The Frequency and Characteristics of Immune Thrombocytopenia at Different Stages of Pregnancy

Abstract: This article analyzes the frequency and characteristics of immune thrombocytopenia at different stages of pregnancy. The article includes innovations that occurred during the study of the frequency of immune thrombocytopenia. In addition, the article describes each of the features of each period of pregnancy separately.

Key words: thrombocytopenia, clinical manifestations, hereditary, lymphocytic leukemia, myelodysplastic diseases.

Introduction.
Thrombocytopenia is a decrease in the number of platelets in the peripheral blood to <150 thousand / ml in the absence of other abnormalities in the count of elements in patients without clinical manifestations of other diseases that can cause thrombocytopenia (HIV infection, systemic diseases, lymphocytic leukemia, myelodysplastic diseases, treatment with certain drugs, hereditary thrombocytopenia). According to the severity, thrombocytopenia is divided into mild (with a platelet count from >100 to <150 thousand/ml), moderate (from >50 to <100 thousand/ml) and severe (<50 thousand/ml).

Literary review and methodology.
The causes of thrombocytopenia are increased destruction or consumption of platelets, as well as insufficient formation of the latter. Thrombocytopenia can be hereditary (associated with changes in the functional properties of platelets) and acquired: immune or as a result of exposure to various damaging factors [1]. The most commonly diagnosed is idiopathic thrombocytopenic purpura (ITP), which accounts for up to 90% of all thrombocytopenias.
Thrombocytopenia can complicate the course of 5 to 10% of pregnancies, while about 75% of newly diagnosed cases of thrombocytopenia are directly related to pregnancy [7, 16].

The main causes of thrombocytopenia during pregnancy are gestational thrombocytopenia, pregnancy-induced hypertension, HELLP syndrome, HIV infection, immune thrombocytopenic purpura, antiphospholipid syndrome, systemic disease, thrombotic thrombocytopenic purpura, DIC, hemolytic uremic syndrome, hereditary thrombocytopenia, folate deficiency, primary dysfunction of the bone marrow [7, 15]. If any thrombocytopenia is detected, especially below 80.0 × 10⁹/l, a pregnant woman needs to be examined as if ITP is suspected.

ITP is an autoimmune disease in which antibodies of the IgG class are produced against platelets’ own membrane glycoproteins. ITP is characterized by destruction of platelets occurring in the reticuloendothelial system, mainly in the spleen, as a result of which the breakdown of platelets prevails over their production [7].

The first description of "spotted hemorrhagic disease" (morbus maculosus haemorrhagicus) was made by the Hanoverian physician P. Werlhof in 1735 (Werlhof’s disease), at the end of the 19th century. the disease was isolated as an independent nosological form. In 2008, the International consensus on the diagnosis and treatment of ITP suggested that Werlhof’s disease be called primary immune thrombocytopenia [11].

The annual detection of ITP is about 2 cases per 100,000 adults [2]. However, the estimated incidence of ITP, especially in children, is difficult to determine, since not all patients seek medical help and are examined. The prevalence ranges from 4.5 to 20 cases per 100,000 population. Men get sick 5-6 times less often than women. More often, people aged 20 to 40 years old - 54% of patients, from 40 to 60 years old - 30%, and very rarely younger than 20 and older than 70 years (5 and 11%, respectively) get sick. ITP trigger factors can be infections (often viral) in 59%, pregnancy in 19%, stress in 15%, surgical manipulations in 4%, physical activity in 2%, vaccinations in 1% patients [13].

The etiology of ITP is not fully understood, but among the specific mechanisms of the disease, the influence of immune disorders at the T-cell level and in the production of cytokines, which are involved in the activation and differentiation of B-lymphocytes into antibody-producing cells, has been proven. The latter leads to overproduction of autoantibodies directed against platelet surface glycoproteins and causing their damage. This leads to the release of new antigens, to which antibodies are formed with the formation of immune complexes, and a vicious circle is formed. Unfortunately, modern methods for the determination of antiplatelet autoantibodies by enzyme immunoassay or immunofluorescent methods are very laborious (including due to the small number of platelets) and are informative only in 60–80% of cases.

