

Idiopathic Thrombocytopenia in Pregnancy

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Abstract

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder in which antiplatelet autoantibodies bind to the antigens on platelet surfaces, resulting in their destruction. It is one of the most common autoimmune disorders that physicians manage today. Although it can present itself at any age, it tends to occur in young women. Hence, it commonly affects women in the childbearing age group. It is a haematological disorder for which diagnostic and treatment strategies are not well defined. In the past decade, there have been attempts for consensus in the management of patients with ITP, resulting in practice guidelines being published. The management of pregnant patients with ITP, however, has its special problems with the added responsibility of caring for 2 lives, the mother and her fetus. The choice of drugs is limited to those without teratogenic risks to the fetus and the overall aim is to prevent haemorrhage in both mother and fetus during the antenatal and peripartum periods. There are more data now to show that invasive procedures do not necessarily reduce fetal bleeding risk and are associated with more maternal morbidities, thus favouring the trend towards more conservative management.

Ann Acad Med Singapore 2002; 31:335-9

Key words: Antiplatelet antibody, Autoimmune disorder, Cordocentesis, Maternal haemorrhage, Neonatal intracranial haemorrhage

Introduction

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder in which platelets are sensitised with an antiplatelet autoantibody and then destroyed by the reticuloendothelial system.¹ Hence, it is also known as primary autoimmune thrombocytopenic purpura. There are two forms of ITP—acute and chronic. The latter is defined as persistence of thrombocytopenia for more than 6 months. Almost all adult patients with ITP have the chronic form. ITP is a relatively common haematological disorder in women of childbearing age. It is easy, but wrong, to label any pregnant woman with a less than normal platelet count to have ITP. Indeed, it is evident now that ITP is an uncommon cause accounting for only 3% of thrombocytopenia in pregnant patients.²

Thrombocytopenia during Pregnancy

In a large, prospective study involving 15,000 mother-newborn pairs, maternal thrombocytopenia occurred in 7% of women.² The causes were incidental thrombocytopenia of pregnancy (75%), thrombocytopenia complicating hypertensive disorders of pregnancy (21%), thrombocytopenia associated with immunological disorders including ITP and systemic erythematosus (4%), and ITP (3%).

Incidental thrombocytopenia of pregnancy or gestational thrombocytopenia is the most common cause of thrombocytopenia in pregnancy.^{2,3} It occurs in up to 5% of pregnant women and accounts for 75% of cases of thrombocytopenia at term.^{2,4} The platelet count falls by about 10% during an uncomplicated pregnancy with the greatest decline during the last trimester. Therefore, gestational thrombocytopenia usually presents during late gestation. The thrombocytopenia is usually mild, above $70 \times 10^9/L$, with the majority between 130 and $150 \times 10^9/L$. Like mild anaemia of pregnancy, this is not a disease but a physiological response that does not require intervention or therapy. The diagnosis is made by exclusion of other diseases that can cause thrombocytopenia. Current evidence does not support exhaustive investigations to differentiate between gestational thrombocytopenia and mild ITP in routine practice since most of the cases show only mild thrombocytopenia that do not require medical treatment.

Hypertensive disorders of pregnancy occur in 10% of pregnancies, presenting usually after 20 weeks of gestation and thrombocytopenia may occur in up to 25% of these patients.^{2,4,5} Other uncommon causes of thrombocytopenia during pregnancy are HELLP syndrome (an acronym for haemolysis, elevated liver function tests and low platelet count), liver diseases and portal hypertension.⁵ These

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diseases are accompanied by obvious clinical and laboratory abnormalities such that these diagnoses are apparent to the managing physicians.

Presentation of ITP

Pregnant patients with ITP may present in several ways. The patients may be asymptomatic and thrombocytopenia diagnosed on routine full blood counts. Some patients have a known history of ITP with some degree of thrombocytopenia at the time of pregnancy or even before the pregnancy. Less commonly, patients may present with bleeding symptoms characteristic of thrombocytopenia such as petechiae, mucosal bleeding and easy bruising. If the thrombocytopenia is chronic, recurrent menorrhagia prior to pregnancy and bleeding gastrointestinal tract (GIT) may lead to iron deficiency anaemia. The most serious and potentially fatal complication is bleeding into the central nervous system; this is fortunately very rare.⁶ Typically, the thrombocytopenia worsens as the pregnancy progress. It is essential to obtain a detailed history and a physical examination to detect diseases other than ITP causing thrombocytopenia.

