Review Article

Thrombocytopenia in pregnancy

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Introduction

Thrombocytopenia is defined as a platelet count of less than 150 x 10^9/l. Normal pregnancy is generally thought not to affect the platelet count, but it has been suggested that the normal range is lower in pregnancy, and that the count falls in the third trimester. This review concentrates on causes of thrombocytopenia with particular reference to pregnancy: most of these involve excessive platelet consumption (Table I).

Failure of platelet production

Demand for folic acid rises to 300–400 µg/day in normal pregnancy, and dietary deficiency may cause thrombocytopenia, particularly where demand is increased by multiple pregnancy, or by an underlying haemolytic state. Combined iron and folate supplements usually provide 350 µg of folate daily.

Aplastic anaemia and paroxysmal nocturnal haemoglobinuria, although rare, do occur in young women, and there is anecdotal evidence for an association of both with pregnancy. Colvin reviews other coincidental causes, such as congenital thrombocytopenias, and malignancies.

Excessive platelet consumption

This is observed in idiopathic (auto-immune) thrombocytopenia (ITP), pre-eclampsia/eclampsia, disseminated intravascular coagulopathy (DIC), and thrombotic thrombocytopenia purpura (TTP). Accelerated platelet activation and consumption characterize normal pregnancy, which may partly explain the common finding of mild thrombocytopenia (platelets 100–150 x 10^9/l), known as pregnancy-associated (PAT), gestational asymptomatic or incidental thrombocytopenia.

Idiopathic thrombocytopenic purpura

Chronic ITP is a common auto-immune disorder in young women. Platelet-associated IgG (PAIgG) is detected in over 90% of cases, and circulating anti-platelet antibodies in about 50%. These are not specific for ITP, however, occurring also in pre-eclampsia, PAT, and possibly in normal pregnancy. In 95% of cases the antibody class is IgG, and 90% of these are IgG, which can cross the placenta. The antibodies are often directed against glycoproteins IIb, IIIa or Ib. ITP may complicate 20% of pregnancies in women with systemic lupus erythematosus (reviewed by de Swiet), and may be the presenting feature in 5–10% of cases of human immunodeficiency virus (HIV) infection.

Management must address the possibility of fetal involvement. Anti-platelet IgG may cross the placenta and cause thrombocytopenia, which if severe (less than 50 x 10^9/l) carries a high risk of

Table I Causes of thrombocytopenia in pregnancy

<table>
<thead>
<tr>
<th>Reduced production</th>
<th>Congenital</th>
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<tr>
<td>Precursor deficiency</td>
<td>Malignancy</td>
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<tr>
<td>Marrow failure</td>
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<tr>
<td>M</td>
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<td>F</td>
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Increased consumption

| Idiopathic (auto-immune) thrombocytopenia | M, F |
| Pre-eclampsia/eclampsia                  | M    |
| Thrombotic thrombocytopenic purpura       | M    |
| Disseminated intravascular coagulopathy  | M    |
| Drugs including heparin                  | M    |
| Alloimmune thrombocytopenia              | F (M)|

M = disease process causes thrombocytopenia in mother;
F = disease process causes thrombocytopenia in fetus.

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intra-cranial haemorrhage during vaginal delivery.\textsuperscript{21} Thirty to 40\% of infants of women with ITP have platelets of less than $100 \times 10^9$/l, and 5–20\%, less than $50 \times 10^9$/l.\textsuperscript{14,22,23} (Earlier reports cited a higher incidence of affected infants\textsuperscript{24,25}). The risk remains similar for subsequent pregnancies. Management therefore depends on whether the fetus is affected, whether antenatal treatment is effective, and which method of delivery is safer.

Treatment of the mother should aim to prevent bleeding, by maintaining a platelet count of over $20 \times 10^9$/l,\textsuperscript{26} and up to $50–100 \times 10^9$/l for delivery.\textsuperscript{27,28} Monitoring the bleeding time (which tends to be disproportionately short for the platelet count in ITP, because the platelets are young and reactive) may help reduce unnecessary therapy.\textsuperscript{28} Corticosteroids (1 mg/kg/day, reducing to a maintenance dose as soon as possible) remain first line treatment, but should be used cautiously, because of a risk of precipitating pre-eclampsia, and of adrenal suppression affecting fetal development;\textsuperscript{26} and immuno-suppression should be avoided.\textsuperscript{6,26,27,29} Second trimester splenectomy proved hazardous, and has largely been discontinued.\textsuperscript{30,31}

