REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Management of Primary Immune Thrombocytopenia in Pregnancy

James B. Bussel, M.D., Ming Hou, M.D., Ph.D., and Douglas B. Cines, M.D.

From the Department of Pediatrics, Weill Cornell Medicine, New York (J.B.B.); the Department of Hematology, Qilu Hospital of Shandong University, Shandong University, Jinan, China (M.H.); and the Departments of Pathology and Laboratory Medicine and Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia (D.B.C.). Dr. Hou can be contacted at houming@medmail.com.cn or at the Department of Hematology, Qilu Hospital of Shandong University, Shandong University, Jinan, Shandong, 250012, China.

N Engl J Med 2023;389:540-8.
DOI: 10.1056/NEJMra2214617

CME at NEJM.org

IMMUNE THROMBOCYTOPENIA (ITP) IS AN AUTOIMMUNE DISEASE IN WHICH IgG antiplatelet antibodies accelerate platelet clearance and reduce platelet production. The prevalence of ITP is approximately 1 to 3 cases per 10,000 persons in the United States, which can be extrapolated to more than 1 million cases globally if the prevalence is similar worldwide. ITP occurs commonly in women of childbearing age. Even during uncomplicated pregnancies, platelet counts may fall, platelet clearance may be accelerated, surgical delivery may be required, some treatments are interdicted, and IgG antiplatelet antibodies not only drive maternal thrombocytopenia but can also be transported across the placenta to the fetus. These factors complicate the diagnosis and management of ITP in pregnancy.

Studies of ITP are also complicated by its substantial clinical heterogeneity. In the absence of biomarkers that can be used to define subgroups, patients are typically characterized on the basis of the clinical trajectory and response to treatments. This heterogeneity intrinsic to ITP is superimposed on the variability that is due to pregnancy. Nonetheless, a consensus has been reached on some key issues involved in managing pregnancy in women with ITP, although uncertainty or unpredictability remains for other issues. In-depth reviews of ITP during pregnancy, including diagnosis[1-3] and management guidelines,[4,5] have been published elsewhere. In this article, we focus on recent insights into risk assessment and management of primary ITP.

PATHOPHYSIOLOGY

Alterations in the immune system at the maternal–fetal interface promote tolerance of shared fetal–paternal alloantigens through a shift toward the predominance of type 2 helper T cells, induction of specific regulatory T cells, and expression of nonclassical HLA-G, HLA-E, and HLA-C molecules by fetal extravillous trophoblasts. However, there is no evidence that pregnancy affects antiplatelet antibody production or platelet destruction by macrophages. Rather, an impairment in platelet production has been suggested on the basis of the observations that serum thrombopoietin levels are higher in pregnant women with ITP than in nonpregnant women with ITP[6,7] and that these elevations may have a placental source.[8,9] One report described megakaryocytic hypoplasia and apoptosis,[6] preliminarily attributed to elevated estradiol levels, a finding that is consistent with high thrombopoietin levels.[10] In addition, glycoprotein IIIa expression on syncytiotrophoblasts as a potential antibody target has not been explored, nor have placentas been examined to look for inflammation (i.e., villitis), although an antibody effect on the placenta has been implicated in fetal and neonatal alloimmune thrombocytopenia.

CASE STUDY

A 34-year old woman who has had ITP for 8 years is referred to us. She currently has a platelet count of 20×10^3 to 30×10^3 per cubic millimeter and is not receiving treatment. She did not have an adequate response to prednisone, had severe headaches when she was receiving intravenous immune globulin (IVIG), and did not have a response to rituximab. She comes for counseling because she would like to become pregnant.

ITP is almost never a contraindication to pregnancy and can be managed with prednisone, IVIG, or both in most cases. However, additional treatment may be required in a subset of cases of ITP that are or become difficult to treat. Pregnant women with ITP that is unresponsive to glucocorticoids and IVIG (e.g., our patient) have a greater risk of bleeding, may require second-line treatment, or both. Management may be especially complicated if a woman has severe, poorly controlled disease or if not all treatment options are available. In such cases, splenectomy or treatment with rituximab 3 or more months in advance of pregnancy[11] may be an option. It is uncommon to counsel any woman against becoming pregnant on the basis of the severity of ITP, but the decision also depends on the availability of specific treatments and the medical personnel available for monitoring and management, including experienced adult and pediatric hematologists, obstetricians, obstetrical anesthesiologists, and neonatologists. The expected benefits and risks among women for whom thrombopoietin-receptor agonists, rituximab, and less commonly used treatments are warranted are discussed below.

