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THE CAUSES, PATHOGENESIS, CLINICAL MANIFESTATIONS, AND LABORATORY DIAGNOSIS OF THROMBOCYTOPENIA IN PREGNANT WOMEN

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Abstract:

Thrombocytopenia in pregnant women is classified into immune thrombocytopenia developed during pregnancy, pre-existing thrombocytopenia unrelated to pregnancy, and secondary or symptomatic thrombocytopenia. Although numerous studies have been conducted on the causes of thrombocytopenia in pregnant women, and various innovations have been proposed and tested, the results remain quite controversial, debatable, and uncertain. These uncertainties may be resolved in the future through targeted, well-designed, controlled trials, pharmacogenomics, and precision medicine research.

Keywords: hemostasis, pregnancy, thrombocytopenia, bleeding.

Idiopathic Thrombocytopenic Purpura (ITP) is an autoimmune disease caused by antiplatelet antibodies and/or circulating immune complexes. These typically target platelet membrane glycoprotein structures, leading to their destruction by reticuloendothelial system cells [20].

In 1915, I. M. Frank proposed that the disease might be associated with an influence located in the spleen affecting megakaryocyte maturation. In 1946, Dameshek and Miller demonstrated that in thrombocytopenic purpura, the number of megakaryocytes does not decrease; rather, it can even increase. They hypothesized that the process of platelet release from megakaryocytes was disrupted. In 1916, Kaznelson proved that in thrombocytopenic purpura, the spleen's destruction of platelets intensifies. For many years, Frank's hypothesis remained more widely accepted [4, 8, 21, 19].

Today, due to adverse environmental factors such as poor-quality food, water, radiation, chemicals, and modern lifestyles, autoimmune diseases are becoming increasingly common. These factors not only directly affect the immune system but can also impair it. As a result, the body, mistakenly identifying its own cells as foreign antigens, produces antibodies against them. These conditions are highly dangerous, as they can begin asymptomatically or mimic other diseases, making early diagnosis challenging. In advanced stages, various complications arise, significantly reducing treatment effectiveness [1, 9, 11, 23].

Immune thrombocytopenic purpura is also an autoimmune disease. Unlike hereditary forms of thrombocytopenic purpura, the reduced lifespan of platelets in this condition is linked to defects in their membranes or structural anomalies in platelets, including impaired activity of glycolytic enzymes or disruptions in the tricarboxylic acid cycle. In cases with an excessive number of antiplatelet antibodies or when antibodies target megakaryocyte antigens not present on platelets, megakaryocyte formation can be disrupted [3, 7, 6, 10].

Thrombocytopenia is a decrease in peripheral blood platelet counts below 150,000/ml in patients without clinical manifestations of other diseases that may cause thrombocytopenia (such as HIV infection, systemic diseases, lympholeukemia, myelodysplastic syndrome, certain medications, or hereditary thrombocytopenia). Thrombocytopenia is classified by severity: mild (platelet count >100,000 to <150,000/ml), moderate (>50,000 to <100,000/ml), and severe (<50,000/ml). Thrombocytopenia can be hereditary (associated with functional changes in platelets) or acquired due to immune or other harmful factors. The most commonly diagnosed form is idiopathic thrombocytopenic purpura (ITP), accounting for 90% of all thrombocytopenias [4, 2, 18].

During pregnancy, a decrease in platelets occurs due to the influence of antiplatelet antibodies. These antibodies cross the placenta and interact with fetal platelets, causing thrombocytopenia in the fetal bloodstream. Platelets bound with antibodies are destroyed by macrophages in the spleen and, to a lesser extent, in the liver. Pregnancy may exacerbate the disease.

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The recurrence of the disease may be associated with the production of antiplatelet antibodies by the fetus's spleen. The risk of bleeding increases during the second pregnancy [12, 23, 25].

In recent years, numerous clinical studies have been published based on retrospective analyses of the frequency of obstetric complications in patients with immune thrombocytopenia (ITP) [9, 14, 16, 19]. M.Yu. Sokolova (2004) acknowledged that ITP can negatively affect pregnancy and fetal viability. Obstetric complications are significantly higher in pregnant women with ITP compared to the general population, occurring on average 2–3 times more frequently: preeclampsia in 37.5% of cases, risk of miscarriage and spontaneous abortion in 56.4%, placental insufficiency in 43.5%, and premature separation of a normally located placenta in 3.6% of cases [2, 6].

