IDIOPATHIC THROMBOCYTOPENIC PURPURA IN PREGNANT WOMEN (LITERATURE REVIEW)

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Abstract: *the review presents data on the frequency, diagnosis and treatment of idiopathic thrombocytopenic purpura. One of the causes of obstetric bleeding is idiopathic thrombocytopenic purpura (ITP), which is an autoimmune disease. Published data indicate the prevalence of ITP among adults and children ranges from 1 to 13 per 100,000 people. Despite significant advances in the study of the clinical picture of ITP and progress in the study of pathogenesis and treatment, a number of important questions regarding the preservation and management of pregnancy remain unresolved. The features of the course of pregnancy, childbirth, the postpartum period, obstetric complications, risk factors for their occurrence, the frequency and causes of adverse pregnancy outcomes for the mother and the fetus require further study. There is no unified view on the possibility of maintaining and managing pregnancy in patients with ITP. Some authors point to the frequent activation of ITP during pregnancy and after delivery.*
Keywords: *idiopathic thrombocytopenic purpura, bleeding, pregnancy.*

ИДИОПАТИЧЕСКАЯ ТРОМБОЦИТОПЕНИЧЕСКАЯ ПУРПУРА У БЕРЕМЕННЫХ (ОБЗОР ЛИТЕРАТУРЫ)

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Аннотация: *в обзоре представлены данные о частоте, диагностике и лечении идиопатической тромбоцитопенической пурпуры. Одной из причин акушерских кровотечений является идиопатическая тромбоцитопеническая пурпура (ИТП), которая представляет собой заболевание аутоиммунной природы. По опубликованным данным, распространенность ИТП среди взрослых и детей колеблется от 1 до 13 на 100000 человек. Несмотря на значительные успехи в изучении клинической картины ИТП и прогресс в исследовании патогенеза и*

лечения, ряд важных вопросов в отношении сохранения и ведения беременности остается нерешенным. Особенности течения беременности, родов, послеродового периода, акушерские осложнения, факторы риска их возникновения, частота и причины неблагоприятных исходов беременности для матери и плода требуют дальнейшего изучения. Отсутствует единый взгляд на возможность сохранения и тактику ведения беременности у больных с ИТП. Одни авторы указывают на частую активацию ИТП при беременности и после родоразрешения.
Ключевые слова: *идиопатическая тромбоцитопеническая пурпура, кровотечение, беременность.*

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For a number of years, it was believed that pregnancy with idiopathic thrombocytopenic purpura (ITP) is contraindicated, since the gestational process contributes to the exacerbation of ITP, which increases the risk of maternal mortality due to obstetric bleeding [9]. Later, with the improvement of diagnostic and therapeutic methods, the view of researchers on this problem has changed. In the literature, reports began to appear about the possibility of pregnancy against the background of ITP, against the background of adequate therapy [3]. However, even now it is almost unambiguously recognized that ITP can have an adverse effect on the course of pregnancy and its outcome [4,12]. In patients with ITP, the frequency of complications such as the threat of termination of pregnancy in the first (30%) and in the second (16%) trimesters, spontaneous miscarriages (17%), the threat of premature birth (18%), pregnancy toxicosis increases 2-3 times (18%) (Sokolova M.Yu., 2002). A number of researchers indicate a high risk of developing preeclampsia (from 22% to 34%) and placental insufficiency (29% -32%) with ITP [11]. Other authors have testified that with ITP there is a high incidence of premature detachment of the normally located placenta (4%), bleeding both during pregnancy and during childbirth (the incidence of bleeding ranges from 13% to 25%) [25]. On average, the incidence of obstetric complications in ITP is 3 times higher than in the population [27].

The data on the course of ITP during pregnancy are contradictory, some authors point to the activation of ITP [15], others believe that during pregnancy there is an improvement in the condition of pregnant women and does not worsen the prognosis of the disease in general. However, most researchers argue that the course of pregnancy and its outcome depends on the course of ITP at the time of conception and on the therapy performed before pregnancy [5].

