



Haematology of Pregnancy

Blood volume changes in pregnancy:

Both red cell mass and plasma volume increase during pregnancy. Since the increase in red cell mass is around 25%, well below the plasma volume increase of 40% (up to 55% in multiple pregnancies) the haemoglobin level falls, particularly between weeks 24 and 32 of pregnancy. This decrease in haemoglobin level occurs even when iron and folate stores are adequate, but is accentuated by deficiencies. The consequent decrease in blood viscosity facilitates placental perfusion. Women who do not exhibit a fall in haemoglobin during a pregnancy have a high incidence of complications such as pre-eclampsia and stillbirth, according to the Swedish Medical Birth Register¹.

Although 110g/l is commonly accepted as the lower limit of normal haemoglobin in pregnancy there are many patients in whom the haemoglobin falls as low as 95g/l without any deleterious effects or evidence of iron or folate deficiency.

Folate status at conception and in pregnancy:

It is now widely accepted that folate deficiency at conception is strongly correlated with neural tube defects. It is strongly recommended that all women take folate supplementation for 3 months prior to conception and throughout pregnancy. Women with a family history of neural tube defect, with diabetes or on anti-epileptiform drugs constitute a high risk group and require a daily 5 mg folate dose. For standard risk women the recommended folate supplement is 0.5mg daily. It should be noted that the standard Fefol tablet only contains 0.3mg of folate, well short of the recommended pre-conception intake.

In addition, since intolerance to the iron in Fefol may hinder compliance, it makes sense to prescribe folate alone initially, switching to a combined iron/folate preparation only if the serum ferritin is reduced.

Folate and Vitamin B12 metabolism in pregnancy:

A slight increase in mean red cell volume (MCV) may occur in normal pregnancy. However, an increase in MCV to over 105fl (given a normal range of 80-100fl) warrants assessment of red cell and serum folate and serum Vitamin B12 levels. Neutrophil hypersegmentation is not a reliable indicator of megaloblastic anaemia in pregnancy due to the tendency for a left shift to occur.

Decreased folate intake due to such causes as vomiting in pregnancy and malabsorption, combined with increased requirements at pregnancy, make folate deficiency a much more common cause of megaloblastic anaemia than Vitamin B12 deficiency. A fall in the inactive transcobalamin I during pregnancy results in a decrease in Vitamin B12 levels which does not accurately reflect either the active transcobalamin II or body stores, which on average last for 2 years. In fact the B12 levels may fall to 100pmol/l or even below without any functional disturbance of B12 metabolism. When the patient has a macrocytic anaemia, a balanced diet, normal folate levels but reduced Vitamin B12, it is worth checking serum homocysteine and urine methylmalonic acid (MMA) levels and anti-parietal cell and anti-intrinsic factor antibodies before giving empiric parenteral Vitamin B12. If genuine Vitamin B12 deficiency is confirmed investigation can then be undertaken at leisure once breast feeding has been completed.

Iron deficiency in pregnancy:

Iron deficiency accounts for 75% of anaemias of pregnancy. The markedly raised red cell mass, together with the requirements of the placenta and foetus necessitate a considerable increase in recommended daily iron intake of around 30mg daily, compared with 15mg daily in the non pregnant state. A serum ferritin estimation at the initial antenatal visit will help to determine whether iron supplementation will be needed and whether this should be taken as Fefol or equivalent or whether iron containing multivitamin preparations will suffice.

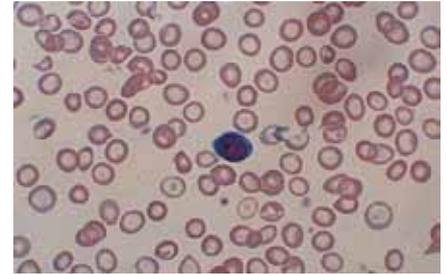


Fig.1 Iron deficient anaemia.

In the second half of pregnancy symptomatic iron deficiency, developing in the setting of intolerance to oral iron can be effectively treated with intravenous total dose infusion (TDI). These infusions are safe and effective but need to be given by experienced staff adhering to a strict protocol.

Additional important causes of a microcytic blood film (MCV<80fl) are thalassaemias/haemoglobinopathies. As thalassaemia trait may be masked by iron deficiency, it is important to check not only Hb electrophoresis and HbH bodies but also serum ferritin. This also avoids the unnecessary administration of iron supplementation to patients whose primary problem is not iron deficiency but thalassaemia. Checking the partner is important once a diagnosis of thalassaemia trait/haemoglobinopathy is confirmed so that genetic advice can be given promptly if appropriate.

Leucocytes in pregnancy:

The normal range of the leucocyte count increases with pregnancy, the upper limit extending from 11.0/nl to 15.0/nl. This increase is largely due to a neutrophilia, which may be accompanied by "toxic" granulation of neutrophils, and left shift with band forms, metamyelocytes and myelocytes. If any symptoms are present, infection, particularly of the urinary tract, needs to be considered. A more extreme left shift with the occasional promyelocyte and myeloblast is occasionally found in a normal pregnancy. The absence of symptoms, normal examination findings and normal platelet count together with serial blood films should allow exclusion of serious disease such as acute leukaemia.

