FOGSI General Clinical Practice Recommendations

Management of Iron Deficiency Anemia in Pregnancy

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Introduction

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 severelyanemic(1). Moreover, 50% cases of anemia are attributable toiron deficiency anemia (IDA) (1).

When hemoglobin concentrations of an individual are below two standard deviations in comparison to the mean distribution of the normal population who are of same age and gender and live in same altitude, such condition is called Anemia. When this condition arises due to the iron deficiency in the body, it is considered as Iron deficiency anemia (2). Iron deficiency anemia is also defined as hemoglobin of less than 11g% in the first and third trimester of pregnancy and less than 10.5g% in the second trimester of pregnancy (3-6).Iron deficiency anemia during pregnancy increases the risk of low birth weight (LBW), preterm birth, maternal and perinatal mortality, and poor Apgar score (7, 8). An estimate by WHO attributes about 591,000 perinatal deaths and 1,15,000 maternal deaths globally to IDA,directly or indirectly (7). According to Lone et al, anemic women as compared to non-anemic women are at 4 foldhigher risk of preterm birth,1.9 fold increased risk of delivering LBW infants, and 1.8 fold increased risk of havingApgar score<5 at 1 min(8).In a systematic review, a dose-response relationship was observed for an increase in dose of iron supplements and reduction in LBW (9).

It is projected that India has the utmost prevalence of anemia i.e. 57-96.2%, among the South Asian countries(10-14).The prevalence and severity of anemia in India are presented in Table 1.

Table 1 Severity of anemia in national surveys

Survey	Anemiaof 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	-	-	-

DLHS, District Level Household & Facility Survey; NNMB, National Nutrition Monitoring Bureau; NFHS, National Family Health Survey

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 (7). Anemia in pregnancy can precipitate several complications. Maternal Hb has a positive relationship with the neonatal measures of weight, length and head circumference (15).Another study indicated that maternal anemia in the second and third trimester of gestation affects postnatal infant growth (16, 17).Losses fromIDAresult in an increase in the costof up to 4.05% of gross domestic product (GDP) in developing countries, and 1.18% of GDP in India (18).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 (19-21).

To combat the high prevalence of IDA, severalGovernment programs and state level schemes were rolled out in various states of the India. National Nutritional AnemiaProphylaxis Program 1970, National AnemiaControl Program 1991, 12/12 initiative 2007 are some of the nationwide initiatives.Few state-specific schemes include Madilu scheme, Thayi bhagya scheme, and Janani surakshayojana.In spite of Government's persistent and prolonged efforts, the problem continues to fester as is documented by therecent survey: National Family Health Survey (NFHS-4, 2015-2016); the prevalence is 23.6-61.4%(14). The prevalence is higher in urban areas (23.6-61.7%) as compared to rural areas (19.6-58.1%) (14).Diverse religions, cultures, languages, food habits, lifestyles,and traditions that 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 theimplementation of cost-effective evidence-based care.

The present Good Clinical Practice Recommendations (GCPR) from The Federation of Obstetric and Gynaecological Societies of India(FOGSI)for the management of anemia in pregnancy are developed by an experiencedpanel of gynecologists, obstetricians, and hematologists from across the country.A literature search was carried out electronically in PubMedand Google Scholar. Specific evidence from India(MedIND/IndMED)wasidentified. Also, a manual search was carried out in key non-indexed journals. Abstracts in the English language

were scanned and includedin theformulation 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)(22).

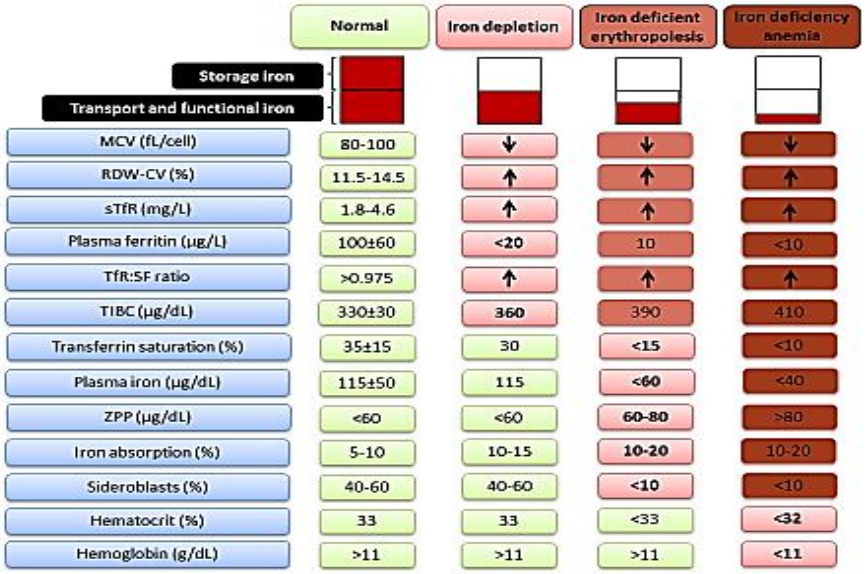
Table 2 Grading of recommendations

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 isattributed to lack of appropriate diagnosis at a suitable age. Iron deficiency (ID) reflects inadequate mobilization of iron stores, leading to impaired “demand to supply” of iron to tissues and red blood cells (RBCs). Therequirement for iron greatly increases with each growing stage, including children below 2 years of age, adolescent, 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 of iron 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(23).



Signs and symptoms

Although Hbtest is recommended at first antenatal visit, examination for signs of pallor of the eyelids, tongue, nail beds, and palm should be regularly used. Some ID patients, with or without clinical signs of anemiamay have alopecia, atrophy of tonguepapillae, or dry mouth due to reduced salivation(24). The symptoms specific to ID include; the syndromes of Plummer-Vinson or Paterson-Kelly (dysphagia with esophageal membrane and atrophic glossitis), gastric atrophy, stomatitis due to rapidly turning over of epithelial cells(25),spoon-shapednails (koilonychia), and pallor. These changes arecaused by a reduction of iron-containing enzymes in the epithelia and gastrointestinal (GI)tract (24). The restless leg syndrome might be striking neurological sequelae prevalent in pregnancy (26). 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 (27-29). Pagophagia (intense desire to eat ice) is quite specific to ID and responds quickly to treatment(30).

