrombotic thrombocytopenic purpura [1]. The above-mentioned symptoms are presented in the following classification of the causes of thrombocytopenia during pregnancy.

Classification of thrombocytopenia in pregnancy

1. Pregnancy-related thrombocytopenia

Gestational thrombocytopenia

Thrombocytopenia in the course of pregnancy-induced hypertension (Gestora)

HELLP syndrome (hemolysis, elevated liver function tests, low platelets count)

Acute fatty liver of pregnancy

2. Thrombocytopenia not related to pregnancy

ITP

Systemic lupus

Phospholipid syndrome

Drug-induced thrombocytopenia (caused by heparin, gold preparations, quinidine, penicillin, cimetidine, digoxin)

Thrombocytopenia in the course of viral infections (viruses that cross-react with platelet antigens, HIV (human immunodeficiency virus)

Epstein-Barr-virus

CMV (cytomegalovirus)

Thrombotic microangiopathy syndromes

Thrombotic thrombocytopenic purpura

Hemolytic-uremic syndrome

DIC (disseminated intravascular coagulation)

Bone marrow dysfunction (bone marrow aplasia)

Leukemias

Aplastic anemia

Nutritional deficiencies

Folic acid deficiency, vitamin B12 deficiency

Hypersplenism

Pseudothrombocytopenia

The basis for the diagnosis of thrombocytopenia in pregnant women is the use of automatic methods for the analysis of blood parameters, in combination with the reticulocytes count and evaluation of peripheral blood smear. Isolated thrombocytopenia is characteristic of both immune thrombocytopenia and gestational thrombocytopenia. There are large platelets in thrombocytopenia, which is indicated by increased platelet ratios - mean platelet volume (MPV) and platelet large cell ratio (P-LCR), which may exceed their norm. An extremely rare reason for the isolated platelet counts during pregnancy is sub-type IIB (2BvWD) and platelet type (PTvWD) of von Willebrand disease (vWD), which is the evidence of congenital thrombocytopenia. Thrombocytopenia with increased reticulocytosis occurs in thrombocytopenia in the course of microangiopathy. The assessment of peripheral blood smears is of great importance in the diagnosis. The presence of fragmentocytes-schistocytes in the smear becomes characteristic of thrombotic microangiopathy. Macrocytosis may be associated with myelodysplastic syndrome (MDS) or deficiency of vitamin B12 and folic acid, and the tear-shaped image of blood cells confirms bone marrow fibrosis. Precise evaluation of WBC makes it possible to diagnose neoplastic diseases of blood that cause thrombocytopenia. It should be noted that on the basis of the changes found in the CBC and peripheral blood smears, a further method of treatment is planned. In the case of isolated thrombocytopenia, the most likely diagnosis is GIT in the second half of pregnancy and ITP in the first half of pregnancy. In both cases, tests should be performed immediately to rule out secondary immune thrombocytopenia and other reasons for isolated reduction of PLT [1]. They are presented in the following list of recommended laboratory tests in pregnant women.

Recommended laboratory tests in pregnant women with isolated thrombocytopenia:

1. Blood count with platelet count and reticulocyte count;
2. Peripheral blood smear;
3. Hepatic enzymes and bilirubin;
4. Direct antiglobulin test;
5. Thyroid function tests;
6. Antiphospholipid antibodies;
7. Antinuclear antibodies;
8. Test confirming infections: Helicobacter pylori, HCV, HBV and HIV;
9. Basic coagulation tests;
10. Diagnostic tests for type 2BvWD and PTvWD von Willebrand disease.

The goal of ITP treatment in pregnant women is to prevent dangerous bleeding. Usually, in the trimester II and III of pregnancy, patients in whom the platelet count (PLT) is above 20-30 G / L do not require treatment – provided that performing an operation or initiating of an invasive procedure is indicated. This treatment includes administration of corticosteroids and intravenous immunoglobulin (IVIG). Due to possible side effects of corticosteroids, it is recommended to start treatment with small doses, e.g. prednisone 10-20mg / day for about 7 days, adjusting the dose to PLT count [20]. In turn, according to the group of experts on Haemostasis of the Polish Society of Hematology and Transplantologists (PTH iT), it is recommended to administer prednisone in the initial dose of 1mg / kg / body weight and its gradual reduction after the platelets count (PLT) increases above 50G / L. If increasing the PLT count is necessary, immunoglobulin should be administered at standard doses of 1g / kg body weight for 1-2 days. After transfusion, the PLT count increases in 24-48 hours and lasts for 2-3 weeks. Of course, the infusion can be repeated to ensure the optimal PLTcount every 2-4 weeks until pregnancy is terminated. In the case of immuno-resistance to first-line drugs, a bone marrow biopsy should be sampled to exclude other causes of thrombocytopenia. If the bone marrow is normal and the isolated thrombocytopenia has been revealed or worsened in late pregnancy, the test for the subtype 2BvWD and PTvWD of von Willebrand disease should be performed. The drug considered safe in pregnancy by the FDA in ITP is

azathioprine at a dose of 1-2mg / kg/ body weight, which has a delayed effect [21]. Another drug approved for the treatment of refractory ITP is cyclosporine (CsA). However, due to the frequent side effects, it is rarely used. The contra-indicated drugs during pregnancy include: cyclophosphamide (CTX), vinca alkaloids, mycophenolate mofetil and danazol [1,22].

Conclusion

Thrombocytopenia in pregnancy is a mild condition and does not require drastic measures, especially if it occurs in the last trimester of pregnancy. Its most common cause is GIT, and in the first trimester - ITP. It should be remembered that thrombocytopenia, despite a mild form, can lead to dangerous complications of pregnancy or exacerbation of a comorbid disease in pregnancy. In order to diagnose the disease, it is essential to take an in-depth history and perform physical examination. In addition, a key element in the diagnosis of thrombocytopenia is to use automated methods for evaluating the blood parameters analysis which affects the increase in diagnoses in the direction of thrombocytopenia in pregnant women.

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Отримана: 03.12.2018 **Прийнята до друку: 24.12.2018**