



Management of immune thrombocytopenia in pregnancy

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Contributions: (I) Conception and design: All authors; (II) Administrative support: JN Poston; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: JN Poston; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Immune thrombocytopenia (ITP) presents unique challenges in the peripartum setting. The diagnosis of ITP is similar to the nonpregnant patient except pregnancy related causes of thrombocytopenia must be considered. Management of ITP will change over the course of pregnancy and closer monitoring is critical as delivery approaches when the recommended platelet goal increases from 20×10^9 – 30×10^9 /L to above 50×10^9 /L for a vaginal delivery. If an epidural is required, the platelet count should be above 70×10^9 /L. The mode of delivery is based on obstetrical indications. First line therapies are glucocorticoids or intravenous immunoglobulin (IVIG). Many second line therapies may be safe in pregnancy. Contraindicated therapies include syk inhibitors, vinca alkaloids, mycophenolate mofetil, cyclophosphamide and danazol. Limited case series report safe administration of the thrombopoietin receptor agonists (TPO-RAs) without adverse fetal outcomes. While the majority of neonates are unaffected, neonatal platelet counts can decline in the first days after delivery and may require therapy. Maternal treatment and platelet count do not appear to predict the risk of neonatal thrombocytopenia; the strongest predictor is a previous sibling's history. ITP is not a contraindication for pregnancy; women with a history of ITP should not be discouraged from becoming pregnant as their ITP can be safely managed with close monitoring and multidisciplinary coordination with obstetrics and pediatrics.

Keywords: Immune thrombocytopenia (ITP); pregnancy

Received: 21 September 2020; Accepted: 02 February 2021; Published: 31 March 2021.

doi: 10.21037/aob-20-58

View this article at: <http://dx.doi.org/10.21037/aob-20-58>

Introduction

Immune thrombocytopenia (ITP) occurs in 0.83 of 10,000 pregnancies (1) and presents unique challenges in the peripartum setting. ITP can develop at any time point during pregnancy and can be difficult to distinguish from other causes of thrombocytopenia in pregnancy such as gestational thrombocytopenia (GT), acute fatty liver of pregnancy and the hypertensive emergencies (preeclampsia and HELLP; hemolysis, elevated liver enzymes, low platelet count) (1,2). Women with pre-existing ITP may have worsening disease during pregnancy, nearly half requiring treatment (2). Treatment of peripartum ITP is indicated depending on signs of bleeding, the degree of

thrombocytopenia and clinical course of the pregnancy; higher platelet count treatment thresholds are required as the mother approaches delivery and is at higher risk for bleeding (3). Careful monitoring of the mother throughout pregnancy is critical to avoid risk to both the mother and neonate. In this review, diagnosis and care of women with peripartum ITP will be discussed.

Diagnosis

Similar to the non-pregnant patient, peripartum ITP is a diagnosis of exclusion; there is no definitive diagnostic test for ITP and presentations can be similar to other causes of thrombocytopenia. Thrombocytopenia should

Table 1 Evaluation of suspected peripartum ITP

Recommended
History & physical exam
Review of blood counts
Reticulocyte count
Blood smear
Coagulation testing
Creatinine
Liver function testing
Thyroid function
ANA
Antiphospholipid antibodies
Quantitative immunoglobulins
H pylori
HIV
HCV
HBV
Recommended under certain situations
Bone marrow biopsy*
Testing for type IIB VWD [^]
ADAMTS-13 [#]
Not recommended
TPO level
Antiplatelet antibodies
Fetal blood sampling

Table is based on recommendations from the updated international consensus report on the investigation and management of primary immune thrombocytopenia (3). *, bone marrow biopsy is recommended only if there are atypical features; ^, consider depending on family history and review of prior platelet counts; #, thrombotic thrombocytopenic purpura (TTP) can present in pregnancy and should be considered in addition to HELLP if there is thrombocytopenia and microangiopathic hemolytic anemia.

first be confirmed by reviewing the peripheral smear to exclude pseudothrombocytopenia or platelet clumping (Table 1). ITP is diagnosed after other causes of acquired thrombocytopenia are excluded such as drug induced thrombocytopenia, cirrhosis and splenic sequestration. Inherited thrombocytopenia should be considered in patients with longstanding thrombocytopenia and

inadequate platelet count responses to glucocorticoids and/or intravenous immunoglobulin (IVIg). An absence of a family history of thrombocytopenia does not definitely rule inherited thrombocytopenia as some are autosomal recessive and *de novo* mutations can occur.