Laboratory tests

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

1.*Red blood cell parameters and indices*

Hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean cell hemoglobin concentration (MCHC),red cell distribution width (RDW), reticulocyte Hb content, % hypochromic cells.Along with the examination of various RBC indices, peripheral blood smear evaluation should also be considered as an essential component of evaluating various hematological disorders (**31**). Furthermore, examination of blood smear could provide important clues in the diagnosis of anemias. Anecdotal evidence suggest that peripheral blood smear could help in differentiating the IDA from megaloblastic anemia and anemia of chronic disease.Macrocytes, oval shaped macrocytes and hyper segmented neutrophils are associated with megaloblastic anemias (folate or cobalamin deficiency),target cells and pencil cells are associated

with IDA (**32, 33**). Presence of target cells frequently in the smear rules out anemia of chronic diseases (**34**). Moreover, poikilocytes (prekeratocytes) are also observed in more numbers in IDA (**34**).

2. Direct measurement of iron stores

Assessment of serum iron, total iron binding capacity (TIBC), % saturation, serum ferritin, bone marrow biopsy

3. Assessment of hemeiron

Estimationof free erythrocyte protoporphyrin (EPP)

4.Assessment of iron uptake

Measuring the soluble serum transferrin receptor (sTfR), and soluble transferrin receptor-log [ferritin] (sTfR-F) index, zinc protoporphyrin(ZPP).

1. *Red blood cell parameters and indices*

A primary step in the diagnosis of IDA is to consider the complete blood count(CBC) including Hb, MCV, MCH, and MCHC (35-37).It is simple, inexpensive, rapid to perform and helpful for early prediction of IDA.

Changes in Hb concentration and hematocrit occur only in late stages as shown in Figure 1; 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 as mentioned in Table 3a and Table 3b by WHO and ICMR, respectively.Indeed, a recent study from India demonstrated that various hematological parameters especially sTfR, serum erythropoietin, serumferritin and sTfR/log ferritin levels correlate with the severity of anemia (**38**).

Table 3a Hemoglobin cut off in pregnancy anemia (WHO)(39)

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	Lowerthan 7
Secondtrimester	10.5 or higher			
Third trimester	11 or higher	10-10.9	7-9.9	Lowerthan 7

Table 3b Hemoglobin cut off for anemia (ICMR)(40, 41)

Normal (g/dL)	Mild (g/dL)	Moderate (g/dL)	Severe (g/dL)	Very Severe (g/dL)
11 or higher	10-10.9	7-10	<7	<4

Altitude above sea level and smoking are the known modifiers of Hb concentration (42). The rising maternal blood volume and iron requirements of the fetus are responsible for the dramatic change in Hb concentration in healthy 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,however, a generic value of -1.0 g/dL has been suggested for unknown trimester. Nonetheless, *Nester P* has developed Hb adjustment table for all trimesters; see table 4 (43). Hemoglobin concentration is the commonest hematological estimation and there is a strong correlation between Hb concentration and serum ferritin levels (44).Generally recommendedmethods of Hb estimation are cyanmethemoglobin and the HemoCue® system(39).

Table 4. Hemoglobin adjustment for pregnant women living at sea level (43)

Stage of Pregnancy (Trimester)	Hemoglobin g/ dL
First	-1.0
Second	-1.5
Third	-1.0
Trimester unknown	-1.0

Mean corpuscular volume is the measure of the average RBC volume, and MCHC is the measure of the concentration of Hb in a given volume of packed RBCs. 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) (24). Red cell distribution width has a better sensitivity than MCV for the diagnosis of IDA (45).

The RDW is a measure of the change in RBC 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 RBC 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 (46, 47). Following treatment, marked reticulocytosis occurs in the first 4 weeks, manifested as a sudden increase in RDW, sometimes to over 30% (48). 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 (37). A few studies have reported sensitivity and specificity, respectively, of RDW in the diagnosis of IDA in pregnancy; Sultana et al, 97.4% and 83.2%; and Tiwari et al, 72.8% and 82.4% (44, 45).

It is noteworthy that microcytosis observed in the peripheral smear may be seen even before abnormalities in CBC are developed. If the patient has coexistent folate or vitamin B12 deficiency, the peripheral smear would show a blend of microcytic and macrocytic hypochromic erythrocytes, along with normal MCV (37). Furthermore, the presence of microcytic hypochromic red cells and typical “photo pencil cells” are indicative of IDA (46).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.

Iron deficiency anemia is characterized by microcytic RBCs. Other conditions causing microcytic RBCs include anemia of chronic disorders, β-thalassemia, and sideroblastic anemia. Differential diagnosis of thalassemia and iron deficiency anemia is of great clinical importance since prognosis and treatment are distinct. Several diagnostic indices have been developed to distinguish IDA from thalassemia trait (47, 48). The development of an index with good diagnostic accuracy based only on parameters derived from the red blood cell count obtained using simple counters would be useful in the clinical routine. Indeed, a meta-analysis demonstrated that the ratio of microcytic to hypochromic RBCs (M/H ratio) (diagnostic odds ratio (DOR) =100.8) and the RBC index (DOR=47.0) have shown good performance in differentiating thalassemia and iron deficiency anemia (49).All the tests described above helps differential diagnosis of various microcytic RBCs etiologies as shown in Table 4.

Table 4 Differential diagnosis of various microcytic RBCs etiologies (50-52)

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	_	-	Normal or decreased
Mentzer index	Increased (>13)	Decreased (<13)	-	-

ACI, acute chronic inflammation; BT, β-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 Mentzer index (MCV/RBC count) has been shown as the most reliable index with high sensitivity (48,53). Mentzer Index>13indicates IDA and <13 indicatesβ-thalassemia. Furthermore, two studies from Middle-East have reported RBC count as above 5×10^6 /mm ^{3}inβ-thalassemiasubjects whereas in IDA patients it is below that value (54, 55).

