FOGSI General Clinical Practice Recommendations

Management of Iron Deficiency Anemia in Pregnancy

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Introduction and rationale

Anemia among pregnant women is a serious global health concern. According to World health organization (WHO) report, about 32.4 million pregnant women suffer from anemia worldwide, of which 0.8 million women are severely anemic (1). Moreover, 50% cases of anemia are attributable to iron deficiency anemia (IDA) (1).

Iron deficiency anemia during pregnancy increases the risk of low birth weight (LBW), preterm birth, maternal and perinatal mortality, and poor Apgar score (2, 3). An estimate by WHO attributes about 591,000 perinatal deaths and 11,5000 maternal deaths globally to IDA, directly or indirectly (2). According to Lone et al, anemic women as compared to non-anemic women are at 4 fold higher risk of preterm birth; 2.2 fold, LBW; and 1.8 fold, low Apgar score (3). In a systematic review, a dose-response relationship was observed for an increase in dose of iron supplements and reduction in LBW (4).

It is projected that India has the utmost prevalence of anemia i.e. 57-96.2%, among the South Asian countries (5-9).

The prevalence and severity of anemia in India are as presented in Table 1.

Table 1 Severity of anemia in national surveys

Survey	Anemia of pregnancy (%)			Severity of anemia (%)		
	Urban	Rural	Total	Mild	Moderate	Severe
DLHS-2* (2002-04)(6)	-	-	96.2	50.7	42.5	3.1
NNMB-2003 (7)	-	-	75%	24.4	45.9	4.3
NFHS-3 (2005-06)(8)	54.6	59.0	57.9	25.8	30.6	2.2
NFHS-4 (2015-16) (9)	23.6-61.7	19.6-58.1	23.6-61.4	-	-	-

In India estimated maternal deaths due to IDA is approximately 3,26,000, with an associated disability-adjusted life years (DALYs) of 12,497,000 (2). Losses from IDA result in an increase in the cost of up to 4.05% of gross domestic product (GDP) in developing countries, and 1.18% of GDP in India (10).

It is known that low socioeconomic status high parity nutritional deficiencies, phytate rich Indian diets, malaria, helminthic infections, and inflammatory or infectious diseases further increase the risks of IDA during pregnancy (11-13).

To combat the high prevalence of IDA several government programs and state level schemes were rolled out in various states of the India. National nutritional anemia prophylaxis program 1970, national anemia control program 1991, 12/12 initiative 2007 are some of the nationwide initiatives. Few state-specific schemes include Madilu scheme, Thayi bhagya scheme, and Janani suraksha yojana. In spite of Government's 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% (9). The prevalence is higher in urban areas (23.6-61.7%) as compared to rural areas (19.6-58.1%) (9). Diverse religions, cultures, languages, food habits, lifestyle, and traditions influence management practices present a challenge to the implementation of the health program. Hence, there is a continuing requirement for county-specific harmonized guideline for the control of IDA in India. It is expected that this practical approach would promote the implementation of cost-effective evidence-based care.

Methodology

The present Good Clinical Practice Recommendations (GCPR) from the Federation of Obstetrician and Gynaecology Society of India (FOGSI) for the management of anemia in pregnancy are developed by an experienced panel of gynecologists, obstetricians, and hematologists from across the country. A literature search was carried out electronically in PubMed and Google Scholar. Specific evidence from India (MedIND/IndMED) was identified. Also, a manual search was carried out in key non-indexed journals. Abstracts in the English language were scanned and included in the formulation of the recommendation. Existing recommendations from national and international guidelines for the management of anemia in pregnancy were also reviewed.

The draft guideline, with proposed GCPR, was reviewed by the members through mail communications and meetings for finalizing consensus on each GCPR for the management of anemia in pregnancy. The modified Grade system was used for classifying the quality of evidence as 1, 2, 3 or 4 (Table 2) (14).

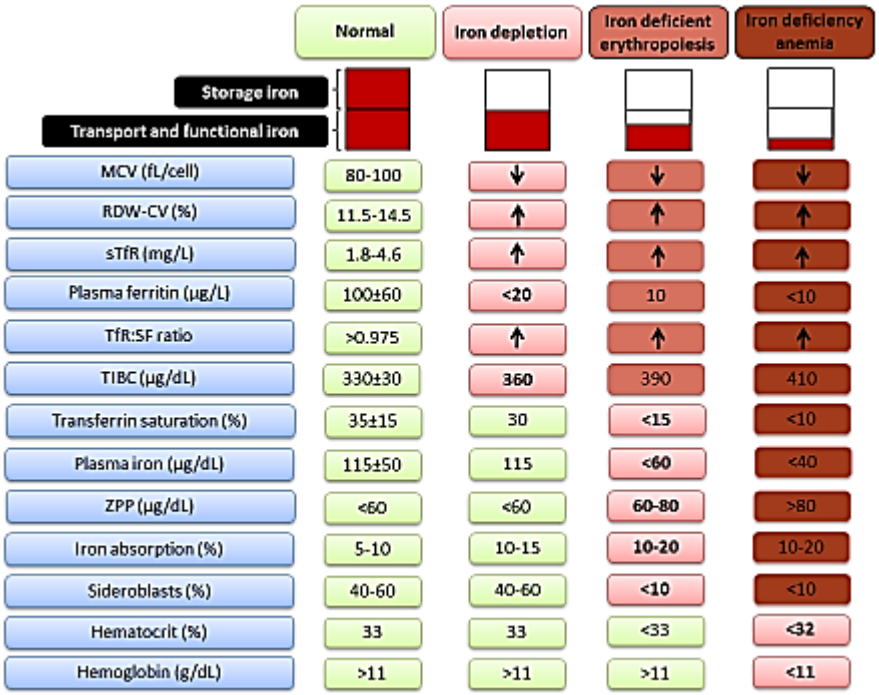
Table 2 Grading of recommendations

Grading of recommendations	
GRADE A	Strongly recommended "RECOMMENDED"
GRADE B	Weaker recommendation "SUGGESTED"
Classification of level of evidence	
1	High-quality evidence backed by consistent results from well-performed randomized controlled trials or overwhelming evidence from well executed observational studies with strong effects
2	Moderate quality evidence from randomized trials
3	Low-quality evidence from observational evidence or from controlled trials with several serious limitations
4 (Practice point)	Not backed by sufficient evidence; however, consensus reached by expert panel group based on clinical experience and expertise

Diagnosis

The continuing problem of IDA in India is attributed to lack of appropriate diagnosis at a suitable age. Iron deficiency reflects inadequate mobilization of iron stores, leading to impaired "demand to supply" of iron to tissues and red blood cells (RBCs). The requirement for iron greatly increases with each growing stage, including children below 2 years of age, adolescents, pregnant and lactating women. Iron deficiency anemia evolves through three distinct stages. Depletion of storage iron occurs in the first phase (stage I), where the total body iron is decreased but red cell indices and hemoglobin (Hb) synthesis remain unchanged. Both these indices change when the supply of iron to bone marrow is reduced (stage II or iron deficient erythropoiesis). In stage III, eventually IDA develops due to insufficient supply to sustain a normal Hb concentration. Different phases of IDA are presented in Figure 1.

Figure 1. Various stages of iron deficiency anemia and their indicators (15).



Signs and symptoms

Although Hb test is recommended at first antenatal visit, examination for signs of pallor of the eyelids, tongue, nail beds, and palm should be regularly used. Some iron deficient patients, with or without clinical signs of anemia, may have alopecia, atrophy of lingual papillae, or dry mouth due to reduced salivation (16). The symptoms specific to the ID include; the syndromes of Plummer-Vinson or Paterson-Kelly (dysphagia with oesophageal membrane and atrophic glossitis), gastric atrophy, stomatitis due to rapidly turning over of epithelial cells (17); spoon-shaped nails (koilonychia) and pallor. These changes were caused by a reduction of iron-containing enzymes in the epithelia and the gastrointestinal (GI) tract (16). The restless leg syndrome might be striking neurological sequelae prevalent in pregnancy (18). Pica, the eating disorder in which there is an appealing desire to lick or eat non-food items, such as gypsum, chalk, soil, ice (pagophagia) or paper, is prevalent in pregnant women (19-21). Pagophagia (intense desire to eat ice) is quite specific to ID and responds quickly to treatment (22).

Laboratory test

There are four groups of tests available for assessment of IDA.

1. Hb, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), red cell distribution width (RDW), reticulocyte Hb content, % hypochromic cells, red cell size factor, and low Hb density;

2. Direct measurement of iron stores through assessment of serum iron, total iron binding capacity (TIBC), % saturation, serum ferritin, bone marrow biopsy iron;

3. Assessment of iron heme 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).

Red blood cell parameters and indices

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

Changes in Hb concentration and hematocrit occur (as shown in Fig.1) only in late stages; both these tests are late indicators of ID. Nevertheless, these tests are important for determining IDA. Low Hb with a reduced MCV is usually the initial finding on a routine CBC. The severity of anemia is based on the patient's Hb/hematocrit level Table 3.

Table 3 Hemoglobin cut off in pregnancy anemia (23).

Pregnancy state	Normal (g/dL)	Mild (g/dL)	Moderate (g/dL)	Severe (g/dL)
First trimester	11 or higher	10-10.9	7-9.9	Lower than 7
Second trimester	10.5 or higher			
Third trimester	11 or higher	10-10.9	7-9.9	Lower than 7

Altitude above sea level and smoking are the known modifiers of Hb concentration (24). The rising maternal blood volume and iron requirements of the fetus are responsible for the dramatic change in Hb concentration in a healthy, iron sufficient women. The Hb concentrations decrease in the first trimester, which continues to decline and reach their lowest point in the second trimester, and start to increase again in the third trimester.

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 (23). Hemoglobin concentration is the commonest hematological estimation, there is a strong correlation between Hb concentration and serum ferritin levels (25). Generally recommended methods of Hb estimation are cyanmethemoglobin and the HemoCue® system(23).

Mean corpuscular volume is the measure of the average red blood cell volume, and MCHC is the measure of the concentration of Hb in a given volume of packed red blood cells. It is important to note that up to 40% of patients with true IDA would have normocytic erythrocytes (i.e. a normal MCV does not rule out IDA) (16). Red cell distribution width (RDW) has a better sensitivity than MCV for the diagnosis of IDA (26).

The RDW is a measure of the change in red blood cell width and is used in combination with the MCV to distinguish an anemia of mixed cause from that of a single cause. Increased RDW represents variance in the red blood cell volume distribution, similar to a peripheral blood smear anisocytosis. In the initial stages of IDA, there is a fall in MCV accompanied with increasing RDW values due to a preponderance of microcytes (27, 28). Following treatment, marked reticulocytosis occurs in the first 4 weeks, manifested as a sudden increase in RDW, sometimes to over 30% (29). Thus, 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 the initiation of therapy (30).

It is common for the platelet count to be greater than 450,000/µL in the presence of IDA, though, the red cell count falls. It is noteworthy that microcytosis observed in the peripheral smear may be seen even before abnormalities in CBC develop. If the patient has coexistent folate and or vitamin B12 deficiency, the peripheral smear would show a blend of microcytic and macrocytic hypochromic erythrocytes, along with normal MCV (30). Furthermore, the presence of microcytic hypochromic red cells and typical “photo pencil cells” are indicative of IDA (31).

A few studies have reported sensitivity and specificity, respectively, of RDW in the diagnosis of IDA in pregnancySultana et al 97.4% and 83.2%; Tiwari et al, 72.8%, and 82.4%.

