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Thrombocytopenic syndromes in pregnancy

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Abstract

The physiological changes in pregnancy result in platelet counts that are lower than in nonpregnant women. Consequently, thrombocytopenia is a common finding occurring in 7–12% of pregnant women. Gestational thrombocytopenia, the most common cause of low platelet counts, tends to be mild in most women and does not affect maternal, fetal or neonatal outcomes. Gestational thrombocytopenia needs to be distinguished from other less common causes of isolated thrombocytopenia, such as immune thrombocytopenia, which affects approximately 3% of thrombocytopenic pregnant women and can lead to neonatal thrombocytopenia. Hypertensive disorders of pregnancy and thrombotic microangiopathies are both associated with thrombocytopenia. They share a considerable number of similar characteristics and are associated with significant maternal and neonatal morbidity and rarely mortality. Accurate identification of the aetiology of thrombocytopenia and appropriate management are integral to optimizing the pregnancy, delivery and neonatal outcomes of this population. Clinical cases are described to illustrate the various aetiologies of thrombocytopenia in pregnancy and their treatment.

Keywords

Thrombocytopenia, pregnancy, immune thrombocytopenia, pre-eclampsia, thrombotic microangiopathy

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Case 1

A 31-year-old gravida 1 para 0 at 24 weeks' gestation has a platelet count of 82×10^9/L. She does not have a personal history or family history of thrombocytopenia. She has never had symptoms suggestive of an underlying bleeding tendency. The current pregnancy has been uncomplicated. She is normotensive, and urinalysis does not demonstrate proteinuria. She does not have other cytopenias. Liver enzymes and serum creatinine are within the normal range.

The normal range for platelet counts is 10% lower in pregnancy than in nonpregnant women because of haemodilution and increased platelet activation and clearance.[1–3] A platelet count of $<150 \times 10^9$/L occurs in 7–12% of the pregnant population.[3,4] However, only 1% of pregnant women have levels $<100 \times 10^9$/L.[5] Approximately 75% of all individuals with thrombocytopenia in pregnancy have gestational thrombocytopenia (GT) or incidental thrombocytopenia of pregnancy. Of these, 15% have hypertensive syndromes, and 3–4% have immune thrombocytopenia (ITP).[5]

Isolated thrombocytopenias

Gestational thrombocytopenia. GT is diagnosed by a reduction in the platelet count in the absence of other clinical, haematological and biochemical changes. With GT, a low platelet count is commonly observed during the second or third trimester, with a nadir platelet count generally greater than 70×10^9/L, although there are reports of women having lower platelet counts.[6] Resolution of thrombocytopenia is prompt, usually within days to two months postpartum.[7] This maternal thrombocytopenia is not associated with fetal thrombocytopenia.[5]

Other causes of isolated thrombocytopenia include pseudothrombocytopenia, viral-associated thrombocytopenia, e.g. hepatitis B virus, hepatitis C virus, human immune deficiency virus, hereditary thrombocytopenia (e.g. Type IIb von Willebrand's disease), vitamin B12/folate deficiency, hypersplenism, drugs, and ITP. These may be differentiated by history, e.g. if there is a family history of a haemorrhagic tendency, examination, laboratory investigations and/or medical imaging (Table 1).

Other laboratory investigations such as screening for antiphospholipid antibodies (aPLs) in patients with thrombocytopenia is debateable and has been advised only when there is suspicion of antiphospholipid antibody syndrome (APS).[2] The rationale for not screening for aPL is because only a small proportion will likely have APS. Previous reports have overestimated the frequency of aPL in patients with thrombocytopenia because of the lack of adherence to criteria to diagnose aPL (e.g. anticaridiolipin immunoglobulin (Ig) G or IgM levels >40 GPL or MPL, respectively, or >99th percentile 12 weeks apart).[8] In addition, the risk of thrombosis in individuals with ITP has not definitively been shown to correlate with the presence/absence of aPL.[9] In contrast, screening for aPL has been advocated as thrombocytopenia occurs in 10–20% patients with aPL,[10,11] and there is potentially a risk of thrombosis in asymptomatic carriers of aPL (5%/year).[12] Accordingly, a careful selection of pregnant patients with thrombocytopenia to screen for aPL, i.e. ITP with a prior fetal loss and the use of established criteria to identify aPL may reduce the incorrect classification of women as having aPL and identify women at higher risk of thrombosis.

