Iron deficiency anaemia in pregnancy

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Introduction :

Anaemia is the most common haematological disorder in pregnancy which has significant maternal as well as perinatal morbidity and mortality. Anaemia among pregnant women is a serious global health concern. According to world health organization (WHO) report, about 32.4 million pregnant women suffer from anaemia worldwide, of which 0.8 million women are severely anaemic. An estimate by WHO attributes about 591,000 maternal deaths globally to IDA, directly or indirectly.Majority of the cases of anaemia in pregnancy is due to nutritional deficiency of whichmore than 50% cases are attributable to iron deficiency anaemia(IDA) followed by folate and Vit-B12 deficiency. Other causes like haemoglobinopathies, autoimmune haemolytic anaemia, aplastic anaemia, chronic infections, rheumatoid arthritis, chronic renal disease though less commonly found clinician should have a suspicion based on symptomatology for the better management of the case.

Definition :

Anemia is defined as decrease in the oxygen carrying capacity of the blood due to decrease in the haemoglobin concentration or due to reduced number of RBC's

Classification of anaemia :

Table 1: Classification of anaemiabased on etiology:

Etiological classification
1. Anaemia with nutritional deficiency Iron deficiency Folic acid deficiency Vitamin B 12 deficiency Combined deficiency 2. Anaemia associated with decreased production of RBC's Bone marrow disorders Hypothyroidism Chronic renal patholody Bone marrow suppression 3. Anaemia associated increased RBC's destruction Haemolyticanaemia's – Inherited and Acquired Sickle cell anaemia Thalassemia Hereditary spherocytosis Autoimmune haemolyticanaemia Haemolytic uremic syndrome TTP Malaria 4. Anaemia due to blood loss Abnormal uterine bleeding GIT bleeding Obstetric haemorrhage

Table 2: Classification of anaemia according to severity

Category of anaemia	**WHO (Hb in g/dl)**	**ICMR (Hb in g/dl)**
Mild	9 - 10.9	10 – 11
Moderate	7 - 8.9	7 – 10
Severe	4 – 6.9	4 – 7
Very severe	< 4	< 4

Table 3: Classification of anaemia according to trimester

Pregnancy state	Hemoglobing/dl)
1st trimester	< 11
2nd trimester	< 10.5
3rd trimester	< 11

Iron metabolism:

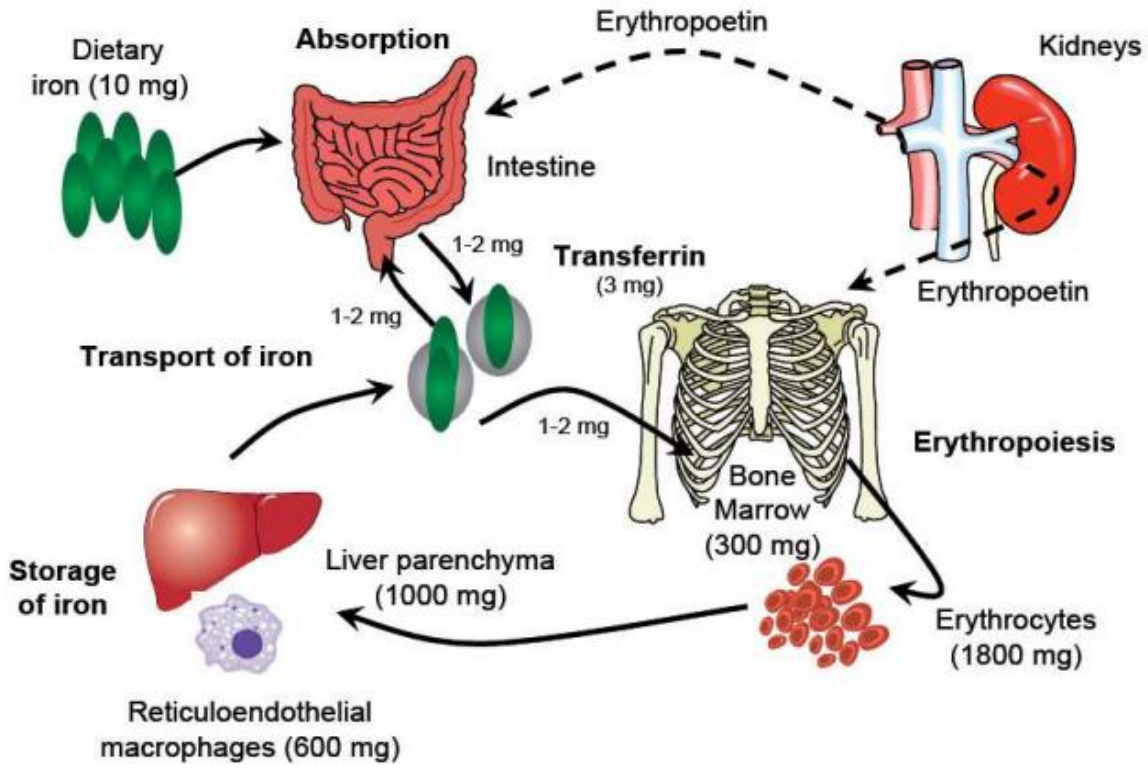
Iron is an essential component of every cell in the body. Although best known for its critical role in the transport and storage of oxygen (in haemoglobin and myoglobin, respectively), within a large variety of enzymes iron also acts as a carrier for electrons, a catalyst for oxygenation, hydroxylation, and is necessary for cellular growth and proliferation. Iron supplements are widely administered to treat iron deficiency anaemia, particularly in chronic diseases such as kidney disease , heart failure or inflammatory bowel disease . Without a sufficient supply of iron, haemoglobin cannot be synthesized and the number of erythrocytes in the blood cannot be maintained at an adequate level.

