Haematology of pregnancy

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Abstract

Women with haematological disease may be at particular risk during pregnancy as the two conditions can mutually impact on each other. The physiological changes that occur during pregnancy to meet the needs of the developing fetus can lead to complications in vulnerable patients. For example, 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. Close proximity of the fetal and maternal circulations enables an effective transfer of nutrients and oxygen; however, passage of certain substances such as maternal drugs can have disastrous consequences for the baby, and passage of fetal antigenic material into the maternal circulation can cause alloimmune sensitization. The growing fetus has an increased demand for iron and other haematinics so maternal deficiencies can arise. Although most pregnancies progress without complication, management of high-risk cases should be coordinated in joint obstetric haematology clinics.

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

Key points

- Women with haematological disease can be at particular risk during pregnancy as the pregnancy can be compromised by the underlying state and/or the haematological condition worsened by the pregnancy. Although most pregnancies progress without complication, management of high-risk cases should be coordinated in joint obstetric haematology clinics and involve anaesthetists, neonatologists and other specialists where relevant
- Iron deficiency is the most common cause of anaemia in pregnancy. A trial of oral iron supplementation is helpful in the presence of anaemia, defined by a haemoglobin <110 g/litre in the first trimester, <105 g/litre in the second and third trimesters and <100 g/litre in postpartum period
- All women should have a risk assessment for venous thromboembolism at booking and throughout pregnancy and the postpartum period
- Maternal haemorrhage remains a significant cause of maternal mortality and morbidity
- Haemolytic disease of the newborn is caused by transplacental passage of maternal alloantibodies against fetal paternally derived red cell antigens, the mother having been sensitized by previous transfusion or pregnancy

Anaemia

In pregnancy there is an increase in red cell mass and plasma volume. The increase in plasma volume is proportionally greater and results in a fall in haemoglobin. 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, exhausting 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 can also increase the risk of intrauterine growth restriction, premature membrane rupture and early delivery.

Diagnosis is difficult as the microcytosis typically associated with iron deficiency anaemia can be masked by the increase in mean cell volume of 5–10 fl in pregnancy. A trial of oral iron supplementation is often helpful in the presence of anaemia, defined by a haemoglobin less than 110 g/litre in the first trimester, less than 105 g/litre in the second and third trimesters and less than 100 g/litre in the postpartum period.[1] True iron

Please cite this article in press as: Robinson S, et al., Haematology of pregnancy, Medicine (2017), http://dx.doi.org/10.1016/j.mpmed.2017.01.002

malabsorption is unusual, and the most common indications for intravenous iron are non-compliance with and intolerance to oral treatment. Some studies have advocated universal iron supplementation 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 mg daily) must be given in the first trimester to reduce the risk of neural tube defects in the fetus. A coexisting iron deficiency can mask the increased mean cell volume of folate deficiency, requiring evaluation of the blood film to aid diagnosis. Vitamin B_{12} requirements also increase, with deficiency being associated with neural tube defects, preterm labour, intrauterine growth retardation (IUGR) and recurrent miscarriage.

Establishing vitamin B_{12} status during pregnancy is complicated by physiological changes such as haemodilution caused by the expanded blood volume, altered renal function, alterations in B_{12} binding proteins and transfer of maternofetal vitamin B_{12}. Serum vitamin B_{12} assays measure the sum of inactive and active B_{12}. Other markers of B_{12} status are also available and are increasingly being adopted as a way to measure functional vitamin B_{12}: holotranscobalamin ('active vitamin B_{12}'), the only form of vitamin B_{12} presented for cellular uptake and used to satisfy metabolic demand; and methylmalonic acid, a by-product of methylmalonyl-CoA metabolism, the serum concentration of which correlates inversely with tissue vitamin B_{12} utilization.

Haemoglobinopathies

Screening for haemoglobinopathies must be carried out as early as possible, to offer 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 variants, depending on the risks identified and the prevalence of the local population. Affected mothers need close multidisciplinary management to support their pregnancy.

Sickle cell disease

Women with sickle cell anaemia and other haemoglobin (Hb) combinations giving rise to sickle cell disease (e.g. HbSC, HbSβ-thalassaemia, HbSD, HbSE, HbSO-Arab) have a high morbidity risk: more than half experience acute painful crisis, and a quarter require peripartum admission to intensive care. In addition to sickle cell crisis and chest syndrome, maternal complications include severe anaemia, infection, especially urinary, hypertension, pre-eclampsia and thromboembolic events. Fetal risks are also higher and include growth restriction, stillbirth and prematurity.

Women should be offered an appointment before conception to screen for end-organ damage, discuss potential complications and offer a management plan. General crisis prevention measures include avoidance of cold, dehydration and overexertion. Compliance with folate supplements (5 mg daily) and continuation of prophylactic antibiotics should be emphasized, along with the need to treat infection promptly and present early in the event of vaso-occlusive crisis. Aspirin is recommended from 12 weeks' gestation to reduce the risk of pre-eclampsia.[2] Non-steroidal anti-inflammatory drugs should only be used between 12 and 32 weeks' gestation. Hydroxycarbamide, which increases fetal haemoglobin (HbF) and therefore reduces the HbS percentage, is teratogenic and should be stopped 3 months before conception.

Routine top-up or exchange transfusion can be useful in reducing painful crises but has not been shown to affect overall outcome. Transfused blood components should be rhesus-matched according to the extended phenotype as well as being negative for Kell-, HbS- and cytomegalovirus-.

Venous thromboembolic (VTE) disease

Pregnancy is a prothrombotic state with a 10-fold increased risk of VTE disease in the antenatal period, increasing to 25-fold in the postpartum period. In addition to venous stasis caused by reduced vascular tone and pressure from the gravid uterus, the haemostatic system undergoes several changes in preparation for delivery:

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

Management of acute VTE disease 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, treatment should be given until the diagnosis is excluded, unless there are major contraindications.[3]

Meta-analysis has shown low-molecular-weight heparin (LMWH) to be at least as effective as unfractionated heparin, with a reduced risk of bleeding. The Royal College of Obstetricians and Gynaecologists guidelines advise a twice-daily dosing regimen 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 postpartum. Warfarin should be avoided as it is a teratogen, affecting facial, skeletal and nervous system development.

Prevention of VTE disease

All women should be risk assessed at booking and throughout the pregnancy and postpartum period.[4] A personal history of unprovoked or oestrogen-related venous thrombosis is a significant risk factor. Other risks include a family history of unprovoked thrombosis, thrombophilia, age >35 years, multiparity, obesity and immobilization.

The most common inherited thrombophilias are heterozygosity for either factor V Leiden or the prothrombin gene mutation, which account for up to 44% and 17% of cases, respectively. However, the relative risk of VTE is most marked with antithrombin deficiency (119 versus 6.9 and 9.5 for heterozygous factor V Leiden and prothrombin gene mutation, respectively).

There is no role for routine thrombophilia screening but this might 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 for factor V Leiden

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