Laboratory Investigations

The choice of laboratory investigations is guided by the clinical scenario.^{7,8} The following tests may be appropriate in the management of patients with suspected ITP:

- 1) Full blood count and a stained peripheral blood smear. The stained peripheral blood film is useful to exclude pseudo-thrombocytopenia from ethylenediamine tetra-acetic acid (EDTA)-induced clumping of platelets. It is also useful in diagnosing thrombocytopenia due to thrombotic thrombocytopenic purpura and pre-eclampsia.
- 2) Thyroid function tests—as a small proportion of patients with ITP have concomitant thyroid dysfunction.
- 3) Serology tests—to exclude autoimmune disorders as other causes of immunological thrombocytopenia such as systemic lupus erythematosus (SLE), rheumatoid arthritis and antiphospholipin syndrome (APS). If there are no symptoms to suggest an autoimmune disorder, an antinuclear antibody (ANA) as a screening test is sufficient.
- 4) Other tests, such as liver and renal function tests, should be ordered based on the clinical picture. Hepatitis and human immunodeficiency virus (HIV) serology is part of a routine antenatal blood test in Singapore and the results should be useful for patients with ITP.

Measurement of platelet-associated IgG (PAIgG) as a diagnostic tool remains unsatisfactory despite improved serological techniques.⁹ It is neither diagnostic of ITP⁹ nor a predictor of pregnancy outcome for patients with ITP.^{10,11} They offer little diagnostic and prognostic information

about patients with suspected ITP. The role of platelet antibodies in predicting infant thrombocytopenia in pregnancy remains unclear. The clinical impact of these antibody tests is controversial.

Bone marrow biopsy is an invaluable test for exclusion of other haematological disorders. It is generally not done for pregnant patients unless other haematological disease is suspected.^{7,8}

Diagnosis

ITP is still a diagnosis of exclusion in both pregnant and non-pregnant patients. The diagnosis of ITP is a clinical one based on the patient's history, physical examination and complete blood count as well as examination of the peripheral blood film. There is no reliable confirmatory laboratory test. The diagnosis of ITP is more difficult during pregnancy because the presentation may closely resemble that of gestational thrombocytopenia. The aim is to exclude as confidently as possible the other causes of thrombocytopenia.

Antenatal Management of ITP in Pregnancy

The management of pregnant patients with ITP is largely extrapolated from data concerning non-pregnant patients.⁶

⁸ In looking after pregnant patients, care must be taken to avoid drugs with teratogenic potentials and to ensure adequate haemostasis for both mother and fetus. Close liaison should be maintained between the obstetrician, haematologist and paediatrician.

Asymptomatic Women with Mild to Moderate Thrombocytopenia

The degree of thrombocytopenia required for haemorrhage varies between 10 and 30 × 10⁹/L.⁶ No specific treatment is required if the platelet count is above 50 × 10⁹/L as there is very little risk in bleeding.⁸ The patients will need vitamin and folic acid supplements as in all other pregnant patients. However, they will require closer follow-up visits for purpose of monitoring their platelet counts. They should be seen at least once a month during the first and second trimesters and once every 2 weeks during the last trimester. A progressive decrease in platelet counts is expected and specific treatment will be recommended if the platelet count is below 50 × 10⁹/L.

Patients with Moderate Thrombocytopenia

The 2 most preferred options as the first-line treatment of moderately severe thrombocytopenia are the use of corticosteroids and intravenous immunoglobulin (IVIG). Corticosteroids work by inhibiting the production of autoantibodies as well as inhibiting the phagocytosis of the sensitised platelets.¹² The starting dose of prednisolone is usually 1 mg per kg body weight, followed by titration

down to the lowest efficacious dose.^{7,8} It is inexpensive and efficacious. It is also considered to be safe with regards to teratogenic potential. Potential fetal toxicity, such as fetal adrenal suppression, is unlikely as prednisolone is almost completely metabolised by the placenta.^{7,8,13,14} However, there are many potential adverse effects to the mother, namely gestational diabetes, hypertension, excessive weight gain, osteoporosis, acne and psychological disturbances.¹⁵ If the duration of treatment is likely to be brief or if there are financial constraints, corticosteroid treatment is an effective option.

