Anaemia in pregnancy is a common and worldwide problem that deserves more attention. For many developing countries, prevalence rates of up to 75% are reported. Anaemia is frequently severe in these situations and can be expected to contribute significantly to maternal mortality and morbidity. After a discussion of definitions, screening for anaemia and prevalence, the relationship between anaemia and maternal mortality and morbidity will be reviewed. Micronutrient deficiency and especially iron deficiency is believed to be the main underlying cause for anaemia. More recently the role of vitamin A deficiency as a contributing factor to anaemia has also been examined. The difficulties of assessment of micronutrient sufficiency or deficiency in pregnancy are described, as is the interaction between infection and micronutrient deficiency states.

Definitions

As a result of the normal physiological changes in pregnancy, plasma volume expands by 46–55%, whereas red-cell volume expands by 18–25%\textsuperscript{1,2}. The resulting haemodilution has, perhaps wrongly, been termed ‘physiological anaemia of pregnancy’. There are in fact insufficient data to give accurate physiological limits for the expected haemodilution. In most published studies, the mean minimum normal haemoglobin in healthy pregnant women living at sea level is 11.0–12.0 g/dl. The mean minimum by WHO criteria is taken to be 11.0 g/dl in the first half of pregnancy and 10.5 g/dl in the second half of pregnancy\textsuperscript{3,4}. In the only well-conducted longitudinal study that could be found of the ‘hydraemia’ of pregnancy in iron-replete healthy pregnant women, 10.4 g/dl was the lowest recorded value\textsuperscript{5}.

Anaemia in pregnancy is further divided into mild anaemia ([Hb] 10.0–10.9 g/dl), moderate anaemia ([Hb] 7.0–9.9 g/dl) and severe anaemia ([Hb]<7.0 g/dl)\textsuperscript{4}. The definition of severe anaemia in the published literature, however, varies and this may also be defined as [Hb]<8.0 g/dl. There is discussion in the literature about the relevance of the various cut-off points, whether different cut-off points should be used for different populations\textsuperscript{5–8} and the need to adjust for populations living at high altitude\textsuperscript{9}.

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Screening

An accepted standard of practice is that all women have at least one haemoglobin measurement during the course of pregnancy. This is usually carried out by electronic (automated) counter. In many developing countries, these methods are not available at Health Centre level and may not be available even at tertiary level. Either screening for anaemia may not be carried out at all or assessment of whether a pregnant woman is anaemic or not may be limited to inspection of the conjunctiva by the nurse or midwife for the presence of pallor during antenatal visits.

There are few published papers reporting on the accuracy of screening for anaemia using clinical inspection of conjunctiva in pregnant women. In a large study conducted in women attending a rural antenatal clinic, sensitivity was 33.2% and 39.7% for haemoglobin values of ≤11.0 and ≤10.0 g/dl, respectively. Values obtained were better for the lower range of haemoglobin values but did not exceed 62.1%10. A study from Mozambique reported a sensitivity of 31.5%, with anaemia defined as a packed cell volume ≤3011. In a smaller study from Kenya, examination of the conjunctiva was reported to have 62–69% sensitivity for detecting severe anaemia ([Hb]<7.0 g/dl) in a study population with a high incidence of severe anaemia (16%)12. Substantial interobserver variability has also been reported13,14. Even when used in combination with a conjunctival—or anaemia—recognition card, sensitivity remains low except when anaemia is severe15,16.

In the absence of a functioning automated (Coulter) counter, several alternative methods for measurement of haemoglobin concentration are available17. A relatively expensive but simple to use portable haemoglobin meter (HemoCue) has been evaluated and found to have a sensitivity of between 80% and 97% and a specificity of between 79% and 99% depending on the cut-off points for haemoglobin concentration used10,18–20. Another method which has been studied in antenatal clinic settings is the copper sulphate method21–24. This method relies on the preparation and availability of a solution of copper sulphate of known specific gravity. There is a fixed range of haemoglobin values for which a blood sample can be tested, e.g. [Hb]<8.0 g/dl or <10.0 g/dl.

In response to the need for a simple, cheap and accurate method for the estimation of haemoglobin concentration, a new Colour Scale was recently developed by the WHO25 which is similar to the Talquist26 scale and consists of a card with 6 colour standards corresponding to the colour of bloodstains of various haemoglobin concentrations (range 4.0–14.0 g/dl). Assessment in an antenatal population with high prevalence of anaemia by comparison with Coulter counter measurements gave sensitivities of 75.4% and 81.6% for cut-off points of [Hb]<11.0 and <10.0 g/dl, respectively. Specificity was 47.2% and 45.3%, respectively.
but improved to 76.4% for [Hb]<8.0 g/dl and 98.5% for [Hb]<6.0 g/dl. The sensitivity of the WHO Colour Scale as a screening tool to detect anaemia was consistently better than if conjunctival inspection was used for screening\textsuperscript{10}.

