Anemia affects an estimated 30% of women of child-bearing age, and more than 40% of pregnant women worldwide. The highest prevalence of anemia in pregnant women is in South-East Asia (48.7%) and Africa (46.3%).

Anemia in pregnancy is defined by the World Health Organization (WHO) as hemoglobin (Hb) less than 110 g/dL in the first and third trimesters, and less than 105 g/dL in the second trimester.

Micronutrient deficiencies are common in women of reproductive age, particularly in developing countries. A systematic review of data from 2005 to 2015 of reproductive age women in Ethiopia, Kenya, Nigeria and South Africa found the prevalence of anemia, iron deficiency, iron deficiency anemia, folate deficiency, zinc, vitamin A and iodine deficiencies to be 18–51%, 9–18%, 10%, 46%, 34%, 4–22% and 22–55%, respectively. The corresponding prevalence rates in pregnant women were 32–62%, 19–61%, 9–47%, 3–12%, 46–76%, 21–48% and 87%. Women of reproductive age in developing countries are particularly susceptible to micronutrient deficiencies due to women prioritizing the health of other family members and, thus, inequitable food distribution within households, lack of availability of food, lack of dietary diversity, and endemic infectious diseases. As a result, women may enter pregnancy with micronutrient deficiencies, which may be further exacerbated by the demands of pregnancy.

Iron deficiency is the most common cause of anemia in pregnancy, accounting for up to 75% of cases. In addition, iron deficiency anemia (IDA) affects 10% of postpartum women. It is estimated that an additional 500 mg of iron is required during pregnancy for expansion of red cell mass, 300–350 mg for the growing fetus and placenta, as well as 250 mg for peripartum blood loss. Physiologic requirements for iron absorbed are estimated to be 0.8 mg/day in first trimester, 5 mg/day in second trimester and 6 mg/day in third trimester. A typical Western diet provides only 50% of daily iron requirements for pregnant women. A significant proportion of women have inadequate iron stores in early pregnancy even in the absence of anemia. An observational study of 102 non-anemic first trimester women in the USA found that 37% were iron deficient based upon a transferrin saturation of less than 20%. Fourteen per cent had ferritin levels <30 ng/mL, 6% had ferritin levels <25 ng/mL, and 5% had ferritin levels <20 ng/mL. A recent study in Indian women
found the prevalence of iron deficiency was 91% in first trimester.\(^6\)

Risk factors for iron deficiency in pregnancy include low dietary intake, malabsorption, blood loss, adolescent pregnancy, obesity, gestational diabetes, hypertension, higher parity, a short interpartum period, and carrying multiple fetuses.

**DIAGNOSING IRON DEFICIENCY**

Serum ferritin is usually adequate for the diagnosis of iron deficiency, with the exception of where there is active inflammation, as ferritin acts as an acute phase reactant. Diagnostic thresholds for iron deficiency in pregnancy vary significantly. While WHO defines iron deficiency anemia based on a serum ferritin <15 ng/mL, pregnant women with serum ferritin levels <30 ng/mL are considered to be at risk for IDA in the United Kingdom, and in Denmark it is suggested that women with serum ferritin <70 g/mL be treated with iron supplements.\(^7\)

Studies correlating the presence or absence of stainable marrow iron with serum ferritin indicated that a level of <30 ng/mL has a 92% sensitivity and 98% specificity for diagnosing iron deficiency, whereas a serum ferritin <10 ng/ml has only a 25% sensitivity in detecting iron deficiency.\(^8\),\(^9\)

In the setting of acute inflammation measurement of transferrin saturation may be useful. Transferrin saturation <16% is considered a marker of functional iron deficiency.