Causes of thrombocytopenia unique to pregnancy must also be considered when diagnosing ITP in the peripartum setting (3). Over the course of normal pregnancy, platelet counts decline due to increased blood volume and cell turn over (4,5). In 5–10% of healthy pregnancies, women develop thrombocytopenia beyond the normal decline in pregnancy due to GT (4,5). GT is the most common cause of thrombocytopenia in pregnancy and most cases are benign with counts generally above $100 \times 10^9/L$ (5). GT often develops in later pregnancy, most frequently immediately prior to delivery (5). It can be difficult to distinguish GT from mild ITP, particularly if thrombocytopenia occurs in the first trimester when ITP is the most common cause of thrombocytopenia in pregnancy (5,6). Unlike ITP, thrombocytopenia of GT will not respond to IVIg or glucocorticoids (7). If the mother does not require treatment, postpartum monitoring may help differentiate as GT will resolve after delivery (8). Although there are rare reports of GT associated with neonatal thrombocytopenia (8), other causes of neonatal thrombocytopenia must be excluded, including neonatal alloimmune thrombocytopenia (NAITP) (9). Mild forms of inherited thrombocytopenia and type IIB von Willebrand disease can present in the mother during pregnancy and then be associated with neonatal thrombocytopenia. Obtaining pre-pregnancy platelet counts and an extensive family and bleeding history is critical for diagnosis.

Additional causes of thrombocytopenia unique to pregnancy include preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count), and acute fatty liver of pregnancy. Signs and symptoms of preeclampsia should be evaluated particularly if the patient develops thrombocytopenia late in pregnancy. Presence of preeclampsia does not exclude a concurrent diagnosis of ITP depending on the patient's history. Furthermore, women with pre-existing ITP can develop pregnancy complications such as preeclampsia or HELLP syndrome.

Although common in pregnancy, anemia should be evaluated beyond iron studies in women with concurrent thrombocytopenia. Testing should include a blood smear and laboratory testing to rule out hemolysis. Concurrent immune mediated hemolysis suggests Evans syndrome. Thrombotic microangiopathies (TMA) should be

considered if there is microangiopathic hemolytic anemia and thrombocytopenia. While HELLP is a pregnancy related TMA, both hemolytic uremic syndrome and thrombotic thrombocytopenic purpura can present in pregnancy. Abnormalities of other cell lines or organ dysfunction may suggest a bone marrow failure syndrome.

Distinguishing ITP from other causes of thrombocytopenia can be diagnostically challenging. Increased platelet counts with glucocorticoids and/or IVIG suggests ITP, but cannot distinguish between primary and secondary ITP. Primary or idiopathic ITP has no known associated disorder. Secondary ITP is ITP associated with an underlying disorder such as a hepatitis C, HIV, rheumatologic disorders (e.g., systemic lupus erythematosus), or a lymphoproliferative disorder. Treating the underlying disorder may resolve thrombocytopenia in secondary ITP.

Diagnostic testing in ITP

Bone marrow biopsy is not required for diagnosis of ITP including in the peripartum setting (3), however, it may be required if there is concern for marrow failure or hematologic malignancy, or if the patient does not have an appropriate response to ITP directed therapies (*Table 1*).

Currently available tests for antiplatelet antibodies have poor sensitivity and specificity and testing is recommended only in the research setting (3). The presence of anti-platelet antibodies does not alter management, nor prognosticate the course of the mother or neonate. While ITP is thought to be primarily an autoantibody driven disease, direct T cell cytotoxicity likely contributes and is not captured with antibody testing (10).

Thrombopoietin (TPO) levels appear to be elevated in patients with ITP during pregnancy (11), however TPO testing is currently not routinely available and not recommended (3) (*Table 1*). In the non-pregnant population, higher TPO levels correlate with non-response to TPO receptor agonists (TPORAs) (12). In the pregnancy setting, TPO levels have not been shown to predict the severity of ITP and it is unknown if TPO levels predict response to recombinant TPO or TPORAs.