Serum ferritin

Ferritin is a sensitive indicator of IDA in pregnant women(45, 56, 57).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 below15 μg/L indicates iron depletion in all stages of pregnancy(58). However, treatment needs to be initiated when the concentration falls below 30μg/L, as this indicates early iron depletion(58, 59).

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(60). Cutoffs of sTfR (and, thus, the sTfR–F) depend on the assay used, which is a key limitation. There is agradual increase in mean sTfR concentration as pregnancy progresses. The increase is mostly influenced by increased erythropoietic activity than by iron depletion(61).

Serum Iron, and total iron binding capacity (TIBC)

Serum iron and TIBC are the other independent indicators of iron stores or availability. The TIBC measures the obtainability of iron-binding sites. Transferrin, a specific carrier protein transports extracellular iron in the body.Therefore, TIBC is the indirect measure of transferrin levels

that rises as serum iron concentration (and stored iron) declines. The TIBC decreases with malnutrition, inflammation, chronic infection, and cancer (62).

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

The erythrocyte ZPP is formed when zinc is incorporated into protoporphyrin in place of iron during the biosynthesis of heme. Short supply of iron as in IDA increases ZPP production and elevates ZPP/heme ratio whereas in normal condition the reaction of ZPP with iron predominates (62). Before the onset of anemia, ZPP/heme reflects iron status and detects ID. This test is most accurately reported as the ZPP or ZPP/heme ratio. It is a sensitive test, but with limited specificity, because ZPP increases in the settings of inflammation, lead poisoning, anemia in chronic disease, and hemoglobinopathies (63).Normal value of ZPP< 2.3 micrograms ZPP/g Hb.

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 (64).

Bone Marrow biopsy

Bone marrow biopsy should be considered to make a definitive diagnosis of IDA when the diagnosis remains ambiguous even after the analysis of laboratory results.It is indicated when there is no response to treatment or to rule out other conditionsThe absence of stainable iron is the ‘gold standard’ for diagnosis of IDA.

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 checkedto rule out microcytic or normocytic anemia before starting iron therapy to avoid iron overload.An increase of at least 1 g/dL in hemoglobin or 0.03 l/l in hematocrit after 1 or 2 months of supplementation shows an adequate response to treatment and confirms the diagnosis of IDA (2, 3, 4, 36, 65,). However, when multiple etiological factors cause anemia, iron supplementation could only correct the hemoglobin deficit partially. Therefore, based on the prevalence of possible etiological factors, concurrent interventions such as using micronutrients other than iron, or control of infections such as malaria or hookworm might be needed (2).

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 (66).

Food-based strategies

Dietary modification/ improvement

The physiological demand for iron during pregnancy is 3 times higher than in non-pregnant women, and it increases as pregnancy progresses(58, 67).The net iron requirements for pregnancy has been calculatedas 840 mgtaking into account the requirements forfetus placenta, expansion of maternal erythrocyte mass, and final losses due to delivery(68).Thoughiron 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/day during the last 6–8 weeks of pregnancy(69).The extent of iron absorption 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 (69).

The dietary modification involves improving intake of iron by increasing the quantity of iron rich food and practices that increase the absorption of iron (70). The etiology of anemia in India is multifactorial with low iron bioavailability as a major etiological factor(71). 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(71). Non-heme 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 (72-75). 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 aregular meal (23.9±11.2% vs 9.7±6.5%, $p<0.05$) (76). Because phytate is a known iron absorption inhibitor, consumption of phytate rich food should be discouragedwith 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(77, 78).

There is evidence that dietary modification and awareness educationamongpregnant women improve maternal and neonatal outcomes (79-82). 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 96.0%) in post-NE group in nutritional status during pregnancy in a study byGargA et al. (83)

Food fortification

Food fortification is the concept of combining a vehicle (probably commonly consumed food items) and a nutrient togetherand is probably the most cost-effective long-term approach in improving the iron status during pregnancy at the national level(84-86).When accompanied with supplementation, food fortification can be an effective way in managing IDA in women with pregnancy (87). Of various fortifying iron compounds, sodium iron ethylenediaminetetraacetic acid (NaFeEDTA) is most frequently used owing to its effectiveness with a diet rich in phytatesuch as sugar, curry powder, soy sauce, fish sauce and maize flour (88-92).Micronized ground ferric pyrophosphate is another iron salt

used for fortification of color-sensitive food vehicles, such as salt in Africa (93)and rice in India (94).Bio-fortification is a recent approach in iron fortification of wheat, bean, cassava, maize, rice, and yam (95).

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(96-105). Double fortified salt (DFS) has been demonstrated to significantly increase mean Hb in pregnant women consuming DFS than women not consuming fortified salt(+0.42 g/dL vs 0.20 g/dL, $p<0.001$). Further,DFS provided additional ~93 mg of iron within 6 months of supplementation(87).

Supplementation

The average daily requirement of iron increases from 4-6 mg/day in the second and third trimesters to 10 mg/day during the last 6–8 weeks of pregnancy(69). These requirements are unlikely to be met by the diet alone because of poor accessibility, availability, and affordability of diversified food (106). Hence, regular iron supplementation is necessaryfor pregnant women to prevent IDA. The supplementation to prevent anemia targets at improving the ID and it may be community-basedinitiative while therapeutic supplementation aims at treating established IDA, which is a part of the healthcare delivery system (2).