DIAGNOSIS

The differential diagnosis of thrombocytopenia in pregnancy has been reviewed in depth elsewhere.[12] ITP is the most common cause of thrombocytopenia in the first and second trimesters and of maternal platelet counts below 80×10^3 per cubic millimeter throughout gestation in otherwise healthy women (Fig. 1).[14-17] ITP is identified for the first time during pregnancy in approximately 10% of pregnant women with ITP in the United States and in a higher percentage of women in countries in which prenatal care is less frequent.[18-20] Obstetrical causes of thrombocytopenia, such as preeclampsia and thrombotic microangiopathies, are usually evident clinically, depending on the degree of illness in such patients. Secondary ITP, pseudothrombocytopenia, hereditary thrombocytopenia, and drug-induced thrombocytopenias should be considered and ruled out, although the exclusion of these conditions may not always be straightforward. Occasionally, in patients with mild thrombocytopenia, it may be difficult to distinguish between newly diagnosed ITP and gestational thrombocytopenia, since both are diagnoses of exclusion.

Gestational thrombocytopenia, which is by far the most common cause of low platelet counts in pregnancy, is often attributed to increased plasma volume, sequestration in the placental vasculature, increased platelet clearance, or a combination of these factors.[21] It has not been determined whether gestational thrombocytopenia results from the fall in platelet counts that occurs during pregnancy in women with a lower baseline count or whether it is a distinct entity. The higher thrombopoietin levels in women with ITP during pregnancy may help distinguish ITP from gestational thrombocytopenia.[6,7] Less than 1% of women with gestational thrombocytopenia have platelet counts below 100×10^3 per cubic millimeter, and 0.1% have counts below 80×10^3 per cubic millimeter[17] (Fig. 2). Gestational thrombocytopenia has not been found to be a cause of maternal bleeding or neonatal thrombocytopenia.

MATERNAL OUTCOMES

Almost all women with ITP have a decrease in the platelet count during gestation, and in many cases, therapy must be reinitiated or intensified, often, but not only, in preparation for delivery.[15,22] In a recent prospective study comparing the outcomes for women with ITP during gestation with those for nonpregnant women with ITP, exacerbations and adjustments in treatment doubled during pregnancy, occurring in any trimester or after delivery.[22] Although platelet counts often fall, counts below 30×10^3 per cubic millimeter are relatively infrequent.[14,15,19] Moreover, although bleeding events are reported in up to a third of nonpregnant women with ITP, among pregnant women with this condition, the incidence of these events is only somewhat higher than that among those with ITP who are not pregnant (hazard ratio, 1.83; 95% confidence interval, 0.91 to 3.65) and severe bleeding is rare.[1,19,22]

