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Complications of idiopathic thrombocytopenic purpura in pregnancy: a review of literature

Complicações da púrpura trombocitopênica idiopática na gravidez: uma revisão da literatura

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ABSTRACT

Introduction: Idiopathic thrombocytopenic purpura (ITP) is an acquired immune disorder that causes a reduction in platelet count, called thrombocytopenia. ITP during pregnancy usually presents some complications that may impair the outcome of pregnancy. **Objective:** This literature review aimed to identify the main complications of ITP in pregnancy and its consequences. **Methodology:** The bibliographic search was performed through scientific articles available in the Scielo and PubMed databases, of which 64 articles were selected, both in Portuguese and English. **Results:** The risk of postpartum hemorrhage, placental abruption, and neonatal thrombocytopenia are some complications that may occur during pregnancy. **Conclusion:** Pregnant women must be properly monitored during pregnancy so that there are no major complications.

Key words: idiopathic thrombocytopenic purpura; complications; diagnosis; hematological complications in pregnancy.

RESUMO

Introdução: *A púrpura trombocitopênica idiopática (PTI) é uma doença autoimune adquirida que causa redução na contagem de plaquetas denominada trombocitopenia. A PTI durante a gestação normalmente apresenta algumas complicações que podem afetar o desfecho da gravidez.* ***Objetivo:*** *Esta revisão da literatura teve como objetivo identificar as principais complicações da PTI na gravidez e suas consequências.* ***Metodologia:*** *A pesquisa bibliográfica foi realizada por meio de artigos científicos disponíveis nas bases de dados Scielo e PubMed. Foram selecionados 64 artigos, tanto em inglês quanto em português.* ***Resultados:*** *O risco de hemorragia pós-parto, descolamento prematuro da placenta e trombocitopenia neonatal são algumas complicações que podem ocorrer na gestação.* ***Conclusão:*** *As gestantes devem ser devidamente acompanhadas durante a gestação para que não ocorram maiores complicações.*

Unitermos: *púrpura trombocitopênica idiopática; complicações; diagnóstico; complicações hematológicas na gravidez.*

RESUMEN

Introducción: *La púrpura trombocitopénica idiopática (PTI) es una enfermedad autoinmune adquirida que causa un bajo conteo de plaquetas en la sangre denominado trombocitopenia. La PTI durante el embarazo normalmente presenta algunas complicaciones que pueden afectar el resultado del embarazo.* ***Objetivo:*** *Esta revisión de literatura tuvo como objeto identificar las principales complicaciones de la PTI en el embarazo y sus consecuencias.* ***Método:*** *Se llevó a cabo una búsqueda bibliográfica de artículos científicos disponibles en las bases de datos Scielo y PubMed. Se seleccionaron 64 artículos, tanto en inglés como en*

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portugués. ***Resultados:*** *El riesgo de hemorragia posparto, desprendimiento prematuro de placenta y trombocitopenia neonatal son algunas complicaciones que pueden ocurrir en la gestación.* ***Conclusión:*** *Las mujeres embarazadas deben ser debidamente supervisadas durante el embarazo para que no ocurran mayores complicaciones.*

Palabras clave: *púrpura trombocitopénica idiopática; complicaciones; diagnóstico; complicaciones hematológicas del embarazo.*

INTRODUCTION

The first clinical description of idiopathic thrombocytopenic purpura (ITP) occurred in 1735, by Paul Gottlieb Werlhof, a German doctor and poet. As Werlhof was the first descriptor of ITP, it is also referred to by its eponym name as Werlhof disease[1].

ITP is an acquired immune-mediated hematological disease, usually of unknown cause, which causes low platelet count (thrombocytopenia)[2-5]. It is defined as thrombocytopenia when the platelet count is lower than 100,000 platelets/mm^3, since the normal count is 150,000 to 400,000/mm^3[4, 6, 7]. Thrombocytopenia in ITP develops because antiplatelet autoantibodies cause premature removal of platelets from circulation by macrophages in the reticuloendothelial system; platelet destruction occurs mainly in the spleen[3, 8, 9]. Some current studies indicate that there are other mechanisms that also contribute to the pathogenesis of ITP, such as the reduction in platelet production caused by antibodies that cross-react with megakaryocytes[10-13].

