Haematology of pregnancy

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Abstract

The physiological changes that occur during pregnancy, to meet the needs of the developing fetus, can lead to complications in vulnerable patients.

Close proximity of fetal and maternal circulations enables effective transfer of nutrients and oxygen but passage of certain substances can also have disastrous consequences for mother or baby. For example, teratogenicity may arise from maternal drugs, and fetal antigenic material passing into the maternal circulation may cause maternal alloimmune sensitization syndromes. Iron deficiency and lack of other haematinics may result from increased demand. The massive increase in uterine blood flow and vascular compliance, necessary to maintain the blood supply for the developing fetus, can lead to significant haemorrhage at the time of placental separation. Changes in coagulation factors help to combat this risk but increase the potential for systemic thromboembolic events. Women with pre-existing haematological disease may be at particular risk during pregnancy or the pregnancy may be compromised by the underlying state. Whilst the majority of pregnancies progress without complication, management of high-risk cases should be coordinated in joint obstetric haematology clinics.

Keywords anaemia; haematology; haemolytic disease; neonatal alloimmune thrombocytopenia; pregnancy; sickle; thrombocytopenia; thrombophilia; venous thromboembolic disease

Anaemia

In pregnancy there is an increase in red cell mass of 25% but a fall in haemoglobin concentration due to a proportionally greater expansion (50%) of plasma volume. This gives rise to the physiological anaemia of pregnancy, which is maximal at 32 weeks.

Iron deficiency

The total iron requirements of pregnancy exceed 1000 mg;[1] this exhausts most women's iron stores. The consequences of iron deficiency include fatigue, reduced resistance to infection, cardiovascular stress, poor tolerance to blood loss at delivery, and an increased need for transfusion. Iron deficiency may also increase the risk of intrauterine growth restriction, premature membrane rupture and early delivery.

Diagnosis is difficult as serum ferritin increases throughout pregnancy and the usual microcytosis can be masked by the physiological increase in mean cell volume (MCV) of 5–10 fl. A trial of oral iron supplementation is often helpful. Absorption is optimized by administration with vitamin C 1 hour before food. True iron malabsorption is unusual and the most common indications for parenteral iron are non-compliance and intolerance. Some studies have advocated universal iron supplementation[2] in pregnancy, but others have questioned the value of this approach.

Folate and vitamin B_{12} deficiency

Folate requirements increase in pregnancy as nucleic acid formation escalates. Folic acid supplements (400 μg daily) must be given in the first trimester to reduce the risk of neural tube defects in the fetus. A co-existing iron deficiency can mask the increased MCV of folate deficiency, requiring evaluation of the blood film to aid diagnosis. Although vitamin B_{12} concentration falls in pregnancy, this usually represents a dilutional effect and an increase in binding globulin, rather than a true tissue deficiency; the concentration returns to normal post-partum without treatment.

Haemoglobinopathies

Screening for haemoglobinopathies must be carried out as early as possible, to allow genetic counselling and prenatal diagnosis if the offspring is at risk of major haemoglobinopathy. Screening should be in accordance with the NHS Sickle Cell and Thalassaemia Screening Programme, using the family origin questionnaire, routine blood cell indices and tests for sickle cell and other haemoglobin (Hb) variants, depending on the risks identified and the prevalence of the local population. Affected mothers will need close multidisciplinary management to support their pregnancy.

Sickle cell disease

Women with sickle cell anaemia and other haemoglobin combinations giving rise to sickle cell disease (such as HbSC, HbSβ-thalassaemia, HbSD, HbSE and HbSO-Arab) have a very high morbidity risk, with more than half experiencing acute painful crisis and a quarter requiring peripartum admission to intensive care.[3]

In addition to sickle cell crisis and chest syndrome, maternal complications include severe anaemia, infection – especially urinary and respiratory[4,5] – hypertension and thromboembolic events. Fetal risks are also higher and include miscarriage, growth restriction, stillbirth and prematurity.

Women should be counselled preconceptually about potential problems, screened for end-organ damage and offered an opportunity to discuss the plan for management. General crisis prevention measures include avoidance of cold, dehydration[5,6] and over-exertion. Compliance with folate supplements (5 mg) and continuation of prophylactic antibiotics should be emphasized along with the need for prompt treatment of infection. Aspirin is recommended from 12 weeks' gestation to reduce the risk of pre-eclampsia.[7] Non-steroidal anti-inflammatory drugs (NSAIDs) should only be used between 12 and 32 weeks' gestation.[8] Hydroxycarbamide, which increases fetal haemoglobin (HbF) and therefore reduces the HbS percentage, is teratogenic and should be stopped 3 months before conception.[8]

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Routine top-up or exchange transfusion may be useful in reducing painful crises but has not been shown to affect overall outcome. Transfused blood should be negative for HbS and cytomegalovirus (CMV) as well as fully Rh phenotyped[8,9] to reduce the development of alloantibodies.

