Bleeding disorders in pregnancy

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Abstract

During pregnancy the physiological changes in the haemostatic system tend to improve mild inherited bleeding disorders. However, thrombocytopenia and coagulation problems unique to pregnancy may occur. In this review, we discuss and provide recommendations for the management of bleeding problems seen in pregnancy, such as thrombocytopenia, von Willebrand disease, haemophilias and thrombotic microangiopathies. In the majority of cases complicated by haematological disease, pregnancy, delivery, and the puerperium should be managed by a multidisciplinary team, which includes obstetricians, haematologists and obstetric anaesthetists.

Keywords bleeding; haemorrhage; postpartum haemorrhage; thrombocytopenia antepartum

Introduction

Within the circulatory system, blood must flow normally and yet if vessels are damaged it must form a clot quickly to restrict excessive bleeding. Due to the competing demands of flow and haemostasis, the coagulation system is necessarily complex. Table 1 provides an aetiological division of bleeding disorders.

Pregnancy results in increased levels of fibrinogen, factors VII, VIII, IX, X and XII, and von Willebrand factor. It also results in decreased levels of factor XI and protein S. Together, these changes lead to a prothrombotic state. Thus, most inherited bleeding disorders tend to improve during pregnancy but worsen immediately afterwards as the haemostatic system reverts quickly to the non-pregnant state. An altered fibrinolytic state is part of a normal physiological response to pregnancy due to an increase in the fibrinolytic inhibitors PAI-1 and PAI-2 and tissue plasminogen activator (t-PA).

We review the management of bleeding disorders in pregnancy and the puerperium. Thrombocytopenia is discussed first, then the thrombotic microangiopathies, and the last part of the review will deal with the most common inherited bleeding disorders and acquired haemophilia.

Thrombocytopenia in pregnancy

Thrombocytopenia is a common finding in pregnancy, occurring in 7–10% of pregnancies (Table 2). 75% of cases are due to

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Causes of bleeding disorders in pregnancy

Platelets

Thrombocytopenia

- Failure of production
  - Decreased megakaryocyte mass —radiation, chemicals, drugs; intrinsic bone marrow abnormalities (aplastic anaemia, leukaemia, myelofibrosis, myelodysplastic syndrome, etc); replacement of bone marrow with carcinoma cells (plasma cells, etc)
  - Ineffective thrombopoiesis —megaloblastic anaemias (B12, folic acid deficiency)
- Increased destruction
  - Immune mechanisms: autoimmune thrombocytopenic purpura (ITP); autoimmune diseases (lupus erythematosus)
  - Splenomegaly (usually secondary to liver disease)
  - Microangiopathies (PET, HELLP, DIC, TTP)
- Pregnancy directly related
  - Acute fatty liver
  - Gestational thrombocytopenia
- Dilutional/uncertain
  - HIV

Platelet dysfunction

- Hereditary
  - Disorders of platelet adhesion (Bernard–Soulier syndrome)
  - Disorders of platelet aggregation (thromboasthenia, Glanzmann)
  - Disorders of platelet secretion (a granule deficiency—Grey platelet syndrome, dense granule deficiency —delta storage pool deficiency, aspirin- like disorders)
  - Disorders of platelet procoagulant activity (Scott syndrome)
- Acquired
  - Drugs—aspirin and other NSAIDs; alcohol, antibiotics (carbenicillin, penicillin, moxalactam, third-generation cephalosporins)
  - Other—uraemia, liver disease, heart bypass surgery, haematological malignancies, myeloproliferative disorders, leukaemia, etc)

Vessel wall

- Drugs (chronic glucocorticoid use, penicillins, sulphonamides)
- Vitamin C deficiency
- Paraproteinaemia
- Henoch–Schönlein purpura and other vasculitis
- Hereditary defects
  - Hereditary haemorrhagic telangiectasia
  - Ehlers–Danlos syndrome

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Table 1 (*continued*)

Coagulation

- Acquired causes
- Inherited causes
- Vitamin K antagonism/deficiency
- Liver disease
- Anticoagulation therapy
- Disseminated intravascular coagulation
- Factor inhibitors
- Factor deficiencies (von Willebrand disease, haemophilia A and B, rare —FXI, FVII, FX, prothrombin deficiency, fibrinogen deficiency/dysfunction)

