Thrombocytopenia in pregnancy

Key content:
- Thrombocytopenia occurs in 8–10% of all pregnancies.
- In pregnancy it is usually mild and benign.
- Rare causes can be associated with severe complications for mother and baby.
- Cases thought to be due to immune thrombocytopenic purpura or microangiopathic processes should be managed in a specialist centre.

Learning objectives:
- To learn about the underlying causes.
- To be aware of the management of the more severe cases.
- To ensure appropriate referral of high-risk cases.

Ethical issues:
- Clear prepregnancy counselling is important to enable women to make informed decisions regarding future pregnancies.
- Women need to understand the percentage risk of recurrence of certain conditions and the risks to fetal wellbeing.

Keywords HELLP syndrome / immune (idiopathic) thrombocytopenic purpura / pre-eclampsia / thrombotic thrombocytopenic purpura

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Introduction
Platelets are involved in primary haemostasis, plugging sites of endothelial damage and acting as a surface for secondary haemostasis via the coagulation pathway. The normal serum level of platelets in pregnancy is 150–400 × 10^9/l. Reduction of serum platelet counts is arbitrarily considered mild if the count is >100, moderate at 50–100 and severe at <50. Low counts can be due to an increase in destruction or consumption of platelets, dilutional effects or (more rarely) lack of production of platelets.

It is unusual to have any clinical signs or symptoms when the platelet count is >50, unless platelet function is also defective. Common signs of thrombocytopenia include petechiae, nose bleeding and, more rarely, haematuria and gastrointestinal bleeding.

During pregnancy there is a general downward drift in platelet count, particularly during the last trimester. This results at term in a level that is approximately 10% less than the prepregnancy level. The mechanisms for this are thought to be a combination of dilutional effects and acceleration of platelet destruction across the placenta. Most women still have platelet counts within the normal range; however, if the starting count is at the lower end of the normal range, or there is a more severe drop, thrombocytopenia occurs. Hence thrombocytopenia is a common finding in pregnancy. Most cases are mild and have no significance for mother or fetus but, in some instances, where thrombocytopenia is part of a complex clinical disorder, there can be profound and even life-threatening results for both mother and baby. The effect of pregnancy on the disorder and, conversely, of the disorder on the pregnancy, must be taken into account. In some instances, the aetiology is unique to pregnancy and the puerperium.

Aetiology and prevalence
A platelet count below the normal range is found in 8–10% of pregnancies. Approximately 75% of these cases are due to a benign process of gestational thrombocytopenia; 15–20% can be attributed to hypertensive disorders; 3–4% to an immune process; and the remaining 1–2% are made up of rare constitutional thrombocytopenias, infections and haematological malignancies. The various causes are listed in Box 1 and discussed in the sections below. In general, counts that are stable and >100 do not require further investigation but should be monitored.

Gestational thrombocytopenia (incidental thrombocytopenia of pregnancy)
Box 2 shows the typical characteristics of this disorder, which is the most common cause of thrombocytopenia in pregnancy, occurring in approximately 75% of cases of thrombocytopenia and 8% of all pregnancies. It is a benign condition usually found incidentally later in pregnancy and there is no bleeding risk to mother or fetus. Counts are typically >70 and usually >100.

Many of the features are similar to mild immune thrombocytopenia and it can be difficult to distinguish between the two disorders. There are no specific diagnostic tests for either and both are diagnoses of exclusion. Rarely, cases of gestational thrombocytopenia with platelet counts as low as 50 have been described. Again, the outcome appears good.

The pathophysiological process is not known but is thought to represent an acceleration of platelet consumption via an exaggeration of the physiological process across the placenta, or possibly via a mild immune process.

Gestational thrombocytopenia resolves quickly after delivery, but it can recur in subsequent pregnancies. A count should be performed 6 weeks postnatally and the result documented.

