

THE OCCURRENCE OF IMMUNE THROMBOCYTOPENIA (ITP) DURING PREGNANCY , CARRYING OUT PREGNANCY AND CHOOSING THE OPTIMAL ROUTE FOR CHILDBIRTH

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Resume : The diagnosis of immune thrombocytopenia (ITP) can be very difficult and dangerous to receive at any time. This is especially true when emotions increase during pregnancy and there is a constant adaptation to the physical demands of pregnancy. A new or reversible diagnosis of ITP during pregnancy can add an additional layer of stress, which is how ITP affects overall health, pregnancy, and the health of the developing baby.

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Epidemiology :

ITP is diagnosed in pregnancy approximately every 1 in 1000-10.000 cases and accounts for 4-5% of all cases of thrombocytopenia associated with pregnancy. Although ITP can manifest itself at any time in pregnancy, it is the most common diagnosis of thrombocytopenia in the first trimester. Gestational thrombocytopenia usually manifests much later in pregnancy, and the platelet count is usually higher than 70,000.

ITP in pregnancy usually manifests with platelet counts below 70,000-80,000. It is also common in individuals who previously had ITPs. The diagnosis of ITP in pregnancy is made through a detailed physical examination and Anamnesis of other possible causes of thrombocytopenia, obtaining a complete prenatal history of present and past pregnancy, and working with blood. A slight decrease in the number of platelets is normal in any pregnancy, since the volume of blood expands. Platelets usually drop to 10% in an average pregnant woman and usually do not cause thrombocytopenia. Pregnancy in women with ITP is not contraindicated.

If you have ITP, you do not need to avoid or stop pregnancy or worry about an increased risk of abortion. About 1/3 of pregnant women with ITP require treatment. There are some medications used to treat ITP that can affect a developing baby. It is important to discuss current medications with the hematologist to ensure that treatment for pregnant women with ITP is not contraindicated for pregnancy.

Management of ITP during pregnancy depends on the severity of thrombocytopenia. If there are no bleeding problems, it may be good to divide the platelet count between 20,000-30,000, but it is

recommended to increase the platelet count to at least 50,000-70,000 for spinal anesthesia and at least 70,000 for epidural. While Vaginal delivery can be done safely with 30,000 platelets, many obstetricians-gynecologists believe that there should be more than 50,000 platelets for caesarean section practice. The procedure for taking childbirth in women with ITP should be based only on Obstetric instructions. Vaginal delivery is safe for the baby.

Against the background of clinical hematological remission, the onset of pregnancy is favorable. The frequency of obstetric complications during pregnancy is higher with the onset of pregnancy against the background of increased ITP, with a constant recurrent course of the disease, with widespread hemorrhagic manifestations and thrombocytopenia <30 thousand/MCL, resistant to therapy or shortly after splenectomy (less than 6 months). Pregnancy itself also affects the ITP course. A number of researchers believed that in 30% of patients, ITP increases against the background of pregnancy, and often the activation of the process occurs in the first and second trimesters, less often after childbirth [26]. If ITP is increased during conception, the risk of exacerbation of the disease increases to 45%. Conversely, exacerbation of the disease during pregnancy, which occurs against the background of clinical-hematological remission, is observed in only 12% of patients [22]. A splenectomy performed at least 6 months before the onset of pregnancy significantly improves the prognosis of the disease.

Many issues of pregnancy, childbirth and the postpartum period with ITP are controversial and unresolved. In 1994, the American Society of Hematology published 42 ITP diagnostics and treatment measures to analyze the published data and develop scientifically based clinical guidelines for ITP diagnosis and treatment. At the time, it became clear that there was very little work among ITP publications with reliable high-quality results, on the basis of which scientifically based recommendations could be proposed. Existing recommendations for pregnancy and birth management are based on clinical experience and consensus decisions of experts (evidence level) [25]. Then the commission decided to turn to the opinion of specialists and develop temporary clinical recommendations. The members of the commission filled out questionnaires, in which the need or expediency of conducting diagnostic or therapeutic activities in various clinical situations on a nine-point scale was assessed (several hundred of them were proposed). The recommended recommendations are based on the personal opinion of the members of the commission, since information about the effectiveness of one method or another was insufficient to develop scientifically based recommendations.

Given the available conditions, there is no agreement 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, pregnancy management with ITP is a complex task that requires close cooperation between the obstetrician and the hematologist. Pregnant women with ITP require careful supervision and should be examined every month in the first and second trimester, every 2 weeks after 28 weeks and every week after 36 weeks. Special attention should be paid to blood pressure, weight, protein content in urine and platelet count in a regular obstetric examination. Although treatment of ITP during pregnancy does not differ significantly from tactics other than pregnancy, there are some differences.

