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Iron Deficiency Anemia in Pregnancy-Recent Updates in Management Based On Evidence

Hafizur Rahman[1]*, Tanma Saikia[2], Ezzat Khalda[3], Kirti Singh[1]

[1]Department of Obstetrics and Gynecology, Sikkim Manipal Institute of Medical Sciences
[2]Department of Obstetrics and Gynecology, Gauhati Medical College and Hospital, Guwahati, India
[3]Department of Radiodiagnosis, Sikkim Manipal Institute of Medical Sciences, Gangtok, India

Address of Corresponding Author

Dr Hafizur Rahman

Professor of Obstetrics & Gynecology, Sikkim Manipal Institute of Medical Sciences, 5th Mile, Tadong, Gangtok, Sikkim-737102, India
E-mail hafizezzy[at]gmail.com

Abstract: ***Anaemia is a global health problem and a major cause of maternal morbidity and mortality. IDA during pregnancy has the risk of low birth weight (LBW), preterm birth, maternal and perinatal mortality, and poor Apgar score. The clinical symptoms of Iron deficiency anemia (IDA) in pregnancy are non-specific and are not reliable for diagnosis. Diagnosis is based on laboratory assessment of red cell indices and measurement of iron stores. All pregnant women should be given appropriate dietary advice to correct iron deficiency. When a woman become iron-deficient in pregnancy diet alone is not adequate to correct deficiency and an oral supplementation should strongly be considered. Ferrous iron salts are the current preparation of choice for oral iron supplementation. WHO recommended prophylactic iron supplementation of all pregnant women with 60 mg iron and 400 µg folic acid daily, till term in pregnancy and continuation of similar dose during lactation for 3 months in countries where prevalence is more than forty percent. Parenteral iron should be considered from the second trimester onwards for women with confirmed IDA who are intolerant of, or do not to respond to, oral iron.***

Keywords: Anemia, iron deficiency, management, update

1.Definition

Anaemia is defined as low haemoglobin concentration, Hb less than 2 standard deviations below the mean for a healthy population. However, there is variation in what are considered normal values for pregnancy. The World Health Organisation (WHO) defines anaemia in pregnancy as a haemoglobin concentration of <11g/dL.[1]

In view of the relative plasma expansion being particularly marked in the second trimester, it would seem reasonable to take 10.5g/dL as the cut-off from 12 weeks onwards.[2] The WHO defines postpartum anaemia as Hb <10.0g/dl.[1]

2.Burden of anaemia in pregnant women

Anaemia is a global health problem and a major cause of maternal morbidity and mortality. According to World Health Organization (WHO), about 32.4 million pregnant women suffer from anemia worldwide, of which 0.8 million women are severely anaemic. Half of these cases of anemia are attributable to iron deficiency anemia (IDA).[3]

IDA during pregnancy has the risk of low birth weight (LBW), preterm birth, maternal and perinatal mortality, and poor Apgar score.[4] Anaemia directly or indirectly attributes about 6 lakh perinatal deaths and 115 thousand maternal deaths globally. [4] Anaemic women compared to non-anemic women are at 4-fold higher risk of preterm birth,1.9-fold increased risk of delivering LBW infants, and 1.8-fold increased risk of having low Apgar score<5 at 1 min 5.[5]

3.Diagnosis of Iron deficiency Anaemia in pregnancy

3.1 Clinical features

The clinical symptoms of IDA in pregnancy are non-specific and are not reliable for diagnosis. Fatigue is the most common presenting symptom. Other complaints may be weakness, headache, palpitations, dizziness, dyspnoea and irritability. Some patients may have alopecia, atrophy of tongue papillae, or dry mouth due to reduced salivation.[6] The symptoms specific to IDA include; the syndromes of Plummer-Vinson or Paterson-Kelly (dysphagia with esophageal membrane and atrophic glossitis), gastric atrophy, stomatitis due to rapidly turning over of epithelial cells, koilonychia (spoon-shaped nails), and pallor. Pica (craving for non-food items) and Pagophagia (intense desire to eat ice) are also considered as symptom specific to IDA.[7]

3.2 Laboratory testing

3.2.1 Red cell Indices

A low Hb, mean cell volume (MCV), mean cell haemoglobin (MCH) and mean cell haemoglobin concentration (MCHC) are suggestive of iron deficiency, but need to be interpreted with caution in view of the physiological increase of MCV in pregnancy, of around 6 fl. Microcytic, hypochromic indices may also occur in haemoglobinopathies.[8]

3.2.2 Direct measurement of iron stores

Assessment of the following

a) Serum iron, total iron binding capacity (TIBC), % saturation, serum ferritin, bone marrow biopsy
b) Serum ferritin-A low serum ferritin is diagnostic of iron deficiency in pregnancy. However, a normal ferritin level does not exclude iron deficiency, as pregnancy is associated with a physiological rise in acute phase proteins (Kaestel et al, 2015) and changes in iron utilisation and metabolism.[9]

Fall in serum concentration below15 µg/L indicates iron depletion in all stages of pregnancy.[10] However; treatment needs to be initiated when the concentration falls below 30µg/L, as this indicates early iron depletion.[10]

3.2.3 Other biomarkers of iron deficiency

Transferrin saturation has not been widely used in pregnancy, outside the context of research but is useful in non-pregnancy settings. Other biomarkers may be promising but have not yet been validated in pregnancy, such as soluble transferrin receptor levels (sTfR) and reticulocyte haemoglobin content.[11]

4.Severity of anemia Classification

The severity of anemia is based on the patient's Hb/haematocrit level. Table below shows severity as per WHO and ICMR.