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 agreater probability of higher Hb concentrations at term and in the postpartum period. Nonetheless, they were at relatively high risk of Hb concentrations >13g% during pregnancy, and at term. Women taking iron supplements had lower incidence of giving birth to LBWbabies (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 23.75g, 95% CI, -3.02 to 50.51). There were no significant differences between groups for congenital anomalies, neonatal death, and maternal death (107).Another systematic review and meta-analysis,which included 44 cohort studies in addition to 48 randomized clinical trials (RCTs)evaluating impact 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, 95% CI, 0.42 to 0.59), ID (RR0.59, 95% CI, 0.46 to 0.79), IDA (RR0.40, 95% CI, 0.26 to 0.60), and LBW (RR 0.81, 95% CI, 0.71 to 0.93) compared to controls. Of particular note, the risk of LBW (adjusted OR 1.29, 95% CI, 1.09 to 1.53) and preterm birth (adjusted OR1.21, 95% CI, 1.13 to 1.30) were higher with anemia in the first and second trimester as shown by ameta-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, 95% CI, 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 g (6.8 to 21.8, linear trend p=0.002) for each 1 g/dL increase in mean Hb(9).

Daily Vs Intermittent

A recent Cochrane systematic review has shown similar maternal and infant outcomes with both intermittent and daily supplementation.Intermittent supplementationwas 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 (108). WHO recommends once a week intermittent iron and folic acid supplementation (120 mg elemental iron and 2.8 mg folic acid) in non-anemic pregnant women and adolescents (109). MoHFW recommend intermittent iron and folic acid supplementation (100 mg elemental iron and 0.5 mg folic acid) in all females of reproductive age (15-45 years) (110).

Iron Preparations

There are various iron salts commonly used for the treatment of anemia in India.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 (111). 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(112)	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	• Rise in Hb was seen with all preparations • ↑Hb at 30 D with CI : from 8.69±0.77 baseline to 10.31±0.71, with FS: from baseline 8.89±0.63 to 9.68±0.74, with FF 8.43±0.89 to 9.12±0.87 ($p<0.05$) • ↑Hb at 60D with CI : from 8.69±0.77 baseline to 11.67±0.68 at 60 D, with FS: from baseline 8.89±0.63 to 10.21±0.73, with FF 8.43±0.89 to 10.03±0.91 ($p<0.05$) • ↑Hb at 60D was higher with CI than FS and FF ($p<0.05$) • GI disturbances less in CI as compared to the others. • **CI is effective and better tolerated than others.**
Singhal SR et al, 2015(113)	250	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(g/dL): 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($p<0.001$) • Mean↑SF at 60D (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($p<0.001$) • % S/E : FS, 32; FF, 40; FA, 22; FB, 26; SoF, 14 • **FA & FB are more effective than FS. SoFless S/E**
Geetha R et al, 2014(114)	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 (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($p<0.05$) • 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(115)	150	FF vs CI : efficacy & tolerability	FF: 152mg (app. 50mg elemental iron) + folic acid 750 µg + zinc sulphate 61.8mg) b.i.d for 12 wks. **Inclusion criteria** Gestational age >14 wks of amenorrhea & pregnancy with Hb (7-10 g/dL) Target Hb: 11 g/dL	CI: (app. 100mg elemental iron)+ folic acid 1500 µg + Vit-B12 10 µg+ zinc sulphate 61.8mg) OD	↑ Hb (2, 4, 8 & 12 wks) ADR	• Mean↑Hb at 12 wks: 3g/dL (FF) & 1.489g/dL(CI) (p<0.0001) • Achieved targetHb: 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) • ADR more in CI group. • **FF is not only significantly superior in efficacy but is better tolerated than CI.**
Saha L et al, 2007 (116)	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 vs65.75±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(117)	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	-	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)

			gelatin capsules			
Prospective study						
Kambar et al,2013 (118)	100	IPC vs FS: efficacy, safety, compliance,& cost effectiveness	IPC: 100mg elemental iron + folic acid 500µg OD for 6 weeks (A) **Inclusion criteria** 14 to 20 wks of gestation, Hb: 6.5-8 g/dL (moderate anemia)	FS: 60mg elemental iron + folic acid 500 µgb.i.dfor 6 wks (B)	After 6w, Hb, PCV, MCHC & Se. iron. ADR	• 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($p<0.001$) • 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 139.98±75.51 ($p <0.001$) • **IPC is better alternative to FS as safe & compliance.**
Patil SS et al, 2013(119)	60	Various iron salts: efficacy, tolerability & cost	FF, FB, & CI (each 100 mg) Folic acid 1.5mg, Vit-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(120)	37	SoF vs FF: efficacy	Group A: SoF (33mg of elemental iron) +Vit-B12 (15µg) +folic acid (1.5mg) b.i.d. Group B: SoF (66 mg of elemental iron) +Vit-B12 (15µg) +folic acid (1.5mg) b.i.d. **Inclusion criteria** Gestational age12-26 wks Hb	Group C: FF (100mg of elemental iron) +Vit-B12 (15µg) +folic acid (1.5mg) b.i.d.	Hb, RBC count, MCV, MCH& MCHC (0, 30, 45, 60 & 75D) SF, se. iron, TIBC &	• 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 b.i.d) produce comparable results as ahigher dose of FF (100mg elemental iron b.i.d) • **SoF appears to be effective in improving Hb profile in pregnant anemic women & is tolerated well.**

			(<10g/dL)		TSAT	
Retrospective study						
Angadi E et al, 2015(121)	150	Various iron salts: efficacy & cost effectiveness	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** Gestational age 14 -24 wks Hb> 8g/dL& severe intolerance of OI	-	Hb (30D) & cost effectiveness	• Mean ↑Hb at 30D was more with A(1.569g/dL), followed by B(1.097g/dL) and C (0.48 g/dL). (p<0.001) • ACER:Rs. 281.12 (C), Rs. 60.16 (B) & Rs. 184.21 (A) per increase in Hb g/dL. • **FF can be considered best cost effective medication 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 effectsIPC, 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(113). The PERFECT trial, a multi-centricRCT, compared the efficacy and tolerability of ferrous fumarate with carbonyl iron for the treatment of IDA in pregnancy, 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) score (1.416vs 1.750, p<0.0001) and patient global assessment of tolerability to therapy (PGATT) score (1.416 vs1.652, p=0.002) scales response (122). A comparable rise in Hb was found in pregnant women treated with low doses of ferrous fumarate than ferrous sulphate in a double-blindRCT in India (120). Few studies have found iron polymaltose complex to be more effective and better tolerated than ferrous sulphate in pregnant women (116, 118, 123). 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 (124). The results were supported by another study, which demonstrated an increase in Hb by 0.8-2 g/dL (125). Delayed release preparations of several ferrous salts are available, e.g. ferrous calcium citrate multi-layered system.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 (126). A subgroup analysis of pooled data from 7 RCTs in a systematic review has demonstrated a statistically significant increased risk of GI side effects with ferrous sulphate (OR3.33, 95% CI, 1.19-9.28, p= 0.02, I^2 = 66.1%) in pregnant women (n=1028). These side effects include diarrhea, constipation, abdominal pain, flatulence, nausea, black or tarry stools and heartburn(127). Drug interactions are also a major concern of oral iron pills as they interact with many drugs (128).