Iron usually exists in the ferrous (Fe 2+) or ferric (Fe 3+) state, but since Fe 2+ is readily oxidized to Fe 3+ , which in neutral aqueous solutions rapidly hydrolyzes to insoluble iron(III)-hydroxides, iron is transported and stored bound to proteins. Effective binding of iron is essential not only to ensure that it is available where and when required, but also because Fe 2+ can catalyse the formation of reactive oxygen species, which cause oxidative stress, damaging cellular constituents.

Total body Fe in man is 4–5g. Daily losses, e.g. in epithelial desquamation from the gastro-intestinal tract or skin, are small. Excretion in urine, bile and sweat is negligible. Thenormal daily Fe requirement is thus only 1mg, increasing with physiological need, as in growth, pregnancy and blood loss: an additional 1000mg Fe is required in pregnancy, and 0·5mg Fe/ml blood loss[3].

Three key proteins regulate the transport and storage of iron. Transferrin transports iron in the plasma and the extracellular fluid. The transferrin receptor, expressed by cells that require iron and present in their membranes, binds the transferrin di-iron complex and internalizes it into the cell. Ferritin is an iron-storage protein that sequesters iron keeping it in a readily available form. About 60% of iron is found in the erythrocytes within haemoglobin, the oxygen transport protein. The remainder is found in myoglobin in the muscles, in a variety of different enzymes (‘haeme’ and ‘non-haeme’), and in storage form. Most stored iron is in the form of ferritin, found in the liver, bone marrow, spleen and muscles.Serum iron (i.e., iron bound to transferrin) represents only a very small proportion of total body iron (<0.2%). Moreover, the

relationship between physiological iron compartments is highly dynamic: Erythrocytes are broken down in the liver and in the spleen, and new red blood cells are produced in the bone marrow. The total serum iron pool is approximately 4 mg, but the normal daily turnover is not greater than 30 mg, such that minor changes in serum level due to exogenous iron administration are clinically meaningless. In this setting, conventional measurements of serum iron concentration provide no relevant information about the availability of functional iron for physiological processes, and other evaluation strategies must be pursued. Schematic representation of iron metabolism[5].



Iron deficiency anaemia:

Iron is essential for normal Hb synthesis to maintain oxygen transport, as well as being necessary for metabolism and synthesis of DNA and enzymatic processes. Iron stores may be measured using severalindices, although serum ferritin and transferrin saturation are the most common.

Iron deficiency anaemia is defined as a low Hb concentrationin combination with iron deficiency, and is characterized by a defect in Hb synthesis, resulting in abnormally small (microcytic) red blood cells with a decreased Hb content (hypochromic), resulting in reduced capacity of the blood to deliver oxygen.The prevalence of Fe deficiency is much higher. Without adequate Fe supplementation, ferritin falls to subnormal levels towards the end of pregnancy even in the industrialized nations[3].

Iron deficiency anaemia evolves through three distinct stages. Depletion of storage iron occurs in 1st phase (stage I), where total body iron is decreased but red cell indices and haemoglobin (Hb) synthesis remains unchanged. Both these indices change when the supply of iron to bone marrow is reduced (Stage II or iron deficient erythropoiesis). Stage III, eventually IDA develops due to insufficient supply sustains a normal Hb concentration.

Table 1: Stages in Development of Iron Deficiency:

Parameters	Normal	Iron depletion	Iron deficient erythropoiesis	IDA
Hemoglobin	150g/L (15 gm%)	130 g/L (13 gm%)	100g/L (10 gm%)	50 g/L (5 gm%)
MCV	N	↓	↓	↓↓
MCHC	N	N	↓	↓↓
Iron stores	Present	Reduced	Absent	Absent
Serum Fe/ TIBC (Mcg/L)	1000/ 3000	75/ 3000	500/ 4500	250/ 6000
Sr ferritin (mcg/L)	100	20	10	<10
RBCs	Normal	Normal	Normal	Hypochromic microcytosis

Signs and symptoms of IDA:

Although Hb test is recommended at 1st antenatal visit, examination for signs of pallor of the palpebral conjunctiva, tongue, nail beds and palm should be regularly used. Some iron deficient patients, with or without clinical signs of anaemia, may have alopecia, atrophy of lingual papillae, or dry mouth due to reduced salivation.