Table 4.1: Severity classification of anaemia in pregnancy according to Hb level (WHO)[12]

Severity	First trimester	Second trimester	Third trimester
Normal (gm%)	≥11	≥10.5	≥11
Mild (gm%)	10-10.9		10-10.9
Moderate (gm%)	7-9.9		7-9.9
Severe (gm%)	<7		<7

Table 4.2: Severity classification of anaemia in pregnancy according to Hb level (Indian Council of Medical Research/ICMR) [13,14]

Severity Classification (gm%)	Hb Level
Normal (gm%)	≥11
Mild (gm%)	10-10.9
Moderate (gm%)	7-9.9
Severe (gm%)	<7
Very Severe (gm%)	<4

5.Management of Iron deficiency Anaemia in Pregnancy

5.1 Dietary advice

The average daily iron intake from food is 10 mg, of which 10-15% is absorbed. Although absorption of iron increases during pregnancy but the requirement of iron also increases from 1-2 mg to 6 mg per day[15], with increasing demand of the mother's system as well as demand by growing fetus. The daily intake of iron for the latter half of pregnancy is doubles to the tune of 27 mg/day. The amount of iron absorption depends upon the amount of iron in the diet, its bioavailability and physiological requirements. Approximately 95% of dietary iron intake is from non-haem iron sources. Vitamin C (ascorbic acid) significantly enhances iron absorption from non-haem foods. Tannins in tea and coffee inhibit iron absorption when consumed with a meal or shortly after. It is recommended that all pregnant women should be given appropriate dietary advice. when a women become iron-deficient in pregnancy repletion through diet alone is not adequate and an oral supplementation should strongly be considered. All pregnant women should be provided with appropriate education and counselling regarding adequate dietary intake in pregnancy but the amount of improvement remains doubtful.[15]

5.2 Oral iron supplementation

Oral supplementation of iron is an effective, cheap and safer way for iron supplementation. Ferrous salts are better to ferric salts because of their poor absorption and bioavailability.[16] Common ferrous salts preparations include ferrous fumarate, ferrous sulphate and ferrous gluconate.

Amount of elemental iron varies by preparation, which should be taken in consideration before prescribing iron preparations. Various multivitamins usually available off the counter have inadequate iron to correct anaemia and, and additionally, often contain other minerals that interfere with iron absorption. Some combined iron and folic acid preparations are also available in market but their efficacy compared to oral iron alone is uncertain. Traditionally, the recommended dose of elemental iron for treatment of iron deficiency has been 100-200 mg daily, however more recent evidence suggest that lower doses or intermittent supplementation of iron may be advantageous.[17]

WHO recommends once a week intermittent iron and folic acid supplementation (120 mg elemental iron and 2.8 mg folic acid) in non-anemic pregnant women and adolescents.[18] Ministry of health and family welfare recommended intermittent iron and folic acid supplementation (100 mg elemental iron and 0.5 mg folic acid) in all females of reproductive age (15-45 years).[19]

5.3 UK guideline on iron deficiency anaemia

Ferrous iron salts are the current preparation of choice for oral iron supplementation. Pending further research optimal dose of elemental oral iron, 40-80 mg every morning is suggested, checking Hb at 2-3 weeks to ensure an adequate response. Women should be counselled as to how to take oral iron supplements correctly. This should be on an empty stomach, with water or a source of vitamin C. Other medications, multivitamins and antacids should not be taken at the same time. Treatment for anaemia should be started promptly by the healthcare professional caring for the woman. Escalation to specialist medical care is required if anaemia is severe (after 34 weeks), or if the

Hb is failing to respond after 2-3 weeks of oral iron correctly taken. In non-anaemic women at increased risk of iron depletion, 40-80 mg elemental iron once a day should be offered empirically, or serum ferritin should be checked and iron offered if the ferritin is <30 lg/l.[20]

A repeat Hb at 2-3 weeks is required to assess response to treatment. The timing of further checks will depend upon the degree of anaemia and period of gestation. Once the Hb is in the normal range, treatment should be continued for a further 3 months and until at least until 6 weeks postpartum to replenish iron stores.