Platelets in pregnancy:

In up to 10% of pregnancies mild thrombocytopenia supervenes after week 20. The platelet count rarely fails below 75/nl and pregnancy proceeds uneventfully. There is typically a history of similar mild thrombocytopenia with previous pregnancies but normal platelet count between pregnancies. For this reason the term gestational thrombocytopenia is usually applied. The baby's platelet count at birth is normal. Platelet antibodies are rarely found, but it remains likely that the transient thrombocytopenia is of autoimmune aetiology.

An autoimmune mechanism also accounts for most cases of severe isolated thrombocytopenia in pregnancy. Immune thrombocytopenia (ITP) which accounts for 5-10% of thrombocytopenias in pregnancy is important as the severity of the thrombocytopenia often posing major problems for pregnancy, delivery and for the baby. Systemic lupus erythematosus (SLE), the antiphospholipid syndrome (APS) and pre-eclampsia and its (HELLP) syndrome variant also need to be excluded. Platelet-specific antibodies are found in over 50% of patients with immune thrombocytopenia. However the presence or absence of antibodies does not correlate with severity. Bone marrow examination is usually noncontributory.

Typically, the platelet count falls, sometimes profoundly, as pregnancy progresses. In severe acute ITP high dose corticosteroid therapy and intravenous immunoglobulin may be required. In the most extreme cases splenectomy may be unavoidable, but can only be performed with acceptable safety to mother and foetus during the second trimester. In the milder acute ITP and in chronic ITP it may be possible to delay treatment until the last few weeks of pregnancy providing there is no active bleeding and the platelet count remains above 25/nl. In the last few weeks of pregnancy however, treatment aimed at increasing the platelet count to 75-100/nl is needed since this enables delivery and epidural anaesthesia to be performed safely. In maternal ITP, particularly in splenectomized patients there is a significant risk of severe neonatal thrombocytopenia. This holds true even when the maternal count is normal or near normal at the time of delivery. In

ITP, the mode of delivery should be determined by obstetric indications.

When the thrombocytopenia is associated with pregnancy-specific causes such as pre-eclampsia, HELLP syndrome and acute fatty liver it is important to perform a coagulation profile including D-dimers to exclude DIC. Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome (TTP/HUS) is an important diagnosis since the disease complex is life threatening but responds rapidly to early intensive plasma exchange therapy. The red cell appearances on the peripheral blood film in TTP are often characteristic, with variable numbers of red cell fragments.

Myeloproliferative disorders (MPD) and other haematological malignancies occur occasionally in pregnancy. Essential thrombocythemia (ET) is the most common of these. Despite the potential hazards of thrombosis and haemorrhage it is usually possible to avoid exposure to myelosuppressive agents during pregnancy.

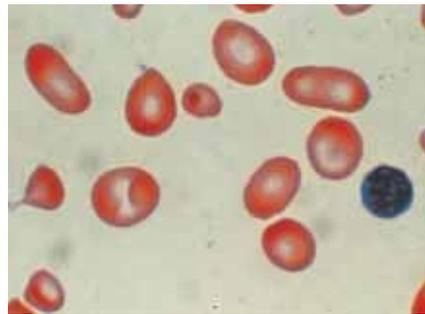


Fig. 2 Megaloblastic anaemia

Thrombosis and haemostasis in pregnancy:

The incidence of venous thromboembolism (VTE) increases three-fold in late pregnancy and ten-fold in the immediate post partum period. This risk reflects a variety of pregnancy induced changes in the haemostatic mechanism including an increase in fibrinogen and Factor VIII, the development of acquired resistance to activated protein C, a reduction in the antithrombotic factor protein S, and reduced fibrinolytic activity. In pregnancy the ESR reflects the hyperfibrinogenaemia and loses its usefulness as a marker for systemic disease.

Inherited thrombophilias, whether due to genetic mutations such as

factor V Leiden and prothrombin, gene mutation or deficiencies of protein C, S and anti-thrombin (AT), increase the risk, not only of VTE in pregnancy and the post-partum period but also of recurrent foetal loss. However, the increase in risk is not considered sufficient to warrant funding of thrombophilia screening for recurrent foetal loss under the Medical Benefits Schedule. Anti-cardiolipin antibodies and lupus anticoagulant, particularly when present at high titre, markedly increase the risk of foetal loss and maternal VTE, and may warrant the use of prophylactic low molecular weight heparin (LMWH) during pregnancy and the puerperium. Patients with homozygous or multiple thrombophilic defects are also at greatly increased risk, and likewise merit LMWH prophylaxis.

If therapeutic anticoagulation is required during pregnancy LMW heparin is the drug of choice for most conditions. In view of the risk of bleeding complicating epidural anaesthesia it is mandatory to obtain expert advice concerning the timetabling of heparin dosage particularly LMW heparin.

Von Willebrand's disease is the most common inherited bleeding disorder, mild (type 1) disease accounting for 90% of cases. In pregnancy, extending through to the immediate post partum period, there is usually a temporary normalisation of the disease, measurable as a return of Factor VIII complex levels and platelet function studies to normal. A check early in the third trimester revealing that these parameters are all within the normal range clears the way for epidural anaesthesia to be performed safely if required. However, a history of PPH in a previous pregnancy may override these considerations and mandate the prophylactic use of specific therapy such as DDAVP (Minirin) or Factor VIII concentrate, depending on the severity of the von Willebrand's disease.

Dr Andrew Barr

Consultant Haematologist

T: (08) 9467 5222

M: 0419 901 329

Reference: ¹Stephansson, O, et al. Maternal haemoglobin concentration during pregnancy and risk of stillbirth. JAMA. 2000;284:2611.