Pseudothrombocytopenia or spurious thrombocytopenia occurs in 0.1–0.2% of the population and is secondary to platelet agglutination induced by ethylenediaminetetraacetic acid (EDTA), a common anticoagulant used in collection tubes for haematological tests.[13] Platelet clumping results in the inability of haematology analysers to estimate an accurate platelet number. Pseudothrombocytopenia is not associated with an increased risk of bleeding, as the platelet number is not reduced. Determining the platelet count in collection tubes using citrate as an anticoagulant, instead of EDTA, will usually provide a more accurate platelet number; however, platelet clumping may persist in 15–20% of samples.[13]

Primary ITP may be difficult to distinguish from GT. Figure 1 highlights the characteristics that differentiate gestational from primary ITP. If the diagnosis is unclear at the time of delivery, intrapartum management should reflect the treatment for ITP.

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Immune thrombocytopenia. ITP is a 'heterogeneous disorder' that induces the development of platelet autoantibodies.[14] Platelet autoantibodies arise from varied immune mechanisms, such as infection (e.g. *Helicobacter pylori*), immune dysregulation (e.g. coexistent immune deficiency) and molecular mimicry following infection.[14] The diagnosis of ITP is considered when the platelet count is consistently below 100×10^9/L.[15] In addition to the investigations in Table 1, quantitative Ig levels, direct antiglobulin testing and screening for *H. pylori* can be considered for individuals with ITP suspected of having primary immune deficiency, concurrent autoimmune haemolytic anaemia or recent onset ITP, respectively.[7] A bone marrow examination is not required for the diagnosis of ITP.[2]

ITP is not infrequently encountered during pregnancy, affecting 2 to 3/1000 pregnancies.[5] Approximately two-thirds of women have a diagnosis of ITP prior to pregnancy.[5] Unlike GT, ITP can occur in the first or early second trimester and is one of the more common causes of thrombocytopenia in early pregnancy (Figure 1).

Pregnancy with ITP

Most women with ITP have mild to moderate thrombocytopenia, and only 30–35% require any intervention during pregnancy.[16,17] Most individuals do not have bleeding symptoms. Mild bleeding symptoms, such as easy bruising and purpura, occur in 10% of individuals, whereas 20% may experience moderate bleeding, defined as epistaxis, bleeding after trauma and mucous membrane bleeding.[16] Of women who are symptomatic, a small proportion (3.4%) may experience severe bleeding, such as gastrointestinal bleeding, haematuria or deep tissue bleeding.[16] Overall, ITP is associated with a low risk of maternal morbidity, and only 10% of individuals experience exacerbation of their disease postpartum.[18]

Table 1. Investigations for isolated thrombocytopenia in the absence of a family history of bleeding.

Complete blood count and film
Liver enzymes
Thyroid function tests
Vitamin B12 and folate[a]
HCV, HIV and HBV
Coagulation screen: aPTT and PT
Antinuclear antibody, anticardiolipin antibodies and lupus inhibitor
Medical imaging to assess spleen size

aPTT: activated prothrombin time; PT: prothrombin time.
[a]Folate deficiency is uncommon in countries with folate fortification.