Immune changes in pregnancy

Pregnancy induced immunomodulation undoubtedly impacts ITP and new onset ITP during pregnancy likely represents a form of secondary ITP. Complex immune changes occur both systemically and at the maternal fetal

interface at the placenta, allowing the maternal immune system to tolerate paternal alloantigens. Reduced exposure to paternal human leukocyte antigens (HLA) may be critical for tolerance; fetal extravillous trophoblasts that migrate into the decidua lack expression of classical HLA class Ia and class II molecules and instead have non classical HLA class Ib molecules (13,14). Maternal tolerance is also regulated by hormones such as increased progesterone and beta HCG, which promote maternal immune cells to shift from an inflammatory (Th1) to regulatory (Th2) cytokine profile (15). While immunomodulation of pregnancy promotes tolerance of the fetus, the maternal immune system is not functionally immunosuppressed and may be more responsive to systemic infections (16). More research is needed to clarify how the immune changes of pregnancy alter autoimmunity.

Pregnancy results in new exposures to alloantigens both at the level of the placenta and systemically as fetal DNA and small populations of fetal cells enter maternal circulation (microchimerism). Microchimerism may be critical for immune tolerance and may impact autoimmunity (17,18). Insufficient fetal microchimerism may increase inflammation with lower levels seen in women with preeclampsia (19). Improvement in rheumatoid arthritis during pregnancy has been correlated with higher levels of fetal microchimerism (20). However, fetal microchimerism may correlate with progressive disease in other autoimmune diseases like systemic lupus erythematosus and systemic sclerosis (21). Further investigation is needed to understand the impact of microchimerism on the maternal immune system particularly in light of persistence of fetal microchimerism in maternal circulation for years after pregnancy. It is unknown how microchimerism affects the risk and course of an autoimmune disease, like ITP.

Prenatal risks and management

ITP often worsens during the course of pregnancy with only 5.6% of women with ITP having improvement in platelet counts during pregnancy (2). The majority of women with pre-existing ITP have worsening thrombocytopenia during pregnancy and nearly half (49%) require treatment (2). Risk factors for severe disease during pregnancy include prior splenectomy, as well as a short duration of response to IVIG and/or inability to taper glucocorticoids (3). Rapidly declining platelet counts suggests worsening ITP: these mothers require closer monitoring than those with stably low counts.

The decision to start therapy is based on the degree of thrombocytopenia, signs of bleeding, and status of the pregnancy. During the first and second trimesters, platelet counts may be safely maintained at 20×10^9 – 30×10^9 /L (3). Higher platelet goals could be considered if there are signs of bleeding or a procedure is required. During the third trimester, the platelet count should be closely monitored. As the mother approaches delivery, platelet counts should be treated to maintain the platelet count above 50×10^9 /L with the least toxicity possible as the risk of bleeding during delivery increases when the platelet count is under 50×10^9 /L (3). While the majority of women with ITP will not have major bleeding during pregnancy, bleeding can occur at any platelet count and the clinical picture must be considered when contemplating therapy,

First line therapies are similar to ITP in the non-pregnant patient. IVIG and glucocorticoids appear to have similar efficacy in peripartum ITP and have minimal risk to the fetus (22). Glucocorticoids should be tapered to the lowest possible dose; higher doses of glucocorticoids (especially >15 mg/day) can increase the risk of maternal diabetes, hypertension and excessive weight gain and the risk of an abnormal fetal weight (23). IVIG is considered safe in pregnancy, however the prothrombotic risk of IVIG is notable given the already increased risk for thrombosis in pregnancy (24). Patients with a shorter duration of response to IVIG may benefit from more frequent dosing such as lower doses given biweekly (3). Combination therapy with both glucocorticoids and IVIG may be effective in women who have insufficient platelet count responses to either treatment as monotherapy. If combination therapy is ineffective, second line therapies should be considered.