It is known that ITP therapy during pregnancy is based on the use of glucocorticosteroid therapy (GCS), immunoglobulins, splenectomy. There have been reports of plasmapheresis, thrombopoietic drugs (Eltrombopag or Romiplostim), as well as the use of cytostatics and immunosuppressants. Due to the lack of reliable evidence of safety, most researchers recommend avoiding prescribing cytostatics and immunosuppressants during pregnancy. The experience of using thrombopoietic drugs during pregnancy is not significant, these studies fall into Category C [23]. Solving the issue of the need to

prescribe therapy depends on both the level of platelets and the presence of hemorrhagic syndrome. Based on the principles of the American Society of Hematology (ASH) and the British committee on hematology standards (BCSH), adequate therapy should be performed for severe thrombocytopenia and/or bleeding-related thrombocytopenia. In the later stages of pregnancy, more intensive treatment tactics are recommended to prepare pregnant women for childbirth, which is often accompanied by peridural anesthesia. Therapy is recommended if the platelet count is below 10,000/c1 during any pregnancy or below 30,000/c1 in the second or third trimester, or bleeding [18]. There is no agreement to treat patients with platelet counts $<30,000 / C1$, but reflects a desire to avoid GCS therapy during pregnancy without bleeding in the first trimester [16, 24].

Due to its effectiveness and low cost, many researchers considered corticosteroids to be first-line drugs to treat ITP during pregnancy [20]. Ha was first used to treat ITP in the 50s, a positive effect was noted (Damcshek W. et al., 1958). The effectiveness of GCS therapy during pregnancy is about 60% [8] and is assessed according to the following criteria: complete primary response (platelet level is not lower than $100.0 \times 10^9/L$) and partial primary response (platelet level is higher than $50.0 \times 10^9/l$). At the same time, complete clinical-hematological remission can be achieved as a result of the use of GCS in only 15-25% of patients [23].

The mechanism of action of the civil code in the ITP is not yet completely clear. Against the background of taking gks, a decrease in the fragility of capillaries, loss of purpura and an increase in platelet levels were noted. This is due to the fact that under the conditions of thrombocytopenia, about half of the capillary endothelium is thinned out, which returns after an average of 4-5 days against the background of taking prednisolone, with the same level of thrombocytopenia. Ha antibody reduces phagocytosis of sensitive platelets [3] neutralizes mechanisms that cause thrombopoiesis depression, reduces endothelial permeability and damage, and has an immunosuppressive effect. In addition, GCS improves the physiological functions of platelets [18]. When prescribing gks, the drugs selected are 43 gestation times prednisone and metipred, given their relatively low ability to penetrate through the fetoplasental barrier and low side effects [8]. In contrast, long-term GCS (dexamethasone, Betamethasone) penetrate through the fetoplasental barrier intact, so their use must be limited [12]. Researchers' views on the purpose of therapy vary. According to some authors, treatment of ITP is aimed at achieving and maintaining complete remission [21]. Others believe that therapy should be aimed at achieving and maintaining safe platelet levels. However, a number of scientists believed that platelet levels were at least $50 \times 10^9/l$ [15] safe, according to other researchers, this parameter should be at least $70 \times 10^9/l$ [10, 17].

In the literature [19] there are data on the development of adrenal insufficiency in newborns whose mothers received GCS during pregnancy. However, in most observations [11] and specially conducted studies, it has been shown that maternal-acquired GKS has no effect on the formation of glucocorticoid function of the adrenal cortex in newborns. The absence of negative effects on the fetus, including the formation of the function of the adrenal cortex in newborns, is explained by the authors by the presence of intrauterine defense mechanisms that ensure the inactivation of steroids in the placenta and fetal enzyme systems [8].

There is no consensus on the dosage and duration of GCS therapy. According to many authors, the average therapeutic dose of Prednisolone is 1 mg/kg per day (taking into account the weight before pregnancy), the dose of which decreases after receiving a response to therapy [20]. However, platelet levels rise within 2-3 weeks and antibodies against platelets decrease [13], which is a satisfactory

response to therapy [22]. Some researchers recommended doubling the dose of the drug in the absence of an effect [17].

There is no consensus on the duration of therapy. Most hematologists considered necessary therapy for at least 4-6 weeks [27], while others adhere to the tactic of reducing the dose of prednisolone after the platelets have reached sufficient levels [10], 10-15 mg / day with the transition to maintenance doses of the drug [25]. Given the toxicity of the drug, the possibility of using low therapeutic doses of 20-30 mg per day was considered in a situation where therapy is indicated, but not very necessary. The effectiveness of glucocorticoid therapy ranges from 50 to 75%. The level of stable remission is relatively small and reaches 5-30% [4]. Recurrence of the disease after discontinuation of treatment develops in 50% -60% of patients [7]. An alternative was proposed as a first - line drug for ITP- intravenous immunoglobulin (VVIT), especially in cases where long-term therapy may not be required (Gill CC, 2000). The mechanism of action of intravenous immunoglobulins in ITP is primarily associated with the neutralization of antibodies against platelets, the rapid elimination of immune complexes formed by strengthening phagocytosis, as well as the capture of over-activated complement factors [11,17]. In addition, Ig blocks certain Fc receptors in phagocytes and thus prevents the destruction of platelets filled with autoantibodies by cells of the reticulo - endothelial system (res) [19].