Management
For the vast majority of cases the pregnancy and delivery should be treated as normal. In cases of moderate or severe thrombocytopenia an anaesthetic

<table>
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<th>Causative diagnosis</th>
<th>Mechanism</th>
<th>Diagnostic features</th>
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<tr>
<td>Gestational thrombocytopenia</td>
<td>Physiological dilution, accelerated destruction</td>
<td>Third trimester, platelets &gt;70 × 10^9/l;</td>
</tr>
<tr>
<td>Immune thrombocytopenic purpura</td>
<td>Immune destruction, suppressed production</td>
<td>incidental finding</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura,</td>
<td>Periarterial consumption, microthrombosis</td>
<td>Diagnosis of exclusion</td>
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<tr>
<td>Haemolytic or renal insufficiency</td>
<td>Periarterial consumption, microthrombosis</td>
<td>Unwell, fever, neurological and renal</td>
</tr>
<tr>
<td>and platelet count syndrome (HELLP syndrome)</td>
<td></td>
<td>dysfunction</td>
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<tr>
<td>Hereditary thrombocytopenia</td>
<td>Bone marrow underproduction</td>
<td>Raised LDH, ALT and bilirubin,</td>
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<tr>
<td>Pseudothyrombocytopenia</td>
<td>Laboratory artefact</td>
<td>haemolytic anaemia +/- pre-eclampsia,</td>
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<tr>
<td>Viral infection/drugs</td>
<td>Multifactorial</td>
<td>DIC</td>
</tr>
<tr>
<td>Leukaemia/lymphoma</td>
<td>Bone marrow infiltration</td>
<td>Family history, abnormal platelets</td>
</tr>
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ALT = alanine aminotransferase; DIC = disseminated intravascular coagulation; LDH = lactate dehydrogenase
consultation is useful to discuss analgesic options, since most units will not consider epidural anaesthesia with platelet counts of <80. A trial of steroids should be considered when the count is 50–70.

Counts should be monitored periodically. When maternal counts are <80 during the pregnancy, a cord sample should be taken to ensure that the baby’s counts are normal. Consider taking further neonatal samples on days 1 and 4, as neonatal thrombocytopenia can present then. Where maternal platelet counts are low, similar management to that of maternal immune thrombocytopenic purpura (ITP) is recommended, because of the small risk of fetal thrombocytopenia. Hence, where possible, fetal scalp electrodes or sampling and high- or mid-cavity operative delivery should be avoided. Caesarean section should be reserved for obstetric indications only.

Immune (idiopathic) thrombocytopenic purpura
Adult ITP is usually a chronic condition, often occurring among young women. The incidence is estimated at 0.1–1/1000 pregnancies, accounting for approximately 3% of cases of thrombocytopenia in pregnancy. It is a diagnosis of exclusion, although in approximately two-thirds of cases the diagnosis is already established before pregnancy, allowing the opportunity for prepregnancy counselling.

The thrombocytopenia in ITP is predominantly caused by antibodies that are specific to platelet surface glycoproteins and which bind to the platelets in the maternal circulation, resulting in immune-mediated platelet destruction. Recent research suggests there is also suppression of platelet production. The antibodies can cross the placenta and cause fetal thrombocytopenia.

Diagnosis
Despite good understanding of the pathological mechanisms, there are no specific diagnostic tests for ITP. Although platelet antibodies can be demonstrated in these cases, the tests lack sensitivity and specificity and, therefore, the diagnosis of ITP is one of exclusion. Careful history, examination and laboratory specimens are helpful in excluding other causes of thrombocytopenia. A bone marrow test is not indicated unless there are unusual features or lack of response to standard treatment. As stated, the main difficulty is differentiation from gestational thrombocytopenia. However, this is not often a problem clinically, since no treatment is required for either condition when the platelet count is >70–80. It is unusual to have a count of <70 in gestational thrombocytopenia.

Management
Women with ITP should receive management in a unit with experience in the care of this condition, preferably in a combined obstetric/hematology setting. The aim of management is to maintain an adequate platelet count that will minimise the risk of bleeding during pregnancy, delivery and postpartum. Bleeding with ITP is unusual, even with very low counts; a general guideline for intervention levels in non-haemorrhagic cases is set out in Table 1. Counts should be closely monitored throughout pregnancy. The majority of women will not require treatment in the antenatal period; treatment is more often required to increase the count before delivery. Prednisolone is the usual first-line choice and it is often administered at lower doses than those recommended for nonpregnant women to minimise the risk of adverse effects on the mother (gestational diabetes, postpartum psychoses). A starting dose of 20 mg daily can be offered, escalating to 60 mg if no or an inadequate response is seen after 1 week. Dosage should then be tapered to the minimum that is effective in maintaining the count within the required range. Where the counts are very low, the woman is experiencing haemorrhage, or there remains an inadequate response to steroids, intravenous immunoglobulin should be considered, as it acts more quickly than steroids. Anti-D immunoglobulin appears to have efficacy equal to that of intravenous immunoglobulin for women who are rhesus positive. Both these options are useful when a rapid increase in platelet count is required. Other options are considered more rarely and include splenectomy and platelet transfusion.