Second line treatment choices must take in to account the expected timing of response and the course of pregnancy. Some second line therapies require months for a response. Cyclosporine, for example, will only be effective by delivery if considered earlier in pregnancy. In emergencies with an urgent need to increase the platelet count, IVIG with or without high dose steroids is recommended. Platelet transfusions may also be helpful. The risk of antifibrinolytic therapies during pregnancy is unknown although it is safe and effective for postpartum bleeding (25).

Additionally, the impact on maternal and fetal outcomes must be considered when selecting second line therapies. Anti-D immune globulin (Winrho®) has been used for RhD-positive women with ITP during the second and third trimesters, however there is a risk of both maternal and fetal hemolysis (depending on the fetus's RhD

status) (26). Rituximab may be considered, but may cause neonatal lymphopenia and impaired response to vaccinations (27). Azathioprine has been used successfully in pregnancy with more extensive data on the use in systemic lupus erythematosus and renal transplantation (28). Splenectomy should be avoided except in the most treatment refractory settings (3,29). If needed, it is preferred to perform a splenectomy during the second trimester when there is the least risk to the fetus from anesthesia and uterine size is not prohibitive (30). Notably, vaccinations against encapsulated organisms will be required and splenectomy will increase the mother's risk for thrombosis (31). Contraindicated ITP directed therapies due to adverse fetal outcomes include: syk inhibitors, vinca alkaloids, mycophenolate mofetil, cyclophosphamide and danazol (3).

Data is emerging on the safety of TPO-RAs and pregnancy. Pregnant women were excluded from the trials of romiplostim and eltrombopag and minimal long term safety data is available on fetal outcomes. Both romiplostim and eltrombopag likely cross the placenta as romiplostim utilizes the fc receptor and eltrombopag is a small molecule. The majority of women with ITP in pregnancy respond to the TPORAs with one case series showing a 77% response rate although most responders (70%) required multiple concurrent ITP therapies (32). Romiplostim appears safe in pregnancy based on a limited safety database from the manufacturer and other case series (3,32). Romiplostim may be preferred over eltrombopag due to the lack of iron chelation and liver toxicity (33). However, the liver effects of eltrombopag may be overreported in the general literature due to the interference effects of eltrombopag on laboratory testing (33). A small case series reported no adverse effects of eltrombopag in pregnancy except for one neonate with thrombocytosis that persisted for weeks after delivery with a mother who continued to take eltrombopag while breastfeeding (32). Human recombinant TPO (rhTPO) has also been successfully used in pregnancy in one case series (34), but is not universally available.

Delivery risks and management

Coordination with each patient and her obstetrician is essential throughout pregnancy but especially close to delivery. ITP can worsen in the third trimester and close monitoring is required especially for women with a rapidly falling platelet count. The route of delivery is based on pregnancy indications (35). Ideally, platelet counts should

be above $50 \times 10^9/L$ prior to vaginal delivery as the risk of postpartum hemorrhage increases below $50 \times 10^9/L$ (2). If a mother desires an epidural or will have an epidural a cesarean delivery, a platelet count above $70 \times 10^9/L$ is recommended (3). In a series of thrombocytopenic patients, the risk of bleeding with an epidural was 0.2% when the platelet count was above $70 \times 10^9/L$ (36). For a spinal block injection, a platelet count of $50 \times 10^9/L$ is considered safe (37). If a mother requires an emergency cesarean, general anesthesia can be safely performed with a platelet count over $30 \times 10^9/L$ (3,7). Postpartum pain control can include NSAIDs unless the platelet count is under $70 \times 10^9/L$ (3,7). Women with ITP remain at risk for venous thrombosis (38) and prophylaxis should be used as indicated in routine pregnancy.