In adults, ITP has an insidious onset and its greatest occurrence is in young women[9, 14]. The prevalence of this platelet disorder is around 9.5-23.6 cases per 100,000 individuals[5, 15-17]. Chronic ITP rarely resolves spontaneously, but it may spontaneously recur or regress, which makes it difficult to predict its evolution[9, 18]. Among the symptoms, petechiae and ecchymosis are common, but there may also occur some hemorrhagic manifestations, such as bleeding from the mucous membranes[8-10].

The clinical diagnosis is one of exclusion, in which patients with previous or severe thrombocytopenia, without anemia nor neutropenia, with no history of drugs and splenomegaly and with normal or increased number of marrow megakaryocytes make the diagnosis of ITP probable[9, 10, 19]. The treatment of chronic ITP aims to maintain the platelet count in a state that does not cause bleeding and other complications (above 50,000/mm^3)[2, 20]. The first-line drugs usually recommended for the ITP treatment include corticosteroid and intravenous immunoglobulin (IVIg) therapy[21]. When there is no response from the patient to corticosteroids and IVIg therapy, splenectomy is indicated as the second option[10, 22, 23].

ITP is estimated to occur around 1 and 2 women for every 1,000 pregnancies, which represents 5% of cases of thrombocytopenia in pregnancy[8, 18, 19, 24-27]. Unlike gestational thrombocytopenia (GT), which usually disappears in the short term, ITP is the most common cause of thrombocytopenia in early pregnancy; in relation to GT, isolated thrombocytopenia is more common in the first and second trimesters[8, 10, 28].

Therefore, the aim of this study was to perform a literature review on ITP in pregnancy and its complications. The search for scientific articles was carried out on Scielo and PubMed platforms, in Portuguese and English. To obtain the most up-to-date information on the topic, we only select materials within a 10-year interval.

ITP IN PREGNANCY

ITP, when presenting for the first time during pregnancy, represents a diagnostic and therapeutic challenge[29, 30]. The diagnosis is toughest when the pregnant woman has thrombocytopenia – as ITP is an exclusion diagnosis, it is necessary to rule out other causes of thrombocytopenia, from the most common, the gestational thrombocytopenia (or incidental) to one of the most serious, the syndrome that presents signs such as hemolysis, elevated liver enzymes and low platelet (HELLP)[4, 19, 21]. Therefore, the ITP diagnosis and its treatment may take time[19].

GT represents a low clinical risk for the mother, as it manifests as mild thrombocytopenia with no major complications. Therefore, a differential diagnosis between ITP and GT is important because a mild maternal ITP can cause thrombocytopenia in the fetus, resulting in subsequent complications; however, GT will not cause thrombocytopenia[31, 32].

A ITP diagnosis is more consistent when there is a low platelet count before pregnancy, relevant thrombocytopenia in the first trimester and a declining platelet count as the pregnancy proceeds. On the other hand, incidental thrombocytopenia is characterized when the pregnant woman develops mild thrombocytopenia in the second or third trimesters, with no correlation with proteinuria or hypertension[10, 29]. Another way to differentiate between GT and

ITP for diagnostic purposes is to consider that GT, in addition to presenting mild thrombocytopenia, shows a platelet count usually above 70,000/mm^3 – which returns to normal 12 weeks after delivery[19, 28, 33].

As the platelet count decreases, the possibility of a patient suffering from ITP instead of incidental thrombocytopenia of pregnancy increases. In addition, as many pregnant women with incidental thrombocytopenia have elevated platelet levels of class G immunoglobulin (IgG), platelet antibody tests do not distinguish between these syndromes. It is essential that pregnant women with suspected ITP undergo complete blood count and platelet count tests during the laboratory investigation, in addition to exclusion tests[10, 34] as shown in the **Chart**.