Indications for maternal treatment for ITP

Treatment for ITP during pregnancy is considered in the first or second trimester, if the platelet count is <20–30×10^9/L in the absence of bleeding and if $<50 \times 10^9$/L in the third trimester, because a platelet count of 50×10^9/L or more is adequate for both vaginal delivery and caesarean section.[2,16]

Similar to the treatment for ITP in the nonpregnant individual, the use of corticosteroids and intravenous immune globulin (IVIG) is the treatment option during pregnancy.[2] A platelet increment in response to corticosteroids occurs after three to seven days. Corticosteroids are associated with a longer duration of response.[19] Corticosteroids may be associated with a small risk of orofacial clefts during embryogenesis and may aggravate maternal hypertension or diabetes later in pregnancy.[20,21] The optimum dose of prednisone has not been determined and lower initial doses of prednisone (10–40 mg daily) in comparison to doses used in nonpregnant individuals have been suggested to reduce the adverse effects of prednisone.[2,7] The lowest effective dose is used during the course of pregnancy.

A rapid increment, within 24–72 h in platelet count, occurs with IVIG but the increase in platelet count is transient usually lasting only two to three weeks. IVIG is administered at the same dose as in nonpregnant individuals, 1 or 2 g/kg over two days. Platelet transfusion is reserved for bleeding patients with platelet counts $<10 \times 10^9$/L, or at delivery if platelet counts are <30 to 50×10^9/L, because transfused platelets are associated with a short duration of response as they are rapidly destroyed.

Second-line treatments for ITP include splenectomy, preferably in the second trimester,[22] azathioprine, anti-D and cyclosporine.[19] Rituximab crosses the placenta and may cause neonatal B cell depression if given within six months of delivery.[23] Vinca alkaloids, cyclophosphamide, danazol and thrombopoietin mimetics should be avoided in pregnancy.[19]

Obstetric management in women with ITP

The mode of delivery should be determined by obstetrical indications as vaginal delivery has not been associated with increased risk of neonatal bleeding.[24,25] However, as antiplatelet IgG antibodies can cross the placenta, resulting in platelet counts $<50 \times 10^9$/L in 10 to 15% of

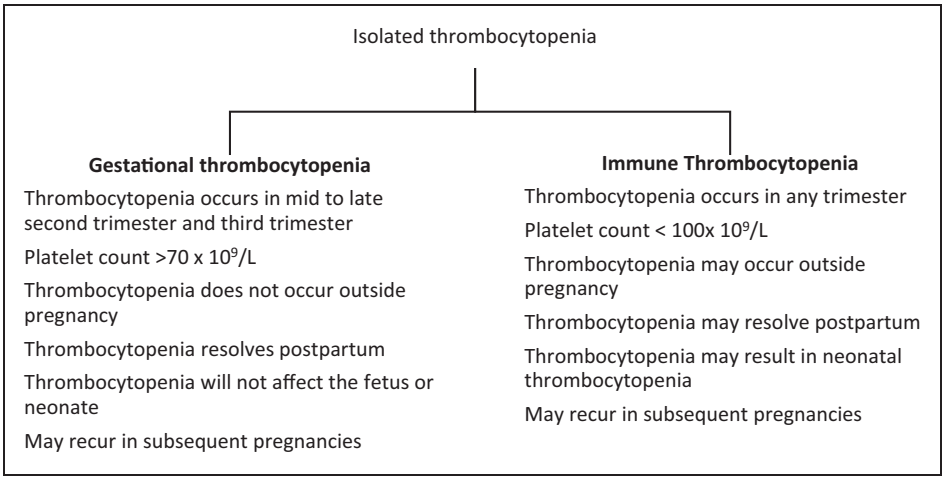

Figure 1. Characteristics differentiating gestational thrombocytopenia from immune thrombocytopenia (printed with permission).

neonates,[16] fetal blood sampling antepartum, the use of fetal scalp electrodes and performing scalp pH or lactate in labour, are not advised as they potentially increase risk of fetal bleeding.[7] In addition, fetal scalp sampling may be inaccurate.[26] Assisted vaginal delivery should be approached cautiously, considering the risks of bleeding to the neonate as compared to the risks associated with a second-stage caesarean section.[27] If assisted vaginal delivery is performed, use of forceps is preferable to use of a ventouse cup, as vacuum-assisted deliveries have been associated with an increase in the risk of neonatal intracranial haemorrhage.[28] The platelet threshold required for neuraxial anaesthesia has not been determined but in practice, most anaesthetists accept a lower limit of platelet count of $50–80 \times 10^9$/L.[2]

Maternal ITP and the neonate

Although the risk of neonatal thrombocytopenia is low, a cord platelet count should be obtained. If the platelet count is $<50 \times 10^9$/L, the decision to administer intramuscular vitamin K is balanced with the risk of haemorrhagic disease of the newborn and the efficacy of oral formulations.