Many researchers recommend using a 2-day BBIg injection at a dose of 1.0 g/kg of body weight, which is recommended in emergency situations where a rapid increase in the number of platelets is necessary, in particular, before surgery. Differences in efficacy and tolerability of the drug compared to 5-day therapy have not been found [9]. At the same time, there are reports in the literature of the development of acute renal failure against the background of high /dose therapy of the drug in patients with ITP who do not suffer from kidney disease, which must be stopped using hemodialysis. Therefore, when prescribing high doses of ig, it is necessary to control kidney function. In addition, a side effect of the recently intravenous drug immunoglobulin in the form of hemolysis was found.

Also, most researchers believe that the short duration of the therapeutic effect of high doses of immunoglobulin, the recovery of thrombocytopenia is observed in 2-4 weeks [25]. Some researchers have shown that VVIT has platelet levels below 20.0 thousand/MCL and can significantly reduce the duration of severe thrombocytopenia with increased bleeding tendency [19]. The effectiveness of VVIT therapy is 80-85%. In recent times, reports of the effectiveness of the use of anti - Rh immunoglobulin for intravenous administration have begun to appear in Rh-positive ITP patients. Based on the results of a multicenter study, the immunoglobulin anti-D dose is 2075 mcg/kg. The effectiveness of treatment was 88%. Contraindications to prescribing anti-D immunoglobulin are the patient's Rh-Negative blood, splenectomy history, and hypersensitivity to plasma components. In addition, immunoglobulin anti-d dosage should be reduced in patients with anemia, as the severity of anemia may increase.

Splenectomy can be considered if there is no response to GCS and BBIg therapy. If necessary, splenectomy is performed in the second trimester, as an early operation can lead to abortion and is accompanied by technical difficulties in the third trimester, as the pregnant uterus prevents surgical entry [5,21].

Laparoscopic splenectomy is preferable during pregnancy [23]. 75% of pregnant women have achieved remission after splenectomy [3,16]. Summarizing the available literary data, it should be concluded that, despite the lack of reliable research and the researchers' unified view of this problem, it is necessary to follow the principles recommended by ASH and BCSH in the management of pregnancy with ITP at the moment. Pregnant women with ITP and platelet count >50k / MCL usually

do not need treatment; they do not need glucocorticoids or immunoglobulin as an initial therapy. If the number of platelets in the I or II trimester of pregnancy is 30-50 thousand/MCL, these drugs should also not be prescribed. Treatment is indicated for all pregnant women with a platelet count of <10,000/MCL, as well as those with bleeding or equal to 10-30,000/MCL in the II or III trimester of pregnancy. In the III trimester of pregnancy, it is recommended to prescribe immunoglobulin as a starting therapy for administration if the platelet count is <10 thousand/MCL or if it is 10-30 thousand/MCL and bleeding occurs. If, despite treatment with glucocorticoids or immunoglobulin in a pregnant woman, the platelet count remains <10 thousand/MCL and bleeding continues, a splenectomy can be performed in the II trimester of pregnancy. Splenectomy should not be performed for pregnant women without clinical signs of ITP with a platelet count of >10 thousand/MCL. The greatest risk in patients with ITP is the birth and early postpartum period [24]. Before the use of prednisolone, the death of both the mother and the fetus was enormous. The greatest danger to the mother is non - stop bleeding. It should be noted that bleeding from the rupture of the soft tissues of the birth canal sometimes causes more problems than uterine bleeding [25].

The issue of platelet levels remains controversial, in which peridural anesthesia is possible, and in this case, bleeding is minimal, both in physiological childbirth and by caesarean section. The American Society of Hematology ash believes that the platelet count of 50,000/C1 is sufficient for vaginal and cesarean delivery. According to the principles of Bcsh, the number of platelets for peridural anesthesia and cesarean section should be equal to 80,000/p1. These criteria are based on a retrospective review in which peridural anesthesia was successfully performed in 30 patients with ITP and between platelet counts of 69,000-98,000/c1 without neurological complications [27]. Thus, although there is no reliable randomized data, most experts consider the number of platelets in the 70,000 / P1 range to be sufficient for 45 peridural anesthesia and vaginal delivery and cesarean delivery. Despite the fact that many researchers recognize the risk of bleeding in the delivery of patients with ITP, there is very little work devoted to this problem, but there is no single point of view on preventive methods, methods of its implementation and the critical level of platelets.necessary.

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