Clinical manifestations of the disease depend on the degree of thrombocytopenia. These are mainly spontaneous or post-traumatic skin hemorrhagic syndrome (single or generalized petechial rash and ecchymosis), petechiae and ecchymosis on the mucous membranes, nasal and gingival bleeding, menorrhagia, and less often gastrointestinal bleeding and hematuria. The diagnosis of ITP is still a diagnosis of exclusion. Diagnostic criteria: isolated thrombocytopenia <100.0×10⁹/l in two blood tests, visual assessment of the number and morphology of platelets, increased or normal number of megakaryocytes in the myelogram, normal size of the spleen, exclusion of other pathological conditions that cause thrombocytopenia, antiplatelet antibodies in high titer [4].

The main methods for diagnosis are:
- history taking: determination of factors preceding the development of thrombocytopenia (infection, vaccination, stress, medication), duration of bleeding after surgical interventions, thrombosis
throughout life, the presence of cardiovascular pathology or other diseases accompanied by thrombocytopenia;
- family history: bleeding, thrombocytopenia, thrombosis and diseases of the hematopoietic system in relatives;
- physical examination: intoxication, fever, hepato- and splenomegaly, swollen lymph nodes, somatic pathology [4, 12];

Laboratory research methods:
1. General blood test with platelet count (including Fonio) and reticulocytes. Also pay attention to the size of cells and aggregates of platelets. In ITP, there is only isolated thrombocytopenia.
2. Biochemical blood test with the determination of all the main parameters.
3. Cytological examination of the bone marrow to exclude thrombocytopenia in myeloproliferative diseases. Bone marrow trepanobiopsy is indicated for recurrent and resistant forms of ITP.
4. Carrying out PCR diagnostics, as well as diagnostic monitoring of viruses of the herpes simplex family, HIV.
5. Diagnosis of Helicobacter pylori using a breath test or determination of H. pylori antigens in feces in patients with a burdened ulcer history and / or clinical manifestations of gastric and duodenal ulcers.
7. Molecular genetic studies (congenital thrombophilia).
8. Ultrasound examinations (ultrasound) of the abdominal cavity and retroperitoneal space, radiography of the chest organs.
9. Determination of specific antibodies to platelet glycoproteins: a high titer confirms the immune genesis of thrombocytopenia, but is not an absolutely informative method [12].
10. Antiphospholipid antibodies, thyroid function assessment, antinuclear antibodies, antibodies to native (double-stranded) DNA (to exclude systemic lupus erythematosus).

The main goal of ITP therapy is to achieve a safe (stopping hemorrhagic syndrome) platelet level, and not to correct the number of platelets to normal levels. A platelet level of 30–50.0 × 10⁹/l is considered safe, which ensures the normal existence of the patient without spontaneous bleeding and does not reduce the quality of life [3, 5]. Therapy of patients with ITP should be based on an individual approach, which should be determined not only by the level of platelets, but also by the severity of the hemorrhagic syndrome, complications from previous treatment, and planned surgical interventions. The platelet count of 100.0×10⁹/l fully provides hemostasis and allows for surgical interventions and delivery without the risk of bleeding. Critical is the content of platelets <10.0×10⁹/l. A platelet level >30–50×10⁹/l is considered safe, which ensures the normal existence of a patient without hemorrhagic syndrome.

Hemorrhagic syndrome and thrombocytopenia 30.0–50.0 × 10⁹/l are staggered ITP. The first line therapy is [2, 3]:
Glucocorticosteroids (GCS):
- prednisolone at a dose of 1 mg/kg body weight orally for 2-4 weeks. After stopping the hemorrhagic syndrome and increasing the number of platelets >50.0 × 10⁹/l, a gradual decrease in the dose of the drug begins, then maintenance therapy is prescribed in small doses (10–15 mg/day), then every other day for up to 8 months;

- methylprednisolone (in tablets of 4 mg), dexamethasone (in tablets of 0.5 mg) are prescribed in full quantitative correspondence of tablets during therapy with prednisolone.

2. Intravenous administration of high doses of polyvalent immunoglobulin, which provides a more rapid increase in platelet count compared to GCS. The hemostatic effect occurs on the 1st-2nd day after administration. The course dose of the drug is 2 g per 1 kg of body weight. A single dose for a 2-day course: 1 g per 1 kg of body weight. Single dose for a 5-day course: 400 mg per 1 kg of body weight.