Intravenous IgG (i.v. IgG: 0.4 g/kg body weight/day for 5 days) was first noted to be effective in childhood ITP in 1981.\textsuperscript{32} Treatment is followed by a consistent rise in the platelet count in almost all patients, which lasts for 2–4 weeks, so delivery can usually be covered by a course of i.v. IgG given at about 38 weeks.\textsuperscript{6} The main drawback is cost. Improved supportive care, i.v. IgG and platelet transfusions for severe bleeding and emergency surgery have reduced maternal risk considerably.\textsuperscript{26}

The fetal platelet count is not predicted by the maternal platelet count, PAIgG, nor presence of circulating antibodies,\textsuperscript{11,15,33,34} and discordant twin pregnancies may occur,\textsuperscript{25} but a history of ITP indicates a significant risk of fetal thrombocytopenia.\textsuperscript{9,14,15} That previous splenectomy has particular significance\textsuperscript{35} is now doubtful.\textsuperscript{23,33,34} The absence of circulating antibodies may predict a very low risk of fetal thrombocytopenia,\textsuperscript{14,36} but there are frequent exceptions, and consistent results are difficult to obtain.\textsuperscript{9}

Attempts to treat the affected fetus have been disappointing. Maternal corticosteroids do not consistently reduce the incidence of fetal thrombocytopenia.\textsuperscript{37,38} Thrombocytopenic infants have been born to mothers whose counts have responded to i.v. IgG pre-delivery.\textsuperscript{39,40} Placental transfer of IgG requires an intact Fc portion, and may take 3 weeks to equilibrate.\textsuperscript{41}

Therefore, at present, there is no effective ante-natal treatment, although some advocate steroids.\textsuperscript{42} The fetal platelet count can be measured directly by fetal scalp blood sampling early in labour,\textsuperscript{24,33,43} or by percutaneous umbilical blood sampling (PUBS).\textsuperscript{11,22,44} The former may be technically impossible, or give falsely low counts.\textsuperscript{23,45,46} PUBS at term appears safe in experienced hands.\textsuperscript{11,22,44} Current treatment options do not justify the increased risks earlier in pregnancy. If the fetal platelet count is below $50 \times 10^9$/l, delivery should be by Caesarean section.\textsuperscript{11,25–28,43} and emergency facilities for this must be available.\textsuperscript{44} The infant’s platelet count often falls further during the first week post-natally, requiring monitoring, and possibly treatment.\textsuperscript{47}

**Pregnancy-associated thrombocytopenia**

Women with asymptomatic thrombocytopenia in pregnancy and platelet counts rapidly returning to normal post-delivery probably have PAT, with a low incidence of fetal complications. PAT is common: in recent series the incidence was 0.4–8.3\%, or more.\textsuperscript{2,10,12,14,15} The platelet count is usually $100–150 \times 10^9$/l, although it may be as low as $50 \times 10^9$/l, and falls slowly.\textsuperscript{2} The fetus is not at risk: none of 330 infants had platelets of less than $50 \times 10^9$/l. The problem is to distinguish PAT from chronic ITP, in order to avoid unnecessary intervention. Laboratory tests are not conclusive, so eliciting a past history of ITP is very important.

Therefore, for all women with a history of ITP predating pregnancy,\textsuperscript{9,14,15} whatever their current count, and probably for women with platelets below an arbitrary number, perhaps $75 \times 10^9$/l, who are more likely to have ITP,\textsuperscript{2,14} corticosteroids and/or i.v. IgG should be used to achieve haemostasis in the mother. A fetal platelet count obtained immediately pre-delivery, and obstetric considerations, should determine the method of delivery.

If there is no history of ITP, and particularly if the maternal count exceeds $100 \times 10^9$/l, there is little risk of a thrombocytopenic infant, and invasive sampling is not necessary.\textsuperscript{9,11,14}

**Alloimmune thrombocytopenia**

This is discussed to compare and contrast it with ITP. About 2\% of women are negative for common platelet antigens, such as PLA\(_1\) (Zwa), and may develop antibodies against the paternally derived antigen on fetal platelets (analogous to Rhesus haemolytic anaemia).\textsuperscript{48} Unlike ITP, the woman is unaffected, unless she develops thrombocytopenia and ‘post-transfusion purpura’ following blood transfusion,\textsuperscript{49} but her fetus may be severely thrombocytopenic. Delivery should be by Caesarean section in known cases,\textsuperscript{50} but management is complicated by increasing recognition of antenatal intracranial bleeds,\textsuperscript{50–52} and because the first child is affected in 50\% of cases,\textsuperscript{53} with severity tending to increase with subsequent pregnancies. PUBS
and in utero platelet transfusions, with PlA1 negative platelets, have been advocated, as has maternal i.v. IgG and antenatal screening for PlA1, to detect women at risk. A woman with a previous affected pregnancy should be managed at a major centre. Management of the thrombocytopenic neonate is discussed by Mueller-Eckhardt.