Favorable is the onset of pregnancy against the background of clinical and hematological remission. The incidence of obstetric complications during pregnancy will be high when pregnancy occurs against the background of

exacerbation of ITP, with a continuously recurrent course of the disease with widespread hemorrhagic manifestations and thrombocytopenia <30 thousand / μL, refractory to therapy, or soon after splenectomy (less than 6 months). The pregnancy itself also affects the course of ITP. A number of researchers believed that in 30% of patients, ITP exacerbates during pregnancy and more often the activation of the process occurs in the first and second trimesters, less often after childbirth [26]. The risk of exacerbation of the disease increases to 45% if at the time of conception there was an exacerbation of ITP. On the contrary, during pregnancy occurring against the background of clinical and hematological remission, exacerbation of the disease is observed in only 12% of patients [22]. Splenectomy performed at least 6 months before pregnancy significantly improves the prognosis of the disease [20].

Many issues of management of pregnancy, childbirth and the postpartum period in ITP remain controversial and unresolved. In 1994, the American Society of Hematology formed an expert panel to review published evidence of diagnostic and therapeutic interventions for ITP and develop evidence-based clinical guidelines for the diagnosis and treatment of ITP. Then it became clear that among the publications on ITP there are very few works with reliable high-quality results, on the basis of which one could offer scientifically based recommendations. The available recommendations for the management of pregnancy and childbirth were based on clinical experience and consensus decisions of experts (level of evidence C [25]. Then the commission decided to seek expert opinion and develop interim clinical guidelines. The members of the commission filled out questionnaires in which, on a nine-point scale, they assessed the need for or the feasibility of carrying out diagnostic or therapeutic measures in various clinical situations (several hundred were proposed.) The proposed recommendations are based on the private opinion of the commission members, since the data on the effectiveness of one method or another was not enough to develop scientifically based recommendations.

Due to the current circumstances, there is no consensus on the management of such patients [16, 20] and the treatment of pregnant women with ITP is a serious problem. In general, according to most scientists, the management of pregnancy in ITP is a complex task requiring close cooperation between the obstetrician and hematologist. Pregnant women with ITP require close monitoring and should be monitored monthly in the first and second trimester, every 2 weeks after 28 weeks, and weekly after 36 weeks. Routine obstetric examinations should pay particular attention to blood pressure, weight, urine protein, and platelet count.

Although treatment of ITP during pregnancy does not differ significantly from treatment outside of pregnancy, there are some differences. It is known that ITP therapy during pregnancy is based on the use of glucocorticosteroid therapy (GCS), immunoglobulins, and splenectomy. There are reports of the use of plasmapheresis, thrombopoietic drugs (Eltrombopag or Romiplostim), as well as

cytostatics and immunosuppressants. Due to the lack of conclusive evidence of safety, most researchers recommend avoiding the use of cytostatics and immunosuppressants during pregnancy. The experience with the use of thrombopoietic drugs during pregnancy is not significant, these studies are classified as category C [23]. The decision on the need to prescribe therapy depends on both the platelet level and the presence of hemorrhagic syndrome. In accordance with the principles of the American Society of Hematology (ASH) and the British Committee for Standards in Hematology (BCSH), adequate therapy should be provided for severe thrombocytopenia and / or thrombocytopenia associated with bleeding. More intensive treatment is recommended later in pregnancy to prepare pregnant women for childbirth, which is often accompanied by epidural anesthesia. Therapy is recommended when the platelet count is below 10,000 / c1 at any gestational age or below 30,000 / c1 in the second or third trimester or when bleeding develops [18]. There is no consensus regarding the treatment of patients with platelet count <30,000 / c1, but no bleeding in the first trimester, reflecting the desire to avoid GCS therapy during pregnancy [16, 24].

Because of their effectiveness and low cost, many researchers believed that corticosteroids were the first line treatment for ITP in pregnancy [20]. For the first time, GC were used for the treatment of ITP in the 50s, a positive effect was noted (Damcshek W. el al., 1958). The effectiveness of GCS therapy during pregnancy is about 60% [8] and is assessed by such criteria as: complete primary response (platelet count is not lower than 100.0 x 109 / l) and partial primary response (platelet count is higher than 50.0 x 109 / l). Moreover, only in 15-25% of patients it is possible to achieve complete clinical and hematological remission as a result of the use of GCS [23].