High-dose IVIG is very efficacious in raising the platelet counts rapidly.^{7,8,16,17} Its mechanism of action is mainly at the reticulo-endothelial cell blockage and acting as anti-idiotypic antibodies.¹⁸ IVIG is certainly superior to corticosteroids in terms of side effects profile. It is given by intravenous infusion at a dose of 1 g/kg body weight over 6 to 8 hours for 2 consecutive days. There are very few adverse effects with IVIG. Headaches, backache, nausea, septic meningitis and fever occur in less than 5% of patients.^{19,20} There are rare but serious complications, such as anaphylaxis, alloimmune haemolysis²¹ and hepatitis C infection.^{22,23} It is important that only virally inactivated products are used. The main disadvantages are the high cost and the transient nature of responses in raising the platelet counts, requiring repeated infusions that will further escalate the cost. If cost is not a problem, IVIG as a first-line treatment is likely to be the preferred option. In situations where prolonged duration of treatment is likely, in the presence of unacceptable side effects of steroids or an unacceptably high maintenance dose of steroids, then the use of IVIG is justified.⁸

Women with Severe Thrombocytopenia

There are some pregnant patients with severe ITP with a platelet count of less than $10 \times 10^9/L$. These patients generally require corticosteroids in addition to periodic high-dose IVIGs.^{7,8} In certain cases, high-dose methylprednisolone or dexamethasone has been used.^{8,24}

Beside corticosteroids, other drugs are used with great caution. Azathioprine may be considered, as it has been used safely in pregnant patients with kidney transplant and pregnant patients with SLE.⁸ The dosages of these medications are titrated with an aim to achieve a clinically acceptable platelet count with minimum medications. There have been reports of successful use of dapsone²⁵ in pregnancy. Vincristine and danazol^{7,8} should not be used as there is a potential risk of fetal teratogenicity.

For patients who are resistant to both IVIG and corticosteroids, splenectomy may be considered during the second trimester as a last resort.^{5,7,8} It is important to remember that although the mother may be in haematological

remission after splenectomy, the fetus may still be at risk due to transplacental passage of the circulating maternal autoantibodies.⁵

Frequency of Thrombocytopenia and Haemorrhage in Infants Born to Mothers with ITP

Previous perception and assumption that ITP was a very serious disorder for both mother and infant were erroneous. Clinically, intrauterine haemorrhage in the fetus has not been reported in ITP in contrast to neonatal alloimmune thrombocytopenia.^{2,26} Severe thrombocytopenia, in presumed maternal ITP, has previously been overestimated. Many patients, in early reports of suspected severe neonatal thrombocytopenia complicating ITP in mothers, were in fact shown to have alloimmune ITP.²⁷ There was also a bias of "worse-case" reporting.^{4,28}

A review of studies between 1990 and 2000 on the issue of neonatal thrombocytopenia and the mode of delivery showed that moderate neonatal thrombocytopenia (platelet count <50) and severe neonatal thrombocytopenia (platelet count <20) occur in 9% and 4%, respectively, of infants born to mothers with ITP.²⁷ Minor bleeding complications such as petechiae, cephalohaematoma, haematuria, mild gastrointestinal bleeding and umbilical bleeding occurred in 3%; major complications such as intracranial haemorrhage (ICH), gastrointestinal bleeding and bloody pericardial effusion occurred in 1% of the infants.

Neonatal ICH is the most feared complication in infants of ITP mothers. There were 11 cases of neonatal ICH described in the 1243 infants delivered to mothers with ITP in 22 prospective and retrospective studies from 1990 to 2000.²⁷ The rate of neonatal ICH was about 0.9%. Two neonates had ICH at normal platelet counts and 2 developed ICH despite being delivered by caesarean section. However, not all neonatal ICHs were caused by thrombocytopenia alone; some were associated with other fetal malformations, fetal distress and prematurity. Hence, it was felt that the true rate of neonatal ICH was lower than 0.9%.