Iron deficiency anemia is characterized by microcytic red blood cells. Other conditions causing microcytic RBCs include anemia of chronic disorders, beta-thalassemia, and

sideroblastic anemias. All the tests described above helps differential diagnosis of various microcytic RBCs etiologies as shown in Table 4 (32, 33).

Table 4. Differential diagnosis of various microcytic RBCs etiologies (32-34)

Indicator	**IDA**	**BT**	**SA**	**ACI**
Hemoglobin	Decreased	Normal or decreased	-	Decreased
Ferritin	Decreased	Normal Increased	Normal or increased	Normal or Increased
Serum iron	Decreased	Normal or increased	Normal or increased	Normal or Decreased
TIBC	Increased	Normal	Normal	Slightly decreased
TS	Decreased	Normal to increased	Normal to increased	Normal to slightly decreased
sTfR	Increased in severe IDA	>100 mg/L	-	Normal
FEP	Increased	Normal	-	Increased
MCV	Decreased	Decreased	Normal	Normal or decreased
RDW	Increased	Normal to increased	Increased	Normal
Reticulocytes	Decreased Increased	_ Decreased	- -	Normal or decreased -

ACI, acute chronic inflammation; BT, beta-thalassemia; IDA, Iron deficiency anemia; FEP, free erythrocyte protoporphyrin; MCV, mean corpuscular volume; RDW, red cell distribution width; SA, sideroblastic anemia; sTfR, soluble transferrin receptor; TIBC, total iron binding capacity; TS,transferrin saturation

However, in low-resource settings like India, where these tests are not easily available, the RBC indices are of great value for primary diagnosis which can reduce unnecessary investigative costs. Of all available indices, the Meltzer index (MCV/RBC) has been shown as the most reliable index with high sensitivity (35, 36).

Serum ferritin

Ferritin has been studied in pregnant patients as a sensitive indicator of IDA (26, 37, 38). Serum ferritin reflects ID in the absence of inflammation, with the advantage of steady concentration even on the recent intake of iron rich foods. **During pregnancy, in women with adequate iron stores, serum ferritin initially rises and later gradually falls by 32 weeks (due to hemodilution), followed by a slight rise in the third trimester. Fall in serum concentration below 15 µg/L indicates iron depletion in all stages of**

pregnancy(39). However, treatment needs to be initiated when the concentration falls below 30µg/L as this indicates early iron depletion (39, 40).

Soluble transferrin receptor (sTFR)

It is a sensitive measure of tissue iron supply but is an expensive test. It is a transmembrane protein which transports circulating iron into the RBCs and is expressed on erythrocyte membranes; sTfR and total transferrin concentrations are directly proportional. The assay is not standardized(41). Cutoffs of sTfR (and, thus, the sTfR–F) depend on the assay used, which is a key limitation. There is a gradual increase in mean sTFR concentration as pregnancy progresses. The increases are mostly influenced by increased erythropoietic activity than by iron depletion (42).

Serum Iron and total iron binding capacity

Serum iron and TIBC are the other independent indicators of iron stores or availability. The TIBC measures the obtainability of iron-binding sites. A specific carrier protein, transferrin, transports extracellular iron in the body. Therefore, TIBC is the indirect measure of measures transferrin levels that rises as serum iron concentration (and stored iron) declines. The TIBC decreases with malnutrition, inflammation, chronic infection, and cancer (43).

Erythrocyte Zinc Protoporphyrin (EPP) and Zinc protoporphyrin (ZPP)

The erythrocyte zinc protoporphyrin assay is used for assessment of iron status. It is formed when zinc is incorporated into protoporphyrin in place of iron during the biosynthesis of heme. (44). It is a sensitive test, but with limited specificity because EPP increases in the settings of inflammation, lead poisoning, ACD, and hemoglobinopathies (43).

Reticulocyte hemoglobin content

Reticulocyte Hb concentration determines the amount of iron presented to the bone marrow for uptake into new RBCs. This test is not commonly available. The sensitivity and specificity of this are analogous to those of serum ferritin (45).

Bone Marrow iron

In order to make a 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 the absence of stainable iron.

Trial of Iron therapy

In situations with low Hb or hematocrit, a presumptive diagnosis of IDA is supported by a response to iron therapy. If the patient is known to have hemoglobinopathies, serum ferritin has to be checked to rule out microcytic or normocytic anemia before starting iron therapy to avoid iron overload. An increase in Hb at week two confirms ID. **Detailed investigations should be done if the individual does not respond to iron supplementation within two weeks** (46).

Management

Management of ID can be achieved at two levels, at the individual patient or at public health level. Prevention strategies developed by WHO comprise food-based approach, iron supplementation, improvement in health services and sanitation. Other strategies, e.g. control of hookworm, malaria, and parasitic infestations are also required to prevent IDA in Indian women (47).

Food-based strategies

Dietary modification/ improvement

The physiological demand for iron during pregnancy is 3 times higher than in non-pregnant, and it increases as pregnancy progresses (39, 48). The net iron requirements for pregnancy has been calculated as 840 mg taking into account the requirements for fetus placenta, expansion of maternal erythrocyte mass and final losses due to delivery (49). Though iron requirements decrease during the first trimester, there is an increase of 4-6 mg/day in the second and third trimesters which may reach to 10 mg/d during the last 6–8 weeks of pregnancy (50). The extent of absorption of iron in pregnancy also needs to be contemplated. The iron absorption has been found to decrease during the first trimester of pregnancy, which rises during the second, and this increase lasts the remainder of pregnancy (50).

The dietary modification involves improving intake of iron by increasing the quantity of iron rich food and practices that increase the absorption of iron (51). The etiology of anemia in India is multifactorial with low iron bioavailability as a major etiological factor(52). Moreover, non-heme iron, a poorly absorbed form of iron, from cereals, pulses, vegetables and fruits contribute about 90-95% of total daily iron in Indian diets (52). Nonheme iron (present in plant-based foods) absorption is inhibited by phytic acid (6-phosphoinositol)

which is found in whole grains, lentils, and nuts. In addition, polyphenols, such as tannic and chlorogenic acids, found in coffee, tea, red wines, and a variety of vegetables, cereals and spices also inhibit iron absorption. They are capable of forming complexes with iron at physiological pH of 7.4 and alter the equilibrium concentration of free iron and thus influence bioavailability. Promoting the use of iron absorption enhancers like ascorbic acid is an effective way of increasing bioavailability of iron and a resultant improvement in Hb level (53-56). Nair et al demonstrated >100% increase in bioavailability with 100 g of guava fruit included in the regular meal. In this study, the iron absorption from the modified meal was greater when compared with a regular meal (23.9% ± 11.2% vs. 9.7% ± 6.5%, $P < 0.05$) (57). Because phytate is a known iron absorption inhibitor, consumption of phytates rich food should be discouraged with meals. Other food items that need to be eluded are tannins present in coffee, cocoa and tea; calcium, particularly in milk and milk products; phosphates in egg yolk; and oxalates in vegetables (58, 59).

There is evidence that dietary modification and awareness education among pregnant women improve maternal and neonatal outcomes (60-63). Individual counseling with nutrition education (NE) along with weekly reinforcement significantly increased mean Hb (g/dL) levels (Post-NE vs Non-NE = 9.65 ± 0.97 vs 7.85 ± 1.58, $p<0.001$) and decreased anemia prevalence (Post-NE vs Non-NE = 78.7% vs 96%) in post-NE group in nutritional status during pregnancy in the study by Garg A et al. (64)

Food fortification

Food fortification is the concept of combining a vehicle (probably commonly consumed food items) and a nutrient together, is probably the most cost-effective, long-term approach in improving the iron status during pregnancy at the national level (65-67). When accompanied with supplementation, food fortification can be an effective way in managing IDA in women with pregnancy (68). Of the various fortifying iron compounds, sodium iron ethylene diamine tetra acetic acid (NaFeEDTA) is most frequently used owing to its effectiveness with a diet rich in phytates such as sugar, curry powder, soy sauce, fish sauce and maize flour (69-73). Micronized ground ferric pyrophosphate is another iron salt used for fortification of color-sensitive food vehicles such as salt in Africa (74) and rice in India (75). Bio fortification is a recent approach in iron fortification of wheat, bean, cassava, maize, rice, and yam (76).

Food fortification was found to be non-inferior to iron and folic acid (IFA) supplementation in improving Hb concentration and decreasing the prevalence of IDA in pregnant women

(77-86). Double fortified salt (DFS) has been demonstrated to significantly increase mean Hb (+0.42 g/dL vs. 0.20 g/dL , p<0.001) in pregnant women consuming DFS than women not consuming fortified salt, and DFS provided additional ~93 mg of iron within 6 months of supplementation (68).

Supplementation

The average daily intake of iron in pregnancy increases from 4-6 mg/day in the second and third trimesters of 10 mg/d during the last 6–8 weeks of pregnancy (50). These requirements are unlikely to be met by the diet alone, because of poor accessibility, availability, and affordability of diversified food (87). Hence, regular iron supplementation is necessary for pregnant women to prevent IDA. The supplementation to prevent anemia targets at improving the ID and it may be community-based initiative while therapeutic supplementation aims at treating established IDA, which is a part of the healthcare delivery system (46).

Oral supplementation

A Cochrane systematic review evaluated the efficacy of daily iron supplementation alone or along with folic acid or other micronutrients compared with placebo or no iron in pregnant women. Prophylactic iron supplementation displayed a significant decrease in the risk of maternal anemia (70%), ID and IDA (57%) at term. Iron treated women had greater probability of higher Hb concentrations at term and in the post-partum period. Nonetheless, they were at relatively high risk of Hb concentrations >13 mg% during pregnancy, and at term. Women taking iron supplements had lower incidence of giving birth to LBW babies (8.4% vs 10.3%, RR 0.84; 95% CI 0.69 to 1.03), preterm babies (RR 0.93; 95% CI 0.84 to 1.03) and also slightly heavier babies (mean difference, 23.75 g; 95% CI -3.02 to 50.51). There were no significant differences between groups for congenital anomalies, neonatal death, and maternal mortality death (88). Another systematic review and meta-analysis, which included 44 cohort studies in addition to 48 RCTs evaluating impacts of prenatal iron supplementation on adverse pregnancy outcomes, found an increase in maternal Hb by 0.459 g/dL, reduction in the risk of anemia (RR 0.50, 0.42 to 0.59), ID (RR0.59, 0.46 to 0.79), IDA (RR0.40, 0.26 to 0.60), and LBW (RR 0.81, 0.71 to 0.93) compared to controls. Of particular note, the risk of LBW (adjusted OR 1.29, 1.09 to 1.53) and preterm birth (adjusted OR1.21, 1.13 to 1.30) were higher with anemia in the first and second trimester as shown by a meta-analysis of cohort studies. The exposure-response (dose response) analysis displayed increase

in birth weight of 15.1 g (6.0 to 24.2, linear trend p=0.005), decrease in risk of LBW by 3% (RR 0.97, 0.95 to 0.98, linear trend p<0.001), for every 10 mg increase in iron dose/day, up to 66 mg/day. Moreover, after adjustment for dose, the duration of the supplement was not significantly associated with the outcomes, as shown by an increase in birth weight by 14.0 (6.8 to 21.8 g, linear trend p=0.002) for each 0.1 g/dL increase in mean Hb (4).

Daily Vs Intermittent

A recent Cochrane systematic review has shown similar maternal and infant outcomes with both intermittent and daily supplementation; intermittent supplementation was associated with fewer side effects, although, the risk of mild anemia near term was increased. Intermittent supplementation has been proposed as a feasible alternative to daily supplementation for those pregnant women who are not anemic and have an adequate antenatal care, (89).