For nausea and epigastric discomfort, alternate day dosing or preparations with lower iron content should be tried. Slow release and enteric-coated forms should be avoided. Repeat Hb testing is required 2-3 weeks after commencing treatment for established anaemia, to assess compliance, correct administration and response to treatment. Once the Hb is in the normal range, replacement should continue for 3 months and until at least 6 weeks postpartum to replenish iron stores. If response to oral iron replacement is poor, compliance should be confirmed and concomitant causes that may be contributing to the anaemia considered, such as folate deficiency or malabsorption.[20]

5.4 Prophylactic iron therapy

WHO recommended prophylactic iron supplementation of all pregnant women with 60 mg iron and 400 µg folic acid daily, till term in pregnancy and continuation of similar dose during lactation for 3 months in countries where prevalence is >40%.[21] The Indian Ministry of Health and Family Welfare (MoHFW) guideline recommends 100 mg of iron and 500 µg of folic acid daily at least for 100 days starting at 14-16 weeks of gestation, followed by the same for 6 months in the post-partum period. [22,23] Daily supplementation of 120 mg of elemental iron and 400 µg of folic acid is recommended by WHO in established mild to moderate anemia in pregnancy. The 2013 MoHFW guideline recommend two IFA tablets per day for at least 100 days for the treatment of mild anemia, intramuscular (IM) iron therapy in divided doses with oral folic acid in moderate anemia. Standard prophylactic doses of iron should be prescribed after the Hb is normalized for remaining term of pregnancy. [22,23]

5.5 FOGSI GCPR

(Federation of Obstetrics and Gynaecological Societies of India, General Clinical Practice Recommendations)[24]

- In pregnant women with mild to moderate anemia and gestation less than 30-32 weeks, and those who respond to a trial of oral iron, the treatment should continue with 100 mg elemental iron twice daily and 500 µg of folic 25 acid with an assessment for the rise in haemoglobin. A repeat haemoglobin test is recommended after 4 weeks of oral iron therapy.[24]
- When target haemoglobin is achieved, a prophylactic daily oral iron supplementation (60-100 mg of iron and 500 µg of folic acid) is recommended for at least 6 months during pregnancy and should be continued in postpartum for another 6 months.[24]
- Pregnant women on oral iron therapy should be counselled to take the tablets before meal or at least one hour after the meal along with supplements like Vitamin C to enhance absorption.[24]

5.6 Intravenous iron therapy

Current evidence found that pregnant women receiving parenteral iron, compared with oral iron, achieved anemia corrections faster and with fewer side effects. [25, 26]

Parenteral iron therapy is indicated when there is noncompliance with, or intolerance of oral iron or malabsorption syndrome or when a rapid Hb response is required. Contraindications are history of anaphylaxis or serious reactions to parenteral iron therapy and first trimester of pregnancy.[25,26]

Parenteral iron should be considered from the second trimester onwards for women with confirmed IDA who are intolerant of, or do not to respond to, oral iron. Parenteral iron should be considered in women who present after 34 weeks' gestation with confirmed IDA and an Hb of <100 g/l.

5.7 Dosing and administration

Traditionally the Ganzoni formula has been used for estimation of iron dose.[27]

Iron requirement (mg) =Total iron deficit (mg) = 2.4 x body weight (kg) x (target Hb (11gm %) −actual Hb (gm %) + storage iron (500 mg).

After calculating the iron deficit, Ferric carboxymaltose is administered with maximal dose per sitting 1000 mg which is diluted in 200ml 0.9% normal saline and administered as an IV infusion over 30 minutes. Subsequent dose if any are planed after one week. Iron sucrose is administered as 200 mg in 200 ml NS over 30 min thrice weekly till complete dosage are administered but not to exceed dose 600 mg per week. Additional doses if any are given next week.

5.8 IDA and mode of delivery

IDA does not decide the mode of birth, and decisions should be made according to obstetric indications. Anaemic women are more prone to develop PPH and lower iron stores for coping with haemorrhage.[20]

Women with Hb <100 g/l near delivery date should have an individualised plan, mandatory institutional delivery and active management of third stage of labour.

After delivery, women with blood loss >500 ml, those with uncorrected anaemia detected in the antenatal period or those with symptoms suggestive of anaemia postnatally should have their Haemoglobin checked within 48 hour of delivery. Women with Hb <100 g/l within 48 h of delivery, who are haemodynamically stable, asymptomatic, or

mildly symptomatic, should be offered oral elemental iron 40-80 mg daily for at least 3 months. Use of IV iron postpartum should be considered in women who are previously intolerant of, or do not respond to, oral iron and/or where the severity of symptoms of anaemia requires prompt management. Obstetric labour wards should have guidelines for the criteria to be used for postnatal red cell transfusion in anaemic women who are not actively bleeding.[20]

6.Conclusion

Oral supplementation of iron is an effective, cheap and safer way for iron supplementation in women with IDA in pregnancy. Recent evidence suggests that lower doses or intermittent supplementation of iron may be advantageous. Accordingly, Ministry of health and family welfare recommended intermittent iron and folic acid supplementation (100 mg elemental iron and 0.5 mg folic acid) in all females of reproductive age (15-45 years). WHO recommended prophylactic iron supplementation of all pregnant women with 60 mg iron and 400 µg folic acid daily, till term in pregnancy and continuation of similar dose during lactation for 3 months. Current evidence found that pregnant women receiving parenteral iron, compared with oral iron, achieved anemia corrections faster and with fewer side effects. IDA does not decide the mode of birth, and decisions should be made according to obstetric indications.

Conflicts of Interest: Disclosure: None of the authors have a conflict of interest

Disclaimers: Nil

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