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MODERN APPROACHES TO THE TREATMENT OF PREGNANTS WITH IMMUNE THROMBOCYTOPENIC PURPURA

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Abstract: Although a number of drugs have been proposed and tested for the treatment of immune thrombocytopenia in pregnancy, the results are controversial, controversial and uncertain. This uncertainty may be resolved in the future through targeted, well-designed, controlled trials, pharmacogenomics, and precision medicine research.

Keywords: hemostasis, pregnancy, thrombocytopenia, bleeding.

The main goal of treating pregnant women with immune thrombocytopenic purpura (ITP) is to prevent and eliminate bleeding. The choice of treatment depends on the clinical presentation, severity of the disease, and the number and quality of platelets in the peripheral blood. Glucocorticoids (GCs), immunoglobulins (IGs), thrombopoietin receptor agonists, cardiocentesis, cesarean section, splenectomy (SE) (depending on vital signs, especially in cases of intracranial hemorrhage and any large localized hemorrhage), and platelet transfusion are the most effective methods of treating thrombocytopenia during pregnancy.

Glucocorticosteroids. In 1997 and 2010, the main principles of ITP treatment in pregnant women were reviewed and published. GCS serve as a cheap and rapid treatment for ITP. According to the results of A. Sugar et al., approximately 40-60% of patients relapsed within 6 months, and 20-30% within 1-2 years [9]. When a favorable clinical and hematological response is achieved, the issue of reducing the dose of the drug is resolved. The use of prednisolone in short courses and low doses is effective and safe for the mother [24]. The additional use of GCS prolongs the effect of treatment. If ITP recurrence is observed in the II and III trimesters of pregnancy, prednisolone is prescribed at a dose of 0.5 mg/kg body weight for no more than 2 weeks, then it is recommended to gradually cancel the dose by 0.5–1 tablet per day under the control of the dynamics of the hemorrhagic syndrome and platelet count [23].

In a study conducted by Jingjing Zhu et al. in 2020, the first-line therapy for primary immune thrombocytopenia is steroids, but one third of the patients did not respond to steroids. The studies conducted showed abnormalities in the growth and development of megakaryocytes and poorly compensated thrombopoiesis. When the effect of megakaryocytes on steroids was studied in 170 adult patients with ITP, 109 were found to be steroid-sensitive and 61 were not responsive to steroids [4].

Prednisolone is metabolized in the placenta, but high doses of the drug may have adverse effects on the fetus. Long-term use of prednisolone may result in a decrease in sensitivity to it. When using this treatment

regimen, all patients have a good hemostatic effect and an increase in platelet count is observed in 80% of cases [17].

Immunoglobulins. The effect of these drugs is aimed at restoring a normal immune response by reducing the effect of antiplatelet antibodies. In addition, the drugs affect B-lymphocytes and plasma cells, thereby reducing the synthesis of autoantibodies and normalizing impaired Treg functions. In refractory ITP, a combination of several therapeutic approaches is required to ensure the restoration of physiological platelet counts in some patients. The effect of the introduction of human immunoglobulins is very rapid, its effectiveness is 80-90% after 2-3 days from the start of therapy, but the increase in platelet counts is temporary (duration 45-60 days). Parenteral administration of immunoglobulins in the third trimester of pregnancy is considered a first-line drug for the treatment of severe thrombocytopenia or thrombocytopenic bleeding [17].

In patients who are resistant to GCS or who have contraindications to GCS and are at risk of severe bleeding, parenteral immunoglobulin is recommended. An increase in platelet count to >50×109/L is achieved in approximately 80% of patients after the first day of intravenous immunoglobulin therapy. It reaches a maximum value at the end of the first week after the end of treatment [21]. However, this effect is transient and does not last more than 3-4 weeks, after which the platelet count may decrease to baseline [12]. In emergency situations with ITP, when there is a need for major bleeding or preparation for urgent surgical intervention, intravenous immunoglobulins can be used to achieve a rapid increase in platelet count [13]. Patients usually tolerate treatment with high doses of immunoglobulin. However, there is evidence that patients with high doses of immunoglobulins develop acute renal failure. Therefore, when prescribing high doses of immunoglobulin, it is necessary to monitor kidney and liver function.

There are also reports of the development of induced hemolysis against the background of the use of immunoglobulins [15].

Thrombopoietin receptor agonists. Despite the long-standing recognition of the involvement of the immune system in the formation of ITP, important discoveries have been made today. Thrombopoietin receptor agonists are a discovery of the last decade, which have shown efficacy and safety in studies and have quickly entered routine clinical practice [1]. However, many unresolved problems remain both in the choice of ITP therapy and in the study of the clinical and biological heterogeneity of patients [16].

Such contrasting groups of patients with ITP, such as those resistant to therapy and those who maintain a long-term stable response after discontinuation of treatment, are still poorly understood [17, 7, 8]. Recently, there have been several publications on the efficacy of thrombopoietin mimetics, a class of agents that stimulate thrombopoiesis, in the treatment of ITP in pregnant women [16]. J. Descroix et al. (2014) described two cases of successful treatment with thrombopoietin in pregnant women with corticosteroid-resistant immune thrombocytopenia without maternal or fetal complications. According to the authors, thrombopoietin, due to its rapid onset of action and high efficacy, may be an important alternative treatment during pregnancy, except in cases of immune thrombocytopenia resistant to first-line therapy [3]. However, more studies are needed to definitively demonstrate its safety in newborns. A pregnant woman with thrombocytopenia who had failed to respond to all available treatments was successfully treated with thrombopoietin at 34 weeks [5].