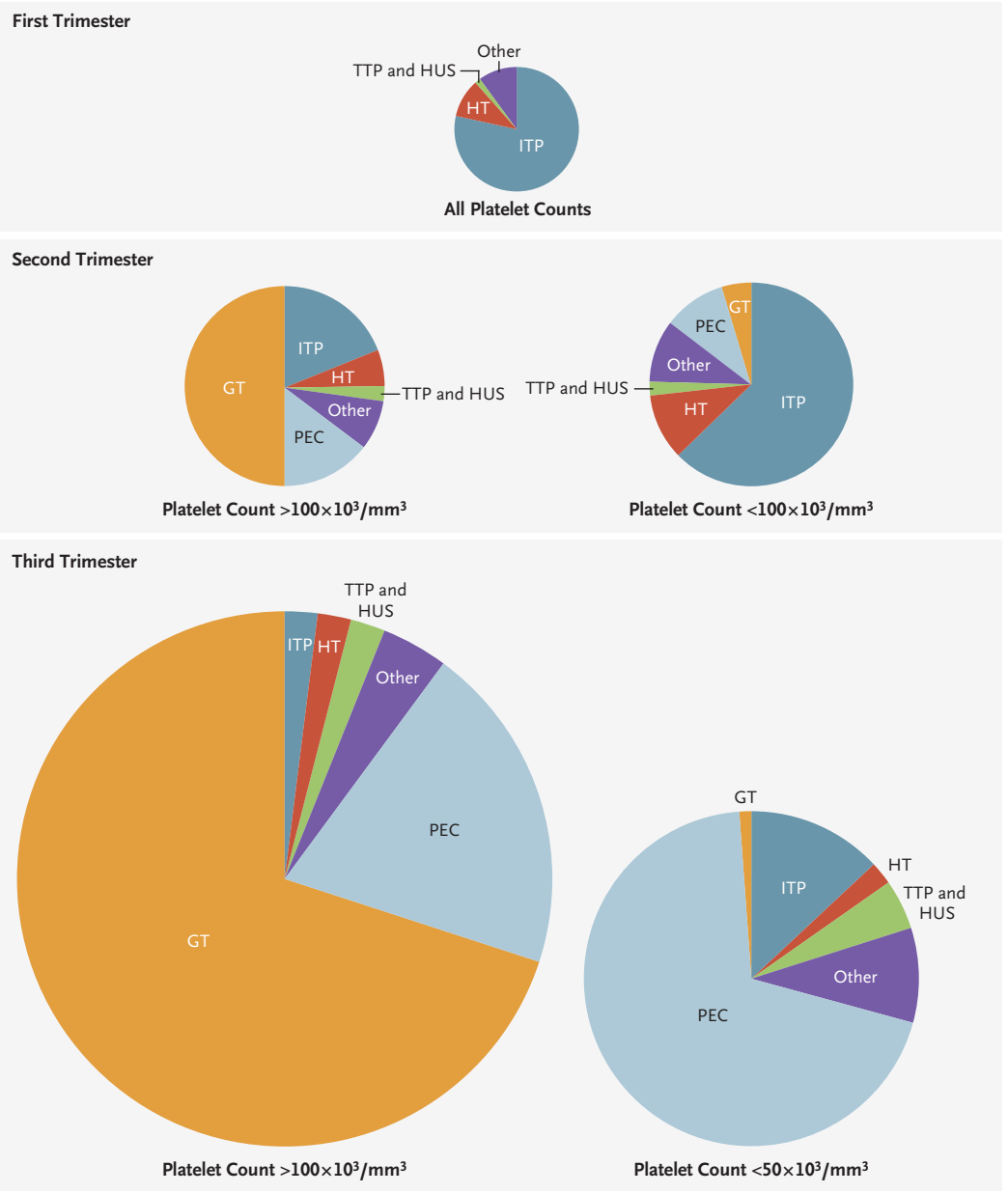

Figure 1. Estimated Prevalence of Causes of Immune Thrombocytopenia (ITP) in Pregnant Women According to the Trimester of Detection and Platelet Count.

The size of each circle represents the relative frequency of all causes of thrombocytopenia during each of the three trimesters of pregnancy. All causes and all platelet counts are considered together in the first trimester, when thrombocytopenia is uncommon. The distribution of causes during the second and third trimesters is subdivided according to the platelet count. All results are estimates based on experience and a review of the literature; the distribution changes as the platelet count falls further from more than 100×10^3 to less than 50×10^3 (not shown). The "other" category includes HELLP (hemolysis, elevated liver-enzyme levels, and a low platelet count), paroxysmal nocturnal hemoglobinuria, and myelodysplastic syndrome. GT denotes gestational thrombocytopenia, HT hereditary thrombocytopenia, HUS hemolytic–uremic syndrome, PEC preeclampsia, and TTP thrombotic thrombocytopenic purpura. Adapted from Cines and Levine.[13]

No maternal deaths from ITP have been reported in recent studies,[1] and most studies have not shown an increase in the most common complications of gestation, including preeclampsia, premature delivery, abruption, and thromboembolic complications.[22] Although an increase in the incidence of postpartum hemorrhage has been suggested,[1,15,19,23,24] we have not observed such an increase with proper management. Platelet counts typically return to prepartum levels after delivery, although in certain newborns and, anecdotally, in some mothers, not until cessation of breastfeeding.[15,22]

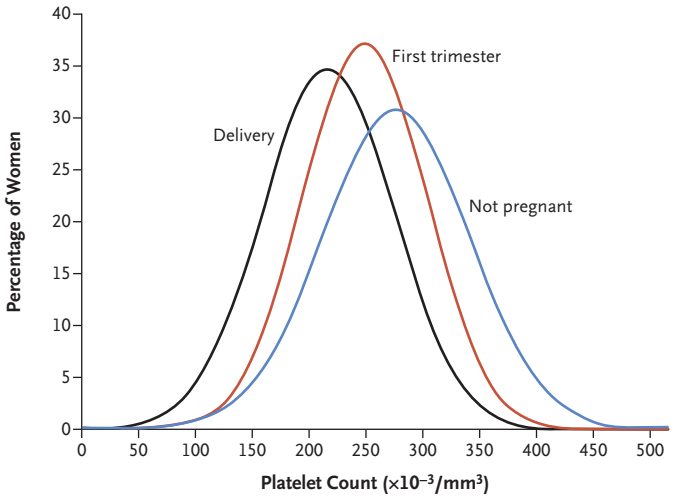

Figure 2. Platelet Counts during Pregnancy.

The distribution of mean platelet counts is shown for nonpregnant women and at two time points for women who had uncomplicated pregnancies: during the first trimester (mean gestational age, 8.7 weeks) and at delivery. Adapted from Reese et al.[17]

MANAGEMENT

OVERVIEW

For routine cases, we follow women with ITP and uncomplicated pregnancies at 4-week intervals during the first two trimesters, then every 2 weeks, and finally, weekly until delivery. Indications for treatment during the first two trimesters are the same as those for nonpregnant women with ITP (i.e., bleeding, platelet counts $<20\times10^3$ to 30×10^3 per cubic millimeter, or procedures such as amniocentesis). The method of delivery is usually based on obstetrical indications. A platelet count of 30×10^3 per cubic millimeter is generally accepted as the minimum count that is sufficient to reduce the risk of untoward bleeding after vaginal delivery,[25] and a count of 50×10^3 per cubic millimeter is the minimum for cesarean section.[26] However, anesthesiologists generally do not perform neuraxial anesthesia in patients with a platelet count below 70×10^3 to 80×10^3 per cubic millimeter,[27] although the procedure appears to be relatively safe at lower platelet counts.[28,29] In rare cases, platelet transfusions are warranted for delivery. Tranexamic acid can be considered after delivery. The use of vacuum extraction and other procedures that may increase the risk of injury to a fetus with thrombocytopenia should be avoided, and forceps should be used judiciously. Data on the risk of thromboembolism during pregnancy and after delivery among women with ITP are lacking. Extrapolating the indications and risk–benefit tradeoffs for prophylactic and therapeutic anticoagulation from studies involving nonpregnant women and the general approach to patients with ITP who are not pregnant, we recommend that the platelet count be maintained above 30×10^3 to 50×10^3 per cubic millimeter, depending on the specific circumstances.