Table 1

Causes of thrombocytopenia in pregnancy

Pregnancy-related	Other
Gestational (or incidental, 75%)	Spurious (EDTA-induced platelet aggregation) send a citrate sample to exclude this Pre-eclampsia (PET)
Pre-eclampsia (PET)	Autoimmune (immune thrombocytopenic purpura,drug-induced, systemic lupus erythematosus, antiphospholipid syndrome)
Haemolysis, elevated liver enzymes and low platelet (HELLP syndrome)	Viral, e.g. HIV, EBV, CMV von Willebrand type IIB disease
Disseminated intravascular coagulation	Haemolytic uraemic syndrome/ thrombotic thrombocytopenic purpura
Acute fatty liver	Congenital/marrow disease/ hypersplenism/liver disease
Folate deficiency	Drugs (not low molecular weight heparins)

Table 2

gestational thrombocytopenia (GT), 15—20% are due to thrombotic microangiopathies (in particular associated with hypertensive disorders of pregnancy), 3—4% are due to immune causes, and <1% are due to other rare causes including constitutional thrombocytopenias, infection, and malignancy.

Gestational thrombocytopenia

The platelet count in pregnancy is generally lower than the non-pregnant state. In 5—8% of all pregnancies, the platelet count at term is below the normal range (150—400 $\times$ 10^9/L). In gestational thrombocytopenia (GT) platelet counts are typically >70 $\times$ 10^9/L, with about two-thirds just below the normal lower limit, between 130 $\times$ 10^9/L and 150 $\times$ 10^9/L. It is exceptional for the platelet count to fall below 80 $\times$ 10^9/L but in rare cases, subsequently confirmed as GT, counts may be as low as 50 $\times$ 10^9/L.

The cause of GT remains uncertain, but the dilutional effect on platelet mass of expanded plasma volume in pregnancy and possibly accelerated destruction of platelets when passing over trophoblasts contribute to the aetiology.

Characteristically GT:

- is mild and asymptomatic;
- is not associated with past non-pregnant medical history of thrombocytopenia in the mother;
- occurs late in pregnancy (second trimester, more pronounced in labour);
- is not associated with fetal thrombocytopenia;
- is not associated with maternal or neonatal haemorrhage;
- resolves spontaneously after delivery (within 7 days—6 weeks postpartum
  - may recur with subsequent pregnancies
- does not affect bleeding times, unless the platelet count falls below 80 $\times$ 10^9/L.

It should be remembered that although fibrinogen is the end point of the coagulation cascade, and directly responsible for fibrin production, it is also the main ligand for platelet aggregation. Thus the increased fibrinogen levels in pregnancy allow pregnant women to tolerate lower platelet counts than non-pregnant women.

Immune thrombocytopenic purpura

Immune thrombocytopenic purpura (ITP) is due to the formation of autoantibodies, usually IgG, against platelet surface glycoproteins, especially glycoproteins Ib—IX and IIb—IIIa, causing their premature destruction by the reticuloendothelial system. The incidence of ITP in the general adult population is 6.6 per 100 000, with 1—5 cases per 10 000 pregnancies. ITP is around 100 times less common than GT in pregnancy. ITP is rarely associated with systemic lupus erythematosus, human immunodeficiency virus (HIV), or drugs.

Due to the increased platelet turnover, the residual platelets are young and more haemostatically active; therefore, the patients rarely bleed and cerebral haemorrhage occurs in less than 1%. In the last 30 years no maternal deaths have been reported due to ITP in the UK, and maternal morbidity is minimal if appropriate therapy is administered during pregnancy and childbirth.

Usually the clinical problem is differentiating GT from ITP (Table 3). This has minor clinical importance for the mother, but is essential for the fetus. Due to the transplacental passage of antibody, ITP may rarely cause thrombocytopenia in the fetus, whereas GT does not. Neonatal thrombocytopenia occurs in up to 14% of pregnancies complicated by ITP: 7.5% have severe thrombocytopenia with platelet counts <50 $\times$ 10^9/L. Furthermore, 4% have platelet counts <20 $\times$ 10^9/L, and are therefore at

Distinguishing immune thrombocytopenic purpura (ITP) from gestational thrombocytopenia (GT)

	GT	ITP
Time of presentation	> Second trimester	From first trimester
Platelet count	>70—80$\times$$10^9$	More severe
Neonatal thrombocytopenia	No	Possible
Resolution after delivery	Yes	No/yes
Platelet size	Normal	Normal/big
Antiplatelet antibodies	No/yes	Yes/no

Table 3

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