Similarly, neonatal intramuscular vaccinations should be delayed until the platelet count has recovered. Although the risk of neonatal intracranial haemorrhage is <1%, neonates with platelet counts $<50 \times 10^9$/L should have a cranial ultrasound to exclude its presence.[10] Fetal/neonatal alloimmune thrombocytopenia should also be considered in neonates with platelet counts $<50 \times 10^9$/L.

The neonatal platelet count usually reaches a nadir three to five days postpartum[2,16] but may be reduced for months.[2] The most consistently demonstrated risk factor for neonatal thrombocytopenia is a sibling with a history of thrombocytopenia, though a mother with ITP refractory to splenectomy may also increase risk. [16,29,30] There is no correlation of neonatal platelet counts with maternal platelet counts[5] or with the maternal use of betamethasone.[31] The neonate's platelet count should be monitored until a normal platelet number is reached.

Case 1 resolution

This individual has a finding of isolated thrombocytopenia in the late second trimester. All investigations have excluded other possible diagnoses. Although the likely aetiology is GT, ITP cannot be reliably excluded. If the platelet count remains at this level, she may have neuraxial anaesthesia safely and delivery is guided by obstetrical indications. As ITP is still considered an alternate diagnosis, antepartum umbilical cord sampling, intrapartum monitoring of scalp pH or lactate and assisted vacuum delivery should be avoided. A cord platelet count and serial monitoring of neonatal platelet counts should be undertaken. In addition, intramuscular injections are generally avoided. Maternal and serial neonatal platelet counts are advised postpartum until thrombocytopenia has resolved.

Case 2

A 31-year-old gravida 1 para 0 at 28 weeks' gestation has a platelet count of 20×10^9/L, haemoglobin concentration of 79 g/L and peripheral blood film demonstrating 10% schistocytes. Her blood pressure is 140/90 mmHg, and she has no neurological deficits. Serum creatinine, liver enzymes and urinary protein levels are normal.

Thrombocytopenia associated with microangiopathic haemolytic anaemia, secondary to endothelial damage, and characterized by schistocytes (fragments) on peripheral blood film occurs with several disorders[32] (Table 2). Laboratory findings, aside from reduction in the haemoglobin concentration and thrombocytopenia, include elevation in lactate dehydrogenase (LDH) concentration, reduction in haptoglobin levels and elevation in indirect bilirubin levels. There is considerable overlap among the syndromes so that the correct diagnosis may not initially be easily identifiable (Table 3).

Table 2. Disorders associated with microangiopathic haemolytic anaemia and thrombocytopenia.[32]

Primary thrombotic microangiopathy syndromes
Hereditary disorders
ADAMTS13 deficiency-mediated TMA (also known as TTP)
Complement-mediated TMA (also known as atypical HUS)
Metabolism-mediated TMA (e.g. B12 deficiency)
Acquired disorders
ADAMTS13 deficiency-mediated TMA (also known as TTP)
Shiga toxin-mediated TMA (also known as Shiga toxin-HUS)
Drug-induced TMA
Complement-mediated TMA
Other disorders
Systemic infection
Systemic cancer
Severe pre-eclampsia, eclampsia, HELLP syndrome
Severe hypertension
Autoimmune disorders (e.g. systemic lupus erythematosus, systemic sclerosis, antiphospholipid antibody syndrome)
Haematopoietic stem-cell or organ transplantation

ADAMTS13: A disintegrin and metalloproteinase with thrombospondin motifs 13; HUS: hemolytic uremic syndrome; TMA: thrombotic microangiopathy; TTP: thrombotic thrombocytopenic purpura.