The symptoms specific to ID include: the syndrome of Plummer-Vinson or Paterson-Kelly (dysphagia with oesophageal membrane and atrophic glossitis), gastric atrophy, stomatitis due to rapidly turning over of epithelial cells, spoon shaped nails (koilonychias) and pallor. These changes were caused by the reduction of iron-containing enzymes in epithelial and gastrointestinal (GI) tract. The restless leg syndrome might be striking neurological squeal prevalent in pregnancy. Pica, the eating disorder in which there is appealing desire to lick or eat non-food items like gypsum, chalk, soil, ice(pagophagia) or paper, is prevalent in pregnant women. Pagophagia (intense desire to eat ice) is quite specific to ID and responds quickly to treatment[4].

Diagnosis of IDA: There are four groups of tests which are available for detection of IDA.

1. Hb, mean corpuscular volume (MCV), red cell distribution width (RDW), reticulocyte Hb content, % hypochromic cells, red cell size factor, and low Hb density.
2. Direct measurements of iron stores through assessment of serum iron, total iron binding capacity (TIBC), % saturation, serum ferritin, bone marrow biopsy iron.
3. Assessment of iron haeme form through assessment of free erythrocyte protoporphyrin (EPP).
4. Assessment of iron uptake by measuring of the soluble serum transferrin receptor (sTfR), and soluble transferrin receptor-log[ferritin] (sTfR-F) index, zinc protoporphyrin (ZPP).

A primary step in diagnosis of IDA is to consider the complete blood count including Hb, MCV, MCH, and MCHC is simple, inexpensive, rapid to perform and help for early prediction of IDA.

Changes in Hb concentration and haematocrit occur only in later stages; both these tests are indicators of ID. Low Hb with a reduced MCV is usually the initial finding on a routine CBC. The severity of anaemia is based on the patient's Hb/haematocrit level.

Altitude above sea level and smoking are the known modifiers of Hb. Currently, the Hb cut-off according to trimester has not been defined by WHO, but it should be recognized that the Hb falls about 0.5 g/dl in the second trimester. Hb concentration is the commonest haematological estimation, there is strong correlation between Hb concentration and serum ferritin levels. Generally recommended methods of Hb estimation are cyanomethemoglobin and HemoCue@ system. RDW has better sensitivity than MCV for diagnosis of IDA. Falling MCV accompanied by a rising RDW should alert the clinician to the presence of possible IDA which is then confirmed by marked RDW increase occurring early after initiation of therapy.

Peripheral smear shows presence of microcytic hypochromic red cells and typical "photo pencil cells" are indicative of IDA. Other than IDA conditions which causes microcytic blood picture are anaemia of chronic disorder, beta-thalassemia and sideroblasticanaemia.

Of all available indices, the Meltzer index (MCV/RBC) has been shown as a most reliable index with high sensitivity.

Fall in serum ferritin concentration below 15 micg/L indicates iron depletion in all stages of pregnancy. However, treatment needs to be initiated when the concentration falls below 30 micg/L as this indicates early iron depletion.

In order to make definitive diagnosis, bone marrow biopsy should be considered, when the diagnosis remains ambiguous even after the analysis of laboratory results. The 'gold standard' for diagnosis of IDA is absence of stainable iron.

Prophylactic measures to prevent IDA in pregnancy

To combat the high prevalence of IDA several government programs and state level schemes were rolled out in various states of India. National nutritional anaemia prophylaxis program 1970, national anaemia control program 1991, 12/12 initiative 2007 are some of the nationwide initiatives.

Few state specific schemes include Madilu scheme, Thayibhagya scheme, and Jananisurakshayojana. In spite of government persistent and prolonged efforts, the problem continues to fester as is documented by recent surveys: National Family Health survey (NFHS-4, 2015-2016): the prevalence is 23.6-61.4%. The prevalence is higher in urban areas (23.6-61.7%) as compared to rural areas (19.6-58.1%). Diverse religions, cultures, languages, food habits and traditions influence management practices present a challenge to the implementation of the health program. Hence, there is a continuing requirement for country-specific harmonized guideline for the control of IDA in India.

As the prevalence of low iron stores and IDA in women of reproductive age is more in developing countries, iron supplementation is essential in all pregnant women for the following reasons –

i) Increase in the demand for absorbed iron
ii) Increase in the maternal requirement
iii) Inadequate dietary intake

Measures to be taken to prevent anaemia in general are :

- Dietary intake is increased by advising diet rich in iron such as green leafy vegetables, sprouts, jaggery, meat and liver
- Cooking in iron vessels , consumption of water boiled in iron containers
- Avoiding of overcooking is advised
- Fortification of the food by iron
- Motivating adolescents and young adults to take iron rich diet
- Screening for anaemia in schools and colleges
- Parasite control measures to prevent hookworm infestations and malaria

Iron supplementation :

According to WHO guidelines –

Iron should be started within first trimester and provided during antenatal visits

For developing countries where prevalence of anaemia is more than 80%, WHO recommends daily supplementation of 60mg elemental iron in the form of ferrous salts along with 400microgram of folic acid for a duration of at least 6 months during pregnancy and 3 months postpartum.