Management of delivery: maternal considerations
The main concern at delivery for the mother is the risk of haemorrhage. Although there is no universally agreed safe platelet count, there is a general consensus that a platelet count of at least 50 is safe for vaginal or operative delivery. Where the maternal platelet count approaches 50, platelets should be available on standby and management should be in close consultation with a haematologist experienced in obstetric cases. The use of epidural anaesthesia is a particular concern, since a small

<table>
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<tr>
<th>Intervention</th>
<th>Platelet count (x 10^9/l)</th>
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<tr>
<td>Antenatal, no invasive procedures planned</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Operative or instrumental delivery</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Epidural anaesthesia</td>
<td>&gt;80</td>
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[Table 1: A general guideline for intervention levels in non-haemorrhagic cases of ITP in pregnancy]
Box 3
Prepregnancy counselling for women with immune (idiopathic) thrombocytopenia

1. ITP may relapse or worsen during pregnancy.
2. If treatment of ITP is required it will carry both maternal and fetal risks.
3. Around one-third of women will require treatment at some stage of pregnancy, most commonly around the time of delivery.
4. There is an increased risk of haemorrhage at delivery but the risk is small even if the platelet count is low.
5. Epidural anaesthesia may not be possible.
6. Although it is not possible to predict accurately whether a neonate will be affected, the risk is high if a sibling has had thrombocytopenia, or the mother has undergone splenectomy.
7. Maternal death or serious adverse outcomes for mothers with ITP are rare.
8. The risk of intracranial haemorrhage for the fetus/neonate is very low.

Management of delivery: neonatal considerations
Since antibodies are of the IgG subtype, they can cross the placenta and cause thrombocytopenia in the fetus and neonate. The main worry is possible intracranial haemorrhage in the neonate. This is an extremely rare but devastating complication. The effect of the antibodies on fetal counts is unpredictable, maternal treatments near term with steroids or intravenous immunoglobulin do not have any effect on the fetal count and there is no correlation between the severity of maternal thrombocytopenia and the fetal count. The incidence of thrombocytopenia among neonates is reported as between 14–37%. Approximately 5% of babies will have counts <20 and a further 10% will have counts of 20–50. Although there are no reliable predictors, fetal or neonatal thrombocytopenia is more likely if there has been a sibling with thrombocytopenia or the mother has had a splenectomy or her platelet count has been <50 during the pregnancy. Fetal scalp samples do not produce reliable counts and should not be taken. Nor is there a role for percutaneous umbilical blood sampling, since the procedure carries a risk of fetal haemorrhage and possibly death of approximately 2%; this is higher than the risk of intracranial haemorrhage, at <1%.

Mode of delivery
Caesarean section is not routinely recommended, as there is no evidence that this will reduce the incidence of intracranial haemorrhage among susceptible babies. Measures should be in place to avoid trauma to the baby’s head during delivery, as stated previously—there should be avoidance, where possible, of fetal scalp electrodes or sampling and of high- or mid-cavity operative delivery. The neonatal team should be alerted to the possibility of a thrombocytopenic baby before the birth. A cord sample should be taken to assess the neonatal platelet count and if low this should be confirmed by capillary sample. If the count is mildly reduced, further samples on days 1 and 4 should be collected, but if the initial result is normal, no further sampling is required.

Intramuscular vitamin K should be avoided until the count is known. Babies with severe thrombocytopenia should be treated with intravenous immunoglobulin; cranial Doppler ultrasound can be helpful. Platelets should be administered in addition to intravenous immunoglobulin if there is life-threatening haemorrhage.

Prepregnancy counselling
Where possible it is useful to discuss the management issues that can arise during the pregnancy. These are listed in Box 3.