Prevalence

It has been estimated that over half the pregnant women in the world have a haemoglobin level indicative of anaemia. In industrialized countries, anaemia in pregnancy occurs in less than 20% of women. This does, however, still reach the level of public health significance (≥10%). Published rates of prevalence for developing countries range from 35% to 72% for Africa, 37–75% for Asia and 37–52% for Latin America\textsuperscript{27}. Not only is anaemia common, it is often severe. From the published reports available, it can be estimated that 2–7% of pregnant women have values <7.0 g/dl, and, probably 15–20% <8.0 g/dl. Those authors who publish their range of haemoglobin values not infrequently report on patients with values well below 5.0 g/dl\textsuperscript{28–30}. Up-to-date information from many countries is, however, still scanty; the few published studies often describe small sample sizes and are usually from hospital-based populations. There is a lack of data from rural areas. It has been suggested that the prevalence of anaemia may depend on the season, increasing in relation to malaria transmission in the wet season or in relation to increased food shortage at the end of the dry season, but published prevalence rates rarely reflect measurements performed all year round.

In 1993, the World Bank\textsuperscript{31} ranked anaemia as the eighth leading cause of disease in girls and women in developing countries. Although anaemia is assumed to be less common in non-pregnant women, there is a lack of data on the prevalence of anaemia in this population group. Studies are also needed to assess the association between anaemia in pregnancy and pre-pregnancy haemoglobin levels.

Anaemia and maternal mortality and morbidity

Each year more than 500,000 women die from pregnancy-related causes, 99% of these in developing countries\textsuperscript{32}. Estimates of maternal mortality resulting from anaemia range from 34/100,000 live births in Nigeria to as high as 194/100,000 in Pakistan\textsuperscript{4,27}. In combination with obstetric haemorrhage, anaemia is estimated to be responsible for 17–46% of cases of maternal death\textsuperscript{33–35}. A review of symptoms associated with maternal deaths in Bangladesh led researchers to conclude that anaemia had played a secondary role in nearly all cases\textsuperscript{36}. 

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Anaemia is probably a chronic rather than acute condition in many cases. There is a resulting compensatory shift of the oxygen dissociation curve to the right. Thus, women with very low haemoglobin concentrations may be seen in the antenatal period without the expected overt symptoms of cardiac failure. They will, however, easily become tired by any form of physical activity and may decompensate, *e.g.* as a result of labour. Should any adverse event such as bleeding occur, their risk of death is high.

The available data on the association between anaemia and maternal survival are limited and there are serious methodological flaws in most of the studies, as pointed out by Rush in his excellent review. It must be noted that pregnancy outcome will also be related to the underlying causes of anaemia, *e.g.* HIV, iron deficiency, recurrent antepartum haemorrhage, *etc.* Most of the published studies report on outcome for hospital-based patients. In developing countries, this is rarely representative of the population as a whole. In particular, conclusions about association or causality drawn from a single measurement during delivery in hospital must be considered flawed. In many cases, haemoglobin concentration may have been measured only because of, for instance, a prior history of bleeding, fever or suspected malaria, which may be the reason for referral to the hospital in the first place.

It must also be noted that there are currently no agreed international standards or sets of criteria for attributing death to anaemia. It is in fact often difficult to establish accurately the cause of death in situations where clinical information is incomplete and data collection is not standardized. Thus, in many cases, the only two laboratory tests that may have been available to clinicians could be a haemoglobin concentration and a peripheral blood slide for malaria parasitaemia. Death from anaemia may sound better than death from haemorrhage, in that the latter could be perceived as the result of the health facility’s inability to provide adequate care. Finally, level of access to emergency obstetric care and in particular to blood transfusion and the quality and speed of care received are of prime determining importance. Thus, a study from Indonesia illustrated the much higher risk of maternal death in anaemic women from rural areas than from urban areas, possibly as a result of problems with timely access to obstetric care.

Morbidity resulting from anaemia is similarly difficult to establish. Diminished work capacity and physical performance have been reported as a result of anaemia.

Iron deficiency anaemia leads to abnormalities in host defence and neurological dysfunction. Increased risks of premature labour and low birth weight have also been reported in association with anaemia in pregnancy. Both are common problems in developing countries and contribute significantly to high perinatal mortality. However, most published work on this comes from industrialized countries.
where anaemia is much less of a problem and much less severe in nature. Confounding factors such as poverty, poor antenatal clinic attendance and recurrent infection, which can result in low birth weight and prematurity, are seldom examined at the same time. Further research on the effect of anaemia *per se* on birth weight and prematurity is therefore necessary to establish a clear causal relationship.