S. Young et al (2008) reported the successful use of Argatroban in a patient with ITP in the third trimester of pregnancy. Generally, direct thrombin inhibitors are used as anticoagulants in patients with heparin-induced thrombocytopenia [2]. The three direct thrombin inhibitors available in the US - argatroban, bivalirudin, and lepirudin - are class B drugs (the drugs have been studied in animals, but there is little data on the safety of these drugs in human pregnancy) [22].

A. A study by Newland et al. (2016) was the first to assess the frequency of remission in patients with early stages of ITP (≤ 6 months from diagnosis) on the background of romiplostim therapy. High doses of intravenous immunoglobulin or GKS can lead to the development of severe gestosis. And when thrombopoietin increases liver enzymes and causes liver failure in patients, splenectomy is not used as a standard method, but is allowed in emergency cases as "despair therapy" [25].

Splenectomy. Clinical and laboratory remission is achieved in 70-90% of patients when SE is performed. The effect of SE is mainly to destroy the source of antiplatelet antibodies [17]. SE practice during pregnancy is carried out according to the instructions of the mother's health. It is preferable to perform this procedure in the second trimester of pregnancy, because SE in the first trimester increases the risk of spontaneous abortion, and in the third trimester, it is technically more difficult, and the rate of premature birth and stillbirth increases. If a clear hemorrhagic syndrome develops in the third trimester of pregnancy, after strong medical preparation, it is performed in combination with Caesarean section [19]. The ITP is not a guideline for cesarean delivery. The choice of delivery method is based on obstetric indicators. Intracranial bleeding is confirmed in 0-1.5% of newborns.

Immediately after birth, the newborn's platelets are measured. If their number is normal, then there is no need to re-count, although parents should be instructed to watch for vague bruises or petechiae in the baby. Spontaneous remission occurs within one week, even when a significant decrease in platelets is observed in newborns [20].

The response rate to SE has been approximately 80% in various studies. K. Kojouri et al reported a sustained increase in platelet count to 150×109/l after SE in 66% of patients over 5 years. Approximately 14% of patients did not respond to SE and 20% developed relapse. Y. According to Najean et al., recurrence of ITP after SE occurs in most patients within the first 2 years after surgery [17].

Caesarean section practice. F. According to a study by Yassaee and co-author (2012), cesarean delivery was 81% among Iranian women with ITP in a clinic in Tehran. Another study reported operative delivery in 63% of women with ITP. H. Hwa et al (1993) suggest that cesarean delivery of patients with ITP may improve neonatal outcomes [11]. The use of fresh frozen plasma in caesarean section is a reasonable approach. It is not advisable to use the mass of platelets for prophylactic purposes, because the life of transfused platelets is 2 days. With severe hemorrhagic syndrome and significant blood loss, mass transfusion is performed before or during surgery. In the postpartum period, the control of the number of platelets should be carried out after 1-3 months

Cordiosynthesis. S. Harmel and co-authors (1995) determined the number of platelets in fetal umbilical cord blood in pregnant women with thrombocytopenia below 90×109/ml. The time interval between cordiosynthesis and delivery was 0-30 days. Fetal and subsequent neonatal platelet levels were correlated in 36 of 37 cases (97%), with 6 of 37 fetuses (16%) having significant thrombocytopenia (<50×109/ml). In these six cases, the method of delivery was Caesarean section. In other cases, vaginal delivery was recommended. According to the authors, such tactics helped to avoid cases of intraventricular hemorrhage in newborns. T. Based on research, Razafint and co-authors recommended planned cesarean delivery in patients with ITP if the number of platelets detected in fetal umbilical cord blood is less than 100×109/l in order to prevent intranatal bleeding [10].

The goal of therapy is to prevent severe bleeding that threatens the patient's life during thrombocytopenia [23]. In the presence of any of the hemorrhagic complications, therapy should be started immediately, regardless of the platelet count. In the absence of hemorrhagic syndrome, treatment of thrombocytopenia is usually not required. In parallel, when examining a pregnant woman, the condition of the fetus should also be monitored [19].

Today, there are still controversial aspects of drug therapy during pregnancy, the risk of hemorrhagic complications, and methods of delivery for the mother and the fetus [9]. Obstetricians and gynecologists rarely object to carrying out pregnancy in women with thrombocytic diseases, because there is no reliable evidence of the need for medical termination of pregnancy due to the threat to the life of the mother [14]. However, it should be noted that pregnant women with thrombocytic pathology need prenatal care and treatment. Management of such patients should be performed by an obstetrician, hematologist, and pediatrician working in close collaboration. At the same time, it is advisable to deliver pregnant women with this pathology in large clinical centers with the participation of a highly qualified medical team [26].

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