The second-line therapy is splenectomy, indications for newly diagnosed ITP: resistance to corticosteroid therapy, intolerance and contraindications to treatment with first-line drugs, the need to obtain a quick effect in urgent situations with massive bleeding (uterine, gastrointestinal, the threat of hemorrhage in brain) and in severe intractable exacerbations of ITP in pregnant women in the I–II trimesters of pregnancy [9].

In addition, in persistent and chronic ITP, romiplostim, rituximab, azathioprine, cyclophosphamide, etc. can be used as second- and third-line therapy [18]. The refractoriness of ITP is determined by the failure to maintain a long-term clinical effect after splenectomy and cannot be diagnosed before it. Refractory ITP is characterized by a severe course and a constant need for specific therapy [10].

Pregnancy planning is one of the most important conditions for its successful course in ITP. The onset of pregnancy should take place in a state of clinical compensation, i.e. in the absence of hemorrhagic syndrome and platelet count above the critical level (50.0×10⁹/l) [13, 16, 17]. Women with a severe, resistant form of ITP should undergo an adequate course of therapy before pregnancy and plan its onset for a period of remission or clinical and hematological compensation of the disease. In severe and refractory forms of ITP, pregnancy is associated with an increased risk for the mother and child, which patients should be warned about. In pregnant women with ITP, the incidence of complications such as threatened miscarriage in the first and second trimesters, spontaneous miscarriages, threatened preterm birth, early toxicosis and preeclampsia increases by 2–3 times, while the incidence of obstetric bleeding is usually low, however it is the main life-threatening condition during childbirth and in the postpartum period [11, 19].

In ITP, the maternal reticuloendothelial system breaks down the platelet–antiplatelet antibody complexes, and antiplatelet antibodies cross the placenta. Neonatal immune thrombocytopenia results from maternal immunization with fetal specific platelet antigens. Thrombocytopenia in the newborn is noted in 20-30% of children born to women with ITP. Thrombocytopenia is more common in infants born to mothers with severe ITP and is more common in low birth weight infants. The number of platelets in the fetus or newborn does not correlate with the number of platelets in the mother, the level of antibodies, or whether the mother had a splenectomy. During childbirth, measures that increase the risk of hemorrhagic complications in the fetus (vacuum extraction and the use of obstetric forceps) should be excluded.

It should be remembered that all pregnant women with ITP should be jointly observed by an obstetrician-gynecologist and a hematologist, and an anesthesiologist before delivery.

In case of thrombocytopenia <80.0×10⁹/l, especially in the third trimester of pregnancy, weekly monitoring of the complete blood count is necessary. The purpose of prescribing therapy is to increase the number of platelets to a minimum level that ensures the safety of gestation and delivery. During
the first two trimesters of pregnancy, indications for therapy are hemorrhagic syndrome of varying severity; platelet count $<20-30.0 \times 10^9/l$. There is no need to prescribe specific therapy to pregnant women with a platelet level $>50.0 \times 10^9/l$ and the absence of hemorrhagic syndrome. The main drugs used for the treatment of pregnant women are the same as in women without pregnancy [6, 7, 9]. These are corticosteroids (prednisolone in lower doses than outside of pregnancy), human immunoglobulin preparations, their combination, splenectomy is performed extremely rarely. Rituximab, cyclosporine, etc. are inappropriate due to the delay in their effect and the lack of evidence of their safety for the fetus. First-line drugs in women with newly diagnosed ITP and relapses are intravenous immunoglobulins (IVIG) and corticosteroids [5, 14]. IVIG is administered as a single dose of 400 mg/kg body weight. The total dose is determined by the immediate effect, the number of procedures varies from 2 to 5. If there is no effect at the maximum IVIG course dose of 2 g/kg of body weight, splenectomy can be performed by transthoracic access [19]. Treatment of corticosteroids is aimed at stopping the hemorrhagic syndrome and a minimal increase in platelets to a safe concentration.

Clinical observation.