These studies concluded that most mothers with ITP gave birth to infants with normal platelet counts. Severe infant thrombocytopenia and spontaneous neonatal bleeding complications were rare.

Predictors of Neonatal Thrombocytopenia and Determination of Fetal Platelet Count

The only useful predictor of severity of neonatal thrombocytopenia has been mothers who gave birth previously to severely affected infants.^{29,30} There was no neonatal thrombocytopenia less than $50 \times 10^9/L$, when the previous infant's platelet count was above $10 \times 10^9/L$.²⁹

Correlation between maternal platelet count and neonatal platelet count is poor.^{2,10,30-38} The level of maternal PAIgG

has not been shown convincingly to predict neonatal thrombocytopenia.³⁹⁻⁴³

Percutaneous umbilical blood sampling (PUBS) or cordocentesis is an invasive technique involving ultrasound-guided removal of fetal blood from the umbilical vein *in utero*. It may be complicated by fetal distress necessitating an emergency caesarean section. It is also associated with fetal bleeding and death.^{34,44-46} A review of this procedure in 195 cases showed severe neonatal thrombocytopenia in 14 infants (7%) with a complication rate of 5%.³⁴ More importantly, the true risk of potentially fatal neonatal bleeding was 1%. In a review of studies on PUBS, a 2% complication rate was noted; these included fetal bradycardia and haematomas as well as cerebral palsy.²⁷ Such complications in a fetus with normal platelet count will appear more disastrous. The significant complication rates need to be balanced against the potential benefits associated with this procedure. The risk of this procedure appears to be higher than the disease itself, and has never been recommended for practice here.

Fetal scalp sampling is the collection of a small amount of fetal blood via a small scalp incision just before delivery. This requires the fetal head to be engaged in the pelvis, the membranes ruptured and the maternal cervix dilated.¹⁴ The platelet counts may not be accurate and false positive results can arise due to clotting in the sample.^{34,36} The difference between the 'scalp blood' platelet count and the true fetal platelet count may differ by as much as 35%. In addition, bleeding complications can occur in the scalp of the infant and the genital tract of the mother. This procedure will not alter the mode of management and is therefore not recommended.

Mode of Delivery

Mothers with ITP are often subjected to caesarean section based on the assumptions that infants of ITP mothers have high risks of neonatal thrombocytopenia and high risks of fetal haemorrhage. In a recent review of 601 infants of mothers with ITP, 307 were delivered by spontaneous vaginal delivery and 247 by caesarean section.³⁴ Six infants had ICH, of whom 2 were delivered by caesarean section.

The results of 4 studies done in the past decade, which included 202 pregnancies, showed that there was a 7% maternal complication rate. These complications occurred mostly in those who had caesarean section.^{34,40,43,47} The maternal complications were mainly procedure related e.g. haemostatic impairment, wound infection, postoperative fever and endometritis. This showed that maternal complications were more commonly seen than fetal complications in pregnant patients with ITP.

Taking all these into considerations, caesarean sections should be restricted for obstetric indications only.

Use of Peripartum Regional Anaesthesia

Studies have shown that epidural or spinal anaesthesia is safe and without complication in mothers with platelet count ranging from 50 to 150 x 10⁹/L.^{48,49} However, it is important to note that some patients with ITP do have concomitant platelet dysfunction that can impair haemostatic function further. Hence, it is important that the anaesthetist must be experienced and comfortable in performing such procedures for patients with higher bleeding risks.

Conclusion

There is a lack of randomised clinical trials to provide definitive, evidence-based recommendations for the management of pregnant patients with ITP. Historical recommendations to predict the fetal platelet count from clinical and haematological parameters, as well as to determine fetal platelet count *in utero* or during early labour and delivery by caesarean section to minimise the risk of neonatal ICH, have been challenged recently.

Now, there is a trend towards more conservative approaches in managing pregnant patients with ITP, reserving either corticosteroids or IVIG to severe cases only. Fetal bleeding complications are not related to the mode of delivery. Caesarean sections should be performed for obstetric indications only.

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