Patient instructions for oral iron supplementation should include

1. Taking tablets on an empty stomach or at least one hour after a meal (in 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 (129). The 2013 Ministry of Health and Family Welfare (MoHFW) guideline recommends 100 mg of iron and 500 µg of folic acid daily at least for 100 days starting after thefirst trimester, at 14-16 weeks of gestation, followed by the same for 6 months in the post-partum period (130, 131). 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,. Both guidelines recommend offering standard prophylactic dose after the Hb is normalized for remaining term of pregnancy (130, 131). These recommendations are summarized in Table 7.

Table 7Summary 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- for 100 days starting after thefirst trimester, at 14-16 weeks of gestation	• Mild anemia- 2 IFA tablets/day-100 days • Moderate anemia- IM iron therapy+oral folic acid •	Daily 100 mg iron+500 µg folic acid- 6 months

Recommendations:

1.1. In pregnant women with established mild to moderate anemia, with a period of gestation less than 30-32 weeks, and those who respond to a trial of oral iron, the treatment should continue with 100 mg elemental iron twice daily and 500 µg of folic

acid with an assessment for therise in hemoglobin. A repeat hemoglobin test is recommended after 4 weeks of oral iron. (Grade A, level 3)

1.2. After achieving the normalization of hemoglobin a prophylactic daily iron supplementation (60-100 mg of iron and 500 µg of folic acid) is recommended for at least 6 months during pregnancy and should be continued in postpartum for another 6 months.

1.3. Pregnant women on oral iron supplements should be counseled to consume the tablets before meal or at least one hour after the meal along with supplements like Vitamin C to enhance absorption.(Grade A, level 3)

Parenteral iron

Indications

A major drawback of oral iron is reducedcompliance owing to poor tolerability and side effects. The GI adverse effects of oral iron may further exacerbate the pregnancy associated GI disturbances which includes indigestion, constipation, nausea, vomiting, and reflux esophagitis (132). Hence, parenteral iron could be an alternative to oral iron in patients who are unable to tolerate oral iron,and are non-compliant(58) or need rapid restoration of iron stores.Parenteral iron may be used from the second trimester and during the postpartum period(58).

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 themanagement of anaphylaxis (133, 134). Sensitivity test prior to infusion is recommended.
Contraindications 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 theuse of IV iron in the first trimester of pregnancy is present. (58, 135, 136).
3. Oral Iron should be stopped at least 24 hours prior to therapy to avoid toxic reaction(137).

Calculation of Dose of Parenteral Iron(138)

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, IMiron (2 or 3 doses of 250 mg iron at monthly intervals) significantly improved ferritin level compared with oral iron and proposed it as an alternative in patients with poor tolerability to oral iron (139, 140). Similar results were obtained in another study which used threeIMdoses of 150 mg each at 4 weekly intervals vsdaily 100mg elemental iron (141). Intramuscular iron preparations available in India are iron sorbitol, iron dextran and iron polymaltose.

Test dose

All new patients planned for dextran should be given a test dose of 25mg and they should be observed at least 1 hour for any adverse event.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.

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 (131).

Adverse effects

Adverse effects include mild joint pains and discoloration at the injection site, severe reactionssuch as allergy, itching, fever, lymphadenopathy, arthralgia, headache, malaise and anaphylaxis(142).

Intravenous iron administration

Iron sucrose is the most commonly used preparation for IV infusion and is safe with fewer adverse events (143). It is rapidly taken up 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(144) and adverse reactions are virtually unknown (142). In an Indian study (n=100), pregnant women with hemoglobin (5-9 g%)and with iron deficiency, intravenous iron sucrose complex (200 mg twice weekly) produced a significant improvement in hemoglobin(Hb raised from 7.63 ± 0.61 to 11.20 ± 0.73 g% ($P<0.001$) after 8 weeks of therapy) (143).A recent systematic review has shown a significant increase inHb (mean difference0.85 g/dL; 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 (144).

Numerous studies in India have evaluated theeffectiveness of IV iron as a first line treatment in moderate to severe anemia duringsecond and third trimester of pregnancy.Therequirement for formulating standard protocols and guidelines on IViron use in pregnancy in India wasperceived following an observational study conducted across two states of India by MoHFW in collaboration with WHO (145). 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 8. Several RCTs (Table 9) have compared safety and efficacy of IV iron sucrose to IM iron.

Table 8Summary of studies on intravenous vs oral iron supplementation

Author /year	N	Objective	Intervention	Comparator	Outcome	Results
RCT						
Goginen i S et al, 2015(14 6)	100	IV vs oral: safety & efficacy	IV infusion: IS (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 before food) (B)	↑Hb% (28, 32, 36 & 40 wks). S/E (40 wks), & cost	• Mean diff. in Hb%(A vs B,): 0.3±0.18 vs 0.12± 0.88 (p=0.13) • S/E (A vs B): 8% vs 66% • Lost compliance (A vs B): 4% vs40%, • Cost (A vs B): Rs.1600/-vs 1500/- • **IVIS is safe in pregnancy as OI is associated with gastric S/E.**
Sunita VN et al, 2015(14 7)	90	IV vs oral: safety & efficacy	IV infusion: IS (dose as per Hb % & BW: approx. 200-950 mg over 1-8 days)(A) Target Hb:11g/dL **Inclusion criteria** Patients with26-32 wks of gestation, Hb(8-10g/dL), SF(<13µg/L)	Oral: (300mg OD 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), 4w; 30.66±4.93 vs 19.96±2.38 (p=0.001), delv; 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 because it is the safest and least expensive.**
Tembhar	200	IV vs oral:	IV infusion: IS (dose as per	Oral: carbonyl	Hb (7	• Mean ↑Hb (A vs B) at 30D: 7.24±1.02 to