**Micronutrients and pregnancy**

Vitamins and minerals are referred to collectively as the ‘micronutrients’. The micronutrient deficiencies which are thought to be of the greatest public health significance globally are iron deficiency, vitamin A deficiency and iodine deficiency. Both iron deficiency and vitamin A deficiency can result in anaemia. Dietary inadequacy is thought to be the major cause for vitamin A and iron deficiency.

**Iron deficiency**

Iron is obtained in the form of non-haem iron from vegetables and as haem iron from meat. Haem iron is absorbed about two to three times better than non-haem iron. A small amount of haem iron in the diet will improve absorption of non-haem iron and thus the diet composition is an important determinant of the amount of iron actually absorbed. Iron is stored in the reticulo-endothelial system as ferritin and haemosiderin. Iron is a component of haemoglobin and iron deficiency ultimately leads to defective erythropoiesis and anaemia.

Pregnant women are particularly vulnerable to iron deficiency as a result of the increased demand for iron. The requirements for iron during pregnancy have been estimated at a total of about 1000 mg\(^1,48\). In response to pregnancy, iron absorption is increased\(^48,49\).

The marked physiological changes that occur in pregnancy influence the laboratory measurements used to evaluate iron status. The expansion of plasma volume, increase in erythropoiesis and increased demand of the fetoplacental unit for iron occur throughout gestation and can vary markedly between individuals. The resulting changes in serum levels of biochemical markers for iron status make it necessary to re-define cut-off values for the diagnosis of iron deficiency in pregnancy\(^50\). Serum ferritin is the most frequently used indicator of iron status.

The range of values for serum ferritin found in non-anaemic individuals is 12–300 µg/l. In the presence of anaemia, values of <20 µg/l are commonly taken as evidence of iron deficiency\(^51\). However, patients with levels of up to 37 µg/l have been shown to have absent marrow
haemosiderin. In pregnancy, serum ferritin is lower and mean values are close to the iron deficient range. More recently, the measurement of serum transferrin receptors and the serum transferrin receptor/ferritin ratio have been proposed as new indices of iron deficiency. Receptor synthesis is up-regulated in iron deprived tissues. It can be argued that assessment of iron status at the tissue level is of more functional importance when examining the effects of iron depletion on the body than an assessment of stores.

Because of the increase in absorption during pregnancy coupled with the mobilization of iron stores, if women of childbearing age have enough iron stores to cope with the demands of pregnancy this could be sufficient and iron supplements may not be necessary. However, if iron stores are low, supplementation may be necessary or indicated. Provision of routine iron supplementation to pregnant women who do not have evidence of iron deficiency and have Hb levels > 10 g/dl has been shown to have a positive effect on women’s iron status. The prevalence of low pre-delivery haemoglobin and low haemoglobin at 6 weeks post partum is reduced. There is more stainable iron in the bone marrow with higher serum iron and ferritin levels.

### Vitamin A deficiency

Vitamin A is a fat soluble vitamin which is obtained from the diet as preformed vitamin A (retinal) and from some of the carotenoid pigments in food that can be cleaved in the body to give retinol. Preformed vitamin A occurs naturally only in animals and the richest dietary sources are liver, fish oils and dairy products. Between 25 and 35% of the dietary vitamin A will come from carotenoids mainly from plant foods such as carrots and dark leafy vegetables. Carotenoids can be converted to vitamin A in the liver where vitamin A is stored. Absorption from plant sources is thought to be low and animal sources may be needed to achieve adequate levels. The digestion and absorption of vitamin A are also closely linked with lipid absorption and therefore low dietary fat intake may interfere with vitamin A absorption.

Vitamin A deficiency is thought to be common in many developing countries. Much of the work on prevalence has been in children and there is comparatively little information about the occurrence in pregnancy. Estimates of the number of people at risk from vitamin A deficiency are often approximations but it is thought that there is a significant problem in most parts of Africa, South and South East Asia and areas of Latin America and the Western Pacific. In case of marginal vitamin A deficiency, the extra demands made by pregnancy could be expected to result in vitamin A deficiency symptoms such as night blindness.
Assessment of vitamin A status in pregnancy is commonly by measurement of serum retinol. However, serum retinol levels are under strict homeostatic control and not a good measure for individual vitamin A status. Dose response tests have recently been developed which assess vitamin A stores in the liver and this is a more accurate method of assessment. In pregnancy, as a result of the physiological changes described above, serum retinol levels have been shown to drop below non-pregnancy concentrations.

Vitamin A is believed to be essential for normal embryogenesis, haematopoiesis, growth and epithelial differentiation. In pregnancy, extra vitamin A is required for growth and tissue maintenance in the fetus, for providing it with reserves and for maternal metabolism. Basal requirements in pregnancy are 370 µg per day, which increase during lactation to 450 µg per day.