Contrary to many researchers, H. Xwa et al. (1993) reported high rates of bleeding during pregnancy (12%) and in the postpartum period (24%) in patients with ITP [22]. Similarly, a study conducted by S. Borna et al. highlighted a high incidence of severe postpartum bleeding (30.7% of cases) in this pathology [9].

There is limited evidence-based information regarding the accuracy and reliability of diagnostic tests used for ITP. According to literature data, a definitive diagnosis requires confirming isolated thrombocytopenia by analyzing patient complaints, medical history, physical examination data, and clinical and laboratory tests, while ruling out other possible causes [24, 15].

Maternal immune and autoimmune diseases can lead to impaired thrombocytopoiesis in newborns, manifested by a decrease in platelet count and resulting in the following forms of thrombocytopenia:

1. Alloimmune or isoimmune thrombocytopenia associated with maternal-fetal blood group incompatibility, when maternal antibodies enter the fetal bloodstream (neonatal).
2. Transimmune thrombocytopenia (maternal antibodies directed against fetal platelets cross the placental "barrier") in cases where the mother has idiopathic thrombocytopenia or systemic lupus erythematosus.
3. Autoimmune thrombocytopenia, characterized by the production of antibodies against one's own platelets.
4. Heteroimmune thrombocytopenia caused by changes in the antigenic structure of blood cells due to viral or other agents affecting the organism [14, 8].

Patients with ITP represent a highly heterogeneous group. Many of them, even with significantly low platelet counts, show no manifestations related to thrombocytopenia, while others may develop bleeding of varying severity from the onset of the disease. Thus, F. Rodeghiero et al. published the results of a study on ITP patients observed in routine clinical practice for more than 12 months. It was found that 40% of them, despite low platelet counts, experienced no bleeding and did not require treatment [21].

The functional state of platelets can be assessed by markers of platelet activation in plasma. The most widely used methods include determining the components of platelet dense granules in plasma, such as anti-heparin factor IV, β-thromboglobulin, and serotonin. Qualitative and quantitative tests often assess von Willebrand factor and, occasionally, platelet factor 3. Normal plasma levels of β-thromboglobulin range from $20–35\times10^{12}$ g/L, and anti-heparin factor IV from $4–6\times10^{12}$ g/L. These values can increase more than tenfold during the activation of the primary hemostatic pathway [5].

Based on studies of 28 patients with ITP, A.V. Seleznev (2004) identified significant changes in the erythrocyte component along with platelets. In this regard, the author proposed focusing on the hemostatic function of red blood cells when diagnosing the disease, including the study of erythrocyte coagulation factors, deformability, and other parameters [10].

Thus, a comprehensive study of ITP patients, including anamnesis, general clinical, and laboratory methods, is of great importance in diagnosing the disease [24].

In clinical practice, evaluating the vascular-platelet system of hemostasis requires not only determining platelet count but also assessing their quality through various tests. For example, methods for determining platelet adhesion and aggregation capacity are frequently used. Comparative thromboelastography using platelet-free plasma and platelet-rich plasma provides precise information about the state of vascular-platelet hemostasis [4].

Aggregation studies are usually conducted using specially configured and equipped photoelectric colorimeters—aggregometers—which provide the results as a graphical representation of the aggregation reaction with various inducers (aggregation curves). Typically, the quality of aggregation is assessed using ADP (at various concentrations), collagen, ristocetin, adrenaline, and several other agents. Summarizing the results of such studies, the total platelet aggregation index is usually determined. For women in the second phase of the

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menstrual cycle, the normal ranges for platelet aggregation are as follows: adrenaline inducer (5 mM) - 45–75%, ADP (5 mM) - 45–75%, collagen - 40–60%, ristocetin (1.2 mg/ml) - 60–100% [2]. Further analysis of aggregation curves based on various parameters provides more detailed insights [13].

In physiological pregnancy, platelet aggregation in the first and second trimesters corresponds closely to the values observed in women during the second phase of the menstrual cycle. However, these values may decrease during the third trimester [24]. Interesting data on the relationship between the predominance of specific morphological forms of platelets in plasma and aggregation results were presented in studies by M.A. Modin [6]. A predominance of "resting" platelets (discocytes) in plasma was associated with a decrease in the maximum slope of the aggregation curve amplitude when ADP was used as the inducer. Similarly, for the same inducer, a positive correlation was noted between the low activation level of platelets (first-degree echinocytes) and aggregation amplitude concentration.