According to MOH (Ministry of health), Government of India – its recommended to give 100mg of elemental iron and 500microgram of folic acid for at least 100 days from 14weeks of gestation for all pregnant women free of cost by Government of India.

Treatment:

1. Food based strategies – dietary modification, food fortification.

2. Supplementation - oral iron therapy, parenteral iron therapy.

Methods to treat iron deficiency

- Oral preparations
- Parenteral preparations
- Dietary iron
- Blood transfusion

Comparison of different methods of iron therapy

	Efficacy	Cost	Side effects
Oral FeSo4	Excellent	Cheap	Abdominal discomfort
Parenteral	Good	Expensive	Fever, rash joint pain shock, death
Dietary iron	Mediocare	Expensive	Weight gain
Blood transfusion	Good	Expensive	TTI - HIV, hepatitis, fever, shock, death

Oral vs. Parenteral iron therapy: It is very well known that oral iron is less than ideal treatment mainly because of

a) gastrointestinal adverse effects (particularly when using ferrous iron compounds)
b) lack of adherence to therapy
c) insufficient length of therapy for the degree of iron deficiency
d) poor duodenal absorption due to concomitant gastrointestinal pathologies (inflammatory bowel disease [IBD] or any other cause of chronic inflammation, malignancy)
e) the long course of treatment needed to resolve anaemia (1-2 months) and replenish body iron stores (another 3-6 months).

Noncompliance to a prescribed course of oral iron is common and even in compliant patients, poor intestinal absorption fails to compensate for the iron need in the presence of on-going blood losses or in inflammatory conditions. In addition to that, adequate iron stores are essential to achieve maximum benefit from erythropoiesis-stimulating agents (ESAs). Decreased iron stores or decreased availability of iron are the most common reasons for resistance to the effect of these agents. Thus, oral iron therapy should not be considered for chronic kidney disease (CKD), patients on haemodialysis and cancer patients receiving ESAs because of the inflammatory state. In this scenario, oral iron is poorly absorbed from the intestinal tract due to up regulation of hepcidin, a peptide hormone that plays a central role in iron homeostasis. In addition to this, in IBD, the possibility that iron may further damage the intestinal mucosa should be a serious indication for the use of IV rather than oral iron therapy.

Recommendations for oral iron therapy :

Best taken in empty stomach early in the morning or 2 hours after food

Absorption is impaired with phosphates, phytates and tanins

Iron absorption increased with Vitamin C, orange or lemon juice

Factors which inhibit iron salts are –

Calcium supplements

Milk and dairy products

Egg, cereals

Proton pump inhibitors

Antacids

H2 receptor antagonists

Oral iron is considered as first-line therapy since it is inexpensive and effective when taken properly.

The recommended oral daily dose for the treatment of iron deficiency anaemia in pregnant women isi n the rangeof**120–200mg/day ofelementaliron**, depending on the severity of anaemia. This may require iron tablets/capsules to be taken two to three times daily.

Ferrous salts are the most appropriate and effective oral iron therapyand the below preparations are commonly used.

Ferrousfumarate:300mg (100 mg elemental iron)per tablet/capsule

Ferroussulfate:150mg/200mg(45mg/60mg elementaliron)per tablet/capsule

Ferrousgluconate:300 mg (30 mg elemental iron)per tablet/capsule

The tablets supplied by the Government of India can beusedtwotimesaday.Theefficacyof allironsaltsmentionedaboveissimilar,andno onepreparationissuperiortothe other. Someenteric-coated,sustained-re-leasepreparationssuchas carbonyliron,iron polymaltosecomplex,andferrousglycine sulfatearealso available.Thesearemoreexpensive butpoorlyabsorbedbecause theydonotrelease the drugin the duodenum whereironis best absorbed.Thesepreparationsare notsuperior tothe ferroussaltsmentionedaboveandarenot recommended.

Sideeffects:Approximately30%ormoreofwomenwillhave gastrointestinalsymptoms:

• Nausea

• Constipationordiarrhoea

• Epigastricdistressand/orvomiting

Women should be reassured that the side effects will usuallysubsideafter10–14 days of continuous usage

Parenteral iron therapy

History of parenteral iron therapy:

The ferric hydroxide preparation was the first iron compound for parenteral use introduced early in the 20thcentury. However, the lack of a carbohydrate shell of this compound resulted in immediate iron release and severe toxic reactions, which led to it being recommended only in extraordinary circumstances. The first high-molecular-weight iron dextran [HMW- ID]) for intramuscular and IV use (Imferon) was introduced in 1954. HMW-ID consists of an iron oxyhydroxide core, which is surrounded by a carbohydrate shell made of polymers of dextran.

