

Anaemia in pregnancy

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Anaemia is one of the commonest illnesses affecting pregnant women with a frequency of approximately 20 per cent in the developed world. It can have a significant effect on a woman's quality of life as well as reducing peripartal blood reserves. Anaemia can also have effects on the fetus leading to an increased risk of growth retardation, prematurity, intrauterine death, amniotic rupture and infection.

In addition to this, anaemia can be anticipated with prenatal screening and treated early, averting serious consequences. In pregnancy, maternal plasma volume expands by approximately 40 per cent (1000ml) and while the total red blood cell mass also increases (by approximately 300mg), this occurs later in pregnancy. Therefore, haemoglobin and haematocrit levels usually fall as a result of this dilutional effect. The resultant low viscosity state is thought to act by facilitating placental oxygen transfer. There is also an associated physiological macrocytosis with an increase of 4fl on average and peaking at term. This should not, however, result in frank macrocytosis (greater than 100fl). In an iron-replete woman these changes have all reversed by six weeks postpartum. Mild anaemia is therefore very common with up to 50 per cent of women having a haemoglobin of below 110g/L at some point.

Iron deficiency anaemia

Iron deficiency is by far the most important cause of anaemia in pregnancy accounting for greater than 90 per cent of cases. The generally lower iron stores in adult women reflect the composite effect of menstrual losses, lower caloric intake and iron losses associated with pregnancy and lactation (about 1000mg each for pregnancy, delivery and nursing). If the dietary iron intake is poor, the interval between pregnancies is short, or the delivery is complicated by haemorrhage, iron deficiency anaemia rapidly develops. The World Health Organization (WHO) defines anaemia in pregnancy as a haemoglobin below 110g/L.

The normal iron content of the body is 3 to 4g with about 65 per cent as haemoglobin, 25 per cent as ferritin and the remainder bound to transferrin, haemosiderin and other proteins such as myoglobin. The iron requirements in pregnancy are represented in Table 1.

Table 1. Iron demands in pregnancy and the puerperium

Increase in the red blood cell mass	400-500mg
Demands of the fetus and placenta	300mg
Blood loss at delivery and placental loss	200mg
Lactation	1mg/day

Women who enter pregnancy in an iron deficient state are then unable to meet the demands of pregnancy by diet alone and require supplementation. Millman *et al* found that 20 per cent of fertile women have iron stores greater than 500mg, which is the minimum required for pregnancy.¹ They also noted that 40 per cent of women have iron stores between 100 and 500mg, and 40 per cent have virtually no iron stores. Based on this data, most women do need some iron supplementation.

A drop in the mean corpuscular volume (MCV), rather than the expected rise, is often the earliest sign of impending iron deficiency anaemia. The blood film may be useful in distinguishing iron deficiency from other aetiologies of anaemia. The presence of a hypochromic microcytosis with marked anisocytosis (variability in size of red cells) is characteristic. Once the haemoglobin falls below 100g/L, poikilocytes (different shaped red cells) will become prominent and the presence of elliptocytes and especially pencil cells is highly suggestive of iron deficiency anaemia. If iron deficiency is combined with folate or vitamin B12 deficiency, normocytic and normochromic red blood cells (RBCs) are observed but the morphology will still be abnormal and sometimes a dimorphic picture (two distinct populations of different-sized red cells) may exist.

Iron studies are expected to demonstrate a low ferritin and transferrin saturation with a high transferrin. The ferritin concentration ranges from 40 to 200ng/mL in normal subjects. All patients with serum ferritin concentrations less than 10 to 15ng/mL are iron deficient, with a sensitivity of 59 per cent and a specificity of 99 per cent.² Provided that an anaemic patient does not have an accompanying infectious or inflammatory disease, a cut-off limit of 41ng/mL provides improved diagnostic efficiency, with a sensitivity and specificity of 98 and 98 per cent.³ It is important to note that pregnancy increases the plasma transferrin concentration and as a result, the transferrin saturation may be low in the absence of iron deficiency.

However, the pitfall with ferritin is that it is an acute phase reactant and is often elevated in patients with recent infectious episodes or inflammatory conditions. The measurement of soluble transferrin receptor has some clinical utility in this situation as it is not affected by inflammatory states. It has a reciprocal relationship with iron stores and therefore should be high in iron deficiency. The exception is that it may be elevated in states of ineffective haematopoiesis such as haemoglobinopathies.

Oral replacement therapy should be started as soon as an iron deficient state is demonstrated. There are multiple preparations available, many which contain folate. It is important to recognise that once iron is supplied to a deficient haematopoietic system, it will consume its other substrates rapidly in a surge of activity and therefore there must be adequate folate supplementation as well.