Iron Preparations

There are various iron salts commonly used for the treatment of anemia in India, the characteristics are as summarized in Table 5.

Table 5 Examples of Some Iron Preparations Available in the Indian Market, Their Compositions, and Costs (90)

Iron salt	Other supplements	Brand	Cost (INR)
Dried ferrous sulphate 60 mg	Folic acid 1.5 mg, vitamin C 75 mg, vitamin B6 1.5 mg, vitamin B12 15 mcg	Festo-TR® (DWD PharmaFesto-TR® (DWD Pharma	30.0
Dried ferrous sulphate (timed release) 60 mg	Folic acid 1.5 mg, ascorbic acid 75 mg, pyridoxine hydrochloride 1.5 mg, cyanocoblamin 15 µg	Conviron- TR® (Ranbaxy)	55.35
Ferrous sulphate 150 mg	Folic acid 0.5mg	COFOL (Cipla)	27.0
Dried ferrous sulphate (timed release) 150 mg	Folic acid 1 mg, nicotinamide 50 mg, vitamin B6 2 mg, vitamin B12 15 µg	Fesovit® spansule (Glaxo Smith Kline)	114.5
Ferrous sulphate 525 mg	Vitamin B12 12.5 µg, liver 100 mg, vitamin C 75 mg, folic acid 1 mg, vitamin B1 4.5 mg, vitamin B2 5 mg, nicotinamide 5 mg, vitamin B6 1.5 mg, calcium pantothenate 5 mg	Iberol® (P. Upjohn)	17.96
Ferrous sulphate 150 mg	Folic acid 0.5 mg	Fefol spansule (GlaxoSmithKline)	51.0
Ferrous sulphate 150 mg	Zinc sulphate monohydrate 6.18 mg, folic acid 0.5 mg	Fefol-Z spansule (GlaxoSmithKline)	98.5
Ferrous fumarate 350 mg	L-lysine monohydrate 150 mg, folic acid 1.5 mg, vitamin B12 15 µg, zinc sulphate 6 mg, copper sulphate 0.2 mg, manganese sulphate 1 mg	Ironate capsule (Chemo)	19.00
ferrous fumarate 165 mg	Folic acid 750 µg, docusate sodium 50 mg, vitamin C 75 mg	Softeron (Aristo)	17.20
Ferrous fumarate 150 mg	L-histidine 4 mg, L-lysine monohydrochloride 25 mg, glycine 10 mg, vitamin B1 5 mg, vitamin B 2 3 mg, vitamin B6 1.5 mg, vitamin B12 2.5 µg, vitamin C 40 mg, zinc sulphate 50 mg, folic acid 0.5 µg	Astyfer® (Tablets)	87.42

Ferrous ascorbate 100mg	Folic acid 1.5mg,	Ferium XT (Emcure)	72.95
Calcium ferrous citrate 556 mg	Folic acid 0.3 mg, with other mineral salts	Raricap combi tab (Strides)	63.0
Ferrous calcium citrate equivalent to 25mg	Folic acid 0.3 mg	Raricap (Strides)	110
Ferrous calcium citrate equivalent to 50mg	Folic acid 0.3 mg	Raricap forte (Strides)	140
Carbonyl iron 100 mg	Folic acid 1.5 mg, vitamin B12 10 µg, selenium 60 µg, vitamin E 15 mg, zinc 11.5 mg	Safiron (Khandelwal)	133.33
Carbonyl iron 90mg	Folic acid 1.5mg, pyridoxine 3mg, cyanocoblamin 15mcg, zinc sulphate monohydrate 27.54mg	GEFER (Strides)	55.0
Carbonyl iron 50 mg	Zinc sulphate monohydrate 61.8 mg, folic acid 0.5 mg	COFOL-Z (Cipla)	59.25
Iron (III) Hydroxide Polymaltose Complex 100 mg	Folic Acid 1500 µg	Globac-PM (Zydus)	39.78
Iron (III) Hydroxide Polymaltose Complex 50 mg	Folic acid 0.5 mg	HEPOFER FORTE (Cipla) (syrup)	68.25
Iron polymaltose complex 100 mg	Folic acid 350 µg	FEGEM (Torrent)	49.0
Iron polymaltose complex 100 mg	Folic acid 350 µg	Orofer chewable tab (Emcure Pharma)	88.55
Elemental iron 100mg	Folic acid 1.5mg	GEFER-XT (Strides)	69.0
Elemental iron 60 mg	Calcium carbonate 1250 mg, Docosahexaenoic acid 200 mg	Trimester combi pack (Strides)	99.0
Controlled-release ferrous iron (as glycine sulphate) 100 mg	Folic acid 0.5 mg	Fecontin-F (Modi-Mundi Pharma)	62.8
Controlled-release ferrous iron (as glycine sulphate) 100 mg	Controlled release zinc sulphate monohydrate 61.8 mg, folic acid 0.5 mg	Fecotin-Z (Modi-Mundi Pharma)	80.4

A systematic review, which included about 10,695 patients, found extended-release ferrous sulphate with mucoproteose to be the most tolerated oral iron supplement of the various formulations evaluated (91). Numerous studies in India have been found to evaluate comparative efficacy and tolerability of different iron supplements as presented in Table 6.

Table 6 Summary of comparative studies in India on oral iron preparations

Author /year	N	Objective	Intervention	Comparator	Outcome	Results
RCT						
Pyarelal, 2015 (92)	90	CI vs FS & FF: efficacy in IDA	CI: 100mg OD for 2 months. **Inclusion criteria** Gestational age 14-20 wks Hb (9 - 11g/dL)	FS: 200mg t.i.d. FF: 200mg b.i.d. For 2 months	↑Hb (30 & 60D). ADR	• ↑Hb at 60D ($p<0.05$) (g/dL): CI, 8.69±0.77 to 11.67±0.68; FS, 8.89±0.63 to 10.21±0.73; FF, 8.43±0.89 to 10.03±0.91. • GI disturbances less in CI as compared to the others. • **CI is effective and better tolerated than others.**
Singhal SR et al, 2015 (93)		Various OI salts: efficacy & safety	FS (100mg), FF (100mg), FA (100mg), FB (30 mg), SoF (33 mg) **Inclusion criteria** Gestational age 16-28 wks Hb (7-10g/dL)	-	↑Hb (30 & 60D), SF (60D) ADR	• Mean↑Hb at 60D($p<0.001$) (g/dlL: FS, 0.93±0.27; FF, 1.06±0.28; FA, 1.13±0.35; FB, 1.11±0.27; SoF, 1.09±0.31 • Mean↑SF at 60D($p<0.001$) (ng/ml): FS, 12.19±5.01; FF, 12.65±5.77; FA, 13.44±7.89; FB, 13.47±7.03; SoF, 11.95±3.95 • % S/E : FS, 32; FF, 40; FA, 22; FB, 26; SoF, 14 • **FA & FB are more effective than FS. SoF les S/E**
Geetha R et al, 2014 (94)	60	CI vs FS vs FF: efficacy & tolerability	CI: 100mg OD for 2 months. **Inclusion criteria** Gestational age>14 wks Hb (9 - 11g/dL)	FS: 200mg t.i.d. FF: 200mg b.i.d. for 2 months	↑Hb (30 & 60D). ADR	• ↑Hb at 60D ($p<0.05$) (g/dL): CI, 8.62±0.74 to 11.8±0.60; FS, 9.12±0.66 to 10.53±0.76; FF, 8.63±0.94 to 10.44±0.98. • GI disturbances less in CI as compared to the others. • **CI showed highly significant ↑Hb & superior in efficacy & better tolerated than others**
Sagaonkar S et al, 2009 (95)	150	FF vs CI : efficacy & tolerability	FF: 152mg (app. 50mg elemental iron) + folic acid 750 µgµg + zinc sulphate 61.8mg) b.i.d for 12 wks. **Inclusion criteria** Gestational age >14 wks of amenorrhea & pregnancy with	CI: (app. 100mg elemental iron) + folic acid 1500 µgµg + Vitamin B12	↑ Hb (2 , 4 , 8 & 12 wks) ADR	• Mean↑Hb at 12 wks: 3g/dL (FF) & 1.489g/dL(CI) ($p<0.0001$). • achieved target Hb: 90.2% (FF) & 20.83%(CI) • FF showed better outcome than CI group with respect to response to therapy ($p<0.0001$) & tolerability ($p=0.002$). • Tolerability: 65.3% (FF) & 34.7% (CI)

			Hb (7-10 g/dL) target Hb: 11 g/dL	10 µg+ zinc sulphate 61.8mg) OD		• ADR more in CI group. • **FF is not only significantly superior in efficacy but is better tolerated than CI.**
Saha L et al, 2007 (96)	100	IPC vs FS: efficacy , safety, compliance & cost effectiveness	IPC: 100mg elemental iron + folic acid 500 µg daily for 8 wks (A) **Inclusion criteria** 14-27 wks gestation, with Hb< 9g/dL & SF< 12 µg/L,	FS: 120mg elemental iron + folic acid 500 µg daily for 8 wks (B)	PCV, MCV, MCH, MCHC, serum iron, & SF (8w)	• Mean ↑Hb (A vs B): 2.72±1.55 vs 2.9±1.08 g/dL • ↑% PCV (A vs B): 26 to 34 vs 25 to 34. • MCH, MCV, MCHC: sign. ↑ from baseline to 8w ($p<0.001$), but no sign. between groups. • S.Iron (A vs B) ($p < .001$): 67.29±9.12 to 105.61±15.22 µg/dL vs 65.75±21.45 to 108.88±42.5 µg/dL • SF (A vs B) ($p < .001$): 10.93±4.14 to 33.52±10.57 ng/ml vs 11.38±8.5 to 28.22±10.40 ng/ml • % ADR (A vs B) ($p < .001$): 31 VS 78. • Compliance (A vs B): 91% vs 87% ($p < 0.05$) • Cost (A vs B): Rs 237.08±47.25 vs Rs 169.98±75.51 ($P < .001$) • **IPC considered as alternative for the treatment of IDA intolerance to other iron (ferrous form)**
Shatrugna V et al, 1999 (97)	115	Various iron formulations: tolerance	FS tablets (60, 120 & 180mg of elemental iron), 60mg of elemental iron (FS salt, FF tablets & syrup) excipients added to pure FS salts, powdered FS tablets, FS gelatin capsules	-	Bioavailability & S/E	• Increasing the dose improves the bioavailability of iron, but associated with unacceptable S/E. • Liquid formulations of iron had a better bioavailability (FF syrup and gelatin capsules most superior)
Prospective study						
Kambar et al, 2013 (98)	100	IPC vs FS: efficacy , safety, complianc	IPC: 100mg elemental iron + folic acid 500µg OD for 6 weeks (A) **Inclusion criteria**	FS: 60mg elemental iron + folic acid 500 µg	After 6w, Hb, PCV, MCHC & Se. iron.	• Mean ↑Hb (A vs B): 1.348 vs 1.05g/dL ($p<0.05$) • Mean ↑% PCV (A vs B): 4.2 vs 3.14 ($p<0.05$) • Mean ↑MCHC (A vs B): 0.99 vs 0.66g/L ($p>0.05$) • Mean ↑Se. iron (A vs B): 3.7 vs 0.5µg/dL($p<0.001$)