The most sensitive and informative test for predicting pregnancy complications such as preeclampsia, fetal growth restriction, and miscarriage is the activity of platelet aggregation induced by ADP [4, 5, 7]. In such cases, a significant increase in spontaneous platelet aggregation is observed [5, 13]. However, several foreign authors [14] refute this view in cases of recurrent miscarriage syndrome. Their studies comparing groups of pregnant women with a history of spontaneous miscarriages and healthy volunteers did not reveal significant differences in ADP-induced aggregation [24].

Data obtained from the analysis of aggregation curves can help predict various pregnancy complications. For example, increased platelet activity and spontaneous aggregation indicate the formation of intravascular aggregates that block microcirculation, including within the mother-placenta-fetus system [15, 8].

The clinical presentation depends on qualitative and quantitative platelet defects—bleeding severity may vary significantly. With mild bleeding, there may be a tendency to bruising with minor injuries, such as at the site of elastic band application, occasional mild nosebleeds, prolonged menstrual bleeding in women, and so on. In cases of severe hemorrhagic syndrome, blood loss may develop to the extent of threatening the life of the fetus [18, 24].

Diagnosing thrombocytopathies is challenging. They are often masked by symptoms like nosebleeds, menorrhagia, and other mucosal bleeding. Therefore, in cases with a history of microcirculatory bleeding, a detailed history and appropriate diagnostic studies are necessary [25, 23].

If clinical signs of thrombocytopathies are present, the second step in diagnosis involves a complete blood count and manual platelet count in smears. A complete blood count may not show abnormalities in thrombocytopathies. However, if platelet size is altered, automatic analyzers may not adjust the true count. Thus, manual counting with subsequent Romanowsky-Giemsa staining of blood smears is essential. Morphological analysis of platelets provides additional information on platelet number and size, the presence of conglomerates, and other features: the absence of alpha granules and a general gray platelet appearance suggest gray platelet syndrome; inclusion in leukocytes indicates MYH9-related disorders; and erythrocyte morphology anomalies point to GATA-1 mutation-associated conditions. If platelet conglomerates are found in smears, differential diagnosis should consider collection-related artifacts. Pseudothrombocytopenia may result from platelet clumping in EDTA tubes, which can be confirmed by collecting blood in a citrate tube [12, 18].

Although relatively few comparative studies of platelet aggregation in adults and children have been conducted, existing data suggest that aggregation differences are present only in children under one year of age. Children aged 1–18 years have no specific age-related norms for platelet aggregation compared to adults [17, 18].

Screening tests indicating disorders in the platelet component of hemostasis include prolonged capillary bleeding time (Duke and Ivy tests) and PFA-100 (an automated platelet function analyzer) [4, 1].

Currently, various platelet aggregation disorders are characteristic of certain thrombocytopathies, helping clinicians establish an accurate diagnosis [14, 20]. Clinically significant thrombocytopathies, which may manifest as congenital or acquired, result from qualitative platelet abnormalities due to drug effects or systemic diseases. However, persistent platelet dysfunction is usually not associated with severe platelet quality defects [16].

Drug-induced platelet dysfunction can have various etiologies. In clinical practice, the most common cause of platelet dysfunction is the use of aspirin or other NSAIDs. Aspirin irreversibly binds and inactivates cyclooxygenase, a key enzyme in prostaglandin biosynthesis. This leads to a disruption of the platelet activation-response mechanism, resulting in the inability to release platelet granules and, more broadly, acquired secretion defects. Once cyclooxygenase is inactivated by aspirin, the platelet remains non-

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functional until it is replaced. Since approximately 100,000–150,000 platelets are replaced every five days, and a concentration of 100,000 platelets/μL ensures normal hemostasis, several days are required to eliminate the defect after the last dose of aspirin. Therefore, surgical and other invasive procedures should be postponed for at least five days after discontinuation of the drug.

Other NSAIDs also exhibit inhibitory effects on cyclooxygenase; however, unlike aspirin, these effects are reversible and dissipate once the drugs are cleared from the plasma. Although the half-life varies for each NSAID, platelet function generally returns to normal within 24 hours [13, 16].

The diagnosis of ITP (immune thrombocytopenia) is made by exclusion [13, 10, 22]. Studies to detect antiplatelet antibodies provide insufficient information, so the specific identification of antigens in immune and pregnancy-related thrombocytopenia is not definitive. Due to insufficient specificity (about 80%) and low sensitivity (approximately 60%), methods for detecting antiplatelet antibodies are not included in international guidelines for examining and treating patients with idiopathic thrombocytopenic purpura [11].