The use of microcytosis in screening will underestimate the prevalence of IDA, as a fall in Hb commonly antedates the fall in mean corpuscular volume.\(^10\) Microcytosis was present in only 27.5–65% of patients with iron deficiency.\(^11\),\(^12\)

Soluble transferrin receptor levels increase in iron deficiency, and are unaffected by inflammation. A meta-analysis of ten studies found that soluble transferrin receptor levels had a sensitivity of 86% and a specificity of 75% in detecting iron deficiency.\(^13\)

The assay is not standardized and not widely available. Hepcidin regulates systemic iron bioavailability, determining how well oral iron is absorbed. Levels of hepcidin fall during pregnancy, women with undetectable levels transferring more maternally ingested iron to their fetus than women with detectable hepcidin. The utility of hepcidin levels as a biomarker of iron deficiency is being evaluated, one recent study suggesting that serum hepcidin is superior to Hb, serum iron, serum ferritin, transferrin saturation, and transferrin iron binding capacity as an indicator of IDA in pregnant women.\(^14\)

Hepcidin may be particularly useful in detecting iron deficiency in the setting of infectious or inflammatory disease.

Based upon measures of erythrocyte and reticulocyte indices including reticulocyte Hb content and percentages of hypochromic erythrocytes and microcytic erythrocytes, Demmers et al. concluded that in contrast to iron-deficient nonpregnant women, low ferritin concentrations in pregnant women are not associated with functional iron deficiency.\(^7\)

Iron metabolism might be differentially regulated for optimal fetal growth and development despite low maternal iron stores.

Portable point-of-care devices (POCD) for the assessment of Hb levels from capillary blood may be useful in remote areas.\(^15\),\(^16\) Detection of iron deficiency using POCD may also be useful particularly in remote areas and developing countries. A mobile phone device-coupled tool measuring serum ferritin using fingerprick blood samples displayed a correlation of 0.92 with a sensitivity of greater than 90% for predicting iron deficiency (ferritin <15 ng/mL) compared with a laboratory standard IMMULITE analysis of whole blood samples.\(^17\)

Similarly an immunochromatographic assay-based point-of-care screening device quantified soluble transferrin receptor from a drop of serum within a few minutes with a correlation of 0.93 compared with ELISA of archived serum samples demonstrating its potential for point-of-care assessment of iron status.\(^18\) Additionally erythrocyte zinc-protoporphyrin/heme ratio was found to be a valid point-of-care biomarker to diagnose iron deficiency anemia.\(^19\)

**PREVENTION OF IRON DEFICIENCY**

Appropriate dietary advice should be given to all women regarding healthy eating. Appropriate surveillance and treatment should be given regarding endemic infections that may cause anemia (e.g. hookworm, malaria).

Fortification of food with iron has met with a number of barriers. Fortified foods are often financially unavailable to the
poorest segments of the population who have the greatest risk of micronutrient deficiencies. Food choices for fortification need to be chosen carefully in order to deliver greatest benefit to those individuals at highest risk. Coverage surveys in four African countries found fortification of wheat, maize and semolina flours contributed only 0–13% of recommended iron intake in women of reproductive age. A study in the Solomon Islands found that the potential benefit of fortification of wheat flour was likely to be limited to urban populations, and that fortification of rice would contribute significantly to the intake of iron, folic acid and zinc by women of reproductive age.

Universal fortification of food with iron may place individuals with hemochromatosis at greater risk. Denmark and Sweden, however, ceased iron fortification of foods in 1987 and 1994, respectively, because of both a lack of evidence of benefit and concerns regarding hemochromatosis. The combined allele frequency of the H63D and C282Y mutations for hemochromatosis is only 2.6% in Africa, 1.9% in South-East Asia and 8.6% in the Indian subcontinent, compared with an allele frequency of up to 30% in Northern European populations, suggesting the benefit far outweighs risks in those areas where iron deficiency is highly prevalent.

Iodized salt is an ideal carrier for food fortification as it is universally consumed independent of economic status. Previous attempts to fortify food with both iodine and iron together have been limited by iron negating the effect of iodine. Microencapsulation based technology enables the addition of iron without degradation or interaction, and currently double-fortified salt is reaching 60 million people in three states in India.

A stable quadruple fortification of salt with iodine, iron, folic acid and vitamin B12 that could provide up to 50% of the recommended dietary allowance (RDA) of folic acid and iron, and 100% of RDA of vitamin B12 and iodine has been pilot tested with high consumer acceptability. It is estimated this formulation would cost less than US$ 0.20 per person per annum.

Fortification of water with iron and vitamin C has been effective in improving ferritin and Hb in a number of studies.