In 1992 and 1996 two new compounds INFeD containing low-molecular-weight iron dextran (LMW-ID) andDexferrum with HMW-ID, respectively; were approved by the Food and Drug Administration (FDA) for clinical use in the United States. These formulations can be administered as an IV bolus or total dose infusion (TDI) with doses up to 1000 mg. Both of them required a test dose and had black box warnings.

In November 2000, iron sucrose (IS) (Venofer) was approved in the United States although it had also been used for a long time in Europe with the greatest experience in published literature with this formulation.

With the introduction of Ferric Carboxymaltose (FCM) as an i.v. iron formulation which can be used at high doses and allows rapid administration (up to 1000 mg in a single dose infused in 15 min) treatment of iron deficiency anemia is becoming further easier. Because it is free of dextran and its derivatives, FCM does not cross-react with dextran antibodies and never needed the administration of a test dose.

Recommendation for parenteral iron therapy:

India has always been a country with a high prevalence of anaemia. Indian obstetricians and nutrition scientists earlier documented that pregnant women were the most vulnerable group for anaemia. They reported adverse health consequences of anaemia in pregnancy on mother child. Obstetricians then embarked on a series of research studies to combat anaemia in pregnancy.

- Daily oral iron folate therapy (100 mg of elemental iron and 500 μg of folic acid) prevented fall in haemoglobin (Hb) levels seen in pregnancy and resulted in some improvement in birth weight, and

- Daily administration of two or maximum tolerated dose of oral iron folic acid (100 mg of elemental iron and 500 µg of folic acid) from the time of diagnosis of anaemia till delivery succeeded in correction of mild anaemia provided the compliance was good.
- Moderate anaemia (seen in about 15-20% of pregnant women majority of whom come to antenatal clinic after 20 wk of gestation) did not respond well to oral iron therapy because
  (i) One or two tablets a day was insufficient to raise the Hb levels beyond 11 g/dl;
  (ii) Attempts to increase the dose resulted in increased side effects and reduced compliance; and
  (iii) Increased dose also increased gut motility and reduced iron absorption

As a result, oral iron therapy was not found useful for treatment of moderate anaemia.

Indications of parenteral iron therapy:

- Reduced compliance of oral iron owing to poor tolerability and side effects.
- Unresponsiveness to oral iron
- The GI adverse effects of oral iron may further exacerbate the pregnancy associated GI isturbances which includes indigestion, constipation, nausea, vomiting and reflux esophagitis.
- Need for quick recovery from anemia
- In patients who need rapid restoration of iron stores.
- Parenteral iron may be used from the second trimester and during the postpartum period.

Prerequisites for parenteral iron therapy:

- Diagnosis of IDA needs to be confirmed before starting parenteral therapy.
- The infusion should be carried out only in a health facility with adequate supervision
- Availability for the management of anaphylaxis.
- Sensitivity test prior to infusion is recommended.

Contraindications to parenteral iron:

1. History of anaphylactic reactions to parenteral iron therapy.
2. First trimester pregnancy, chronic liver disease and active infection (acute or chronic). No evidence of use of IV iron in the first trimester of pregnancy is present.
3. Oral iron should be stopped at least 24 hours prior to therapy to avoid toxic reaction.

Calculation of total iron dose:

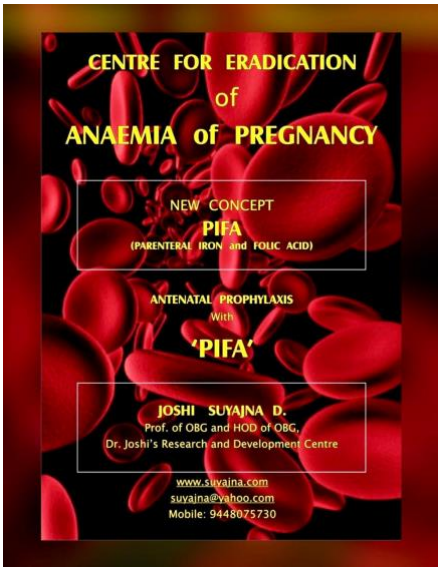
The total iron dose was calculated by formula, rounded to nearest multiple of 100.

Total Iron Dose = Weight (kg) x [Target Hb (gm/l) – Actual Hb (gm/dl)] x 0.24 + 500mg

The target Hb was taken as 12 gm/dl because of physiological haemodilution during pregnancy. Actual Hb was Hb at the time of inclusion, 0.24 was correction factor and 500 mg is average stored iron in adults.