ITP can worsen after delivery, especially in women with a history of a splenectomy (2), and all should be closely monitored for postpartum hemorrhage. The incidence of postpartum hemorrhage varies by case series from 1.9% to 22% (6) with rates up to 24% in women with platelet counts under $50 \times 10^9/L$ (6). The majority of women with ITP do not have bleeding complications beyond what is expected during pregnancy as the most important mechanism of hemostasis after delivery is the normal contraction of the uterus after delivery

Risks for the neonate and management

After delivery, close monitoring of the neonate is required as 21% to 28% will develop thrombocytopenia presumably from passive transfer of maternal autoantibodies against platelet antigens (6). The majority have mild thrombocytopenia without life threatening bleeding. Less than 1% of neonates develop intracranial hemorrhage (3,39). Risk for thrombocytopenia is increased if siblings had thrombocytopenia at delivery or if the mother has had a splenectomy (39). Except for one retrospective case series (40), most data suggest the mother's treatment and platelet counts during pregnancy do not impact the risk of thrombocytopenia in the neonate (32,39). Attempts to measure the fetal platelet count by percutaneous umbilical blood sampling is not recommended as there is a risk of hemorrhage and fetal loss comparable to non-intervention (*Table 1*). Fetal scalp vein sampling also has a risk of hemorrhage and may result in a falsely low platelet count.

Although most infants are unaffected, it is critical to avoid trauma to the infant during delivery and the use of forceps or vacuum should be discouraged. After birth,

a cord blood platelet count should be sent. If this is less than $100 \times 10^9/L$, a peripheral blood platelet count should be drawn and followed until the platelet count stabilizes above $100 \times 10^9/L$. Pseudothrombocytopenia should be excluded as it is common with cord blood draws due to a higher rate of clotting in the sample (3). Platelet counts may decline during the first 1–3 days of life (3). Treatment with IVIG is indicated if the infant has signs of bleeding and/or a platelet count under $30 \times 10^9/L$ (3,7). If there is an intracranial hemorrhage, the platelet count should be kept above $100 \times 10^9/L$ for one week and then above $50 \times 10^9/L$ in the second week (3). Platelet transfusions may also be used although they may increase the risk of intracranial hemorrhage if used when the platelet count is at or above $50 \times 10^9/L$ (33).

Breastfeeding and ITP

The majority of women with ITP may breastfeed if desired. Rarely, breastfeeding may cause persistent neonatal thrombocytopenia that resolves when breastfeeding is stopped (3,39). If there is persistent neonatal thrombocytopenia, breastfeeding should be discontinued. If the mother would like to resume breastfeeding after the baby's platelet count recovers, then the mother should be advised to express breast milk to maintain her ability to breastfeed. Breastfeeding may be resumed if the baby's platelet count improves and remains stable once restarted. The mother's ITP treatment may also impact counseling around breastfeeding as some medications are secreted in breast milk such as glucocorticoids (41). Eltrombopag may also be secreted in breastmilk as persistent thrombocytopenia after birth was noted in one infant whose mother breastfed while on eltrombopag (32).

Conclusions

ITP can be successfully managed in the peripartum setting with close monitoring and coordination with obstetrics and pediatrics. Although mothers are at risk for worsening ITP as pregnancy progresses and nearly half require treatment, ITP is not a contraindication for pregnancy. Frontline therapy consists of glucocorticoids or IVIG. Combination therapy can be used if there is an inadequate response to frontline therapies. Second line therapies can be successful, but require discussion with the mother regarding potential risks to herself and her baby. Limited case series suggest the TPORAs and rhTPO are safe in pregnancy. Additional

investigation is needed to understand the impact of immune modulation of pregnancy on the development and severity of ITP in the peripartum setting.

Acknowledgments

Funding: Dr. Poston received a 2019 HTRS/Novo Nordisk Clinical Fellowship Award in Hemophilia and Rare Bleeding Disorders from the Hemostasis and Thrombosis Research Society (HTRS), which was supported by an educational grant from Novo Nordisk Inc.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (John W. Semple and Rick Kapur) for the series “Treatment of Immune Thrombocytopenia (ITP)” published in *Annals of Blood*. The article was sent for external peer review organized by the Guest Editors and the editorial office.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/aob-20-58>). The series “Treatment of Immune Thrombocytopenia (ITP)” was commissioned by the editorial office without any funding or sponsorship. JNP reports grants from Novo Nordisk/HTRS, outside the submitted work. TBG reports personal fees from Amgen Corporation, personal fees from Novartis Corporation, outside the submitted work. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/aob-20-58

Cite this article as: Poston JN, Gernsheimer TB. Management of immune thrombocytopenia in pregnancy. *Ann Blood* 2021;6:5.