FIRST-LINE THERAPY

No treatment of ITP in pregnancy has been approved by regulatory agencies. Prednisone is given at the lowest effective dose, usually with an initial dose of 10 to 20 mg daily (Table 1). Dexamethasone is likely to affect the fetus,[31] whereas prednisone is almost completely inactivated by the placenta.[32] IVIG (at a dose of 400 mg per kilogram of body weight per day, given for up to 5 days, or 1000 mg per kilogram per day, given for 1 or 2 days) may be added, if a hemostatic response to glucocorticoids is not attained or to prepare for delivery. The timing of treatment and delivery may be crucial if a platelet count above 80×10^3 per cubic millimeter is desired for epidural anesthesia.

SECOND-LINE THERAPY

There is no consensus on second-line treatment options, other than to use them as sparingly as possible. The use of rituximab (375 mg per square meter of body-surface area, given weekly for 4 weeks) in pregnancy has drawbacks. For example, the response may be slow (up to 8 weeks until a response is seen), rituximab compromises the response to vaccinations for 6 to 12 months, and it may increase the risk of neonatal hypogam-

Table 1. Treatment of Maternal Immune Thrombocytopenia (ITP) during Pregnancy.*

Treatment	Dose	Most Common Reason for Use of Agent during Pregnancy	Patients with Response	Time to Response	Drug-Related Adverse Events of Particular Concern	
					Women	Infants
			%			
First line						
Prednisone	Initial dose: 10–20 mg/day	ITP, SLE, allergies	40–70	3–14 days	Diabetes, hypertension, premature delivery, sleeplessness, weight gain, fluid overload	Hypoglycemia, prematurity
IVIG	0.4 g/kg/day for up to 5 days or 1 g/kg/day for 1 or 2 days	ITP, CVID, FNAIT	40–80	1–3 days	Fluid overload, hypertension, possible worsening of headache and aseptic meningitis	
Second line†						
Thrombopoietin-receptor agonists‡		ITP	70–80	7–14 days	Thrombocytosis, possibly thrombosis (reported in 3 cases[30])	Thrombocytosis
Romiplostim	1–10 μg/kg once weekly				Myalgias and headaches	
Eltrombopag	25–75 mg/day				Elevated liver-enzyme levels, which may simulate HELLP	
rhTPO	300 U/kg/day				Pain at injection site, development of antibodies to rhTPO	
Rh_0(D) immune globulin	50–75 μg/kg	ITP	70	4–5 days	Hemolysis, anemia, infusion reactions	Anemia, jaundice
Rituximab	375 mg/m^2 weekly for 4 wk	ITP	40–60	1–8 wk	Infusion reactions, hypogammaglobulinemia, infection	Reduction in B cells, hypogammaglobulinemia
Azathioprine	50–75 mg/day	ITP, renal transplantation	Too few cases to calculate	8–16 wk	Transaminitis, neutropenia, infection	
Dapsone	100 mg daily	ITP, leprosy	40–50	7–14 days	Hemolysis, anemia (may be aggravated by malaria, G6PD deficiency, or HIV infection)	Prematurity; anemia (may be aggravated by malaria or G6PD deficiency)
Cyclosporine	3–5 mg/kg/day	ITP, solid-organ transplantation, IBD	Too few cases to calculate	4–12 wk	Renal injury, tremor, hypertension, hypertrichosis, gingival hyperplasia	
Splenectomy (laparoscopic)	Early in second trimester	ITP, AIHA	50–80	1–60 days	Bleeding, infection, thrombosis, miscarriage, preterm labor and premature rupture of membranes	Prematurity

maglobulinemia if administered in the third trimester. On the positive side, studies[33-35] suggest better responses in women of childbearing age.

Splenectomy can be performed early in the second trimester (although many general surgeons are reluctant to do so). Whether the results are similar to those in nonpregnant women is unknown.

Safety data for azathioprine, dapsone, and cyclosporine are based almost entirely on the use of these agents in patients with other diseases (Table 1). Dapsone has been used in more than 1000 pregnant women without ITP, but the safety is not well established. Rh_0(D) immune globulin, in the intravenous WinRho SDF preparation, is the only form of immune globulin used for ITP in pregnancy.[36] Vinca alkaloids, cyclophosphamide, mycophenolate mofetil, danazol, and fostamatinib are contraindicated. Alternative second-line options have been even less well studied (Table 1).