CHART – Laboratory evaluation recommended for differential diagnosis of thrombocytopenia in pregnancy

Antiphospholipid antibodies (Lupus anticoagulant, anticardiolipin IgG or IgM, and anti-beta-2-glycoprotein I)
Coagulogram
Antinuclear factor
Helicobacter pylori
CBC and reticulocyte count
Quantitative measurement of immunoglobulin levels
Serology for systemic lupus erythematosus
Direct Coombs test
Liver function tests
Thyroid function tests
Viral screening (HIV, hepatitis C and B virus, cytomegalovirus)

Source: created by the author with adaptations[21, 28].

IgG: immunoglobulin G class; IgM: immunoglobulin M class; CBC: complete blood count; HIV: human immunodeficiency virus.

In the same way that pregnancy is a known risk factor for the evolution of newly diagnosed ITP, it also represents a risks that induce crises of other diseases in patients with chronic ITP[35]. Women who were previously diagnosed with ITP may experience exacerbation or relapse during pregnancy[6, 21]. In 2017, in France, Comont *et al*. (2017)[35] conducted a study that evaluated the effects of pregnancy in 39 women considered in complete remission. As a result, although serious complications were not noticed, relapses were observed during pregnancy in some of them; therefore, patients considered cured may have relapses[35]. Pregnancies complicate by up to 10% due to thrombocytopenia, resulting in the most varied causes[8, 10, 24, 36], such as preeclampsia, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, and sepsis[19, 37-39]. The interval of manifestation of these pathologies during pregnancy and their symptoms accumulate, which makes the diagnosis even more difficult[10, 34], as shown in **Tables 1** and **2**.

TABLE 1 – Symptoms of ITP and other causes of thrombocytopenia in pregnancy

Cause	Symptoms	Thrombocytopenia
ITP	Hematoma, petechiae, epistaxis, gingivorrhagia	Severe
Gestational thrombocytopenia	Asymptomatic	Mild
Preeclampsia	Hypertension, proteinuria, edema	Mild
HELLP syndrome	Nausea, upper abdominal pain, elevated liver enzymes, increased LDH	Severe
Gestational hepatic steatosis	Nausea, abdominal pain, jaundice, dehydration	Mild
Thrombotic thrombocytopenic purpura	Fever, neurological abnormalities, enal dysfunction	Severe
Hemolytic-uremic syndrome	Microangiopathic hemolytic anemia, bloody diarrhea, kidney failure	Moderate

Source: Adapted with modifications[10, 32].

ITP: idiopathic thrombocytopenic purpura; HELLP: hemolysis, elevated liver enzymes, low platelets; LDH: lactate dehydrogenase.

TABLE 2 – Causes of specific and pregnancy-related thrombocytopenia

Specific causes	Frequency	Pregnancy trimester
Gestational thrombocytopenia	75%	2nd or 3rd trimester
Preeclampsia	3%-14%	2nd or 3rd trimester
HELLP syndrome	0.5%-0.9%	3rd trimester
Gestational hepatic steatosis	1:7,000-1:20,000	3rd trimester
Pregnancy-related causes	Frequency	Pregnancy trimester
Thrombotic thrombocytopenic purpura	1:25,000	Peripartum period
Hemolytic-uremic syndrome	Rare	3rd trimester or postpartum
Disseminated intravascular coagulation	20% of all cases associated with HELLP syndrome	Unknown data

Source: Adapted with modifications[10, 24, 29, 34].

HELLP: hemolysis, elevated liver enzymes, low platelets.