Because of the importance of adequate pre-pregnancy iron stores, WHO guidelines recommend once-weekly supplementation with 60 mg elemental iron and 2.8 mg folic acid in all non-pregnant women of reproductive age living in regions with a greater than 20% prevalence of anemia (most developing countries). This together with regular deworming has been shown to be effective in increasing iron stores, stabilizing Hb and reducing soil transmitted helminth infections over periods of several years. The equivalent of 60 mg of elemental iron is 300 mg of ferrous sulfate heptahydrate, 180 mg ferrous fumarate or 500 mg ferrous gluconate.

In countries where anemia prevalence is over 40%, WHO recommends daily elemental iron supplementation of 60 mg in pregnant women together with folic acid 0.4 mg. Routine supplementation with 15–30 mg/day of elemental iron is recommended in pregnancy in North America. Weekly therapy with 120 mg of iron appears to be an effective and safe alternative to daily therapy. UK guidelines differ in that routine supplementation of all pregnant women is not recommended, instead screening for anemia is performed in early pregnancy and at 26 weeks' gestation. The bioavailability of non-heme iron in foods of plant origin is low, and vegetarian women should be offered iron supplements at a recommended dosage of 30 mg/day.

In a study in which 133 pregnant African women were injected with 5-ml iron dextran complex in each buttock at their first antenatal visit, 84% of the treated group showed an improvement in Hb level (mean rise 1.025 g/dL) compared with 56% of women in a control group (mean rise 0.26 g/dL). Oral iron therapy commonly causes constipation, diarrhea and nausea, and non-adherence rates of prescribed oral supplements in pregnancy have been reported to be 27–46%. Recommendations for universal iron supplementation have not resulted in a consistent reduction in the incidence of iron deficiency anemia in pregnancy. Intermittent supplementation (2–3 times a week on non-consecutive days) produced similar maternal and infant outcomes to daily supplementation.

Iron salt preparations containing equivalent amounts of elemental iron have similar rates of side-effects. Controlled-release iron formulations have lower rates of epigastric pain and nausea, but no difference in discontinuation rates compared with ferrous sulfate. Absorption of iron may be increased by concurrent administration of vitamin C. Oral iron is likely to be ineffective in the setting of inflammatory bowel disease, and not absorbed in women who have
undergone bypass bariatric surgery.

It is unclear as to whether iron supplementation in malaria endemic areas may increase the risk of infection. A 2015 systematic review and meta-analysis of pregnancy concluded that iron supplementation in pregnancy was associated with a temporal increase in Plasmodium vivax infections without a clear effect on Plasmodium falciparum risk. A 2018 review of clinical trials, however, concluded that iron supplementation in pregnancy did not increase the risk of malaria. In malaria-endemic areas, iron supplementation should occur in conjunction with appropriate malaria prevention, diagnosis, and treatment measures.

TREATMENT OF IRON DEFICIENCY

Where a woman is diagnosed with anemia in pregnancy, the daily dose of oral elemental iron should be increased to 120 mg per day until Hb is at least 110 g/dL.

A study comparing intramuscular administration of iron dextran (250 mg thrice weekly) to pregnant women with IDA resulted in more rapid improvement in Hb at 2, 4 and 6 weeks than oral ferrous sulfate (200 mg 3 times per day with vitamin C). The relative cost of parenteral iron dextran treatment was 4–8 times that of oral ferrous sulfate. In addition, intramuscular therapy required transport of the pregnant woman to and from the local hospital for administration in case of anaphylaxis, and was associated with pain at the injection site in 17%, skin staining in 3%, nausea in 10%, and headache in 7%. Intramuscular iron is therefore not recommended as first-line therapy.

A meta-analysis revealed pregnant women with anemia are 2.7 times more likely to achieve their target Hb with iron infusion (FeI) than oral iron, and to do so more rapidly and with less risk of adverse effects. Systematic reviews of oral and intravenous iron therapy for iron deficiency anemia in pregnancy demonstrated significant improvement in hematologic parameters though no improvement in clinically relevant outcomes. A possible contributor to the failure of FeI to improve maternal and fetal outcomes is the late administration – recent retrospective observational Australian studies reported administration of FeI to healthy women at a mean gestation of 34.6 weeks. FeI is usually avoided in first trimester because of uncertainty regarding teratogenicity. Twenty-two cases of intravenous iron administration in healthy women in first trimester have been described without adverse pregnancy outcome. Additionally, more than 600 pregnancies have been reported in women receiving chronic hemodialysis. Individuals being managed with hemodialysis typically receive 100 mg of intravenous iron weekly. The mean time at which pregnancy is diagnosed in women receiving chronic hemodialysis is 8 weeks, with the fetal malformation rate the same as in the general population, suggesting that intravenous iron in doses used for dialysis patients is not teratogenic in human pregnancy.