Hypertensive disorders of pregnancy
See Table 2. These comprise pre-eclampsia and eclampsia; the combined haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome; thrombotic thrombocytopenic purpura (TTP); and haemolytic uraemic syndrome.

Pre-eclampsia
Diagnostic criteria for pre-eclampsia include new onset, hypertension and proteinuria (>300 mg/24 hours) at >20 weeks of gestation. The estimated incidence is 5–10% of all pregnancies worldwide with increased incidence among primigravidae or multigravidae with new partners. The aetiology is not fully understood, but there is an association with the presence of laboratory thrombophilia and a known genetic predisposition.

There is increased endothelial cell activation leading to the activation of platelets and the coagulation cascade. In general, women with pre-eclampsia have lower platelet counts than normal: approximately 15% within the thrombocytopenic range. The condition resolves quickly after delivery; therefore conservative management is appropriate for mild or moderate pre-eclampsia. Severe thrombocytopenia occurs among <5% of women with pre-eclampsia, but it can be associated
with disseminated intravascular coagulation. This requires aggressive management and correction of the coagulopathy with fresh frozen plasma, cryoprecipitate and platelet transfusions.

HELLP syndrome
This is a combination of haemolysis, elevated liver enzyme levels and low platelet counts which can complicate severe pre-eclampsia in about 10% of cases. It occurs most frequently in the third trimester, but it can get worse initially postpartum or, occasionally, present at this time. The syndrome can occur without hypertension or proteinuria and the diagnosis may be missed in these circumstances. The presenting symptoms can be very vague, with nausea, malaise and epigastric or right upper quadrant pain. Staff should have a high level of suspicion and check the full blood count and liver function. The pathophysiology of this condition involves endothelial damage with release of tissue factor and coagulation activation. A full blood count shows anaemia and thrombocytopenia, with fragments present on the blood film (microangiopathic haemolytic anaemia). Liver function tests show a raised lactate dehydrogenase, increased bilirubin and abnormal liver enzymes. Disseminated intravascular coagulation may be present in approximately 20% of cases and abruption occurs in approximately 16%. The central nervous and renal systems are usually unaffected by this condition, in contrast to TTP (see below). The neonatal outcome depends on the duration of gestation at delivery: neonatal mortality rates consequent on the necessity of very early delivery are 10–20% and fetal growth restriction is common. Some women will have incomplete forms of HELLP and there are different classifications of this syndrome, based on the platelet count and liver function abnormality.

As delivery is the mainstay of treatment for the mother, steroids should be given (to help mature the baby’s lungs) and supportive care with fresh frozen plasma with or without cryoprecipitate if disseminated intravascular coagulation is present. The platelet count should be maintained at >50. The condition usually improves quite quickly after delivery, although it may worsen during the first 24–48 hours postpartum. Depending on the clinical scenario, e.g. worsening maternal condition or severe fetal growth restriction, delivery may be indicated at any time from 20 weeks of gestation. Conservative management for very early HELLP is controversial and a difficult decision sometimes has to be made between gaining extra time for the baby and the maternal risks.

Microangiopathies
Thrombotic thrombocytopenic purpura
This is a rare, life-threatening disorder with a characteristic pentad of signs and symptoms, which include microangiopathic haemolytic anaemia, thrombocytopenia, neurological symptoms (varying from headache to coma), renal dysfunction and fever. Often only some of these features are present.

Aetiology
Thrombotic thrombocytopenic purpura has been shown to be due to a severe deficiency of von Willebrand’s factor—cleaving protein (ADAMTS 13). This is most commonly an acquired deficiency caused by an autoantibody or, rarely, a congenital deficiency caused by a genetic defect. The two types can be distinguished by measurement of ADAMTS 13 antigen activity and inhibitor—inhibitor is absent in the congenital form.

The lack of ADAMTS 13 leads to persistence of ultra-large multimers of von Willebrand’s factor that unfold and react with platelet receptors, resulting in microthrombi in many organs, particularly in the kidneys, brain and heart, and causing microangiopathic haemolytic anaemia and thrombocytopenia.