e A et al, 2015(148)		Efficacy in IDA	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)	elemental iron 60mg each 4 wks + 5mg FA + Albendazole 800mg for 1 wk)(B)	&30D), SF (30D)	10.93±0.92 g/dL 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 S et al, 2015(149)	100	IV vs Oral: treatment of IDA	IV infusion: IS (dose as per Hb % & BW)+ FA (500µg OD)(A) Target Hb:11g/dL **Inclusion criteria** Single pregnancy, gestational age (12-36wks), Hb(6-9g/dL)	Oral: 200mg b.i.d for 6 wks.+ FA (5mg/day) (B)	After 6 wks, Hb, RBC's indices, SF & TSI. Compliance and S/E	• ↑SF: significant (p<0.001) in group A • ↑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 had a more favorable improvement in clinical features with fewer S/E, and more effective in later months of pregnancy.**
Abdulla h A et al, 2014(150)	200	IV vs oral: safety & efficacy in moderate anemia	IV infusion: IS; 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),follow 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),follow 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 groups. • **IVIS is more effective in achieving target Hb & timely use will reduce maternal & fetal complications and risk of transfusion.**
Abhilashini GD et al, 2014(151)	100	IV vs oral: safety & efficacy	IV infusion: IS; (dose as per Hb % & BW:200mg alt. days; max 600mg/wk.) (A) Target Hb: 11g/dL **Inclusion criteria** Patients with gestational age (30- 34 wks) with IDA (Hb: 6-8g/dL)	Oral: 200 mg t.i.d (B)	Hb, %PCV, MCV, reticulocyte count (2, 4 & 37 wks). S/E	• ↑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; 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(152)	100	IV vs oral: safety & efficacy	IV infusion: IS; (dose as Hb % & BW:200mg alt. days; max 600mg/wk.)(A) Target Hb:11g/dL	Oral: 200mg t.i.d for 4 wks (B)	Hb (7D, 14D, 28D & delv.), SF (28D)	• ↑Hb (A vs B): 14 D; 0.58 vs 0.23 g/dL (p= 0.004), 28 D; 1.9 vs 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

			Inclusion criteria single pregnancy, 24-34 wks of gestation,Hb(7- 9 g/dL), SF(<15µg/L)		S/E	(p<0.001). • S/E (A vs B): 10% vs 46%. • **The ↑Hb is faster with IVIS than OI, which can be beneficial at a later period of gestation and also very well tolerated.**
Mehta MN et al, 2014(153)	150	IV vs oral: efficacy in treatment of IDA	IV infusion: IS, (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= 0.284). • 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(154)	198	IV vs oral: response & efficacy	IV infusion: IS, 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=0.000), 4w; 70.85±46.25 vs 18.34±3.15(p=0.000), 8w; 33.85±12.7 vs 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 than OI.**
Kochhar PK et al, 2013(155)	100	IV vs oral: Efficacy & safety	IV infusion: IS 200mg alt. day (A) **Inclusion criteri** Patients with Hb(7-9 g/dL), SF(<15µg/L), MCV (<85 fL)	Oral: 200mg: t.i.d (4 wks.) (B)	↑Hb (7D, 14D, 21D, 30D & delv.), SF (30D&delv.	• ↑Hb: A (5.1 g/dL), B (3.1g/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,**

					).S/E	**without severe S/E.**
Meenal C et al, 2013(156)	484	IV vs oral: response & efficacy	IV infusion: IS 200mg: 24 hrs apart) + 400mg Albendazole (A) **Inclusion criteria** Anemic (Hb: 5-10g %) in $2^{nd}/3^{rd}$trimesterswith no other risk factors	Oral: 200 mg: b.i.d (4 wks.) + 400mg Albendazole (B)	After 4 wks, Hb &ADR	• ↑Hb:in A group, 71.64% patients showed ↑ 2-2.9g/dL, whereas in B group, 77.4% patients showed ↑0.6-0.9g/dL of Hb. • Both group shows minor ADR. • **IVIS can correct anemia in a short period even in advanced pregnancy and prevent associated maternal and perinatal complications.**
Neeru S et al, 2012(157)	100	IV vs oral: efficacy & tolerance	IV infusion: IS (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). • ↑% 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% vs 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(158)	200	IV vs oral: safety & efficacy for IDA	IV infusion: IS (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(pregnancy)	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 vs26.6 ± 8.56).

			SF(<15µg/L)	(B)		• S/E (A vs B): 13 vs 22 patients. • **IVIS elevates Hb and restores iron stores faster than OI, with no severe ADRs.**
Prospective studies						
Tandon A et al, 2015 (159)	400	IV vs oral: efficacy	IV infusion: 200mg elemental iron diluted in 100ml of 0.9% normal saline, given on alternate days. Total amount was calculated according to iron deficit, based on body weight. **Inclusion criteria** Patients with Hb ≤8 gm%, serum ferritin ≤15 microg/L and dimorphic anemia or microcytic hypochromic anemia.	200 mg FeSo4 tablets per day for 4 weeks.	Hb, SF, Hematocrit and general blood picture are observed 4 weeks after the last dose was given.	• Baseline and 4 weeks values for various parameters in IV vs oral groups: Hb (gm/dl): 6.17±0.47 & 10.08±0.66 vs 6.92±0.59 & 8.38±1.05 (p=0.004); SF (µg/l): 9.47±1.01 &285.5±45.1 vs 10.0±1.70 & 162.8±33.1 (p<0.0001); Hematocrit (%): 16.8±1.76 & 46.06±1.99 vs 18.6±1.36 & 33.45±3.17 (p=0.004); MCHC (%):25.01±1.73 & 34.1±0.97 vs 24.6±2.06 & 32.08±1.41 (p=0.009); MCV (fl): 70.28±0.96 & 93±1.13 vs 70.1±1.96 & 85.8±3.97 (p<0.0001). • **IV therapy is safe, convenient and more effective than oral iron therapy to treat IDA**
Retrospective studies						
Raut SV et al, 2015 (160)	200	IV vs oral: Efficacy in moderate anemia	IV infusion: IS (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 OI.**
Mani P et al, 2015 (161)	229	IV vs oral: Efficacy& tolerance	IVIS 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 =0.000). • IVIS in pregnant women was well tolerated. • **IVIS elevates Hb and restores iron faster than OI**