Fel products consist of a polynuclear iron core with a surrounding shell of carbohydrate for stability. In contrast to the high rate of adverse reactions to high molecular weight iron dextrans, current formulations have a low incidence of side-effects. The risk of major infusion reactions due to activation of the complement system has been estimated to be 1 in 200,000. Minor reactions requiring slowing of the infusion rate occur in 1 in 200. No increased risk of infection or precipitation of cardiac failure has been reported. Ferric carboxymaltose may be associated with hypophosphatemia in up to 50% of patients regularly tested post FeI. Onset occurred approximately 1 week after FeI, peaking in frequency at 2 weeks post FeI, and persisted for up to 5 weeks. The vast majority of cases of hypophosphatemia are asymptomatic – only nine cases of severe hypophosphatemia with musculoskeletal complications having been described to date, none of these in pregnancy. Fel products appear to have equivalent efficacy and safety. Formulations that may be given as a single infusion, such as ferric carboxymaltose, iron polymaltose and low molecular weight iron dextran, may be preferable.

Response to iron therapy is usually seen as a reticulocytosis within 1 week, a rise in Hb within 2 weeks, and an increase in serum ferritin within 3 weeks.

Lactoferrin is an iron-binding protein present in large quantities in colostrum, breast milk, external secretions and leucocytes. Its functions include gastrointestinal absorption of iron as well as antimicrobial, antioxidant, anti-inflammatory and anti-neoplastic activity. Lactoferrin has been approved by the FDA and European Food Safety Authority as a supplement in food products. Lactoferrin is taken orally twice a day. A meta-analysis of randomized trials found lactoferrin was significantly more effective than oral ferrous salts in improving Hb level after 4 weeks in pregnant women.
with moderate iron deficiency anemia, and was better tolerated. In a randomized controlled trial lactoferrin with health education resulted in a similar improvement in anemia to total dose infusion of iron dextran 4 weeks after treatment. The cost of lactoferrin may be a significant barrier to its widespread use. In an Egyptian study the cost of 4 weeks of lactoferrin therapy was $7.20US compared with $0.41US for treatment with ferrous sulfate. Several animal studies have demonstrated significant improvement in serum iron and Hb levels in IDA with the use of dissolving microneedle patches containing ferric pyrophosphate and iron dextran. Transdermal delivery of iron may be an alternative to intravenous and oral therapy in remote areas. Nasal delivery of nano-liposome encapsulated ferric ammonium citrate has been used to increase iron content in the brain of the rat without affecting the respiratory system.

**FOLATE DEFICIENCY**

Folate deficiency complicates approximately 30% of pregnancies worldwide. The folic acid requirement during pregnancy increases by 50% to 150 mg per day. Dietary folate is absorbed in the jejunum. The total body content of folate is estimated to be 15–30 mg, half of these being in the liver, the remainder in blood and body tissues. Folate stores last approximately 3 months before deficiency occurs. Folic acid fortification of foods (providing approximately 163 mg/day in the US) has resulted in a reduction in neural tube defects (NTD) in many countries. The neural tube closes around day 26 of gestation. Causes of folic acid deficiency include diets high in organic foods or low in carbohydrate, interference of absorption due to medications or medical conditions (celiac disease, inflammatory bowel disease, gastric bypass surgery), liver and renal disease, and alcohol excess.