Thus, an ITP diagnosis should be established only after excluding other causes and conditions associated with thrombocytopenia. The absence of antiplatelet antibodies does not rule out ITP [17, 19]. Modern enzyme-linked and immunofluorescent methods for detecting antiplatelet antibodies are time-consuming and yield limited information (only 60–80% of cases). A more informative method, radioimmunoassay, allows the detection of antiplatelet antibodies in 80–90% of cases [12].

Detection of antiplatelet antibodies indicates the presence of an autoimmune process, which can result from connective tissue diseases, infections, hepatitis, immune deficiencies, or oncological hematological diseases. In ITP, these antibodies can cross the placental barrier, leading to thrombocytopenia in the fetus [13].

To confirm an ITP diagnosis, the following criteria are required: a decrease in platelet count to less than 100 × 10^9/L, the presence of characteristic clinical features, and confirmatory laboratory tests. Peripheral blood smear analysis in patients with ITP often reveals a significant number of large platelets; in severe cases, fragmentation of platelets and red blood cells is frequently observed. The outcome of hemorrhagic syndrome often leads to the development of iron deficiency anemia.

Patients with ITP are not characterized by significant changes in leukocyte counts. However, eosinophilia and relative lymphocytosis may appear in the leukocyte formula, along with atypical lymphocyte forms. In such cases, sternal puncture is essential to confirm the diagnosis. ITP is characterized by an increase or normal number of megakaryocytes with normal or giant morphology, without morphological abnormalities. The diagnosis of immune thrombocytopenia is also confirmed when antiplatelet antibodies are detected in plasma or platelets [3].

REFERENCES

1. Babadjanova Sh.A., Zaynutdinova D.L. Frequency and characteristics of immune thrombocytopenia at different stages of pregnancy // Journal of Theoretical and Clinical Medicine. 2021. №5. B. 9-12. ISSN 2091-5853
2. Cines DB, Levine LD. Thrombocytopenia in pregnancy. Blood. 2017 Nov 23;130(21):2271-2277. doi: 10.1182/blood-2017-05-781971. Epub 2017 Jun 21. PMID: 28637667; PMCID: PMC5701522.
3. Jingjing Zhu, Rongrong Chen, Shuqi Zhao, Lixia Zhu, Xueying Li, Mixue Xie, & Xiujin Ye. A megakaryocyte morphological classification-based predictive model for steroid sensitivity in primary immune thrombocytopenia // Platelets, 2020; 31(7): 939–944.
4. Nuriddinova N.F., Kurbonova Z.Ch., Zaynutdinova D.L., Bekchanova N.I. Karimova A.A. Platelet properties after anti-virus therapy in chronic hepatitis and liver cirrhosis with hcv etiology // Patient-Centered Approaches to Medical Intervention Proceedings of International Conference September 27&28, London. 2024. – P.358-361.
5. Scully M. How to evaluate and treat the spectrum of TMA syndromes in pregnancy. Hematology Am Soc Hematol Educ Program. 2021 Dec 10;2021(1):545-551. doi: 10.1182/hematology.2021000290. PMID: 34889427; PMCID: PMC8791125.
6. Subbaiah M., Kumar S., Roy K.K., Sharma J.B., Singh N. Pregnancy outcome in patients with idiopathic thrombocytopenic purpura. Arch Gynecol. Obstet. 2014 Feb; 289 (2):269-73.
7. Townsley D.M. Hematologic complications of pregnancy. Semin Hematol. 2013 Jul; 50 (3): 222-31.
8. Zaynutdinova D.L. Homiladorlikning turli bosqichlarida gemoglobin, eritrotsit va rang ko'rsatkich nazorati // Journal of Cardiorespiratory research. – 2022. – №SI-1.1 – 366-369-b. (14.00.00; (23) SJIF 2022: 5.937)
9. Zaynutdinova D.L., Babadjanova Sh.A. Hemogram changes in postkovid syndrome in