Halimi S et al, 2011 (162)	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 IS (dose as per Hb % & BW) (B)	S/E (15th D) & Hb (30th D)	• ↑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.**

**, highly significant; 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; TSI, total serum iron; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; TIBC, total iron binding capacity; PCV, packed cell volume; ADR, adverse drug reaction; IS, Iron sucrose

Table 9 Summary of studies on intravenous vsintramuscular iron supplementation

Author /year	N	Objective	Intervention	Comparator	Outcome	
RCT						
Suguna V et al, 2015(163)	200	IVIS vs IMIS: Efficacy & safety compariso n	IV infusion: 200mg t.i.w. **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) 7.63±0.42 to 10.56±0.52 • Mean ↑%PCV (IV vs IM 26.5±3.11 to 32.7±2.22 • Mean ↑SF (IV vs IM) at 7.5±1.82 to 22.4±2.12 • FBW (IV vs IM): 2.7±0. • ADR (IV vs IM):16 vs 2 • **IVIS was safe for corre**
Sujatha V et al,2014 (164)	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 v • Mean time taken for targ (p<0.01). • ADR (IV vs IM): 10% v • **IVIS is safe, convenien therapy than IMIS the anemia.**
Singh S et al, 2013(165)	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 v • Mean time taken for targ (p<0.01). • ADR (IV vs IM): 8 % vs
Dhanani JV et al, 2012(166)	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 vs 1.45 (p>0.05). • % Hemocrit at 28D: IV; IM;27.73±4.22 to 31.08 • MCV(fL) at 28D: IV; 70 68.65±9.01 to 72.18±8.6 • MCH (pg) at 28D: IV; 2 20.89±4.52 to 22.52±4.2 • SF (ng/ml) at 28D: IV; 6 9.32±8.37to 20.13±11.3 • ADR(IV vs IM): 2 vs 31 • **Efficacy same but ADR**

IVIS, intravenous iron sucrose; S/E, side effects; IMIS, intramuscular iron sorbitol; SF, serum ferritin; FBW, fetal birth weight; ADR, adv intramuscular iron sorbitol citric acid; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; TIBC, total iron binding ca

Management of postpartum anemia

Untreated IDA during thepostpartumperiod is a cause of maternal morbidities such as tiredness, lethargy, dizziness, headaches, lactation failure,and postpartum depression167, 168). Prevalence of postpartumIDA is very high in India(169, 170). The maternal mortality rates are also significant(171). The importance of prevention and treatment of IDA in postpartum period should be given further thrust in the maternal health programs. The WHO guideline recommends postpartum prophylactic iron supplementation of 60 mg elemental iron + 400 µg folic for 3 months (172, 173).Universal iron supplementation was demonstrated to be effective in reducing the prevalence of anemia among low-income postpartum women (174). The MoHFW guideline recommendsdaily iron (100mg elemental iron with 500µg folic acid) for all non-anemic women in postpartum period for 6 months, whereas the same tablet is advised to be taken twice daily for mild to moderately anemic postpartum women(130, 131).Generally anemia in postpartum represents a dire need for iron supplementation, in such anemic patients parenteral iron supplementation was found to be more effective in treating anemia, as compared to oral iron supplementation (159, 175-178). Among the various preparations of parenteral iron supplementation ferric carboxymaltose was found to be superior to all other parenteral iron supplementation products (179-181).Ferric carboxymaltose (FCM) is a dextran free IV iron preparation that allows rapid administration of high dosesof iron (up to 1000 mg iron in 15 min).FCM administration in postpartumhas been found to be safe and effective in improving the mean Hb level (181-184). Compared to other parenteral iron preparations FCM has several advantages: It has fewer side effects, single high dose administration is possible and it can reduce the frequency of hospital visits (185).

Postpartum IV iron therapy has been found to avoid demand for blood transfusions (186), and it rapidly replenishes iron stores compared with oral iron (175, 177, 183, 187-192).This is more cost effective option(193). A summary of all postpartum iron intervention studies conducted in India is presented in Table 10.