On the other hand, a relationship has been suggested between the incidence of birth defects and high vitamin A intakes during pregnancy with an apparent threshold of 10,000 IU per day. However daily doses of up to 10,000 IU or weekly doses of 25,000 IU after day 60 of pregnancy are safe, especially in areas where vitamin A deficiency is common.

Vitamin A is essential for haematopoiesis. A diet devoid of vitamin A results in decreased haemoglobin levels. Antenatal supplementation with both iron and vitamin A was shown to reduce anaemia prevalence in a study from Indonesia but other studies conducted in sub-Saharan Africa were not able to obtain the same positive result. The mechanism whereby vitamin A supplementation could improve haemoglobin and iron status has not been fully elucidated but it has been suggested that vitamin A is required for the mobilization and utilization of iron for haemoglobin synthesis. An anti-infective role has also been suggested as infection is known to be associated with decreased serum iron levels, suppressed erythropoiesis and lower haemoglobin concentration. An important and large study from Nepal has recently generated discussion about the role of vitamin A in the possible reduction in maternal mortality. A clear biological explanation could not be given and anaemia was not studied as an outcome in this trial. Further trials are currently under way to address these issues. Currently, WHO recommends routine vitamin A supplementation during pregnancy or at any time during lactation in areas with endemic vitamin A deficiency (where night blindness occurs).

### Micronutrient deficiency and anaemia

Relatively few studies have comprehensively assessed the aetiological factors responsible for anaemia in pregnancy and this is especially so
for developing countries where anaemia is more prevalent and more severe and likely to have a greater contribution to maternal mortality and morbidity than in industrialized countries. This is probably for three main reasons. (1) The lack of adequate diagnostic facilities in many institutions in developing countries. (2) The frequent complexity of the aetiological pattern, such that, for example, infection and nutritional deficiency coexist. (3) The relative contribution of each aetiological factor can be difficult to assess in pregnancy when maternal physiological changes alter the parameters used to diagnose deficiency or sufficiency.

Chemical measurements of iron status are influenced by inflammation, and there is a lack of clearly defined and validated cut-off points for the diagnosis of deficiency in these circumstances. Evaluation of suitably stained bone marrow aspirates may then be necessary to provide meaningful results.

Despite the lack of stringent criteria and definitional problems, pregnancy anaemia in sub-Saharan Africa is most often believed to be the result of nutritional deficiencies, especially iron deficiency. Folate deficiency has been described in West Africa. Studies from Indonesia indicate that vitamin A deficiency may contribute to anaemia in pregnancy. Vitamin B12 deficiency was found to be an unrecognized but important cause of anaemia in Zimbabwe. It must be noted that micronutrient deficiencies are often studied in isolation but in actual fact are very likely to occur together and in many cases there is a multiple micronutrient deficiency state.

In many developing countries, it is difficult to meet daily nutrient requirements with diet alone especially for pregnant women. Animal products and fats are often relatively expensive and in addition, there may be food taboos which influence dietary intake in pregnancy. The benefit of multiple micronutrient supplements is therefore being considered.

Although the contribution of malaria is generally acknowledged, the role of other chronic infections has been discussed but not extensively studied in pregnant women. In the last decade, HIV infection has become more prevalent and it must now be considered a possible aetiological factor. A recent study from Malawi illustrates the complex interaction between multi-micronutrient deficiency and infection.

Thus, possible aetiological factors responsible for anaemia are multiple and their relative contributions can be expected to vary by geographical area, as well as by season. Knowledge of the relative importance of different causes should form the basis for intervention strategies.
Key points

- In many areas of the world, as many as 75% of women are anaemic during pregnancy by WHO standards ([Hb] < 11.0 g/dl). Many have severe anaemia ([Hb] < 7.0 g/dl or < 8.0 g/dl). It is not known whether most women enter pregnancy already anaemic or whether anaemia develops primarily during pregnancy. Detection of anaemia often relies solely on conjunctival inspection, which is probably insufficient. The introduction of cheap but accurate screening tools should be encouraged.

- There is a lack of studies measuring haemoglobin levels prospectively before and during pregnancy with assessment of maternal mortality and morbidity. Thus, it is not possible to indicate which level of haemoglobin is particularly associated with adverse outcome. However, on the basis of the available evidence, it seems reasonable to assume that the risk of maternal mortality in developing countries is increased, especially with severe anaemia.

- In many pregnant women, anaemia is probably caused by a combination of disease including both micronutrient deficiency and infection. The complex pattern of interaction between the two requires further study. Haemoglobin concentration should perhaps be regarded as a ‘marker of morbidity’ in these situations.

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