Table 4:Administration Guidelines for Parenteral Iron Products

	Iron dextran	Iron sucrose	Ferric gluconate
Concentration	50 mg/mL (2-mL vial)	20 mg/mL (5-mL vial)	12.5 mg/mL (5-mL ampule)
IV injection (maximum rate	NTE 50 mg/min	NTE 20 mg/min	NTE 12.5 mg/min
Test dose	Required on first infusion	Physician discretion	Physician discretion
Test dose	25-mg IV slow push	25-mg IV slow push	25-mg IV slow push or 25 mg in 50 mL of NS IV over 60 min
Dosing	100mg	100mg	125mg
IV injection	100 mg over 2–5 min	100 mg IV over 5 min	125 mg IV over 10 min
Maintenance dose	Daily until calculated total amount required has been reached	1–3 times week	1,000 mg over 8 dialysis sessions
Minimum cumulative dose	Based on iron replacement calculations	1,000 mg	1,000 mg
Stability	Not reported	48 hr (concentration of 0.5–2 mg/mL)	Not reported
Diluent	0.9% sodium chloride	0.9% sodium chloride	0.9% sodium chloride
Total dose infusion	Yes	No	No
Infusion	Dilute dose in 250–1,000 mL of 0.9% NS infuse over 1–6 hr	100 mL 0.9% NS IV over 15 min	125 mg in 100 mL of NS IV over 1 hr
Routes	IM (INFed) IV infusion	IV injection IV infusion	IV injection IV infusion



PIFA: Parenteral Intravenous iron & Folic Acid : PIFA Prophylaxis: by Suyajna Joshi D.

In pregnant women, oral iron is often used for prophylaxis of iron deficiency and is recommended as first-line treatment for pregnant women with iron deficiency anaemia . However, oral iron substitution has shown to be insufficient for the treatment of severe iron deficiency anaemia and is often associated with gastrointestinal side effects . Therefore, guidelines recommend that physicians consider intravenous (i.v.) iron administration in pregnant women with severe iron deficiency anaemia (Hb< 9.0g/dL), and in case of intolerability to oral iron as well, insufficient Hb increase after oral iron treatment or if there is a need for rapid Hb reconstitution .

Ferric Carboxymaltose (FCM) is an i.v. iron formulation which can be used at high doses and allows rapid administration (up to 1000 mg in a single dose infused in 15 min). Because it is free of dextran and its derivatives, FCM does not cross-react with dextran antibodies and never needed the administration of a test dose. More recently, the European Medicines Agency (EMA) concluded that no test dose should apply to i.v. iron products authorized in the European Union; yet staff and facilities to evaluate and manage anaphylactic or anaphylactoid reactions should be immediately available . At least four postpartum studies compared the safety and efficacy of FCM versus oral iron [26– 29]. Faster and greater Hb-responses were achieved in FCM- treated patients compared to those receiving oral iron and FCM replenished iron stores efficiently. Rather few studies or cases with limited numbers of FCM-treated pregnant women have been reported .

When Christian Brymann started using Inj. Iron Sucrose IV we had a new hope and there was no looking back. In 1995-96 we did a RCT at VIMS comparing Inj.Imferon with Inj. Iron Sucrose IV, the results were more than encouraging. In spite of satisfactory increase in Hb% the suboptimal dose, multiple infusions with its adverse patient compliance were some of the inhibitory factors of IV Iron Sucrose.

We introduced Inj. Ferric Carboxymaltose in pregnancy in the face of reservations by conventional EBM dependent obstetricians. We at KSTP - Ballari had visualized that PIFA (Parenteral Intravenous Iron & Folic Acid) by a Single dose 1000 mg of Inj. FCM is a holistic approach for eradication for Pregnancy anaemia and started as a community programme by 2012, we have started reaping the results. As an established antenatal prophylaxis for anaemia of pregnancy - PIFA with 1000 mg of Inj. FCM intravenous is given to all pregnant women with completion of 12 weeks of gestation. PIFA Prophylaxis by Suyajna Joshi has become the mainstay in Eradication of Pregnancy Anaemia project.

Newer intravenous iron formulations:

In the last 2 years, three new IV iron compounds have been released for clinical use in patients with IDA. Two are currently approved for use in Europe [ferric carboxymaltose (FCM) and iron isomaltoside 1000 (Monofer®)] and one in the United States [Ferumoxytol (FeraHeme®)]. In their pre-registration trials, all of these three new compounds potentially had better safety profiles than the more traditional IV preparations, particularly because these products may be given more rapidly and in larger doses than their predecessors with the possibility of complete replacement of iron in 15-60 minutes.

Ferric carboxymaltose (FCM):

FCM is a new parenteral dextran-free iron product and the first of the new agents approved for rapid and high-dose replenishment of depleted iron stores. FCM is an iron complex that consists of a ferric hydroxide core stabilized by a carbohydrate shell. The design of the macromolecular ferric hydroxide carbohydrate complex allows controlled delivery of iron to the cells of the RES and subsequent delivery to the iron-binding proteins, ferritin and transferrin, with minimal risk of releasing large amounts of ionic iron into the serum. FCM is a stable complex with the advantage of being non-dextran-containing and with a very low immunogenic potential and therefore the risk of anaphylatic reactions is low. Its properties permit the administration of large doses (15 mg/kg; maximum of 1000 mg/infusion) in a single and rapid (15-minute) infusion without the requirement of a test dose.