Pre-eclampsia and pregnancy-induced hypertension

Thrombocytopenia occurs in 17–50% of pre-eclamptic women and may precede the development of hypertension, or occur without it. There is increasing evidence of the pivotal role of platelets in the development of pre-eclampsia and intra-uterine growth retardation, and of the effectiveness of anti-platelet agents in preventing these. Platelet lifespan is reduced, and activation increased as shown by raised beta-thromboglobulin levels. Changes in platelet calcium flux may be detectable as early as the first trimester in women who later develop pre-eclampsia. Overt DIC is uncommon, and standard coagulation assays are usually normal, but platelet dysfunction may be reflected by a prolonged bleeding time.

The treatment for progressive pre-eclampsia, including thrombocytopenia, remains delivery, and the thrombocytopenia then rapidly resolves. The ongoing CLASP trial should determine whether low-dose aspirin can prevent pre-eclampsia, which would represent a major advance in managing this problem.

The HELLP syndrome (haemolysis, elevated liver function tests, low platelet counts) is a serious complication of pre-eclampsia, affecting about 8.5% of severe pre-eclamptics, and perinatal mortality may approach 50%. It is vital to recognize the syndrome, even in the absence of marked hypertension, as recovery may necessitate immediate delivery, despite fetal immaturity. Following delivery, the illness resolves rapidly. Close monitoring of a stable patient may allow fetal maturation.

Infants of pre-eclamptic women are unlikely to be thrombocytopenic, except when they have other complications of prematurity.

Thrombotic thrombocytopenic purpura – haemolytic uraemic syndrome

TTP is rare, and the cause is unknown. The pentad of features (fever, neurological disturbances, renal impairment, thrombocytopenia and microangiopathic haemolytic anaemia) is due to intravascular platelet clumping. The closely related haemolytic uraemic syndrome usually presents postnatally with acute renal failure. TTP has been linked to pregnancy, and oral contraceptive medication, and there may also be an association with HIV.

Prior to 1980 the disease was usually fatal, but prompt delivery did not affect the outcome, but two recent series with a total of 210 patients report successful treatment of 71% and 91% of cases respectively. The most effective treatment was plasma exchange with fresh frozen plasma (FFP) replacement, ± high dose prednisone. Nine pregnant women presented with TTP in the third trimester; they all survived and delivered unaffected babies, and five subsequently had normal pregnancies. A high molecular weight fraction of FFP, requiring smaller infusion volumes, may also be useful. Platelet transfusions are contra-indicated.

Disseminated intravascular coagulopathy

Obstetric problems are important causes of DIC, which may complicate placental abruption, pre-eclampsia, intra-uterine death or infection, uterine rupture and amniotic fluid embolism. Management is that of the underlying cause, with supportive therapy, including platelet and factor replacement as required. Heparin is advocated in cases where the vascular tree is intact, such as amniotic fluid embolism and the chronic DIC accompanying retention of a dead fetus. Heparin is also important in the prevention of gangrene in the rare and serious post-partum complication of Gram-negative septicaemia and DIC, purpura fulminans.

DIC and thrombocytopenia are also features of acute fatty liver of pregnancy. The maternal and fetal mortality (both around 80%) in this rare syndrome appear reduced by prompt delivery, and so recognition of impending hepatic and renal failure in the third trimester is vital.

Heparin

In 0.6–9% of patients, heparin induces anti-platelet IgG, which can cause thrombocytopenia and thrombosis, often arterial, due to complement-mediated platelet activation. This action is heparin-dependent, and as heparin does not cross the placenta, the fetus is not affected. It occurs 7–14 days after the initiation of heparin therapy, and can complicate even low-dose therapy, with significant mortality and risk of amputation. If heparin is unavoidable, heparin from a different source may be safer.

Thrombocytopenia during pregnancy has also been reported as complicating mild type IIb von Willebrand’s disease, and chorioangioma of the placenta, and as spurious due to EDTA-induced platelet clumping.
guish serious causes from benign PAT, and to manage the mother and fetus appropriately.

Conclusion
Thrombocytopenia is a common finding in pregnancy, and careful diagnosis is important to distin-

References


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