The occurrence of severe thrombocytopenia is more common when ITP is diagnosed in pregnancy than when the pregnant woman already has a previous history of chronic ITP. This is probably due to the delay in diagnosis[19]. Risks of postpartum hemorrhage and placental abruption are some frequent events in patients with severe thrombocytopenia (20,000 platelets/mm^3)[13,36]. The rate of gestational diabetes (GD) in pregnant women with ITP is higher than in other women, and postpartum hemorrhage is usually a recurrent concern for them[18]. The increase in this index is tipically associated with the use of corticosteroids during

pregnancy[18, 19, 29, 32]. ITP may cause an increase in intrapartum or postpartum bleeding, even though there is still no evidence that this platelet disorder worsens during pregnancy[18].

A case report by Ferreira *et al*. (2018) [27] described the history of a woman at 25 weeks pregnant, with previous ITP and very severe thrombocytopenia (3,000 platelets/mm^3). The pregnant woman presented some hemorrhagic symptoms because of the lower platelet count, which was interpreted as a relapse of ITP after performing differential diagnosis by exclusion, in addition to failure to respond to most therapies. At 27 weeks pregnant, the drug Eltrombopag, a thrombopoietin receptor agonist (TPO), was administered to the patient, who showed improvement and increase in platelet count. In addition to the complications described above, the pregnant woman also ended up presenting, in the 37th week of pregnancy, proteinuria and high blood pressure, developing preeclampsia, which resulted in labor induction. Despite these complications, the patient gave birth to a healthy child through vaginal delivery, with normal blood loss. The newborn only needed phototherapy because she develops jaundice, and the mother presented only asymptomatic anemia with normal platelet count, with no other complications. Three weeks after delivery, both continued to be monitored and were stable, with normal platelet counts (as well as in the third subsequent month).

Controlling pregnancy in ITP can be difficult due to the imminent risk of bleeding for the pregnant woman, especially during childbirth[19]. The increase in the incidence of premature birth and perinatal mortality in women with ITP was described by Belkin *et al*., in 2009[25]. In these cases, the risk of neonatal thrombocytopenia is greater because circulating antiplatelet antibodies can cross the placenta[19, 31]. Although maternal outcomes in pregnant women diagnosed with ITP are usually favorable, the risk of neonatal thrombocytopenia must be considered[14, 30, 40].

NEONATAL THROMBOCYTOPENIA

Neonatal thrombocytopenia occurs when maternal platelet IgG autoantibodies cross the placenta, causing thrombocytopenia in the fetus and/or newborn (NB). Consequently, the risk of intracranial hemorrhage in the newborn may increase[41-45]. Neonatal thrombocytopenia is defined as a platelet count below 150,000/mm^3[46].

During pregnancy or childbirth, the reduction in the number of maternal platelets is not associated with neonatal thrombocytopenia at birth[10, 41, 43, 47, 48], as mothers' antiplatelet antibodies are not always detectable in infants with neonatal thrombocytopenia[30, 45].

Maternal splenectomy, time elapsed since maternal diagnosis and previous delivery of a child with thrombocytopenia are some existing predictors that increase the risk of developing neonatal thrombocytopenia[32, 41, 45]. Some authors indicate that, regardless of the maternal ITP status, the previous history of splenectomy was related to the occurrence of neonatal thrombocytopenia. In contrast, other researchers reported that this correlation is observed only in patients who did not obtain remission from ITP after splenectomy[30, 40, 49, 50]. Other evidence suggests that, from all the parameters studied, a history of thrombocytopenia in a previous delivery is the safer way to predict neonatal thrombocytopenia[10, 20, 24, 29, 45, 51-53].

The levels of maternal platelet antibodies, as well as the platelet count or the mother's response to treatment, do not correlate with neonatal thrombocytopenia[10, 31, 53, 54]. Maternal platelet count does not predict neonatal platelet count, as well as the number of platelets in the newborn can be predicted by a fetal blood sample collected from the scalp during labor or by percutaneous umbilical cord blood sampling (PUBS) before delivery[10, 18]. However, both procedures are largely invasive, fraught with complications and their use is no longer recommended[10, 18, 51].