		e & cost effectiven ess	14 to 20 wks of gestation, Hb: 6.5-8 g/dl (moderate anemia)	b.i.d for 6 wks (B)	ADR	• ADR (A vs B): 20% vs 51% (p<0.001). • Compliance (A vs B): 91% vs 87% (p < 0.05) • Cost (A vs B): Rs 207.08±47.25 vs Rs 139.98±75.51 (p <0.001) • **IPC is better alternative to FS as safe & compliance.**
Patil SS et al, 2013 (99)	60	Various iron salts: efficacy, tolerability & cost	FF, FB, & CI (each 100 mg) Folic acid 1.5mg, Vitamin B12 10µg administered OD to all. **Inclusion criteria** Gestational age 12-22 wks, Hb <10g/dL & microcytic hypocromic anemia Study period- 3 months	-	Hb, MCV, retic count (1, 2, 3 months) & SF (3 months). ADR	• Significant ↑Hb in all groups (p<0.001) • ↑SF with FF significantly more than others (p<0.05). • Nausea (p<0.05) & epigastric pain (p<0.001) was significantly high with FF as compared with other. • FF (Rs. 1.14/unit) cheapest drug than others. • **FF considered as best cost effective medication & tolerable S/E for treatment & prevention of IDA.**
Sarkate P et al, 2007 (100)	37	SoF VS FF: efficacy	Group A: SoF (33mg of elemental iron) + Vitamin B12 (15µg) +folic acid (1.5mg) b.i.d. Group B: SoF (66 mg of elemental iron) + Vitamin B12 (15µg) +folic acid (1.5mg) b.i.d. **Inclusion criteria** Gestational age12-26 wks Hb (<10g/dL)	Group C: FF (100mg of elemental iron) +Vitamin B12 (15µg) +folic acid (1.5mg) b.i.d.	Hb, RBC count, MCV, MCH&MCHC (0, 30, 45, 60 & 75D) SF, se. iron, TIBC & TSAT	• Mean ↑Hb at 75 D (p < 0.05) (g/dL):1.79 (A), 1.84 (B) & 1.63 (C). • Low doses of SoF (33mg and 66mg of elemental iron given twice daily) produce comparable results as a higher dose of FF (100mg elemental iron given twice daily). • **SoF appears to be effective in improving Hb profile in pregnant anemic women & is tolerated well.**
Retrospective study						
Angadi E et al, 2015 (101)	150	Various iron salts: efficacy & cost effectiven ess	Group A: FA 100mg + Folic acid 1.5mg, Group B: FF 100mg + Folic acid 1.5mg, Group C: IPC 100mg + Folic acid 1.1mg. **Inclusion criteria**	-	Hb (30D) & cost effectiven ess	• Mean ↑Hb at 30D (p<0.001): 1.569g % (FA), 1.097g/dL (FF) & 0.48 g/dL (IPC). • ACER: Rs. 281.12 (IPC), Rs. 60.16 (FF) & Rs. 184.21 (FA) per increase in Hb g/dL. • **FF can be considered best cost effective medication**

	Gestational age 14 -24 wks Hb> 8g/dL & severe intolerance of OI	**for treatment & prevention of IDA.**

ACER, average cost-effectiveness ratio; CI, carbonyl iron; FS, ferrous sulphate; OD, once daily; ADR, adverse drug reaction ; FF, ferrous fumarate; FA, ferrous ascorbate; FB, ferrous bisglycinate; SoF, sodium feredetate; OI, oral iron; SF, serum ferritin; S/E, side effects IPC, iron polycarboxymaltose; PCV, packed cell volume ; MCV, mean corpuscular volume ; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; TIBC, total iron binding capacity TSAT, transferrin saturation

In an RCT, comparing various iron supplements in pregnant women, ferrous ascorbate and bisglycinate were more effective (mean Hb rise in g/dL, 1.13±0.35, p =0.024; 1.11±0.27,p=0.014; respectively) and better tolerated than ferrous sulphate (93). The PERFECT trial, a multi-centric, randomized and controlled trial, compared the efficacy and tolerability of ferrous fumarate with carbonyl iron for the treatment of IDA in pregnancy, which demonstrated a significantly greater increase in Hb in the patient with ferrous fumarate compared with carbonyl iron. Ferrous fumarate was better tolerated than carbonyl iron as shown by patient global assessment of response to therapy (PGART) (1.416 vs. 1.750, p<0.0001) and patient global assessment of tolerability to therapy (PGATT) (1.416 vs. 1.652, p-0.002) scales response (102). A comparable rise in Hb was found in pregnant women treated with low doses of ferrous fumarate vs. ferrous sulphate in a double blind - RCT in India (100). Few studies have found iron polymaltose complex to be more effective and better tolerated than ferrous sulphate in pregnant women (96, 98, 103). Ferrous calcium citrate has been shown to increase Hb by 0.46 to 0.5 g/dL per week with no GI side-effects in a clinical trial (104). The results were supported by another study, which demonstrated an increase in Hb by 0.8-2 g/dL, and with almost no GI side-effects (105). Delayed release preparations of several ferrous salts are available, e.g. ferrous calcium citrate multi-layered system. It has a sugar coating which enhances patient acceptability, while Vit. B12 layer assists in hematopoiesis, and the gastric resistant coating dissolves only in intestine releasing the innermost content i.e. Vit B complex, folic acid, and ferrous calcium citrate. Moreover, ferrous calcium citrate has an additional advantage in the presence of phosphate and phytate-rich diet. Calcium citrate has a higher affinity for phytates than iron, hence when released in the intestine, it complexes with phytates and spares iron. This would ultimately improve iron absorption (106). Present evidence does not allow for arriving at any conclusion on the most effective and better-tolerated iron formulation for use in pregnant women in India.

The GI side effects have been reported to be associated with poor compliance to iron supplementation in pregnant women in India (107). A systematic review has demonstrated a statistically significant increased risk of GI side effects for ferrous sulphate (OR = 3.33, 95% CI 1.19-9.28, p = 0.02, I^2 = 66.1%) in a subgroup analysis of pooled data from 7 RCTs in pregnant women (n = 1028). These side effects include diarrhoea, constipation, abdominal pain, flatulence, nausea, black or tarry stools and heartburn (108). Drug interactions are also a major concern of oral iron pills as they interact with many drugs (109).

Patient instructions for oral iron supplementation should include

1. taking tablets on an empty stomach or one hour after a meal (in the case of vomiting, nausea or gastritis) for better absorption,
2. avoiding consumption with tea, coffee, milk or calcium tablets,

Iron Prophylaxis

Prophylactic 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% is recommended by WHO (110) . The 2013 Ministry of Health and Family Welfare (MoHFW) recommend 100 mg of iron and 500 µg of folic acid daily for 100 days for 6 months during pregnancy, followed by the same for 6 months in the post-partum period (111, 112). 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, and intravenous (IV) sucrose in severely anemic pregnant patients. Both guidelines recommend offering standard prophylactic dose after the Hb is normalized for remaining term of pregnancy (111, 112). These recommendations are summarized in Table 7. The common iron preparations commonly available in Indian market is as summarized in but not limited to Table 8.

Table 7 A summary of recommendations by WHO and MoHFW

	During pregnancy		**Postpartum**
	Prophylaxis	Treatment	
WHO	Daily 60 mg iron+400 µg folic acid till term	Daily 120 mg iron+400 µg folic acid till term	Daily 60 mg iron and 400 µg folic acid- 3 months
MoHFW	Daily 100 mg iron+500 µg folic acid- 6 months	• Mild anemia- 2 IFA tablets/day-100 days • Moderate anemia- IM iron therapy+oral folic acid • Severe anemia- IV sucrose	Daily 100 mg iron+500 µg folic acid- 6 months

Table 8 Examples of Some Iron Preparations Available in the Indian Market, Their Compositions, and Costs (90)

Iron salt	Other supplements	Brand	Cost (INR)
Dried ferrous sulphate 60 mg	Folic acid 1.5 mg, vitamin C 75 mg, vitamin B6 1.5 mg, vitamin B12 15 mcg	Festo-TR® (DWD PharmaFesto-TR® (DWD Pharma	30.0
Dried ferrous sulphate (timed release) 60 mg	Folic acid 1.5 mg, ascorbic acid 75 mg, pyridoxine hydrochloride 1.5 mg, cyanocoblamin 15 µg	Conviron- TR® (Ranbaxy)	55.35
Ferrous sulphate 150 mg	Folic acid 0.5mg	COFOL (Cipla)	27.0
Dried ferrous sulphate (timed release) 150 mg	Folic acid 1 mg, nicotinamide 50 mg, vitamin B6 2 mg, vitamin B12 15 µg	Fesovit® spansule (Glaxo Smith Kline)	114.5
Ferrous sulphate 525 mg	Vitamin B12 12.5 µg, liver 100 mg, vitamin C 75 mg, folic acid 1 mg, vitamin B1 4.5 mg, vitamin B2 5 mg, nicotinamide 5 mg, vitamin B6 1.5 mg, calcium pantothenate 5 mg	Iberol® (P. Upjohn)	17.96
Ferrous sulphate 150 mg	Folic acid 0.5 mg	Fefol spansule (GlaxoSmithKline)	51.0
Ferrous sulphate 150 mg	Zinc sulphate monohydrate 6.18 mg, folic acid 0.5 mg	Fefol-Z spansule (GlaxoSmithKline)	98.5
Ferrous fumarate 350 mg	L-lysine monohydrate 150 mg, folic acid 1.5 mg, vitamin B12 15 µg, zinc sulphate 6 mg, copper sulphate 0.2 mg, manganese sulphate 1 mg	Ironate capsule (Chemo)	19.00
ferrous fumarate 165 mg	Folic acid 750 µg, docusate sodium 50 mg, vitamin C 75 mg	Softeron (Aristo)	17.20
Ferrous fumarate 150 mg	L-histidine 4 mg, L-lysine monohydrochloride 25 mg, glycine 10 mg, vitamin B1 5 mg, vitamin B 2 3 mg, vitamin B6 1.5 mg, vitamin B12 2.5 µg, vitamin C 40 mg, zinc sulphate 50 mg, folic acid 0.5 µg	Astyfer® (Tablets)	87.42
Ferrous ascorbate 100mg	Folic acid 1.5mg,	Ferium XT (Emcure)	72.95

Calcium ferrous citrate 556 mg	Folic acid 0.3 mg, with other mineral salts	Raricap combi tab (Strides)	63.0
Ferrous calcium citrate equivalent to 25mg	Folic acid 0.3 mg	Raricap (Strides)	110
Ferrous calcium citrate equivalent to 50mg	Folic acid 0.3 mg	Raricap forte (Strides)	140
Carbonyl iron 100 mg	Folic acid 1.5 mg, vitamin B12 10 µg, selenium 60 µg, vitamin E 15 mg, zinc 11.5 mg	Safiron (Khandelwal)	133.33
Carbonyl iron 90mg	Folic acid 1.5mg, pyridoxine 3mg, cyanocoblamin 15mcg, zinc sulphate monohydrate 27.54mg	GEFER (Strides)	55.0
Carbonyl iron 50 mg	Zinc sulphate monohydrate 61.8 mg, folic acid 0.5 mg	COFOL-Z (Cipla)	59.25
Iron (III) Hydroxide Polymaltose Complex 100 mg	Folic Acid 1500 µg	Globac-PM (Zydus)	39.78
Iron (III) Hydroxide Polymaltose Complex 50 mg	Folic acid 0.5 mg	HEPOFER FORTE (Cipla) (syrup)	68.25
Iron polymaltose complex 100 mg	Folic acid 350 µg	FEGEM (Torrent)	49.0
Iron polymaltose complex 100 mg	Folic acid 350 µg	Orofer chewable tab (Emcure Pharma)	88.55
Elemental iron 100mg	Folic acid 1.5mg	GEFER-XT (Strides)	69.0
Elemental iron 60 mg	Calcium carbonate 1250 mg, Docosahexaenoic acid 200 mg	Trimester combi pack (Strides)	99.0
Controlled-release ferrous iron (as glycine sulphate) 100 mg	Folic acid 0.5 mg	Fecontin-F (Modi-Mundi Pharma)	62.8
Controlled-release ferrous iron (as glycine sulphate) 100 mg	Controlled release zinc sulphate monohydrate 61.8 mg, folic acid 0.5 mg	Fecotin-Z (Modi-Mundi Pharma)	80.4

Parenteral iron

Indications

Though oral iron has its place in the management of IDA, it has a major drawback of reduced compliance owing to poor tolerability and side effects. The GI adverse effects of oral iron may further exacerbate the pregnancy associated GI disturbance which includes indigestion, constipation, nausea, vomiting, and reflux esophagitis (113). Hence, parenteral iron could be an alternative to oral iron in patients who are unable to tolerate oral iron, are non-compliant (39) or need rapid restoration of iron stores. Parenteral iron may be used from the second trimester and during the post-partum period (39).