Most pregnant women with folate deficiency anemia do not manifest macrocytosis. Red cell folate levels are a more accurate measure of folic acid deficiency than serum folate. A POCD using a fluorescence lateral flow assay to measure serum folate has been described and may be useful for measuring levels in areas remote to laboratory facilities. For the prevention of neural tube defects empiric supplementation with 0.4 mg folic acid per day is recommended from 3 months prior to attempting conception continuing throughout pregnancy and breastfeeding. In women with medical conditions predisposing to low folate levels as above, pregestational diabetes, medications that may lower folic acid levels (e.g. sulfasalazine, trimethoprim, triamterene), or a family history of NTD in second or third degree relatives, a dose of 1 mg folic acid per day is recommended pre-conception/first trimester, reducing to 0.4 mg per day at 12 weeks' gestation and continuing until cessation of breastfeeding. With maternal therapy with carbamazepine or sodium valproate, a parental or previous offspring history of NTD, or sickle cell anemia or thalassemia, 4–5 mg folic acid per day is recommended preconception/first trimester. A preconception/first trimester 1 mg/day dose is also recommended where there is a family history of cleft lip/palate, congenital heart defects, limb defects, urinary tract abnormalities and congenital hydrocephalus, as these may also represent folate-sensitive congenital malformations.

In the treatment of anemia due to folate deficiency, replacement may be achieved with a daily 5 mg oral dose for 4 months or 0.5–1 mg two or three times daily. Holotranscobalamin levels should always be measured prior to treating megaloblastic anemia, as therapy with folic acid may mask diagnosis of vitamin B12 deficiency increasing the risk of neurologic or hematologic complications.

**COBALAMIN DEFICIENCY**

Cobalamin deficiency is far less common than folate deficiency in pregnancy as substantial amounts of vitamin B12 are stored in the liver, enough to maintain supply for 3–6 years. Primary dietary sources of vitamin B12 are meats, fish, shellfish, and dairy products, absorption of B12 occurring in the terminal ileum. Dietary deficiency of B12 is common in vegans and those with low meat intake. The reported prevalence of B12 deficiency in early pregnancy is up to 70% in India. Women of South Asian ethnicity living in Vancouver demonstrated substantially lower vitamin B12 levels and higher rates of vitamin B12 deficiency and inadequacy in first trimester than women of European ancestry. Levels of B12 are lower in smokers, individuals with heavy alcohol intake, and in obese women. Low B12 is seen in more than
10% pregnant women with previous bypass bariatric surgery or sleeve gastrectomy. The long-term (>2 years) use of metformin may induce biochemical vitamin B12 deficiency, though whether this correlates with anemia or neurological complications is unclear. The prevalence of vitamin B12 deficiency in metformin-treated type 2 diabetic patients in a tertiary institution in Nigeria was 41%. Metformin used in the treatment of gestational diabetes mellitus did not result in lower holotranscobalamin levels than in insulin-treated women.

B12 deficiency may manifest as maternal neurological or hematological complications, or as growth restriction, hypotonia, NTDs or loss of neuromotor skills in the neonate. Folate treatment may mask B12 deficiency by correcting megaloblastic anemia, while allowing neurological complications to progress. Thus, B12 levels should always be measured before commencing folate therapy.

Serum total vitamin B12 falls significantly in 20% of healthy women in pregnancy due to reduction in holohaptocorrin. Holotranscobalamin (active B12), the fraction of B12 that is available to cross the placenta, does not change and should be used as a guide to B12 deficiency in pregnancy. Methylmalonic acid (MMA) is a more specific functional indicator of B12 status than homocysteine, as the latter is also determined by folate and other B-vitamins. MMA and homocysteine assays are more expensive than B12 assays. Vitamin B12 levels vary significantly between different ethnicities, thus reference intervals during pregnancy need to be population and laboratory specific. A mobile POCD for measuring B12 was limited by a significant incubation time (3 h), multiple pipetting steps, and requirements for off-chip blood sample processing.

The dietary requirement for vitamin B12 is 2.6 mg/day during pregnancy, and 2.8 mg/day during lactation. B12 therapy may be administered orally, sublingually, intranasally, transdermally or parenterally. In women treated with oral cobalamin 1000 mg/day serum levels should be monitored to ensure adequate replacement. Sublingual therapy was more effective in increasing vitamin B12 levels than the standard intramuscular regimen. A daily low dose (50 mg) sublingual regimen was more effective than a 2000 mg once-weekly regimen in improving vitamin B12 levels in those with marginal deficiency.