The therapeutic efficacy of IV FCM has been evaluated in several randomized, open-label, controlled, multicentre trialsunder different conditions associated with absolute or functional

iron deficiency with or without anemia, including patients with IBD, heavy uterine bleeding, postpartum IDA, chronic heart failure and CKD patients on hemodialysis or not.

Most of these trials compared FCM with oral iron and found it to have a better efficacy in terms of improving Hb levels and particularly with regards to the body iron replenishment; it was significantly faster and higher than with ferrous sulfate. FCM is approved in Europe, Asia, and Australia, but has not yet been approved by the FDA due to unexplained hypophosphatemia two weeks after infusion in patients with CKD and an imbalance in cardiovascular events and deaths in the treatment compared to the placebo arm. However, it should be noted that none of the deaths in the submitted data were considered related to the administration of this IV iron.

The benefit of FCM is the efficacy of IV iron administration without the inconvenience of multiple small- dose injections and long infusion times. For example, if a patient requires 1000 mg of IV iron to correct the iron deficiency, this can be administered 20 times more rapidly with FCM than with iron dextran (0.25 hours versus 2.7 hours). The administration time for 1000 mg of FCM in 250 ml of NS in 15 min in one visit compared with 161 minutes needed for IS administration. The resulting efficiency ratio is over 10 times better for FCM versus IS. Moreover, FCM effectiveness is associated with real cost-saving benefits for hospitals, healthcare providers and patients (less frequent and shorter hospital visits).

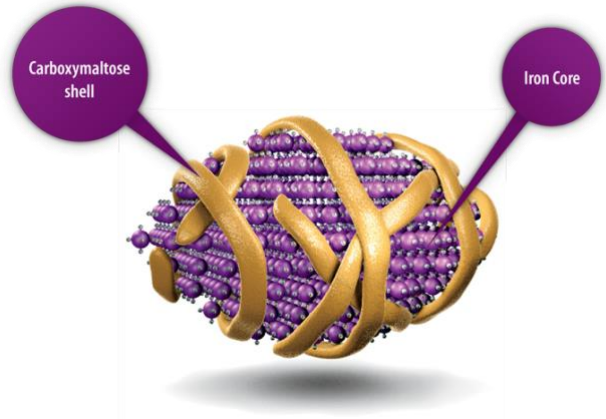


Image 3: structure of FCM

Ferumoxytol (FeraHeme®):

This formulation was approved by the FDA in 2009 for iron replenishment in CKD patients with IDA. It can be administrated as a relatively large dose (max 510 mg) in a rapid (< 20 seconds) session without test dose requirement. The published safety profile of ferumoxytol is consistent with that of LMW-ID, FG and IS. However, thisproduct is not currently approved in Europe and the FDA is continuing to evaluate Ferumoxytol due to reports of serious cardiac disorders. In addition, ferumoxytol administration may transiently interfere with diagnostic ability of magnetic resonance imaging which is frequently used for the diagnosis and follow-up of IBD; consequently this does not seem to be an appropriate IV iron compound for IBD patients. A warning about potentially life threatening events was added to the instructions for use of ferumoxytol in a recently mandated change.

Iron isomaltoside 1000 (Monofer®):

The newest IV iron agent, iron isomaltoside 1000 (Monofer®), was introduced into Europe in 2010. This formulation is a non-branched, non-anaphylactic carbohydrate, structurally different from the branched polysaccharides used in iron dextran. Iron isomaltoside 1000 has a very low immunogenic potential and a very low content of free iron and can therefore be administered as a rapid high dose infusion of up to 2000 mg without the application of a test dose, which offers considerable dose flexibility, including the possibility of providing full iron repletion in a single infusion (one- dose iron repletion). Most IV iron agents are colloids with spheroidal iron- carbohydrate nanoparticles. Each particle consists of a carbohydrate shell that stabilizes the iron-oxyhydroxide core (Fe [III]). However, the structure of Monofer® is somehow different, as the linear oligosaccharide isomaltoside 1000 allows the formation of a matrix with interchanging iron and carbohydrate, instead of a classical spheroidal iron carbohydrate nanoparticle.

Image 4: Matrix structure of iron isomaltoside 1000 which enables controlled and slow release of iron.

The availability of stable parenteral iron compounds allowing for higher dose infusion may greatly facilitate iron replacement therapy in IDA patients. The use of these stable compounds carries benefits for both the patient (less disruption of life, less time away from home/work, reduced injections, few side effects, etc.) and the hospital/health service (reduced visits, reduced physician and nurse time, improved out-patient management, improved cost-effectiveness, etc.). Other benefits of high dose or TID (three times daily) infusions are the significant reduction of treatment period and the higher ferritin obtained, which may be important to delay the recurrence of IDA.

Monitoring of response to treatment:

Response to treatment should be monitored using Hb concentration and serum ferritin levels after 3, 6 and 8 weeks and there should be improvement in those parameters. Other measures were improvement in serum iron level, reticulocyte count, TIBC, MCV.