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 and availability for the management of anaphylaxis. Sensitivity test prior to infusion is recommended

Contradictions to parenteral iron are

1. A history of anaphylactic reactions to parenteral iron therapy,
2. First trimester of pregnancy, chronic liver disease and active infection (acute or chronic). No evidence on the use of IV iron in the first trimester of pregnancy is present. (39, 114, 115).
3. Oral Iron should be stopped at least 24 hours prior to therapy to avoid toxic reaction (116) .

Calculation of Dose of Parenteral Iron (117)

Required iron dose (mg) = (2.4 × (target Hb-actual Hb) × pre-pregnancy weight (kg)) + 1000 mg for replenishment of stores

Intramuscular administration

Intramuscular iron has been shown to be more effective than oral iron in some RCTs. In two RCTs, IM iron (2 or 3 doses of 250 mg Iron at monthly intervals) significantly improved ferritin compared with oral iron and proposed it as an alternative in patients with poor tolerability to oral iron (118, 119). Similar results were obtained in another study which used three IM doses of 150 mg each at 4 weekly intervals vs. daily 100 mg elemental iron (120).

Adverse effects and test dose

All new patients planed for dextran should be given a test dose of 25mg and they should be observed for any adverse event for at least 1 hour. Uneventful test doses do not eliminate a probability of experiencing hypersensitivity reactions later with either the first dose or subsequent doses. A repeat test dose is advised in patients with an interval of no treatment who have been prescribed repeat doses of iron dextran. Mild joint pains and discoloration at the injection site, severe reactions such as allergy, itching, fever, lymphadenopathy, arthralgia, headache, malaise and anaphylaxis (121).

The MoHFW guidelines for treatment of IDA in pregnancy recommend IM iron following a test dose as treatment of choice for moderate anemia in pregnancy (112).

Intravenous iron administration

Iron sucrose is the most commonly used for intravenous infusion and is safe with fewer adverse events (122). It is rapidly up taken by the bone marrow for erythropoiesis and the reticuloendothelial system for storage. The advantage of iron sucrose is that it does not require to administer a test dose (123) and adverse reactions are virtually unknown (121).

A recent systematic review has shown a significant increase in Hb (mean difference in g/dL 0.85; 95% CI 0.31–1.39; $p = 0.002$) and ferritin levels (mean difference 63.32; 95% CI, 39.46–87.18; $p < 0.00001$), with fewer adverse effects (RR, 0.50; 95% CI, 0.34–0.73; $p = 0.0003$) in the IV compared to oral group. Intravenous iron sucrose was more efficacious with few adverse effects than oral formulation in pregnant women with poor tolerability of oral iron and who required immediate replenishment of iron stores (124).

Numerous studies in India have evaluated the effectiveness of IV iron as a first line treatment in moderate to severe anemia in the second and third trimester of pregnancy. The requirement for formulating standard protocols and guidelines on IV iron use in pregnancy in India was perceived following an observational study conducted across two states of India by MoHFW in collaboration with WHO (125). Intravenous iron supplementation has shown good efficacy and tolerability in the treatment of moderate to severe anemia with good compliance rate in these studies as presented in Table 9.

Several RCTs (Table 10) have compared safety and efficacy of IV iron sucrose to IM iron.

Table 9 Summary of studies on intravenous vs. oral iron supplementation

Author /year	N	Objective	Intervention	Comparator	Outcome	Results
RCT						
Goginen i S et al, 2015 (126)	100	IV vs oral: safety & efficacy	IV infusion: (200mg; 20–27, 28–32, 33–36 wks)(A) **Inclusion criteria** Patients with 20-24 wks of gestation	Oral: (100mg of Ferrous ascorbate OD, 1 hr prior to food) (B)	↑Hb% (28, 32, 36 & 40 wks). S/E (40 wks), & cost	• Mean diff. in Hb% (A vs B, p=0.13): 0.3±0.18 vs 0.12± 0.88 • S/E (A vs B): 8% vs 66% • Lost compliance (A vs B): 4% vs 40%, • Cost (A vs B): 1600/-vs 1500/- • **IVIS is safe in pregnancy as OI is associated with gastric S/E.**
Sunita VN et al, 2015 (127)	90	IV vs oral: safety & efficacy	IV infusion: (dose as per Hb % & BW: approx. 200-950 mg over 1-8 days)(A) target Hb:11g/dl **Inclusion criteria** Patients with 26-32 wks of gestation, Hb(8-10g/dL), SF(<13µg/L)	Oral: (300mg/D throughout pregnancy)(B)	↑Hb (14D, 28D & delv.) & SF level (28D & delv.) FBW	• ↑Hb (A vs B, p=0.0001) (g/dL)): 2w-baseline; 1.2±0.05 vs 0.3±0.02, 4w- 2w; 1.01±0.01 vs 0.50±0.001, delv. – 4w; 0.70±0.11 vs 0.50±0.03. • SF (A vs B) (µg/L): baseline; 11.7±1.47 vs 11.5±1.37 (p=0.5325), day 28; 30.66±4.93 vs 19.96±2.38 (p=0.001), d 28.78±5.18 vs 27.32±3.81 (p=0.1624). • Attaining target Hb(A vs B): 57.1% vs 35.1% (p=0.0001) • Complications: 3 folds more in group B (p=0.001) • FBW (A vs B, p=0 0.72): 2590±508.3 vs 2700±492g. • **The choice of treatment of IDA is OI replacement becaus it is the safest and least expensive.**
Tembhar e A et al, 2015 (128)	200	IV vs oral: Efficacy in IDA	IV infusion: (dose as per Hb% & BW: 200mg t.i.w) (5mg FA + Albendazole 800mg for 1 wk)(A) **Inclusion criteria** single pregnancy, >20 wks of gestation, Hb(<10g/dL) , SF(<15µg/L)	Oral: carbonyl elemental iron 60mg each 4 wks + 5mg FA + Albendazole 800mg for 1 wk)(B)	Hb (7 & 30D), SF (30D)	• Mean ↑%Hb (A vs B) at 30D: 7.24±1.02 to 10.93±0.92 g/L vs 7.76±0.45to 8.85±0.52 g/dL(p<0.0001) • Mean rise in SF (A vs B) at 30D: 9.75±2.15 to 53.77±6.53 ng/ml (p< 0.0001) vs 10.74±2.00 to 12.70 ±1.43 ng/ml (p<0.05) • **IVIS significantly improves the Hb and SF on 30D.**
Tripathi	100	IV vs	IV infusion: (dose as per Hb	Oral: 200mg	After 6 wks,	• ↑SF: significant (p<0.001) in group A

S et al, 2015 (129)		Oral: treatment of IDA	% & BW)+ FA (500µg OD)(A) target Hb:11g/dL **Inclusion criteria** single pregnancy, gestational age (12-36wks), Hb(6-9g/dL)	b.i.d for 6 wks.+ FA (5mg/day) (B)	Hb, RBC's indices, SF & TSI. Compliance and S/E	• ↑TSI (A vs B): 10.1 vs 4.5µg/dL (p<0.001) • ↑Hb (A vs B): 2.3 vs 2.2g/dL • RBC's indices: no diff., S/E (A vs B): 6% vs 40% • **IVIS replenishes iron stores much better than OI and ha more favourable improvement in clinical features with fewer S/E, and more effective in later months of pregnan**
Abdulla h A et al, 2014 (130)	200	IV vs oral: safety & efficacy in moderate anemia	IV infusion: 2 dose of 200mg 3-5D apart + 500µg FA OD) (A) **Inclusion criteria** Single pregnancy, Moderate anemia (7-10.9g %)	Oral: 100mg elemental iron+ 500µg FA OD (B)	After 4 wks, Hb, Hematocrit, MCH, MCHC, MCV, serum iron, TIBC, SF values. S/E & Perinatal outcomes	• Hb status (A vs B) (g/dL): initial; 9.3±0.7 vs 9.5±0.6 (p= 0.130), fallow up; 11.0±0.8 vs 10.8±0.6 (p= 0.007) • Hematocrit (A vs B): initial; 28.6±2.7 vs 29.1±1.7 (p=0.095 follow up: 33.1±2.4 vs 32.6±4.2 (p=0.704) • MCH (A vs B): Initial; 26.1±3.2 vs 25.5±3.4 (p= 0.222), fol up; 30.0±3.1 vs 30.5±2.7 (p= 0.165) • MCHC (A vs B): Initial; 30.1±3.0 vs 30.6±3.2 (p= 0.253),follow up; 34.7±2.9 vs 34.5±3.0 (p= 0.615) • MCV (A vs B): Initial; 79.4±6.4 vs 79.8±6.0 (p= 0.638), fol up; 87.0±6.7 vs 87.0±5.6 (p= 0.950) • Serum iron(A vs B): Initial; 56.5±7.3 vs 55.5±4.0 (p= 0.539),follow up; 73.8±5.1 vs 71.6±4.7 (p= 0.121) • TIBC (A vs B): Initial; 434.9±69.8 vs 449.6±48.9 (p= 0.394),follow up; 345.4±46.0 vs 350.0±51.8 (p= 0.741) • SF (A vs B): Initial; 11.8±2.0 vs 11.0±1.8 (p= 0.153),follow up; 26.2±6.3 vs 16.5±3.7 (p<0.001) • S/E & Perinatal outcomes: no significant diff. between grou • **IVIS is more effective in achieving target Hb & timely us will reduce maternal & fetal complications and risk of transfusion.**
Abhilash ini GD et al, 2014 (131)	100	IV vs oral: safety & efficacy	IV infusion: (Dose as per Hb % & BW: 200mg alt. days; max 600mg/wk.) (A) Target Hb: 11g/dL **Inclusion criteria**	Oral: 200 mg t.i.d (B)	Hb, %PCV, MCV, reticulocyte count (2, 4 & 37	• ↑Hb (A vs B) (g/dL): 2w; 1.266±0.431 vs 1.068±0.447 (p= 0.026), 4w; 2.594±0.718 vs 1.992±0.676 (p<0.001), term; 3.954±0.563 vs 2.930±0.565 (p<0.001). • ↑% PCV (A vs B): 2w; 4.090±1.985 vs 3.356±1.718 (p= 0.051), 4w; 7.938±3.334 vs 6.644±2.300 (p=0.026), term;