THROMBOPOIETIN-RECEPTOR AGONISTS

Thrombopoietin-receptor agonists are not approved by their manufacturers or by the Food and Drug Administration or the European Medicines Agency for use in pregnancy. Nor has the use of these agents in pregnancy been endorsed in guidelines for the management of ITP.[4,5] Both eltrombopag, a small molecule, and romiplostim, containing a human IgG-Fc receptor, cross the placenta. Avatrombopag and hetrombopag are expected to cross the placenta as well, whereas recombinant human thrombopoietin is a full-length glycosylated molecule that is not predicted to do so.[37] Exposure to thrombopoietin-receptor agonists throughout pregnancy in nonprimate models, albeit at doses well above those used clinically, has been associated with maternal complications, neonatal thrombocytosis, and fetal anomalies in some studies[38] but not in others.[39,40] An effect of thrombopoietin on decidual cells in vitro has been reported[9]; however, the clinical effect, if any, is unknown.

Thrombopoietin-receptor agonists are widely used as second-line options in nonpregnant patients with ITP and are now increasingly used during pregnancy. In a prospective study in China involving 31 pregnant patients with a platelet count below 30×10^3 per cubic millimeter or bleeding that did not respond to glucocorticoids, IVIG, or both, 74.2% of the patients with ITP had a response to a fixed daily 300-U dose of recombinant

* If marked thrombocytopenia is detected in the infant of a mother with ITP, ultrasonography or magnetic resonance imaging should be performed to detect intracranial hemorrhage, with computed tomography considered if other imaging studies are insufficient or unavailable. Treatment in the infant includes intravenous immune globulin (IVIG) at a dose of 1 g per kilogram of body weight per day for 1 to 3 days, until the platelet count is above 30×10^3 to 50×10^3 per cubic millimeter, depending on the specific circumstances. Intravenous methylprednisolone is given at a dose of 1 mg every 8 hours during treatment with IVIG (without tapering). In an infant with intracranial hemorrhage of grade 2 or higher, the platelet count should be maintained at a level above 50×10^3 to 100×10^3 per cubic millimeter, depending on the specific circumstances. Platelet transfusion is performed if the platelet count is below 20×10^3 per cubic millimeter or if there is bleeding, with repeat transfusion as needed. Breast-feeding should be discontinued if neonatal thrombocytopenia persists for 1 week without improvement. AIHA denotes autoimmune hemolytic anemia, CVID common variable immunodeficiency, FNAIT fetal and neonatal alloimmune thrombocytopenia, G6PD glucose-6-phosphate dehydrogenase, HELLP hemolysis, elevated liver-enzyme levels, and a low platelet count, HIV human immunodeficiency virus, IBD irritable bowel disease, rhTPO recombinant human thrombopoietin, and SLE systemic lupus erythematosus.

† Hydroxychloroquine is commonly continued in the event of pregnancy in patients with rheumatologic disease and appears to be safe. Approximately 50% of patients with antinuclear antibody–positive ITP have a response to hydroxychloroquine (200 mg daily, with or without a loading dose). However, data on the use of this agent during pregnancy in patients with ITP are lacking.

‡ Data on avatrombopag or hetrombopag are lacking.

human thrombopoietin in the second or third trimester; this response was similar to that seen among nonpregnant patients with ITP.[28] No clinically significant adverse events were observed in the mothers or neonates, who were followed for 1 year after delivery.[37] Five of the 31 infants had subnormal platelet counts, although none had marked thrombocytopenia (<50×10^3 platelets per cubic millimeter). A response was observed in 77% of patients in a retrospective study involving 17 pregnant women who were treated with eltrombopag or romiplostim after treatment with glucocorticoids and IVIG had failed. Four women with chronic ITP were receiving thrombopoietin-receptor agonists when they became pregnant, 3 were given eltrombopag for 9 to 12 weeks, beginning in the first trimester for symptomatic ITP that did not respond to standard therapy, and 10 received thrombopoietin-receptor agonists just in preparation for delivery. No thromboembolic events in the women or serious neonatal complications were reported; thrombocytosis developed in one infant whose mother was treated with romiplostim.[41]

A recent safety study focused on treatment with romiplostim during pregnancy in 186 women. Five of the neonates had abnormalities, none of which occurred more frequently than expected, nor was an unexpected increase in maternal complications noted, although three cases of venous thrombosis were reported.[41] Multiple case reports support the safety (except for the increased risk of neonatal thrombocytosis) and efficacy of thrombopoietin-receptor agonists given in the third trimester, often as a means to increase platelet counts before delivery.[30,42] Data are insufficient to assess the safety of thrombopoietin-receptor agonists given at conception,[43,44] although 71 women in the pregnancy surveillance program were receiving treatment with romiplostim when they became pregnant.[41] Among the relatively few women who were treated throughout gestation, there were no known maternal or fetal complications.[45] Thrombopoietin-receptor agonists have also been safe and effective during pregnancy in several women with hereditary thrombocytopenias.[3,46] Administration of these agents during pregnancy has not been shown to prevent neonatal ITP or to mitigate its severity or duration, although isolated cases of neonatal thrombocytosis are consistent with findings in studies in animals.[47-49] Romiplostim has been detected in breast milk and can lead to postnatal thrombocytosis during breast-feeding.[50]

In summary, thrombopoietin-receptor agonists can be recommended only for use in the third trimester to prepare for delivery, and most of the reported studies have evaluated romiplostim. The safety of these agents for use throughout pregnancy in women with otherwise unresponsive disease requires further study.