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-42, January 2025
ISSN: 2749-3644

pregnant women // Central Asian journal of medicine. – 2022. – №4. – P. 118-123. (14.00.00)
10. Zaynutdinova D.L., Babadjanova Sh.A. Homiladorlarda gemorragik sindrom xarakteristikasi // Toshkent tibbiyot akademiyasi axborotnomasi. – 2022. –110-113-b. (14.00.00; №13)
11. Zaynutdinova D.L., Babadjanova Sh.A. Sayfutdinova Z.A., Nuriddinova N.N. Homilador ayollarda trombotsitar gemostaz patologiyalarining zamonaviy talqini // Nazariy va klinik tibbiyot jurnali. – 2022. – №5. – 67-70-b. (14.00.00; №3)
12. Zaynutdinova D.L., Babadjanova Sh.A. The incidence and morphological features of thrombocytopenia in pregnancy // Central Asian journal of medicine. – 2022. – №3. – P. 127-132. (14.00.00)
13. Zaynutdinova D.L., Babadjanova Sh.A., Bekchanova N.I., Nuriddinova N.F. Assessment of thrombocytopenia and thrombocytopathies in pregnant women // Patient-Centered Approaches to Medical Intervention Proceedings of International Conference September 27&28, London. 2024. – P.478-480.
14. Zaynutdinova D.L., Babadjanova Sh.A., Ergasheva M.M. Trombotsitlar patologiyasi bo'lgan homilador ayollarning akusherlik tarixi // Doktor axborotnomasi. – 2023. – №3 (111). – 42-47-b. (14.00.00; №20)
15. Zaynutdinova D.L., Babadjanova Sh.A., Ergasheva M.M. Trombotsitopatiyalar bilan kasallangan homilador ayollarning akusherlik klinikasi // Gumanitar va tibbiy fanlar jurnali. – 2023. – №5 (11). Vol.1 – 30-35-b. (14.00.00)
16. Zaynutdinova D.L., Babadjanova Sh.A., Musayeva N.B., Islamova Z.S. Trombotsitopeniyalarning homilador ayollarda aniqlanish chastotasi, muammoning umumiy holati // Tibbiyotda yangi kun. – 2022. – №12 (50). – 463-467-b. (14.00.00; №22)
17. Zaynutdinova D.L., Babadjanova Sh.A., Nuriddinova N.F., Bekchanova N.I. Enhancing Treatment Effectiveness for Pregnant Women with Thrombocytopenia // Patient-Centered Approaches to Medical Intervention Proceedings of International Conference September 27&28, London. 2024. – P.478-480.
18. Zaynutdinova D.L., Babadjanova Sh.A., Nuriddinova N.F., Bekchanova N.I. Significance of Endothelial Markers in Thrombocytopenia and Thrombocytopathy in Pregnancy // American Journal of Medicine and Medical Sciences. – 2024. – №14(11). – P.2909-2911. (14.00.00; №2)
19. Бессмельцев С.С. Первичная иммунная тромбоцитопеническая пурпура: подходы к терапии согласно новым клиническим рекомендациям американской гематологической ассоциации и международного консенсусного доклада // Вестник гематологии, том XVI, № 2, 2020. С 4-29.
20. Егорова Я.А., Заболотнов В.А., Рыбалка А.Н. Тромбоцитопеническая пурпура при беременносты. Здоровье женщины №5 (91)/2014
21. Зотова И. И., Грицаев С. В. Патогенетическое обоснование терапии идиопатической тромбоцитопенической пурпуры (первичной иммунной тромбоцитопении) у взрослых // Казанский медицинский журнал, 2018 г., том 99, №2. С 279-286.
22. Меликян А.Л., Пустовая Е.И., Цветаева Н.В. и др. Национальные клинические рекомендации по диагностике и лечению первичной иммунной тромбоцитопении (идиопатической тромбоцитопенической пурпуры) у взрослых (редакция 2016 г.). Гематол. и трансфузиол. 2017; 62 (1, suppl. 1): 1–24.
23. Фитцпатрик К.Е., Хиншоу К., Куринчук Дж.Дж., Найт М. Факторы риска, лечение и исходы гемолиза, повышенных ферментов печени и синдрома низкого уровня тромбоцитов и повышенного уровня ферментов печени, синдрома низкого уровня тромбоцитов. Акушерство Гинекол. 2014; 123:618–27.
24. Цхай В.Б., Гребенникова Э.К. Идиопатическая тромбоцитопеническая пурпура у беременных. Акушерские и перинатальные риски. Акушерство, гинекология и репродукция. 2015; 2: 72-79.
25. Шапошникова Е.В. Изучение показателей системы гемостаза у беременных с хронической плацентарной недостаточностью на фоне экстрагенитальной патологии // Медицинский альманах № 5 (24) ноябрь 2012