OTHER ELEMENTS

Other elements which may be a factor in nutritional anemia include zinc, copper, magnesium, B group vitamins, and vitamins A, C and E.

Zinc requirements increase by 40% during pregnancy. The recommended daily allowance (RDA) is 11 mg per day, only 25% of which is absorbed. It is estimated that 25% of the world population is at risk of inadequate zinc intake, and deficiency is common in South Asia and Sub-Saharan Africa. Diets high in phytates and/or low in animal protein provide limited amounts of zinc. Zinc deficiency may also occur as a result of alcoholism, reduced absorption (celiac disease, bariatric surgery), gastrointestinal loss (Crohn's disease), and diuretic therapy. Zinc is an important co-factor in iron metabolism, and zinc deficiency aggravates IDA. Maternal zinc deficiency may also be associated with miscarriage, premature birth, intrauterine growth restriction, birth defects and neurological disorders. Point-of-care testing for serum zinc has been developed for the management of pediatric septic shock, giving a result in 10–20 minutes.

Copper is involved in Hb synthesis, neurotransmission, iron oxidation and the formation of connective tissue disease. Copper deficiency may result in anemia, neutropenia, optic neuropathy, myelopathy, neuropathy and other neurologic dysfunction. Copper deficiency has been reported in 29–34% of pregnant women in India. Foods rich in copper include organ meats such as liver and kidney, shellfish, grains, nuts and seeds. The RDA for pregnancy is 1 mg per day. Causes of acquired copper deficiency include intake of excessive amounts of zinc and iron (which reduce copper absorption), previous upper gastrointestinal surgery, malabsorption syndromes, alcohol excess and malnutrition. Serum copper and ceruloplasmin levels rise approximately two-fold in healthy pregnancy compared with non-pregnant women. Twenty-four hour urine copper levels may be useful in the diagnosis of copper deficiency in pregnancy.

Hypomagnesemia (hypoMg) is common in pregnancy in developing countries and low-income communities. Maternal hypoMg has been reported in 40–60% of pregnant women in South Asia, and 57% of pregnant women in the Sudan. It is unclear as to whether hypoMg may represent a direct cause, a consequence of other disease processes, or an...
epiphrenomenon in adverse pregnancy outcomes. Mg absorption occurs primarily in the ileum and colon. Mg intake depends on the Mg concentration in drinking water and foods. Green leafy vegetables, grain, cereal, nuts and legumes are rich in Mg. Intermittent concentrations of Mg are found in fruit, meat and fish, and low Mg concentrations are present in dairy products. Refining and cooking of foods result in significant loss of Mg. There is a physiological decline in serum Mg in healthy pregnancy from a preconception mean of 0.93 mmol/L to a nadir mean of 0.63 mmol/L in third trimester. Several studies have shown a joint effect between magnesium and iron intake in relation to anemia. The China Health and Nutrition survey found serum magnesium was inversely associated with anemia in men and women. A high intake of magnesium was associated with a lower prevalence of anemia. In Sudanese women in early pregnancy low magnesium and low ferritin were associated with anemia. Gestational magnesium deficiency may be associated with hematological and teratogenic damage. Magnesium-deprived rats manifest a microcytic anemia with intense reticulocytosis suggestive of hemolysis. A high-magnesium diet improved anemia in a murine model of β-thalassemia.

Riboflavin (vitamin B2) deficiency is endemic in populations where the staple diet consists of rice and wheat, with minimal or no consumption of dairy products or meat. Vegans and vegetarians are at highest risk of deficiency. Vitamin B2 degrades in light, and is also lost by the boiling or cooking of vegetables and grains. Deficiency of riboflavin tends to occur in combination with deficiency of other B group vitamins. Symptoms and signs include normocytic normochromic anemia with reticulocytopenia, atrophic glossitis, dermatitis and cheliosis. Bone marrow examination revealed selective hypoplasia of erythroid precursors, and ferrokinetics showed marked reduction of incorporation of iron into red blood cells. Pyridoxine (vitamin B6) deficiency is an uncommon cause of anemia in pregnancy. Vitamin B6 deficiency is typically associated with a hypochromic microcytic anemia, and should be considered where anemia in pregnancy is unresponsive to iron therapy. Two cases of vitamin B6 responsive megaloblastic anemia in pregnancy have also been reported.