Venous thromboembolic disease

Pregnancy is a prothrombotic state with a 10-fold increased risk of venous thromboembolic disease (VTE) in the antenatal period,[10,11] increasing to 25-fold in the post-partum period. In addition to venous stasis due to reduced vascular tone and the pressure from the gravid uterus, the haemostatic system undergoes several changes in preparation for delivery:

- increased coagulation factors, including VII, VIII, fibrinogen and vWF (von Willebrand factor)
- reduction in anticoagulation activity, including a decrease in free protein S concentration and an increased resistance to activated protein C
- increased concentration of inhibitors of fibrinolysis.

Management of acute VTE in pregnancy

Objective diagnosis is crucial but difficult, as there is a progressive elevation in D-dimer concentration with pregnancy and a need to avoid potentially harmful imaging techniques. Once VTE is suspected, unless there are major contraindications, treatment should be given until the diagnosis is excluded.[10] Meta-analysis has shown low-molecular-weight heparin (LMWH) to be at least as effective as unfractionated heparin, with a reduced risk of bleeding.[10] The Royal College of Obstetricians and Gynaecologists (RCOG) guidelines advise a twice daily dosing regimen[10] to minimize peak and trough concentrations. Anti-Xa activity should be measured if there is renal impairment or extreme body weight. Treatment should continue for at least 3 months and until at least 6 weeks post-partum.[10] Warfarin should be avoided as it is a teratogen, affecting facial, skeletal and nervous system development.

Prevention of VTE

All women should be risk assessed at booking and throughout the pregnancy and post partum period. A personal history of unprovoked or oestrogen-related venous thrombosis is a significant risk factor.[12] Other risks include a family history of unprovoked thrombosis, thrombophilia, age greater than 35 years, multiparity, obesity and immobilization.[11,13]

The most common inherited thrombophilias are heterozygosity for either factor V Leiden (FVL) or prothrombin gene mutation (PTGM), which account for up to 44 and 17% of cases, respectively. However, the relative risk (RR) of VTE is most marked with anti-thrombin (AT) deficiency, which has a relative risk of 119 compared to 6.9 and 9.5 for heterozygosity for FVL and PTGM, respectively.[14]

There is no role for routine thrombophilia screening but this may be indicated if the result would justify a change in management (i.e. provision of pharmacological thromboprophylaxis).

If required, testing should include:

- antithrombin concentration
- protein C concentration
- polymerase chain reaction (PCR) for FVL and PTGM. The genetic test for FVL is preferable to a phenotypic test for activated protein C resistance as the latter is affected by the physiological changes to the coagulation system in pregnancy
- anti-phospholipid syndrome (APS) screen (only if there is a personal history of VTE).

Protein S concentration falls in pregnancy and should be tested after 3 months post-partum.

Management of at-risk pregnancies includes advice on general deep vein thrombosis (DVT) prevention, including leg care, compression stockings, mobilization and hydration, along with prophylactic LMWH as indicated.

The duration of LMWH depends on the cumulative inherited and acquired risk factors. Some women may require treatment only in the post partum period but if antenatal thromboprophylaxis is indicated this should start as soon as the pregnancy is confirmed as studies have shown that thrombotic risk is elevated in all trimesters.

Anti-phospholipid syndrome

Anti-phospholipid syndrome (APS) is an autoimmune disorder and an acquired thrombophilic state. The clinical features vary significantly but include placental insufficiency, recurrent fetal loss, thrombocytopenia and thrombotic events, both arterial and venous. Definitions for pregnancy morbidity include:

- three or more unexplained consecutive spontaneous abortions at less than 10 weeks' gestation
- one or more unexplained death of a fetus at 10 weeks' gestation or longer.[15]

Laboratory testing includes detection of anti-cardiolipin antibodies, a lupus anticoagulant or antibodies to β_2-glycoprotein, on two or more occasions distant from the clinical event and more than 12 weeks apart. The use of aspirin and prophylactic LMWH in pregnancy has improved the rates of live birth from 10 to 70%.[16]

Prosthetic heart valves and pregnancy

Anticoagulation for prosthetic heart valves is one indication for continuing warfarin throughout pregnancy, but the potential for teratogenic effects, especially with doses greater than 5 mg a day during weeks 6–9, must be considered. An alternative option is to switch to therapeutic LMWH,[17] either for the duration of pregnancy or for the period up to 14 weeks and after 36 weeks. Monitoring with anti-Xa concentration is required. Joint management between haematology, obstetrics and cardiology, is essential along with full pre-pregnancy counselling.

Bleeding disorders

Inherited

Pregnant women with von Willebrand's disease (vWD) or carriers of haemophilia have an increased risk of bleeding. Factor VIII[18] and vWF increase from 6 to 8 weeks' gestation, reaching levels of three- to fivefold baseline by term. Whilst this provides protection for delivery for women with haemophilia A carrier status and most cases of vWD, they remain vulnerable in early pregnancy and in the puerperium, when levels may fall abruptly. DDAVP (desmopressin) can be used to cover first-trimester procedures and the post-partum period. Oral tranexamic acid is useful to prevent excessive post partum bleeding. Factor IX level does not change in pregnancy and women with a low factor IX