NEONATAL THROMBOCYTOPENIA

Approximately 9 to 15% of neonates are born with marked thrombocytopenia (platelet count at birth, <50×10^3 per cubic millimeter),[2] but prediction of which neonates will be born with this condition is imprecise. The most consistently identified predictor is a history of neonatal thrombocytopenia, when that information is available.[22,51-53] Some but not all studies have shown an association between neonatal thrombocytopenia and severe maternal disease, with severity assessed on the basis of the platelet count or therapy at or near the time of delivery[22,52,54-56]; maternal splenectomy[15,52,53,56,57]; and circulating antiplatelet antibodies.[52] Management of neonatal thrombocytopenia is described in Table 1 and has been reviewed elsewhere.[58]

CASE STUDY REVISITED

Our patient is is now pregnant and not receiving treatment for ITP. We discuss the risks of pregnancy for her and her neonate and the pros and cons of treatment options, recognizing that typical first-line agents (prednisone and IVIG), as well as rituximab, are not likely to be useful. Since we expect her platelet count to fall, we will follow her at more frequent intervals than usual. If her platelet count falls to less than 20×10^3 per cubic millimeter, she has bleeding, or a procedure is required, we will initiate treatment with a thrombopoietin-receptor agonist, preferably romiplostim, because most of the published safety data are for that agent. If necessary, we may combine this treatment with low-dose prednisone.

At week 32 of pregnancy, the patient's platelet count decreases to 17×10^3 per cubic millimeter, and treatment with romiplostim (3 μg per kilogram [1 vial of 250 μg]) per week is started to keep the count above 20×10^3 per cubic millimeter. Romiplostim maintains the patient's platelet