The mechanism of action of HA in ITP is still not fully understood. Back in the 50s. it was proved that against the background of taking corticosteroids, capillary fragility decreases, purpura disappears and an increase in platelet levels is noted. This is due to the fact that under conditions of thrombocytopenia, thinning of the capillary endothelium is observed by about half, which returns to the initial one on average after 4-5 days while taking prednisolone, with the same degree of thrombocytopenia. HA reduce the phagocytosis of antibody-sensitized platelets [3], neutralize the mechanisms that inhibit thrombopoiesis, reduce permeability and damage to the endothelium, and have an immunosuppressive effect. In addition, GCS improve the physiological functions of platelets [18]. The drugs of choice when prescribing GCS during pregnancy are prednisolone and metipred, given their relatively low ability to penetrate the fetoplacental barrier and fewer side effects [8]. On the contrary, long-acting corticosteroids (dexamethasone, betamethasone) penetrate the fetoplacental barrier without being destroyed, so their use should be limited [12]. Researchers differ in their views on the purpose of therapy. According to some authors, the treatment of ITP is aimed at achieving and maintaining

complete remission [21]. Others believe that therapy should be aimed at achieving and maintaining a safe platelet level. However, a number of scientists considered a safe platelet level of at least 50×10^9 / l [15], according to other researchers, this parameter should be at least 70×10^9 / l [10, 17]. There is information in the literature [19] about the development of adrenal insufficiency in newborns whose mothers received GCS during pregnancy. However, in most observations [11] and specially conducted studies, the absence of the effect of GCS taken by the mother on the formation of glucocorticoid function of the adrenal cortex in newborns was shown. The absence of negative effects on the fetus, including on the formation of the adrenal cortex function in newborns, these authors explain by the presence of prenatally acting protective mechanisms that ensure the inactivation of steroids in the placenta and the enzyme systems of the fetus [8].

There is no consensus regarding the doses and duration of GCS therapy. According to most authors, the average therapeutic dose of prednisolone is 1 mg / kg / day (considering the weight before pregnancy), the dose of which is reduced after receiving a response to therapy [20]. In this case, within 2-3 weeks, the level of platelets rises and antiplatelet antibodies decrease [13], which is a satisfactory response to therapy [22]. Some researchers have recommended doubling the dose of the drug in the absence of effect [17, 28].

There is no consensus regarding the duration of therapy. Most hematologists considered the necessary therapy for at least 4-6 weeks [27], while others adhere to the tactic of reducing the dose of prednisolone after reaching a sufficient platelet level [10], with a transition to maintenance doses of the drug 10-15 mg / day [25]. Considering the toxicity of the drug, the possibility of using low therapeutic doses of 20-30 mg / day in a situation where therapy is indicated, but not extremely necessary, was considered. The effectiveness of glucocorticoid therapy ranges from 50 to 75%. The frequency of stable remission is relatively low and reaches 5-30% [4]. Recurrence of the disease after stopping treatment develops in 50% -60% of patients [7]. Intravenous immunoglobulin (IVIT) has been proposed as an alternative first-line treatment for ITP, especially in situations where long-term therapy may not be required (Gill KK, 2000). The mechanism of action of intravenous immunoglobulins in ITP is primarily associated with the neutralization of antiplatelet antibodies, the rapid elimination of the formed immune complexes by increasing phagocytosis, as well as the capture of excess activated complement factors [11, 17]. In addition, Ig blocks certain Fc receptors on phagocytes and thereby prevents the destruction of platelet-loaded autoantibodies by cells of the reticuloendothelial system (RES) [19].

However, there is no consensus in the literature on the indications, methodology, efficacy of IVIT in patients with ITP as monotherapy or in complex treatment in combination with GCS. There is no consensus on the use of these methods in pregnant women with this pathology.

A number of authors propose treatment of ITP during pregnancy with intravenous immunoglobulin at a dosage of 2 grams / kg for more than 2-5 days, considering that this therapy is an effective means of rapidly increasing platelet count (Teeling JL, 2001). Compared to corticosteroids, BBIg are less likely to cause side effects such as hypertension [24]. According to ASH guidelines, BBIg is the drug of choice for severe thrombocytopenia, or thrombocytopenia with bleeding in the third trimester [16, 28]. However, the effect of BBIg therapy can be temporary, which requires repeated courses of therapy and leads to a significant increase in its cost. A number of patients did not respond to monotherapy with either GCS or BBIg, but when treated with a combination of 1 gram methylprednisolone and BBIg l-2gm / kg, a therapeutic effect was noted [20, 28].