			Patients with gestational age (30- 34 wks) with IDA (Hb: 6-8g/dL)		wks). S/E	11.666±2.470 vs 10.040±1.685 (p<0.001). • ↑MCV (A vs B) (fL): 2w; 12.25±6.821 vs 11.02±5.381 (p= 0.317). • S/E (A vs B):4% vs 42% • **IVIS treated IDA faster, effectively than OI without any ADRs.**
Gupta A et al, 2014 (132)	100	IV vs oral: safety & efficacy	IV infusion: (dose as Hb % & BW: 200mg alt. days; max 600mg/wk.)(A) target Hb:11g/dl **Inclusion criteria** single pregnancy, 24-34 wks of gestation ,Hb(7- 9 g/dL), SF(<15µg/L)	Oral: 200mg t.i.d for 4 wks (B)	Hb (7D, 14D, 28D & delv.), SF (28D) S/E	• ↑Hb (A vs B): 14 D; 0.58 vs 0.23 g/dL (p= 0.004), 28 D; 1.9 1.3 g/dL (p \0.001), delv; 3.53 vs 2.43 g/dL (p<0.001). • SF (A vs B): 37.45±5.73 vs 13.96±1.88ng/ml (p<0.001). • S/E (A vs B): 10% vs 46%. • **The ↑Hb is faster with IVIS as OI, which can be benefici at a later period of gestation and also very well tolerated**
Mehta MN et al, 2014 (133)	150	IV vs oral: efficacy in treatment of IDA	IV infusion: (dose as Hb % & BW: 100mg alt. days). target Hb:10g/dl(A) **Inclusion criteria** gestational age (<34 wks with IDA(Hb<8g/dL)	Oral: 200 mg 2 tablet t.i.d (B)	After 6 wks ↑Hb, achieving target Hb, S/E	• Mean ↑Hb (A vs B) (g/dL): 3.93±0.60 vs 3.45±0.68 (p= 0.2 • target Hb (A vs B): 88% vs 76% patients (p =0.055) • S/E (A vs B): 35% vs 47% • **IVIS is safe and as effective as OI in the treatment of IDA**
Dubey S et al, 2013 (134)	198	IV vs oral: response & efficacy	IV infusion: 200mg alt. days (A). target Hb:11g/dl **Inclusion criteria** single pregnancy,20-34 wks of gestation ,Hb(7-9 g/dL) , SF(<15µg/L)	Oral: 100mg elemental iron t.i.d throughout pregnancy (B)	↑Hb & SF (2w, 4w & 8w), achieving target Hb, ADR	• ↑Hb (A vs B) (g/dL): 2w; 1.7±0.92 vs 0.71 ± 0.40 (p=0.000) 4w; 2.80±1.03 vs 1.68±0.86 (p=0.000), 8w; 2.46±1.09 vs 1.84±0.77 (p=0.163). • ↑SF (A vs B) (ng/ml): 2w; 155.33±57.4 vs 20.8±9.5 (p=0.00 4w; 70.85±46.25 vs 18.34±3.15 (p=0.000), 8w; 33.85±12.7 24.2±4.6 (p= 0.016). • Achieving target Hb (A vs B): 62% vs 5% (4w) • ADR (A vs B): 6 vs 18 patients. • No significant diff. in mode of delv. (p=0.055) & FBW (p=0.100). • **IVIS has been safe, ↑ Hb & restores iron stores faster tha**

						OI.
Kochhar PK et al, 2013 (135)	100	IV vs oral: Efficacy & safety	IV infusion: 200mg alt. day **Inclusion criteria** Patients with Hb(7-9 g/dL) , SF(<15µg/L), MCV (<85 fL)	Oral: 200mg: t.i.d (4 wks.)	↑Hb (7D, 14D, 21D, 30D & delv.), SF (30D & delv.).S/E	• ↑Hb: oral (3.1g/dL), IV (5.1 g/dL) (p=0.002) & SF 30 D (p= 0.005) • S/E: more in oral group & neonatal outcomes comparable. • **IVIS is a safe for correction of anemia, without severe S/**
Meenal C et al, 2013 (136)	484	IV vs oral: response & efficacy	IV infusion: 200mg: 24 hrs apart) + 400mg Albendazole **Inclusion criteria** Anemic (Hb: 5-10g %) in secondsecond/ third trimesters with no other risk factors	Oral: 200 mg: b.i.d (4 wks.) + 400mg Albendazole	After 4 wks, Hb & ADR	• ↑Hb: in IV group, 71.64% patients showed ↑ (2-2.9g %), whereas in oral group, 77.4% patients showed ↑0.6-0.9g/dL Hb. • Both group shows minor ADR. • **IVIS can correct anemia in a short period even in advan pregnancy and prevent associated maternal and perinata complications.**
Neeru S et al, 2012 (137)	100	IV vs oral: efficacy & tolerance	IV infusion: (Dose as per Hb % : 200mg alt. days) (A) target Hb:11g/dL **Inclusion criteria** Patients with 14-36 wks gestation.	Oral: Ferrous fumarate 300mg (B)	After 1 month, % Hb, % PCV, % MCV, % MCH, % SF, S/E & compliance, perinatal outcomes	• ↑%Hb (A vs B): 23.62±14.95 vs. 14.11±10.66 (p= 0.001). • Rise in % SF (A vs B): 2032.54±1974.43 vs 180.69±308.39 (p= 0.000). • ↑% PCV (A vs B): 20.94±13.55 vs 13.36±12.56 (p= 0.008). • ↑% MCV (A vs B): 10.21±9.60 vs 5.47±6.49 (p= 0.008). • ↑% MCH (A vs B): 13.46±12.32 vs 7.18±9.68 (p= 0.009). • Compliance (A vs B): 90% vs 88%. S/E (IV vs oral): 13% v 23%. • Perinatal outcomes: no sign. diff. (p = 0.121–1.000) • **IVIS is safe, effective & stores iron better compared with OI.**
Shafi D et al, 2012 (138)	200	IV vs oral: safety & efficacy for IDA	IV infusion: (Dose as per Hb % & BW: 200mg alt. days) (A). target Hb:12 g/dL **Inclusion criteria** Patients with 28-37 wks of gestation, Hb(6-10g/dL),	Oral: Ferrous ascorbate 100mg (elemental) + 1.1mg of FA, b.i.d	Hb conc. & SF (2, 4 & 6 wks) ADR	• ↑Hb (A vs B) (g/dL) (p=0.000): 2w; 1.72±0.484 vs 0.5750±0.456), 4w; 2.18±0.865 vs 1.39±0.4402, 6w; 2.89±0.599 vs 1.9±0.3020). • ↑SF (A vs B) (ng/ml) (p=0.000**): 2w; 40.020±17.02 vs 8.5±4.5), 4w; 2.612±19.88 vs 15.23±8.09), 6w; 78.53±19.82 26.6 ± 8.56). **- highly significant.

			SF(<15µg/L)	(pregnancy) (B)		• S/E (A vs B): 13 vs 22 patients. • **IVIS elevates Hb and restores iron stores faster than OI, with no severe ADRs.**
Retrospective studies						
Raut SV et al, 2015 (139)	200	IV vs oral: Efficacy in moderate anemia	IV infusion: (3 dose of 200mg in alt. days)(A) **Inclusion criteria** Single pregnancy with > 20 wks of gestation, Hb (8-10 g/dL), hematocrit (<30 %)	Oral: Ferrous ascorbate 100mg elemental iron one tab. OD for 8 wks)(B)	After 8 wks., Hb. Tolerance and S/E	• Mean ↑%Hb (A vs B): 1.6g/dL vs 0.87g/dL (P < 0.001). • S/E (A vs B): 2 vs 42 patients. • **IVIS therapy is much effective in correcting IDA than O**
Mani P et al, 2015 (140)	229	IV vs oral: Efficacy& tolerance	IV infusion(A) Target Hb: 12 g/dL	Oral (B)	Hb & SF estimation (2, 4 & 6 wks.)	• A vs B: change in Hb ≥ 1.5g/dL at 4wks, SF raised (p =0.00 • IVIS in pregnant women was well tolerated. • **IVIS elevates Hb and restores iron faster than OI**
Halimi S et al, 2011 (141)	100	Oral vs IV: safety & efficacy	Oral: 240mg elemental iron for 4 wks(A) **Inclusion criteria** 26-30 wks of gestation, Hb (<11 g/dL), hematocrit (<33 %)	IV infusion (Dose as per Hb % & BW)(B)	S/E (15^{th} D) &Hb (30^{th} D)	• Rise in Hb (A vs B) (g/dL) (p=0.0001): 1.85±0.28 vs 3.45±1.06. • S/E (A vs B): 46% vs 52%. • **IVIS therapy is a better choice to correct IDA.**

BW, body weight; OI, oral iron; SF, serum ferritin; FBW, fetal birth weight; S/E, side effects; IDA, iron Deficiency anemia; FA, folic acid; OD, once daily; TS total serum iron; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; TIBC, total ir binding capacity; PCV, packed cell volume; ADR, adverse drug reaction

Table 10 Summary of studies on intravenous vs. intramuscular iron supplementation

Author /year	N	Objective	Intervention	Comparator	Outcome	Results
RCT						
Suguna V et al, 2015 (142)	200	IVIS vs IMIS: Efficacy & safety comparison	IV infusion: 200mg twice wkly. **Inclusion criteria** Patients with Hb(5-9 g/dL), and SF <15 µg/L	IM injection: 2.5ml [150mg] twice monthly.	Hb & RBC indices (2, 4wks & delv.) & SF (delv.) ADR & perinatal outcome	• Mean ↑%Hb (IV vs IM) at delv: 7.42±0.72 to 11.52±0.65 vs 7.63±0.42 to 10.56±0.52. • Mean ↑%PCV (IV vs IM) at delv: 25.6±3.51 to 36.56±5.47 vs 26.5±3.11 to 32.7±2.22 • Mean ↑SF (IV vs IM) at delv (µg/L): 9.39±2.8 to 32.78±4.6 vs 7.5±1.82 to 22.4±2.12 • FBW (IV vs IM): 2.7±0.32 vs 3.1±0.25 Kg • ADR (IV vs IM):16 vs 27 patients. • **IVIS was safe for correction of anemia without serious S/E.**
Sujatha V et al, 2014 (143)	100	IVIS vs IMIS: safety & efficacy target Hb (11 g/dl)	IV infusion: (dose as Hb% & BW: 150mg every 3D) **Inclusion criteria** 14-32 wks of gestation with Hb≤ 8g/dL, se. iron < 60µg/dL &TIBC > 400µg/dL	IM injection: (Dose as Hb% & BW: 1.5 ml till cal. dose).	After 4 wks ↑ Hb, time taken for target Hb, ADR	• Mean ↑Hb (4 wks) (IV vs IM): 3.61 vs 2.36 g/dL (P<0.01) • Mean time taken for target Hb (IV vs IM): 6.42 vs 9.09 wks (P<0.01). • ADR (IV vs IM): 10 % vs 20% • **IVIS is safe, convenient and also more effective, faster acting therapy than IMIS therapy in treating moderate to severe anemia.**
Singh S et al, 2013 (144)	100	IVIS vs IMIS: safety & efficacy target Hb	IV infusion: (dose as Hb% & BW: 150mg every 3D) **Inclusion criteria** 14-32 wks of	IM injection: (Dose as Hb% & BW: 1.5 ml till cal. dose).	After 4 wks ↑ Hb, time taken for target Hb, ADR	• Mean ↑Hb (4 wks) (IV vs IM): 3.52 vs 2.33 g/dL (P<0.01) • Mean time taken for target Hb (IV vs IM): 6.37 vs 9.04 wks (P<0.01). • ADR (IV vs IM): 8 % vs 24%(p= 0.027) •