Only approximately ten per cent of oral iron is absorbed. One 325mg tablet of ferrous sulfate daily provides adequate prophylaxis. It contains 105mg of elemental iron, 10mg of which is absorbed. An acid environment in the duodenum helps this absorption. Therefore, the frequent ingestion of antacid medications, chronic use of H₂ blockers and the use of proton pump inhibitors decreases the absorption of iron. Vitamin C may increase the acid

environment of the stomach and increase absorption and one of the preparations available combines this for convenience. Side effects are dose related and therefore will improve with dose reduction. There is little place for intravenous iron as it carries a small but real risk of anaphylaxis, increased cost and no marked benefit to oral replacement.

Megaloblastic anaemia

Megaloblastic anaemia is the second commonest cause of anaemia in pregnancy with folate deficiency accounting for many more cases than vitamin B12 deficiency. As vitamin B12 and folate are required for the synthesis of new DNA, demand increases up to ten times during pregnancy. Vitamin B12 deficiency is really only seen in those with pernicious anaemia or in strict vegans because of its ubiquity in common foods and our large stores. Folate deficiency, however, develops rapidly because folate stores are minimal.

Megaloblastic anaemia should be suspected when there is a macrocytic anaemia and oval macrocytes on the blood film. Neutrophil hypersegmentation is a late sign and implies severe deficiency. Thrombocytopenia may accompany megaloblastic anaemia in contrast to the thrombocytosis which may be seen with iron deficiency. The serum folate level is a short-term measurement and reflects recent intake, therefore the red cell folate should be measured as it is thought to reflect a time-averaged value of folic acid availability. Serum cobalamin levels below 200pmol/L will detect B12 deficiency with a high specificity. If there remains doubt, measurement of the serum concentrations of the metabolic intermediaries homocysteine and methylmalonic acid is extremely useful, but is only available at a handful of laboratories throughout Australia.

In the case of folate deficiency, replacement should be with 5mg of folic acid daily and a rise in the reticulocytes should be watched for. If this fails to occur, malabsorption is likely and gastrointestinal problems may exist. In the case of B12 deficiency, intramuscular cobalamin is required initially every day for one week at a dose of 1000mcg followed by monthly injections. In strict vegans, three-monthly injections of 1000mcg should prevent deficiency.

Haemoglobinopathies

Haemoglobinopathies can be divided into thalassaemias, where there is decreased globin chain production and haemoglobin variants (for example, sickle cell anaemia). Severity is variable with these conditions and it may not be until pregnancy's increase in demands on haematopoiesis that anaemia becomes clinically significant. Patients with thalassaemia major will have been transfusion dependent since early childhood and they may have complex cardiac, hepatic and endocrine issues necessitating that they receive prenatal care in consultation with a haematologist and preferably at a hospital with a thalassaemia centre.

Discovery of a microcytic anaemia with normal iron studies in an individual with a family history or Middle Eastern, Mediterranean or South East Asian ancestry should prompt testing. A blood film examination in addition to haemoglobin analysis by high performance liquid chromatography should be performed and will allow detection of variant haemoglobins and beta thalassaemia. The finding of a normal haemoglobin analysis with persistent microcytosis should prompt genetic testing for alpha thalassaemia. There are four genes required for alpha chain production. South East Asians with alpha thalassaemia minor frequently lack two genes from one chromosome and therefore are at risk of producing offspring with all four globin chains missing, resulting in hydrops fetalis.

The necessity for transfusional support varies greatly amongst patients with beta thalassaemia. Patients with beta thalassaemia minor (beta thalassaemia trait) usually require no specific therapy, but transfusions are occasionally required when women develop a more severe 'physiologic' anaemia of pregnancy. Thalassaemia intermedia more frequently requires transfusional support and the frequency of transfusions in patients with thalassaemia major may need to increase.

Other causes

Microangiopathic anaemia may be seen in the pregnancy-related conditions preeclampsia, eclampsia and the HELLP syndrome as well as in thrombotic thrombocytopenia purpura (TTP)/haemolytic anaemic syndrome which may occur in the third trimester of pregnancy. It is suspected when fragmentation is seen on the blood film and supported by the finding of an elevated lactate dehydrogenase and bilirubin and a decreased haptoglobin. It is a medical emergency and requires definitive treatment in the form of delivery or in the case of TTP/haemolytic-uremic syndrome (HUS) urgent plasmapheresis.

Autoimmune haemolytic anaemia occurs four times more frequently in pregnant than in non-pregnant women for unknown reasons. Its diagnosis requires the demonstration of a positive direct antiglobulin test with an elevated lactate dehydrogenase (LDH) and bilirubin and low haptoglobin. In most cases, it is quite mild but it may be severe and fatal. It requires treatment with steroids at a dose of 1 mg/kg and usually resolves spontaneously upon delivery.⁴

Aplastic anaemia occurs rarely during pregnancy. It is associated with neutropenia and thrombocytopenia and when severe carries a very poor fetal and maternal prognosis. Finally, acute leukaemia occurs in one in 75,000 pregnancies and in most situations there will be multiple cytopenias as well as blasts in the peripheral blood.

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