count at a level above 30×10^3 per cubic millimeter, and prednisone is not needed. Two weeks before scheduled delivery at week 36, we increase the dose of romiplostim to 6 μg per kilogram (1 vial of 500 μg) per week, and the platelet count increases to approximately 100×10^3 per cubic millimeter in 1 week. The patient delivers vaginally 1 week later without incident and has a healthy-appearing baby who has a platelet count of 123×10^3 per cubic millimeter.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Gonzalez-Porras JR, Palomino D, Vaquero-Roncero LM, Bastida JM. Bleeding complications associated with pregnancy with primary immune thrombocytopenia: a meta-analysis. TH Open 2022;6(3):e230-e237.
2. Eslick R, McLintock C. Managing ITP and thrombocytopenia in pregnancy. Platelets 2020;31:300-6.
3. Rodeghiero F, Marranconi E. Management of immune thrombocytopenia in women: current standards and special considerations. Expert Rev Hematol 2020; 13:175-85.
4. Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv 2018;2: 3360-92.
5. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010; 115:168-86.
6. Zhang X, Zhao Y, Li X, et al. Thrombopoietin: a potential diagnostic indicator of immune thrombocytopenia in pregnancy. Oncotarget 2016;7:7489-96.
7. Frölich MA, Datta S, Corn SB. Thrombopoietin in normal pregnancy and preeclampsia. Am J Obstet Gynecol 1998;179: 100-4.
8. Segerer S, Kammerer U, Kapp M, Dietl J, Rieger L. Upregulation of chemokine and cytokine production during pregnancy. Gynecol Obstet Invest 2009;67:145-50.
9. Segerer SE, Martignoni F, Bogdan A, et al. Thrombopoietin modulates the proliferation, migration and cytokine profile of decidual cell subsets during early gestation. Mol Hum Reprod 2013;19:361-8.
10. Chen Q, Liu F-Q, Sun X-Y, et al. High level of estradiol induces megakaryocyte apoptosis and impairs proplatelete formation via MST1-FOXO1 axis during pregnancy in patients with immune thrombocytopenia. In: Proceedings and abstracts of the 2021 European Hematology Association Congress, June 4–17, 2021. Virtual: European Hematology Association, 2021.
11. Rezk M, Masood A, Dawood R, Emara M, El-Sayed H. Improved pregnancy outcome following earlier splenectomy in women with immune thrombocytopenia: a 5-year observational study. J Matern Fetal Neonatal Med 2018;31:2436-40.
12. Pishko AM, Levine LD, Cines DB. Thrombocytopenia in pregnancy: diagnosis and approach to management. Blood Rev 2020;40:100638.
13. Cines DB, Levine LD. Thrombocytopenia in pregnancy. Blood 2017;130:2271-7.
14. Li J, Gao Y-H, Su J, Zhang L, Sun Y, Li Z-Y. Diagnostic ideas and management strategies for thrombocytopenia of unknown causes in pregnancy. Front Surg 2022;9:799826.
15. Loustau V, Debouverie O, Canoui-Poitrine F, et al. Effect of pregnancy on the course of immune thrombocytopenia: a retrospective study of 118 pregnancies in 82 women. Br J Haematol 2014;166:929-35.
16. Fadiloglu E, Unal C, Tanacan A, Portakal O, Beksac MS. 5 years' experience of a tertiary center with thrombocytopenic pregnancies: gestational thrombocytopenia, idiopathic thrombocytopenic purpura and hypertensive disorders of pregnancy. Geburtshilfe Frauenheilkd 2020;80:76-83.
17. Reese JA, Peck JD, Deschamps DR, et al. Platelet counts during pregnancy. N Engl J Med 2018;379:32-43.
18. Care A, Pavord S, Knight M, Alfirevic Z. Severe primary autoimmune thrombocytopenia in pregnancy: a national cohort study. BJOG 2018;125:604-12.
19. Comont T, Moulis G, Delavigne K, et al. Re: severe primary autoimmune thrombocytopenia (ITP) in pregnancy: a national cohort study primary immune thrombocytopenia management during pregnancy. A French study. BJOG 2018;125:629-30.
20. Rottenstreich A, Israeli N, Roth B, et al. Risk factors associated with neonatal thrombocytopenia in pregnant women with immune thrombocytopenic purpura. J Matern Fetal Neonatal Med 2020;33:1572-8.
21. Habas E Sr, Rayani A, Alfitori G, Eldin Ahmed G, Elzouki AY. Gestational thrombocytopenia: a review on recent updates. Cureus 2022;14(3):e23204.
22. Guillet S, Loustau V, Boutin E, et al. Immune thrombocytopenia and pregnancy: an exposed/nonexposed cohort study. Blood 2023;141:11-21.
23. Huang QS, Zhu XL, Qu QY, et al. Prediction of postpartum hemorrhage in pregnant women with immune thrombocytopenia: development and validation of the MONITOR model in a nationwide multicenter study. Am J Hematol 2021;96: 561-70.
24. Gilmore KS, McLintock C. Maternal and fetal outcomes of primary immune thrombocytopenia during pregnancy: a retrospective study. Obstet Med 2018;11:12-6.
25. Fujimura K, Harada Y, Fujimoto T, et al. Nationwide study of idiopathic thrombocytopenic purpura in pregnant women and the clinical influence on neonates. Int J Hematol 2002;75:426-33.
26. Webert KE, Mittal R, Sigouin C, Heddle NM, Kelton JG. A retrospective 11-year analysis of obstetric patients with idiopathic thrombocytopenic purpura. Blood 2003; 102:4306-11.
27. Bauer ME, Arendt K, Beilin Y, et al. The Society for Obstetric Anesthesia and Perinatology interdisciplinary consensus statement on neuraxial procedures in obstetric patients with thrombocytopenia. Anesth Analg 2021;132:1531-44.
28. Lee LO, Bateman BT, Kheterpal S, et al. Risk of epidural hematoma after neuraxial techniques in thrombocytopenic parturients: a report from the multicenter perioperative outcomes group. Anesthesiology 2017;126:1053-63.
29. Bailey LJ, Shehata N, De France B, Carvalho JCA, Malinowski AK. Obstetric neuraxial anesthesia at low platelet counts in the context of immune thrombocytopenia: a systematic review and meta-analysis. Can J Anaesth 2019;66:1396-414.
30. Bussel JB, Cooper N, Lawrence T, et al. Romiplostim use in pregnant women with immune thrombocytopenia. Am J Hematol 2023;98:31-40.
31. Wang J, Chen F, Zhu S, et al. Adverse effects of prenatal dexamethasone exposure on fetal development. J Reprod Immunol 2022;151:103619.
32. Murphy VE, Fittock RJ, Zarzycki PK, Delahunty MM, Smith R, Clifton VL. Metabolism of synthetic steroids by the human placenta. Placenta 2007;28:39-46.
33. Chapin J, Lee CS, Zhang H, Zehnder JL, Bussel JB. Gender and duration of disease differentiate responses to rituximab-dexamethasone therapy in adults with immune thrombocytopenia. Am J Hematol 2016;91:907-11.
34. Oved JH, Lee CSY, Bussel JB. Treatment of children with persistent and chronic idiopathic thrombocytopenic purpura: 4 infusions of rituximab and three 4-day cycles of dexamethasone. J Pediatr 2017;191:225-31.
35. Marangon M, Vianelli N, Palandri F, et al. Rituximab in immune thrombocytopenia: gender, age, and response as predictors of long-term response. Eur J Haematol 2017;98:371-7.