The risk of intracranial hemorrhage is the most feared consequence of fetal thrombocytopenia and, theoretically, this risk is expected to increase when head trauma occurs during the passage of the fetus through the birth canal at the time of vaginal delivery[10, 20, 24]. Despite this complication, the risk of fetal intracranial hemorrhage in children of patients with ITP is very low, around 1% to 1.5%[10, 41, 47].

Although neonatal thrombocytopenia is able to increase the risk of cerebral hemorrhage in NB, there is insufficient data to guarantee the hypothesis that cesarean delivery is safer for the neonate than vaginal delivery[18, 29, 31, 48, 55]. Furthermore, there is no correlation between the risk of neonatal hemorrhagic complications and the methods of delivery[24, 44, 47, 48]. Thus, it is recommended that the mode of delivery should be based only on obstetric considerations[6, 24, 28, 29, 32, 41, 48, 56, 57]. Recent guidelines, such as that from the British Committee for Standards in Hematology (BCSH), ensure that the platelet count required for safe vaginal and cesarean delivery is at least 50,000/mm^3; for epidural anesthesia, a count from 80,000/mm^3 is ideal[19, 32, 43, 54]. If the NB has a platelet count below 50,000/mm^3, it is recommended to perform a head ultrasound to rule out the risk of intracranial hemorrhage[24, 28, 29, 32].

TREATMENTS

The American Society of Hematology (ASH) recommends, in the second and third trimesters of pregnancy, the beginning of treatment for platelet count below 30,000/mm^3, or in case of bleeding[19, 54]. Treatment is also indicated by the ASH at any time during pregnancy, when the number of platelets is lower than 10,000/mm^3[24, 54]. The indication of treatment for ITP in pregnant women is equivalent to the therapy of the non-pregnant population[34, 48, 54]. Treatment measures are indicated taking into account the patient's symptoms, such as the presence of bleeding[19, 22, 26]. **Table 3** shows the main therapies for ITP and when each one is indicated.

Corticosteroids, such as prednisone, are considered the first line therapy for ITP[18, 19]. However, risk of premature birth, GD, hypertension, among other maternal complications, were related to its use during pregnancy[18-20, 58].

A study carried out in 2014[19] described the higher incidence of premature birth and postpartum infection in women who needed corticosteroid therapy in pregnancy compared to those who have not been treated with the drug. In addition, when corticosteroids are used in the first trimester of pregnancy, congenital anomalies, such as orofacial clefts, may occur as a consequence of their use[32, 50].

As an alternative, intravenous immunoglobulin (IVIg) is suggested as a first-line treatment for ITP associated with pregnancy, especially when long-term therapy is not required[10, 20, 59]. IVIg rapidly increases platelet counts, but it is a temporary event[24, 28, 38, 59]. Compared to corticosteroids, IVIg is less predisposed to induce toxicities[5, 24, 59]. ASH guidelines state that IVIg is an appropriate first-line agent for severe thrombocytopenia or bleeding due to thrombocytopenia in the third trimester of pregnancy[10].

A recent study suggested that corticosteroids and IVIg therapy are more effective in non-pregnant women than in pregnant women with ITP[50]. If some patients during pregnancy do not show a satisfactory response to corticosteroids and IVIg, better results can be obtained if both are administered in combination and in high doses[10, 20].

Since the spleen is known to be a reservoir of platelets, it can sequester approximately one third of platelets under normal conditions. Therefore, splenectomy is also indicated as a treatment option to prevent platelets from being removed by the spleen[57, 60, 61]. In pregnant women undergoing splenectomy, a high chance of lasting or complete remission can be achieved[58, 60]. It is recommended that splenectomy be performed, when necessary, in the second trimester of pregnancy, as it may cause premature delivery if surgery is carried out in the first three months. On the other hand, if it is performed later, occlusion of the surgical field by the enlarged volume of the uterus will make it difficult to carry out the procedure[10, 12, 20, 29]. In pregnant women, laparoscopic splenectomy can usually achieve favorable results[12, 58].