The patient, 38 years old, was admitted with a diagnosis of “Pregnancy 32–33 weeks; transverse position of the fetus; uterine scar after caesarean section in 2009 and 2020 immune thrombocytopenia. Presentation of the loops of the umbilical cord (ultrasound). Congenital malformation of the fetus - agenesis of the corpus callosum, internal hydrocephalus. Thrombophilic mutations (a tendency to hyperfibrinogenemia due to fibrinogen gene polymorphism). The tendency to decrease the fibrinolytic activity of the blood, due to the PAI1 4G/4G genotype. Defect in the platelet receptor gene for collagen. MTFHR gene defect. Gestational diabetes. Varicose veins”.

From the anamnesis it is known that the diagnosis of immune thrombocytopenia was established since 2017, while until 2020 the patient received treatment with prednisolone 1 mg/kg, after which a stable remission was noted. This pregnancy, VII, came on its own.

Previous pregnancies: I (1992) ended in timely delivery, a boy weighing 3800 g was born, the postpartum period was complicated by endometritis, curettage of the walls of the uterine cavity was performed three times, after the third curettage, bleeding opened, requiring a transfusion of 1 dose of erythrocyte mass. Since 2003, Asherman's syndrome was diagnosed, and hysteroscopy was performed. II pregnancy ended in spontaneous miscarriage at 7-8 weeks of gestation; III pregnancy - an emergency caesarean section at a gestational age of 30 weeks due to premature detachment of a normally located placenta, a girl weighing 1700 g was removed, who died after 16 hours. During caesarean section, 1 dose of plasma was transfused. IV pregnancy (2000) also ended with an emergency caesarean section at 34 weeks' gestation for premature placental abruption. A girl weighing 2000 g was taken out, she is healthy. One month after the operative delivery, hematometers were diagnosed, the walls of the uterine cavity were scraped, during which a transfusion of 1 dose of plasma was required. V-VI pregnancies (2003, 2009) - non-developing pregnancies 6-7 weeks - curettage of the walls of the uterine cavity, without features.

This pregnancy proceeded in the first trimester with the threat of termination, the patient was hospitalized, in the second trimester she had anemia, for which she received iron preparations, she did not receive corticosteroid therapy until 28 weeks, she was not observed by a hematologist. She was hospitalized at a gestational age of 28 weeks due to threatening premature birth, a clinical and laboratory examination was carried out, and therapy aimed at prolonging the pregnancy was started. A diagnosis of gestational diabetes mellitus was established, and insulin therapy was started. Repeatedly consulted by a hematologist, prednisolone was prescribed at a dose of 40 mg/day. The minimum platelet level was 20×10^9/l. After 7 days of inpatient observation, regular labor activity developed. The platelet level was 1×10^9/l. Taking into account the development of regular labor activity in a
A multiparous woman with a uterine scar after two previous caesarean sections, presentation of umbilical cord loops, aggravated somatic history, a caesarean section was performed under conditions of reinfusion of autoerythrocytes. Taking into account the chronic course of immune thrombocytopenia and refractoriness to prednisolone therapy, it was decided to perform simultaneous laparoscopic splenectomy. A live premature boy weighing 2740 g, 44 cm long was removed. Apgar score was 6/7. The total blood loss was 1200 ml, auto-erythrocytes were reinfused with 300 ml with a hematocrit of 55%.

In the postoperative period, antibacterial, uterotonic therapy was carried out, the patient was observed by a hematologist, prednisolone was prescribed at a dose of 40 mg, on the 2nd day after delivery, solumedrol was administered at a dose of 125 mg. On the 10th day the patient was discharged home after normalization of the platelet count, the child was discharged on the 16th day.

Conclusion.
Thus, this experience indicates the need for preconception counseling to confirm the state of remission, as well as training in order to create conditions for entry into pregnancy in a situation favorable for gestation and childbirth. Pregnancy in women with ITP may be accompanied by a high risk of complications, therefore, from an early date, patients should be under the supervision of specialists from top-level medical institutions. In the vast majority, the course of the disease during pregnancy is benign, but sometimes the disease can become severe with refractoriness to therapy. Compliance with the algorithm for monitoring the course of the gestational process contributes to the achievement of a favorable outcome of pregnancy.

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