Thrombocytopenia associated with systemic disease

Primary thrombotic microangiopathies. The thrombotic microangiopathies (TMAs) are a group of disorders characterized by microangiopathic haemolytic anaemia, thrombocytopenia and organ injury.[32] This includes A disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13)-deficient TMA (thrombotic thrombocytopenic purpura (TTP)) and complement-mediated TMA (atypical haemolytic uremic syndrome). TTP is caused by a deficiency in the von Willebrand factor cleaving protease ADAMTS13 that cleaves multimeric von Willebrand factor. This results in ultralarge von Willebrand factor multimers that lead to platelet thrombi in small vessels. Complement-mediated TMA is due to from over activation of the alternative pathway of complement.[32]

ADAMTS13-deficient TMA (TTP). TTP occurs in 1 in 25,000 pregnancies.[19] A marked reduction in ADAMTS13 activity (<10%) and evidence of thrombocytopenia and microangiopathic haemolytic anaemia are suggestive of TTP. The presence of anti-ADAMTS13 antibodies in addition to very low levels of ADATMS13 establishes the diagnosis of acquired TTP, whereas the absence of ADAMTS13 antibodies suggests hereditary TTP. A mild reduction in ADAMTS13 levels in the absence of other findings may also occur with normal pregnancy.[33]

Hereditary TTP can occur in any trimester,[34] but acquired TTP usually manifests in the second and third trimesters.[33] The platelet nadir with TTP tends to be lower than seen with haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, with platelet counts $<20 \times 10^9$/L suggesting TTP.[35] Maternal survival has improved markedly since the implementation of treatment with plasma infusion and plasma exchange, ranging between 88 and 100%.[33,34] However, fetal survival is approximately 60%, with the majority of fetal loss occurring when TTP occurs in the first or second trimester.[33–35] The risk of recurrence in subsequent pregnancies is estimated to be 50%.[33]

TTP is a medical emergency. Plasma infusion is used as a replacement for ADAMTS13 for hereditary TTP, while plasma exchange and immune suppressants (e.g. corticosteroids) are used for acquired TTP.

Table 3. Comparison of features of disorders with thrombocytopenia and microangiopathy in pregnancy.[7,19,32–36,38,39]

	Pre-eclampsia	HELLP syndrome	Catastrophic antiphospholipid antibody syndrome	Acquired ADAMTS13 deficiency-mediated TMA	Complement-mediated TMA
Timing	After 20 weeks' gestation	Predominantly third trimester and within 48 hours postpartum	Anytime, may be precipitated by infections and medications	Frequently in the second trimester and third trimester	Predominantly postpartum
Hypertension	Present	Predominantly present	Present/absent	Present/absent	Present/absent
Proteinuria	Predominantly present	Predominantly present	Absent	Absent	Present/absent
Abdominal Pain	Present in severe disease	Often present	Absent	Absent	Absent
Neurologic symptoms	Present in severe disease	Present/absent	Present/absent	Present/absent	Uncommon
Renal involvement	Present/absent	Present/absent	Present/absent	Present/absent	Present
Liver enzymes	Elevated/normal	Elevated	Normal	Elevated/normal	Normal
Haemolysis	Present or absent	Present	Present/absent	Present/absent	Present
Treatment	Delivery	Delivery	Heparin corticosteroids ± IVIG ± plasma exchange	Plasma exchange/plasma infusion and immune suppression	Anticomplement agent and plasma infusion/exchange

Note: ADAMTS13: A disintegrin and metalloproteinase with thrombospondin motifs 13; DIC: disseminated intravascular coagulation; HELLP: haemolysis, elevated liver enzymes and low platelets; IVIG: intravenous immune globulin; TMA: thrombotic microangiopathy.

Antenatal use of low-dose aspirin and low-molecular-weight heparin has been recommended in individuals with platelet counts above 50×10^9/L but is not considered a standard regimen.[35] Serial ultrasound scans for fetal growth and well-being should be instituted in the late second and third trimesters, given the risk of intrauterine growth restriction and intrauterine fetal demise.