Vitamin A deficiency has been reported in 15% of pregnant African women and 24% of pregnant Egyptian women. Eight per cent of pregnant women in Africa have night blindness. Daily requirements for vitamin A increase during pregnancy, the RDA being 800 mg/day. Vitamin A deficiency was associated with a 1.8 times greater risk of anemia than women without vitamin A deficiency in Bangladesh. The mechanism of anemia with vitamin A deficiency is unclear, postulated mechanisms including effects on erythropoietin gene transcription, modulation of iron metabolism and anti-infective properties. Vitamin A supplementation has been shown to improve Hb concentrations and reduce maternal anemia in communities where vitamin A deficiency is common.

Vitamin C deficiency has been reported in up to 80% of pregnant women in Nigeria, 68% of pregnant women in Uganda, 31% of parturients in Brazil, and 75% of adults in rural India. Symptoms and signs of vitamin C deficiency include arthralgia, myalgia, follicular hyperkeratosis, spontaneous bleeding, gum hyperplasia, mood disturbance, jaundice, fever and anemia. Adult scurvy should be particularly considered in the setting of spontaneous petechiae, ecchymoses and mucosal bleeding. Scurvy-associated anemia may be microcytic, normocytic or macrocytic, and may be associated with hemolysis. The findings on blood film and bone marrow biopsy do not help differentiate scurvy-related anemia from the other megaloblastic anaemias, and measurement of vitamin C level is the gold standard for establishing diagnosis.

Vitamin E deficiency is rare, occurring predominantly in the setting of fat malabsorption, rare disorders of fat metabolism and premature birth. Individuals in developing countries are at greater risk of vitamin E deficiency due to poor nutritional status and higher prevalence of oxidative stressors such as HIV infection and malaria which accelerate vitamin E depletion. Vitamin E deficiency is characterized by peripheral neuropathy, ataxia and anemia. Vitamin E may have a role in preventing stress-induced premature erythrocyte lysis by prevention of oxidation of polynsaturated fatty acids and thus stabilizing the red blood cell membrane. Vitamin E deficiency is common in many hereditary hemolytic anemias. Supplementation with vitamin E reduces hemolysis and improves Hb in individuals with sickle cell disease, thalassemia and glucose-6-phosphate dehydrogenase deficiency. Vitamin E supplementation may also have a role in improving anemia in premature infants and patients with chronic kidney disease. A preliminary study of 30 mildly
anemic adults found vitamin E supplementation for 3 months increased Hb. Major dietary sources of vitamin E include vegetable oils, nuts, whole grains and green leafy vegetables. The RDA for α-tocopherol in pregnancy is 15 mg/day.

**CONCLUSION**

Nutritional anemia is extremely common in women of worldwide, particularly in developing countries. Women of reproductive age frequently have micronutrient deficiencies at the time of conception, which may be further exacerbated by the demands of pregnancy and the fetus. Prevention of nutrient inadequacies may be best achieved by multiple nutrient fortification of water supplies and dietary substances which are cheap and are consumed universally such as salt. Point-of-care diagnostic testing may have a significant role in the diagnosis of nutritional anemias in remote areas. Treatment of nutritional anemia must consider the optimal mode of delivery taking medication side-effects, adherence, cost, the frequency of delivery, need for patient travel and administration supervision into account.

**PRACTICE RECOMMENDATIONS**

1. Nutritional anemia in women of reproductive age is highly prevalent, particularly in Africa and South-East Asia.
2. Iron deficiency is the most common cause of anemia in pregnancy.
3. Diagnostic thresholds for iron deficiency vary significantly.
4. There is a high prevalence of non-adherence with oral iron therapy because of gastrointestinal side-effects.
5. Significant reactions to intravenous iron in second and third trimester are extremely rare.
6. More research is needed regarding the safety of intravenous iron infusions in first trimester.
7. Microcytosis is not a good screening test for iron deficiency.
8. Most individuals with anemia due to folate deficiency do not manifest a macrocytosis.
9. Point-of-care devices may enable testing for micronutrient deficiencies in remote areas.

**CONFLICTS OF INTEREST**

*Author statement awaited.*
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