		(11 g/dL)	gestation with Hb≤ 8g/dL, se. iron < 60µg/dL & TIBC > 400µg/dL.			
Dhanani JV et al, 2012 (145)	60 (52)	IVIS vs IMISCA: safety & efficacy	IV infusion: (dose as Hb% & BW: 200mg alt. days) (Brand: IMAX-S) **Inclusion criteria** Patients with Hb<8.5 g/dL	IM injection: (dose as Hb% & BW: 75mg/D for 4 D) (Brand: JECTOCOS)	↑Hb (14D, 28D), Hemocrit, MCV, MCH, SF (28D). ADR	• Mean ↑Hb (g/dL) (IV vs IM): 2w; 0.74 vs 0.89 (p>0.05), 4w; 1.66 vs 1.45 (p>0.05). • % Hemocrit at 28D: IV; 26.95±4.33 to 29.81±4.49 (p<0.001), IM;27.73±4.22 to 31.08±3.80 (p=0.001) • MCV(fL) at 28D: IV; 70.26±11.74 to 73.81±10.0 (p=0.05), IM; 68.65±9.01 to 72.18±8.68 (p<0.001) • MCH (pg) at 28D: IV; 21.10±5.56 to 22.89±5.10 (p<0.05), IM; 20.89±4.52 to 22.52±4.28 (p<0.001) • SF (ng/ml) at 28D: IV; 6.59±3.03 to 20.33±16.58 (p<0.001), IM; 9.32±8.37 to 20.13±11.39 (p<0.001). • ADR(IV vs IM): 2 vs 31 patients • **Efficacy same but ADR more in IM group.**

IVIS, intravenous iron sucrose; S/E, side effects; IMIS, intramuscular iron sorbitol; SF, serum ferritin; FBW, fetal birth weight; ADR, adverse drug reaction; BW, body weight; IMISCA, intramuscular iron sorbitol citric acid; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; TIBC, total iron binding capacity

Management of postpartum anemia

Untreated IDA during the post-partum period is a cause of maternal morbidity such as tiredness, lethargy, dizziness, headaches, lactation failure, post-partum depression (146, 147). Prevalence of postpartum IDA is very high in India (148, 149). The maternal mortality rates are also significant (150). The importance of prevention and treatment of IDA in postpartum period should be given further thrust in the maternal health programs. WHO recommends post-partum prophylactic iron supplementation of 60 mg elemental iron + 400 µg folic for 3 months (151, 152). Universal iron supplementation was demonstrated to be effective in reducing the prevalence of anemia among low-income postpartum women (153). MoHFW guidelines recommend daily iron (100mg elemental iron with 500µg folic acid) for all non-anemic women in post-partum period for 6 months, whereas the same tablet is advised to be taken twice daily for mild to moderately anemic postpartum women (111, 112).

Postpartum intravenous iron therapy has been found to avoid demand for blood transfusions (154), and it rapidly replenishes iron stores compared with oral iron (155-163). This is more cost effective option (164). A summary of all post-partum iron intervention studies conducted in India is presented in Table 11.

Table 11 Summary of postpartum iron intervention studies in India

Author /year	N	Objective	Intervention	Comparator	Outcome	Results
RCT						
Pal SR et al. 2015 (155)	100	IV-IS vs oral Feso4	IV-IS: 200mg thrice a week (group A) **Inclusion criteria** ID with Hb% < 11.0g/dL and serum ferritin level ≤ 20.0 µg/L	Oral Feso4 (group B): 60mg bid for 6 weeks	↑ in Hb & ferritin (Day 1, 15, 42)	• Mean ↑in Hb (A vs B) (g/dL) at day 1: 7.62 ± 1.12 vs 8.50 ± 0.72 (p<0.001) • Achievement of target Hb after 42 days (A vs B) 13.05 ± 0.7 vs 10.65 ± 0.64 (p<0.001) • Mean ↑in ferritin (A vs B) (µg/L) at day 1: 10.95 ± 4.63 vs. 15.55 ± 3.43 (p<0.001); at day 42**:** 119.56 ± 11.18 vs. 71.04 ± 10.01 (p<0.001) • **IV-IS safe, well tolerated, replenishment of both iron store and Hb**
Vijayalakshmi S et al. 2015 (156)	120	IV-IS vs oral Feso4	IV-IS: 300-600mg 2 or 3 divided doses, alternate day for 3 days **Inclusion criteria** Hb less than 10 g/dL within 48 h postpartum	300 mg (100mg elemental iron) Feso4 for 28 days	↑ in Hb (g/dL)	• Mean ↑in Hb in IV-IS after 28 days 8.8+/-0.6 to 11.1+/-0.8 • Mean ↑in Hb in Feso4 after 28 days 8.7+/-0.9 to 10.6+/-0.9 • **IV-IS effective, safe, well tolerated**
Jain G et al. 2013 (157)	40	IV-IS vs oral Ferrousfumarate	300–600 mg of IV-IS every alternate day for 3 days (group A) **Inclusion criteria** Hb less than 8 g/dl	300 mg ferrous fumarate orally daily-14 days (group B)	↑ in Hb	• Mean ↑in Hb in IV-IS after 14 days 2.4 g/dL • Mean ↑in Hb in ferrous fumarate after 14 days 1.2 g/dL • **IV-IS effective, safe, well tolerated than oral ferrous fumarate in postpartum anemia**
Swati et al. 2013 (158)	50	Oral Feso4 vs. IV-IS	Oral Feso4: 200mg 3 times a day for 4 weeks (group A)	IV-IS: 100mg daily for 3 days (group B)	Hb, Serum Ferritin	• Mean ↑in Hb in Feso4: 7.43±0.46 to 8.2±0.48 g/dL • Mean ↑in Hb in IV-IS: 7.27±0.4 to 8.5±0.49 g/dL • Mean ↑in hematocrit Feso4: 0.72± 0.33% • Mean ↑in hematocrit in IV-IS: 0.93±0.34% • **IV-IS effective, safe, well tolerated**

Rohini et al. 2012 (159)	50	Oral Feso4 vs. IV-IS	IV-IS: 200mg elemental iron for 4 weeks (group A)	Oral Feso4: 200 mg iron sulphate tablets t.d.s 4 weeks (group B)	postpartum day 2 or 3, Hb ≤7gm%	• Mean ↑in Hb (A vs B) at day 1: 6.27±0.48 vs. 5.94±0.62 • Mean ↑in Hb (A vs B) after 4th week- 12.35±0.66 g/dL vs. 11.48±1.05 0.004 g/dL • Mean ↑in Hematocrit % (A vs B) at day 1: 18.8±1.46 vs. 17.8±1.76 • Mean ↑in Hematocrit % (A vs B) at 4th week: 37.06±1.99 vs.34.45±3.17 • **IV-IS effective, safe, well tolerated**
Kharde PS et al, 2012 (160)	100	Oral Feso4 vs. IV-IS: efficacy in IDA	**IV-IS:** 200mg (2nd & 4th day) (A) **Inclusion criteria** Hb <10 g/dl but > 6g/dL at 24 to 48 hrs post delv. & SF< 15µg/LL.	Oral Feso4 (B): 200 mg b.i.d for 6 wks.	Hb, SF (5, 14 & 40D) ADR	• Mean ↑in Hb (A vs B) at 40D (p<0.001): 7.47±0.7678 to 11.41±0.7908 g/dL vs 7.76±0.7137 to 10.78±0.7679 g/dL • Mean ↑in SF (A vs B) at 40D (µg/L): 11.47±1.655 to 53.47±5.011 vs 11.35±1.559 to 15.40±1.049 • ADR (A vs B): 8 vs 13 patients • **IV-IS ↑Hb & SF more rapidly, without any serious ADR i comparison with OI.**
Verma S et al, 2011 (161)	150	IV-IS vs oral Feso4: efficacy & safety	**IV-IS:** 600mg (A) **Inclusion criteria** Hb <8 g/dL after 24 hrs of delv.	Oral Feso4 (B): 200mg b.i.d for 4 wks.	Hb (1, 2, 3, 4wks)& ADR	• Mean ↑in Hb (A vs B) at 30D(g/dL): 7.58 to 11.5 vs 7.42 to 10.09 • **IV-IS is an effective mode of treatment with no S/ E & fas recovery in comparison with OI.**
Garg R et al, 2015 (162)	100	IV-FC vs IV-IS in PP with severe IDA: efficacy & safety	IV-FC: 1000mg (A) **Inclusion criteria** All normal & casarean delv. Patients with IDA. Target Hb = 11 g %	IV-IS: 200mg elemental iron alt. days up to 5D.(B)	↑ in Hb & ADR(2w, 4w, 8w, & 12 w)	• Mean ↑in Hb (A vs B) at 4 wks: 3.95 g/dL vs 3.32 g/dL • Achievement of target Hb after 12 wks (A vs B): 100% vs 98 • ADR (A vs B): 12% vs 20% (grade 1). • **IV-FC is safe, convenient, more effective and faster acting than IV-IS for the treatment of severe IDA during PP period.**
Hol KKV et al, 2015 (163)	100	IV-IS vs IV-FC in PP: efficacy & safety	Mild (9-11 g %): IV-IS: 500mg (200mg alt.day)& IV-FS : 500mg single dose (A) **Inclusion criteria** Patients with Hb (7-11 g %) at 24-48 hrs. after delv. With	Moderate (7-9 g %): IV-IS: 1000mg(200 mg alt.day)& IV-FS : 1000	↑Hb & SF at 6 wks	• Mean ↑in Hb (A vs B): 2.30 g % with IS & 2.52 g % with FC (p=0.180) vs 4.58 g % with IS & 4.73 gm% with FC (p=0.31 • Mean ↑in SF (A vs B): 37.97 with IS & 38.70 with FC (p=0.7 vs 43.65 with IS & 44.40 with FC (p=0.788). • No diff. observed in ADRs in both groups. • **IV-IS & IV-FC is equally effective in treating mild &**