Complement-associated TMA. Complement-associated TMA predominantly occurs postpartum, and renal involvement is more common.[36] Since it can be difficult to distinguish from TTP, plasma exchange remains the first-line treatment. If an individual does not respond to plasma exchange, or the ADAMTS13 level is normal, then complement-associated TMA is suspected and a complement inhibitor, such as eculizumab, is instituted. The risk of recurrence of complement-associated TMA in subsequent pregnancies is approximately 20%.[36]

Pre-eclampsia

Pre-eclampsia affects approximately 6% of all pregnancies.[19] Pre-eclampsia is a systemic disorder characterized by new-onset hypertension (≥140/90 mmHg) after 20 weeks' gestational age, with involvement of at least one other system. This may be renal, hepatic, neurological, fetal or haematological. Fifty percent of patients with pre-eclampsia will have platelet counts $<150 \times 10^9$/L.[37]

The HELLP syndrome represents a severe manifestation of pre-eclampsia. HELLP occurs in approximately 10 to 20% of women with pre-eclampsia[38] and is often accompanied by right upper quadrant or epigastric pain, whereas hypertension and proteinuria may be mild or absent.[39] HELLP predominantly occurs in the third trimester; however, 30% of women may present within 48 h postpartum.[19] The perinatal mortality rate is high, between 7 and 34%.[38]

Pre-eclampsia and HELLP resolve within days to months after delivery. Corticosteroids have not been shown to improve clinical outcomes.[40] If HELLP does not improve or deteriorates after three days postpartum, has onset more than seven days postpartum or is accompanied by persistent or worsening neurological or renal dysfunction, an alternative diagnosis such as a primary TMA must be considered.[25]

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is a syndrome characterized by a 'maladaptive' activation of coagulation in response to injury.[41] Pregnancy-specific precipitants of DIC include intrauterine fetal demise, pre-eclampsia, HELLP syndrome[41] and acute fatty liver of pregnancy.[42] The characteristics of DIC are prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), low platelet counts, low fibrinogen concentration and elevated products of fibrin degradation, e.g. D-dimer. As the PT and aPTT are shortened during pregnancy secondary to increased coagulation factors, a prolongation in the PT or aPTT from baseline may be indicative of DIC, even if the PT and aPTT are within the normal range. Thus, a change in levels is more important than the absolute result.[41]

The cornerstone of DIC management is to correct the underlying precipitant as DIC will then usually subside. In the absence of haemorrhage, correction of coagulopathies is not warranted. In the presence of bleeding or if emergent delivery is required, platelets are administered if the platelet count is $<50 \times 10^9$/L. Plasma is administered at a dose of 15 to 20 mL/kg for coagulopathies, whereas hypofibrinogenemia may be corrected by administering cryoprecipitate or fibrinogen concentrate depending on component availability. Cryoprecipitate at a dose of two pools and fibrinogen concentrate at a dose of 2–4 g are used to target a fibrinogen level of more than 1.5–2.0 g/L.[41] Red cell transfusion is advised in a haemorrhaging patient to maintain haemodynamic stability.

Case 2 resolution

Additional investigations in this individual show an increased LDH level, markedly reduced haptoglobin concentration and elevated indirect bilirubin, consistent with haemolysis. The peripheral blood film suggests microangiopathy. The absence of proteinuria and normal liver enzymes diminishes the likelihood of HELLP, and the normal creatinine concentration excludes the diagnosis of complement-mediated TMA. The diagnosis is most consistent with TTP. Because the results of ADAMTS13 testing are not available immediately in most laboratories, plasma exchange should be instituted immediately. If plasma exchange is not available, plasma infusion is used until transfer can be arranged to a centre that offers plasma exchange.

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Contributorship

MY and NS drafted and revised the manuscript. AKM revised the manuscript.

Patient consent

The cases are hypothetical.

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