Incidence
Thrombotic thrombocytopenic purpura occurs in about 1 in 25 000 pregnancies. In addition to new cases, TTP (or haemolytic uraemic syndrome) that occurs initially outside pregnancy may relapse during subsequent pregnancies. The time of onset in pregnancy is variable, ranging from the first trimester to several weeks postpartum. In a review of 166 pregnancy-associated cases, 55% occurred in the second trimester. Maternal mortality was highest among the newly presenting cases, particularly where pre-eclampsia was present.

There can be major difficulties in the differential diagnosis of TTP, haemolytic uraemic syndrome, HELLP and severe pre-eclampsia. The typical features of each disorder are listed in Table 2.

Management
Despite the difficulties of diagnostic certainty, plasma exchange needs to be commenced urgently and good clinical judgement is required. By using this procedure antibodies are removed and 1–1.5 l fresh frozen plasma containing the absent enzyme is infused daily until the platelet count is normal and the lactate dehydrogenase level is reduced. The number of treatments required is extremely variable and high doses of steroids may be indicated. Rituximab, a monoclonal antibody against CD20, has been used successfully when improvement has been slow. About 25% of women affected experience recurrent episodes. In the rare congenital cases,
infusion of fresh frozen plasma rather than plasma exchange is carried out, since these women do not have antibodies. Platelet transfusions are contraindicated because they are known to precipitate or exacerbate central nervous symptoms. A central line should be placed without platelet support, as the risk of bleeding is low in this condition. Predictors of relapse include previous clinical presentation and low levels of ADAMTS 13 while in remission.

Haemolytic uraemic syndrome
This is a similar syndrome, with microangiopathic haemolytic anaemia and thrombocytopenia but with predominant renal involvement. In childhood the disorder is usually associated with *Escherichia coli* infection and a good outcome. In adulthood and in pregnancy there is a poor response to plasma exchange.

Microangiopathies and neonatal issues
The prognosis for the baby in all the microangiopathies described is poor because of extensive placental ischaemia. Disseminated intravascular coagulation can complicate the picture or exist secondary to another cause and is usually associated with bleeding.

Other causes of maternal thrombocytopenia

**Antiphospholipid syndrome**
Thrombocytopenia can be associated with antiphospholipid syndrome but this is rarely severe. In primary antiphospholipid syndrome and systemic lupus erythematosus with antiphospholipid antibodies, women need aspirin and Clexane® (enoxaparin sodium) (Rhone-Poulenc Rorer, Guildford, UK) during pregnancy, as this has been shown to give a better outcome. Occasionally, thrombocytopenia can make this treatment more difficult to achieve.

**Viral infection**
Almost any virus can cause a reduction in platelet count. This is usually very transient, but there may be a more prolonged reduction for a number of weeks. HIV and cytomegalovirus infections are particularly associated with thrombocytopenia and should be sought when appropriate.

**Medication**
Medication is an important cause of thrombocytopenia: it is a frequent adverse effect of commonly used drugs. Heparin-induced thrombocytopenia can, rarely, occur with the administration of unfractionated heparin in pregnancy, but has not been described with the use of low molecular weight heparin in pregnancy.

Other causes of thrombocytopenia
These are rare and include constitutional thrombocytopenias and those due to haematological malignancy.

**Fetal and neonatal thrombocytopenia**
This topic deserves a separate review; however, it needs to be emphasised that thrombocytopenia in pregnancy affects the fetus.

The reduction in neonatal platelet count that can occur in maternal ITP has already been described. Infections of the fetus can also lead to a reduced platelet count. A serious cause of fetal and neonatal thrombocytopenia is fetal and neonatal alloimmune thrombocytopenia (FNAIT). In this condition the maternal platelet count is usually normal, but antigens on the fetal platelets that are not present on the maternal platelets cause the development in the mother of antibodies that cross the placenta to destroy fetal platelets. This is the platelet equivalent of rhesus haemolytic disease of the newborn. Intracranial haemorrhage is a devastating consequence of the condition; a large literature review identified its occurrence in 26% of cases. Approximately 80% of the haemorrhages occur before birth, 14% before 20 weeks of gestation. Prompt recognition of FNAIT in the neonate and treatment with appropriate matched platelets improve outcome. Counselling of parents regarding recurrence should be undertaken. Various antenatal management regimens are in use, none of which are ideal. These include high doses of intravenous immunoglobulin with or without prednisolone (0.5 g/kg), or serial fetal platelet transfusions.
References