			IDA.	mg (500mg alt.day) (B)		**moderate IDA in PP patients. IF-SC has better patient satisfaction**
Patel J et al, 2015 (165)	30	IV-IS vs IV-FC in pregnant vs PP: efficacy & safety	IV-IS: 200mg on day 2 & 4. **Inclusion criteria** Pregnant: gestational age 12-32 wks & Hb<9 g/dL PP : Hb< 10.5 g/dL	IV-FC: 1000 mg /500mg wkly.	↑Hb & SF (8D & 15D). S/E& tolerance	• Mean↑Hb on 15D (IV-FC vs IV-IS) : 5.2 & 5.4 vs 4.1 & 4.9 g/l (pregnancy &PP) • Mean↑SF on 15D (IV-FC vs IV-IS): 9.1 & 9.9 vs 9.4 & 8.3 (pregnancy & PP). • ADR(IV-FC vs IV-IS): 16.67% VS 40% • **IV-FC ↑Hb & stores iron more rapidly as IV-IS, well tolerated, safe & effective to blood transfusion in the PP period.**
Rathod S et al, 2015 (166)	366	IV-FC vs IV-IS vs OI: safety & efficacy on PPA	IV-FC: 1000mg/wk **Inclusion criteria** Patients with Hb<10 g/dL, with PPA.	IV-IS: 300mg alt.day OI: 100mg OD.	Hb & SF on 2w & 6w. ADR	• Mean ↑Hb: 0.8, 2.4, & 3.2 g/dL (2w), 2.1, 3.4, & 4.4 g/dL (6w in OI, IV-IS &IV-FC. (p< 0.0001). • Mean ↑SF: 2.5, 193.1, & 307.1(2w), 14.2, 64, & 106.7 ng/l ml(6w) in OI, IV-IS & IV-FC. (p< 0.0001). • ADRs less in IV-FC compared with others. (p< 0.001) • **IV-FC ↑Hb & restore iron quick than others, without ADI**
Prospective study						
Mishra VV et al, 2015 (167)	158	IV-FC (pregnant vs PP): efficacy & safety	**IV-FC: ≤** 1000mg/wk or 15 mg/kg. **Inclusion criteria** Gestation age >20-36 wks & PP patients with Hb 6-11 g %.	-	Improvement in Hb & iron stores (3 wks). Safety	• Improvement after 3 wks (p<0.001): Hb; 8.97±1.05 to 11.34±0.90, PCV; 29.78±21.20 to 36.41±3.01, TIBC (µg/dL) 402.57±97.28 to 275.59±47.24, SF (ng/ml); 18.30±16.39 to 104.10±32.46, S.Iron (µg/dL); 47.23±18.87 to 92.89±26.93. • Patients with local ADRs (4) & systemic ADRs (5). • **IV-FC should offered to all IDA women to ↓maternal morbidity & mortality**
Retrospective study						
Khandale SN et al, 2015 (168)	121	IV-FC in PPA: efficacy & safety	IV-FC in PPA	-	↑ in Hb & ADR	• Mean↑ Hb: 2.76±1.00 g/dL (p<0.0001). Max. ↑in patients wit baseline Hb 6.1-8g/dL. • patients reported treatment-related ADRs: headache (1); rash/urticaria(1) • **IV-FC was effective in improving Hb in PPA patients & w well tolerated.**

IV-FC, intravenous ferric carboxymaltose; IV-IS, intravenous iron sucrose; IDA, iron Deficiency anemia; ADR, adverse drug reaction; PP, post-partum; SF, serum ferritin; IS, iron sucrose; FC, ferric carboxymaltose; S/E, side effects; OI, oral iron; PPA, post-partum anemia; PCV, packed cell volume; TIBC, total iron binding capacity

Blood transfusion

Severe anemia in last trimester does not permit iron supplementation to completely replenish iron levels, hence, blood transfusion is the treatment of choice for immediate improvement in Hb status (169). The recent RCOG blood transfusion guideline recommends blood transfusion in labor or immediate post-partum period if the Hb is < 7 g/dL (170). The indications for blood transfusion are presented in Table 12

Table 12 Indications of blood transfusion in pregnancy (170, 171)

Antepartum Period
1. Pregnancy <34 weeks
a. Hb <5 g/dL with or without signs of cardiac failure or hypoxia
b. 5-7 g/dL – in presence of impending heart failure
2. Pregnancy >34 weeks
a. Hb <7 g/dL even without signs of cardiac failure or hypoxia
b. severe anemia with decompensation
3. Anemia not due to hematinic deficiency
a. Hemoglobinopathy or Bone marrow failure syndromes
b. Hematologist should always be consulted
4. Acute Hemorrhage
a. Always indicated if Hb <6 g/dL
b. If the patient becomes hemodynamically unstable due to ongoing hemorrhage.
Intrapartum Period
a. Hb <7 g/dL (in labor)
b. Decision of blood transfusion depends on medical history or symptoms
Postpartum Period
a. Anemia with signs of shock/acute hemorrhage with signs of hemodynamic instability.
b. Hb <7gm% (postpartum):Decision of BT depends on medical history or symptoms

Deworming

The prevalence data on soil-transmitted helminthiasis is not uniformly available in India, but clinical experience shows the high burden of worm in the community. Intestinal helminthiasis and Hb concentrations are known to have an inverse relationship (172); hence, administration of anthelmintic agents has been recommended as an additional intervention to reduce anemia. A systematic review of RCTs evaluating the effect of anthelmintic drugs on Hb demonstrated mean Hb increase of 1.71 g/dL (173).

A recent Cochrane review found insufficient evidence to recommend deworming in pregnancy, (174), though there is a demonstrable benefit of deworming in endemic areas (175). In hookworm-endemic areas, WHO risk–benefit analysis confirmed the benefits of deworming in endemic areas – this is evidenced by improved infant birth weight and survival (176) and reduced maternal anemia (177). For soil-transmitted helminthiasis, WHO recommend offering albendazole or mebendazole to pregnant women in the second and third trimesters of pregnancy and to lactating women as a preventive chemotherapy interventions in areas where the prevalence of any soil-transmitted helminth infection (hookworm infection, ascariasis, and trichuriasis) exceeds 20% (178). The national guidelines for deworming in pregnancy by the MoHFW, Government of India, recommend a single dose of 400 mg of Albendazole tablet after the first trimester, preferably in the second-trimester (179).

Malaria

According to the WHO global estimates, there are about 207 million cases of malaria, and 6, 27,000 deaths attributable to malaria in 2012 (180). The report finds approximately 80% of these cases in African countries and 13% in South East Asia Region (SEAR) countries (180), of this, India contributes to 61% of malaria cases and 41% deaths due to malaria (181). The reported prevalence of malaria in pregnancy varies from 46-51% in India (182-186).

Malaria increases the risk of maternal anemia, placental parasitemia, stillbirth, spontaneous abortion, LBW and neonatal deaths (112, 187). WHO recommends a three-pronged approach to the prevention and management of malaria during pregnancy, which includes: insecticide-treated net (ITNs), intermittent preventive treatment (IPTp), effective care management of malarial illness (188). The IPTp with at least 2 doses of sulphodoxinepyrimethamine has been found to reduce the prevalence of maternal anemia and placental parasitaemia, and the incidence of LBW in the second and third trimesters of pregnancy in several studies conducted in Africa (189-192). Further, use of a combination of SP and INTs during second and third trimester can result in better control of malaria in the high prevalence area (193). However, we could not find the evidence on IPTp in India. The 2013 guideline on diagnosis and treatment of malaria in India recommends chloroquine for the treatment of *Plasmodium vivax* during pregnancy. Quinine is recommended for *Plasmodium falciparum* malaria during the first trimester and artemisinin combination therapy in the second and third trimesters of pregnancy (194).

Co-supplementation with other micronutrients

Folic acid or folate insufficiency during pregnancy is directly associated with adverse pregnancy complications and poor birth outcomes. This includes the risk of preterm birth, LBW, intrauterine growth restriction (IUGR) and neural tube defect (NTD) in the neonates (195). Folate supplementation and fortified food can reduce the incidence of NTD by 46% and neonatal death by 13% (196). Therefore, addition 500µg of folic acid or folate during antenatal period is necessary to avoid the maternal and perinatal complications.

Maternal Vitamin B12 deficiency is directly associated with adverse pregnancy complications and poor birth outcomes, e.g. LBW (197), IUGR (198), & NTD (199). A 2.6 µg & 2.8 µg of vitamin B12 daily during pregnancy and lactation, respectively, need to be added to avoid the maternal & neonatal complications (200).

When taken along with the iron rich foods, vitamin C increases the iron absorption, especially the non-heme-iron (49). One study in India reveals that the addition of vitamin C in the lunch increases the Hb level and supports in reducing the IDA (201). However, the recommended dietary allowance (RDA) of vitamin C is sufficient enough to bring this action so an extra amount of supplement may be undesirable (49). Moreover, recent Cochrane data do not support preventive vitamin C supplementation alone or in combination with other supplements to reduce poor fetal growth, fetal or neonatal death, pre-eclampsia, and preterm birth (202). Vitamin C usage other than enhancing the absorption of iron, its routine supplementation in iron deficiency anemia is not advised.

A systemic review of 13 RCTs shows no advantage in reducing maternal mortality with vitamin A compared with placebo or when added to iron supplements (203). A prophylactic Vitamin A supplementation to prevent maternal and infant morbidity and mortality is not recommended (204).

Appendix I. Iron rich food, iron (mg) (per 100gms) **(205)**

1. **Cereal grains and products**
   Whole Wheat flour atta (4.9), Ragi (3.9), Jowar (4.1), Samai (9.3)
2. **Pulses and legumes**
   Bengal gram roasted (9.5), Bengal gram dhal (5.3), Cow pea (8.6), Green gramwhole (4.4), Horse gram whole (6.77), Lentil (7.58), Dry peas (7.05), Soya bean (10.4)
3. **Leafy vegetables**
   Amaranth Polygonoides (Ramdana or Rajgeera)((27.3), Amaranth tristis (38.5), Beet greens (16.2), Bengal gram leaves (23.8), Cauliflower greens (40.0), Mustard leaves (16.3), Radish leaves (18.0)
4. **Roots and Tubers**
   Beet root (1.19), Carrot (1.03), Mango ginger (2.6), Onion small (1.2), Potato (0.48), Radish table (1.0)
5. **Other vegetables**
   Beans (2.6), Cowpea pods (2.5), Onion stalks (7.43)
6. **Nuts and oil seeds**
   Almond (5.09), Cashewnuts (5.81), Coconut dry (7.8), Garden cress seeds (100), Gingelly seeds (9.3), Groundnut (2.5), Niger seeds (56.7)
7. **Fruits**
   Ambada (3.9), Apricot dry (4.6), Currants, black (8.5), Dates dried (7.3), Watermelon (7.9), Peaches (2.4), Pineapple (2.42), Seethaphal (4.31)
8. **Meat and poultry**
   Beef meal (18.8), Egg, hen (2.1), Liver, sheep (6.3), Mutton, muscle (2.5)
9. **Milk and milk products**
   Cheese (2.1), khoa (5.8)

Abbreviations

WHO	World health organization
IDA	iron deficiency anemia
ID	iron deficiency
LBW	low birth weight
DALYs	disability-adjusted life in years
GDP	gross domestic product
DLHS	District Level Household Survey
NNMB	National Nutrition Monitoring Bureau
NFHS	National Family Health Survey
GCPR	Good Clinical Practice Recommendations
FOGSI	Federation of Obstetrician and Gynecology Society of India
RCTs	randomized clinical trials
RBCs	red blood cells
Hb	hemoglobin
MCV	mean corpuscular volume
MCH	mean corpuscular hemoglobin
MCHC	mean cell hemoglobin concentration
RDW	red cell distribution width
TIBC	total iron binding capacity
EPP	erythrocyte zinc protoporphyrin
sTfR	soluble serum transferrin receptor
sTfR-F	soluble transferrin receptor-log [ferritin]
ZPP	zinc protoporphyrin
CBC	complete blood count
DMT-1	divalent metal transporter-**1**
ACD	anemia in chronic disease
NE	nutrition education
NaFeEDTA	sodium iron ethylene diamine tetra acetic acid
IFA	iron and folic acid
DFS	double fortified salt
USPSTF	U.S. Preventive Services Task Force
PGART	patient global assessment of response to therapy
PGATT	patient global assessment of tolerability to therapy
GI	gastro intestinal
MoHFW	Ministry of Health and Family Welfare
IM	intramuscular
IV	intravenous
FCM	ferric carboxymaltose
IV-FCM	intravenous ferric carboxymaltose
RDA	recommended dietary allowance
SGA	Small for gestational age

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