Due to iron metabolic pathways, a rise in reticulocyte count will occur during the second week and thereafter, provided bleeding is not excessive, one can expect a rise in haemoglobin of approximately 1.5g/week.

Intravenous iron therapy is safe, convenient and more effective then oral iron therapy in treatment of iron deficiency anaemia and when compliance is the problem and when patients are coming from difficult geographical conditions and approaching the hospital late in pregnancy. A decrease in the rate of transfusion use post partum. Limitations with intravenous iron replacement include the need for medical supervision in the setting of limited healthcare resources.

Parenteral iron therapy helps in achieving target haemoglobin levels in anaemic patients and if given in time parenteral iron therapy will help to reduce the risk of anaemia and subsequent maternal and foetal complications as well as risk of blood transfusion during pregnancy and at the time of delivery. Moreover the compliance of patients with parenteral iron is much better due to reduction of gastrointestinal side effects. So the current guidelines for the management of iron deficiency anaemia should incorporate parenteral iron therapy as effective and safe treatment in pregnant women with IDA.

BLOOD TRANSFUSION :

Indications for blood transfusion in pregnancy are –

- Severe anaemia at any gestational age
- Moderate anaemia beyond 36weeks gestational age
- Failure of response to iron therapy
- Obstetric haemorrhage
- Sickle cell anaemia and thalassemia in pregnancy
  Properly grouped and cross matched Packed cell volume is used for transfusion which is administered slowly over 4-6 hours

MANAGEMENT DURING LABOUR :

Apart from the general management protocols of labor monitoring –

- Fluid overload should be avoided taking care of the adequate nutrition and hydration
- Vigilant monitoring for signs and symptoms of congestive cardiac failure and pulmonary oedema
- Continuous/intermittent oxygen inhalation based on severity of anaemia
- AMTSL should be carried out to prevent the blood loss as even milder degree of blood loss in anaemic patients may jeopardise the maternal health

Postpartum anaemia: Symptoms of anaemia in the postpartum period include dyspnoea, lethargy, palpitations, and maternal infections, which may influence the ability to care for and bond with a new-born. In addition, there are longer term effects of postpartum haemorrhage related to postpartum anaemia, including impaired quality of life, poor cognitive performance, emotional instability, increased risk for postpartum depression, and poor

lactation, these occur remote from delivery, and constitute a significant health problem in women of reproductive age. Lactation also results in loss of iron via breast milk.While postpartum anaemia is typically seen subsequent to postpartum haemorrhage, it is most commonly associated with antepartum iron deficiency anaemia combined with blood loss at delivery. While there currently is no clear classification of postpartum anaemia, it is generally described as an Hb concentration < 100 g/L at 24 to 48 hours after delivery. Approximately 15% of women will have a blood loss > 500 mL at the time of delivery. It is generally recommended that antepartum anaemia caused by iron deficiency and postpartum anaemia should be treated. Parenteral iron has been shown to produce a faster and greater increase in Hb concentration than oral supplementation without the risks associated with a blood transfusion. Parenteral iron is emerging as an alternative treatment for significant postpartum anaemia.

CONTRACEPTION :

Advisable to enable birth spacing and to replenish iron stores. Injectable contraception, COC pills or progesterone only pills are used. Though Intrauterine copper T devices are not contraindicated , better avoided as it can be a cause for heavy menstrual bleeding.

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3. The Use of Parenteral Iron Therapy for the Treatment of Postpartum Anemia: Christopher M. Nash, MD, FRCSC, Victoria M. Allen, MD, FRCSC: J ObstetGynaecol Can 2015;37(5):439–442
4. Parenteral iron therapy in obstetrics: 8 years experience with iron–sucrose complex: G. Perewusnyk et al: British Journal of Nutrition (2002), 88, 3–10
5. The Pharmacokinetics and Pharmacodynamics of Iron Preparations: Peter Geisser and Susanna Burckhardt: Pharmaceutics 2011, 3, 12-33; doi:10.3390/pharmaceutics3010012
6. Intravenous iron therapy: how far have we come?: Rodolfo DelfiniCançado, Manuel Muñoz: Rev Bras HematolHemoter. 2011;33(6):461-9
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8. Parenteral Iron Therapy Options: Scott B. Silverstein and George M. Rodgers: American Journal of Hematology 76:74–78 (2004)

9. Anemia in Pregnancy: J.B.Sharma, Meenakshi Shankar: JIMSA October - December 2010 Vol. 23 No.4

RECOMMENDED BOOKS :

1. Iron Deficiency and Other Hypoproliferative Anemias
John W. Adamson ; Harrison's principles of internal medicine; 20th Edition

2. Essentials of Obstetrics by Lakshmi Seshadri ; First Edition

3. Ian Donald's practical obstetric problems ; 7th Edition

4. Gabbe's Obstetrics : Normal and problem pregnancies ; 6th Edition