TABLE 3 – Therapies for ITP and indications

Treatment	Indication	Complications
Corticosteroids	First option; no hemorrhagic symptoms	Hypertension, placental abruption, orofacial clefts
IVIg	No response to corticosteroids; severe thrombocytopenia or bleeding in the third trimester	No complications are reported
Splenectomy	No response to corticosteroids and IVIg; 2nd trimester of gestation, with platelet count < 10,000/mm^3	Infection, bleeding, thrombosis
Azathioprine	Second-line therapy	Neonatal hematological and immunological impairments
Cyclosporine	Second-line therapy	No complications/toxicity are reported
Platelet transfusion	Bleeding with platelet count < 10,000/mm^3; 30,000/mm^3 at delivery	-
Eltrombopag	No response to corticosteroids, IVIg, and splenectomy	Maternal thrombocytosis and hepatotoxicity. Expected to cross the placenta
Rituximab	Resistance to first-line treatments	Expected to cross the placenta
Romiplostim	Splenectomy refractory conditions	Severe thrombocytopenia after treatment interruption, thrombocytosis. Expected to cross the placenta
rHuEPO	Resistance to first-line treatments	Fever, upper respiratory infection, dizziness, thrombosis. Expected to cross the placenta

Source: created by the author with adaptations[21, 22].
ITP: idiopathic thrombocytopenic purpura; IVIg: intravenous immunoglobulin; r-HuEPO: recombinant human erythropoietin.

Second-line therapies include azathioprine and cyclosporine, immunosuppressants that have no teratogenic effects, but have a late onset (action from weeks to months) and a low response rate. Azathioprine has been used during pregnancy as an immunosuppressive agent presenting no toxicity risks[13, 29, 56, 57].

When the first and second line treatments fail, platelet transfusions should be administered to avoid hemorrhagic complications and keep the platelet count threshold within the ideal range[27]. Some therapies such as danazol, vinca alkaloids, and cyclophosphamide are considered cytotoxic and are not recommended during pregnancy[29, 52, 56, 57].

Eltrombopag (Revolade®) is indicated when the patient does not react to treatment with corticosteroids, immunoglobulins or splenectomy[27, 62]. Rituximab, an anti-CD20 monoclonal

antibody, is also recommended in cases of resistance to first-line treatments[27, 63]. However, the response time is usually long and it may cross the placenta[29, 39, 57, 64]. Romiplostim is indicated for conditions resistant to splenectomy. This TPO receptor agonist stimulates both the megakaryocytes in the bone marrow and the production of platelets. It also guarantees a high response rate and an accelerated onset of action; on the other hand, it may cross the placenta[63]. Recombinant human erythropoietin (rhuEPO) is another potentially efficient and safe treatment option for ITP during pregnancy[13].

FINAL CONSIDERATIONS

In view of the aspects addressed, the patient with ITP must have her pregnancy properly monitored, from the moment of diagnosis until delivery. Monitoring of the mother and fetus is required to avoid the risk of complications that interfere or impair the pregnancy. The pregnant woman should be informed about the risks of pregnancy, such as side effects of the medication, if treatment is needed, and the possibility of relapse, if she has previously been diagnosed with ITP.

Corticosteroids, despite their adverse effects and complications, remain indicated as the first treatment option. These drugs are still used due to their low cost and high effectiveness; however, they need to be replaced by better therapies that achieve the same effectiveness and cost value, where possible.

Despite the complications described and their potential risks, such as neonatal thrombocytopenia, pregnancy in ITP usually shows successful results. However, more published studies on maternal and fetal follow-up and outcomes after the postpartum period are needed to be aware of the treatment outcome. We have not found in the literature a broad and detailed approach on the complications of ITP in pregnancy. Most studies and reviews only mentioned the complications or described them briefly, with little comparison or tabulation about them.

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