Many researchers recommend the use of 2-day BBIg injections at a dose of 1.0 g / kg of body weight, which is advisable in urgent situations when a rapid increase in platelet count is required, in particular, before surgery. At the same time, no differences were found in the effectiveness and tolerability of the drug compared to 5-day therapy [9]. However, there are reports in the literature on the development of acute renal failure during therapy with high doses of the drug in patients with ITP who have not previously suffered from kidney disease, which had to be stopped by hemodialysis. Therefore, when high doses of Ig are prescribed, renal function should be monitored. In addition, recently, side effects of the intravenous immunoglobulin preparation in the form of induced hemolysis have been revealed. Also, most researchers point to the short duration of the therapeutic effect of high doses of immunoglobulin, the resumption of thrombocytopenia is observed after 2-4 weeks [25].

Some researchers have shown that IVIT can significantly reduce the duration of severe thrombocytopepia with platelet counts below 20,000 / μL and an increased tendency to bleed [19]. The effectiveness of IVIT therapy is 80-85%. Recently, reports have begun to appear on the effectiveness of anti-Rhesus immunoglobulin for intravenous administration in Rh-positive patients with ITP. The dose of anti-D immunoglobulin, according to a multicenter study, is 20-75 μg / kg. The effectiveness of the treatment was 88%. Contraindication to the appointment of anti-D immunoglobulin is the patient's Rh-negative blood, a history of splenectomy and hypersensitivity to plasma components. In addition, in patients with anemia, the dose of anti-D immunoglobulin should be reduced, as the severity of the anemia may worsen.

If there is no response to GCS and BBIg therapy, splenectomy may be considered. If necessary, splenectomy is performed in the second trimester, since early surgery can lead to abortion, and in the third trimester, it is accompanied by technical difficulties, since the pregnant uterus creates obstacles to surgical access [5,21]. Laparoscopic splenectomy is preferred during pregnancy [23]. In 75% of pregnant women, remission was achieved after splenectomy [3, 16].

Summarizing the available literature data, it should be concluded that despite the lack of reliable studies and a unified point of view of researchers on this problem, at present, in the management of pregnancy in ITP, the principles recommended by ASH and BCSH should be followed. Pregnant women with ITP and platelet counts> 50,000 / μL usually do not need treatment; they should not be given glucocorticoids or IV immunoglobulin as initial therapy. If the platelet count is 30-50 thousand / μl during the first or second trimester of pregnancy, these drugs should also not be prescribed. Treatment is indicated for all pregnant women with a platelet count <10 thousand / μl, as well as those who have it equal to 10-30 thousand / μl in the II or III trimester of pregnancy or have bleeding. It is advisable to prescribe intravenous immunoglobulin as an initial therapy when the platelet count is <10 thousand / μl during the third trimester of pregnancy or when it is 10-30 thousand / μl and there is bleeding. If in a pregnant woman, despite treatment with glucocorticoids or immunoglobulin, the platelet count remains <10 thousand / μl and bleeding continues, then splenectomy can be performed in the second trimester of pregnancy. Splenectomy should not be performed in pregnant women without clinical symptoms of ITP with platelet counts> 10,000 / μL. Childbirth and the early postpartum period are the most dangerous in patients with ITP [24]. Before the use of prednisone, the mortality of both the mother and the fetus was extremely high. The greatest danger to the mother is uncontrolled bleeding. It should be noted that bleeding from ruptures of the soft tissues of the birth canal is sometimes a greater problem than bleeding from the uterus [25].

The question of the level of platelets at which epidural anesthesia is possible and at which bleeding will be minimal both during physiological childbirth and during cesarean section remains controversial. The American Society of Hematology, ASH, estimates that a platelet count of 50,000 / c1 is sufficient for both vaginal and caesarean delivery. According to BCSH principles, a platelet count of 80,000 / p1 must be achieved for epidural anesthesia and caesarean section. These criteria are based on a retrospective review in which epidural anesthesia was successfully performed without neurological complications in 30 patients with ITP and platelet counts between 69,000–98,000 / c1 [27].

Thus, although there are no reliable randomized data, most experts consider platelet counts in the 70,000 / p1 range to be sufficient for epidural anesthesia and both vaginal and caesarean delivery. Despite the fact that most researchers recognize the danger of bleeding during delivery of patients with ITP, there are very few works devoted to this problem, and there is no common point of view on the methods of prevention, methods of its implementation and the critical level of platelets at which it is necessary.

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