36. Michel M, Novoa MV, Bussel JB. Intravenous anti-D as a treatment for immune thrombocytopenic purpura (ITP) during pregnancy. Br J Haematol 2003;123:142-6.
37. Kong Z, Qin P, Xiao S, et al. A novel recombinant human thrombopoietin therapy for the management of immune thrombocytopenia in pregnancy. Blood 2017;130:1097-103.
38. Nieto M, Calvo G, Hudson I, et al. The European Medicines Agency review of eltrombopag (Revolade) for the treatment of adult chronic immune (idiopathic) thrombocytopenic purpura: summary of the scientific assessment of the Committee for Medicinal Products for Human Use. Haematologica 2011;96(9):e33-e40.
39. Nakai K, Misugi T, Kitada K, et al. Effect of thrombopoietin receptor agonist on pregnant mice. Pharmaceutics 2022;14:514.
40. Liu Y, Wang R, Han P, et al. Effect of recombinant human thrombopoietin on immune thrombocytopenia in pregnancy in a murine model. Int Immunopharmacol 2019;67:287-93.
41. Michel M, Ruggeri M, Gonzalez-Lopez TJ, et al. Use of thrombopoietin receptor agonists for immune thrombocytopenia in pregnancy: results from a multicenter study. Blood 2020;136:3056-61.
42. Agarwal N, Mangla A. Thrombopoietin receptor agonist for treatment of immune thrombocytopenia in pregnancy: a narrative review. Ther Adv Hematol 2021;12:20406207211001139.
43. Howaidi J, AlRajhi AM, Howaidi A, AlNajjar FH, Tailor IK. Use of thrombopoietin receptor agonists in pregnancy: a review of the literature. Hematol Oncol Stem Cell Ther 2022;15:1-6.
44. Purushothaman J, Puthumana KJ, Kumar A, Innah SJ, Gilvaz S. A case of refractory immune thrombocytopenia in pregnancy managed with elthrombopag. Asian J Transfus Sci 2016;10:155-8.
45. Suzuki N, Hiraga J, Hariyama Y, et al. A low birth weight infant with no malformations delivered by a primary immune thrombocytopenia patient treated with eltrombopag. Int J Hematol 2018;108:109-11.
46. Mendicino F, Santoro C, Martino E, et al. Eltrombopag treatment for severe immune thrombocytopenia during pregnancy: a case report. Blood Coagul Fibrinolysis 2021;32:519-21.
47. Favier R, De Carne C, Elefant E, Lapusneanu R, Gkalea V, Rigouzzo A. Eltrombopag to treat thrombocytopenia during last month of pregnancy in a woman with MYH9-related disease: a case report. A A Pract 2018;10:10-2.
48. Heenan JM. Management of refractory immune thrombocytopaenia in pregnancy. BMJ Case Rep 2021;14(10):e244656.
49. Harrington P, Nelson-Piercy C, Williamson C, Cooper N, Kesse-Adu R, Robinson S. Refractory severe immune thrombocytopenia in a twin pregnancy. Obstet Med 2018;11:35-8.
50. Roy S, Labrecque AA, Dufour A, et al. First-in-human detection of romiplostim drug levels in cord blood, breastmilk and blood in a woman with ITP and her newborn infant. Blood 2022;140:Suppl:2697-8.
51. Christiaens GC, Nieuwenhuis HK, Bussel JB. Comparison of platelet counts in first and second newborns of mothers with immune thrombocytopenic purpura. Obstet Gynecol 1997;90:546-52.
52. Khaspekova SG, Shustova ON, Golubeva NV, Naimushin YA, Larina LE, Mazurov AV. Circulating antiplatelet antibodies in pregnant women with immune thrombocytopenic purpura as predictors of thrombocytopenia in the newborns. Platelets 2019;30:1008-12.
53. Valat AS, Caulier MT, Devos P, et al. Relationships between severe neonatal thrombocytopenia and maternal characteristics in pregnancies associated with autoimmune thrombocytopenia. Br J Haematol 1998;103:397-401.
54. Kashyap R, Garg A, Pradhan M. Maternal and fetal outcomes of pregnancy in patients with immune thrombocytopenia. J Obstet Gynaecol India 2021;71:124-30.
55. Wegnelius G, Bremme K, Lindqvist PG. Efficacy of treatment immune thrombocytopenic purpura in pregnancy with corticosteroids and intravenous immunoglobulin: a prospective follow-up of suggested practice. Blood Coagul Fibrinolysis 2018;29:141-7.
56. Mazzucconi MG, Petrelli V, Gandolfo GM, et al. Autoimmune thrombocytopenic purpura in pregnancy: maternal risk factors predictive of neonatal thrombocytopenia. Autoimmunity 1993;16:209-14.
57. Yamada H, Fujimoto S. Perinatal management of idiopathic thrombocytopenic purpura in pregnancy: risk factors for passive immune thrombocytopenia. Ann Hematol 1994;68:39-42.
58. Bussel JB, Vander Haar EL, Berkowitz RL. New developments in fetal and neonatal alloimmune thrombocytopenia. Am J Obstet Gynecol 2021;225:120-7.