Table10 Summary of postpartum iron intervention studies inIndia

Author /year	N	Objective	Intervention	Comparator	Outcome	
RCT						
Pal SR et al. 2015 (187)	100	IV-IS vs oral Feso4	IV-IS: 200mg t.i.w (A) **Inclusion criteria** ID with Hb% < 11g/dL and serum ferritin level≤20 µg/L	Oral Feso4 (B): 60mg b.i.d for 6 weeks	↑ in Hb& ferritin (Day 1, 15, 42)	• Mean ↑in Hb (8.50 ± 0.72 (p • Achievement (13.05 ± 0.72 v • Mean ↑in ferri 4.63 vs 15.55 11.18 vs 71.04 • **IV-IS safe, we iron stores an**
Vijayala kshmi S et al. 2015(18 8)	120	IV-IS vs oral Feso4	IV-IS: 300-600mg 2/3 divided doses in alternate day for 3 days (A) **Inclusion criteria** Hb <10 g/dL within 48 h postpartum	Oral Feso4: 300 mg (100mg elemental iron) for 28 days (B)	↑ in Hb (g/dL)	• Mean ↑in Hb (11.1±0.8 (p<0 • **IV-IS effectiv**
Jain G et al. 2013(18 9)	40	IV-IS vs oral Ferrousfumar ate	300–600 mg of IV-IS every alternate day for 3 days (A) **Inclusion criteria** Hb<8 g/dL	Oral: 300 mg ferrous fumarate OD for 14 days (B)	↑ in Hb	• Mean ↑in Hb (1.2 g/dL(p<0. • **IV-IS effectiv fumarate in p**
Swati et al. 2013 (190)	50	Oral Feso4 vs IV-IS	Oral Feso4: 200mg t.i.d for 4 weeks (A)	IV-IS: 100mg OD for 3 days (B)	Hb, Serum Ferritin	• Mean ↑in Hb vs7.27±0.4 to • Mean ↑in hem 0.93±0.34% (• **IV-IS effectiv**
Rohini et al. 2012(19 1)	50	Oral Feso4 vs IV-IS	IV-IS: 200mg elemental iron for 4 weeks (A)	Oral Feso4: 200 mg tablets t.d.s 4 weeks (B)	postpartu m day 2 or 3, Hb ≤7g%	• Mean ↑in Hb (vs5.94±0.62 • Mean ↑in Hb (g/dLvs11.48± • Mean ↑in Hem vs 17.8±1.76 • Mean ↑in Hem 37.06±1.99 vs • **IV-IS effectiv**
Kharde PS et al, 2012(17 7)	100	Oral Feso4 vs IV-IS: efficacy in IDA	**IV-IS:** 200mg (2^{nd}& 4^{th} day) (A) **Inclusion criteria** Hb <10 g/dL but > 6g/dL at 24 to 48 hrs post delv. & SF< 15µg/L.	Oral Feso4: 200 mg b.i.d for 6 wks (B)	Hb, SF (5, 14 & 40D) ADR	• Mean ↑in Hb (to 11.41±0.79 10.78±0.7679 • Mean ↑in SF (53.47±5.011 v • ADR (A vs B) • **IV-IS ↑Hb & ADR in comp**
Verma S et al,	150	IV-IS vs oral Feso4:	**IV-IS:** 600mg (A) **Inclusion criteria**	Oral Feso4: 200mg b.i.d	Hb (1, 2, 3, 4wks)&	• Mean ↑in Hb (7.42 to 10.09

2011(175)		efficacy & safety	Hb <8 g/dL after 24 hr of delv.	for 4 wks (B)	ADR	• **IV-IS is an eff E & faster rec**
Garg R et al, 2015(192)	100	IV-FC vs IV-IS insevere IDA: efficacy & safety	IV-FC: 1000mg (A) **Inclusion criteria** All normal &casareandelv.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 (g/dL • Achievement c 100% vs 98%. • ADR (A vs B) • **IV-FC is safe, acting than IV during PP per**
Rathod S et al, 2015(185)	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 g/dL (6w) in C • Mean ↑SF: 2.5 ng/ml(6w) in C • ADRs less in I • **IV-FC ↑Hb & without ADR.**
Prospective study						
Mishra VV et al, 2015(194)	158	IV-FC: efficacy & safety	IV-FC: ≤ 1000mg/wk or 15 mg/kg. **Inclusion criteria** Gestation age >20-36 wks & PP patients with Hb 6-11 g%.	-	↑Hb & iron stores (3 wks)Safety	• Improvement a 11.34±0.90, PC (µg/dL); 402.5 18.30±16.39 to 47.23±18.87 to • Patients with l • **IV-FC should ↓maternal mo**
Hol KV et al, 2015 (183)	100	IV-IS vs IV-FC efficacy & safety in PPA	IV-IS: 500mg to mild anemia group (Hb 9-11 g%); 1000mg to moderate anemia group (Hb 7-9 g%). **Inclusion criteria** PPA patients with Hb 7-11 g% at 24-48 hrs after delivery. Only IDA patients are considered	IV-FC: 500mg and 1000mg to mild and moderate anemia groups respectively.	↑Hb & SF 6 weeks after therapy	• Mean ↑ in Hb = 0.180 for me 4.58 vs. 4.74 (• Mean ↑ in SF 38.70 (p = 0.75 anemia group: difference). **IV-IS and IV- treating mild patients.**
Singh S et al, 2017 (181)	200	IV-IS vs IV-FC efficacy & safety in PPA	IV-IS: 500mg divided in three doses (200mg + 200mg + 100mg) and given on alternate days.(Group 1) **Inclusion criteria** Postpartum patients with Hb ≥7 and <10 gms (10 days post- delivery) and serum ferritin 15 ng/dl (38 weeks of gestation)	IV-FC: 500mg as single dose (Group 2).	↑ in Hb and SF from baseline	• % of patients v 2 vs. Group 2: • % of patients v Group 1: 24 vs • SF rose signifi compared to g • **FC is an effici**
Joshi SD et al, 2017 (182)	200	IV-FC vs IV-	Single dose IV-FC of	IV-IS:	↑Hb and	• ↑ Hb (g/dl) IV- • Mean ↑ in SF

Sharma N et al, 2017 (184)	120	IS efficacy & safety IV-FC vs IV-IS efficacy & safety in PPA	1000mg. **Inclusion Criteria** Patients with Hb ≥6 g/dl and ≤11 gm/dl at 10 days post-delivery. Fixed dose of 1000mg of FC was given within 10 days of delivery. **Inclusion Criteria** Patients with Hb<10 g%, with PPA	1000mg divided into 5 doses of 200mg each, given on 0,2,4,6 and 8 days. Fixed dose of 1000mg of IS was given within 10 days of delivery.	SF on day 0 and 30 from the last dose of parenteral iron. Hb & SF 14 days post transfusi-on	71.07±27.23 • **FC is a better ultra-short du reactions and** • Mean increase (p value 0.000 superior to IS • **FC was very concentration stores in patie**
Patel J et al, 2015 (176)	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 1 vs 4.1 & 4.9 g/ • Mean↑SF 9.4 & 8.3 • ADR(IV-FC v • **IV-FC ↑Hb & well tolerated in the PP peri**
Retrospective study						
Khandal e SN et al, 2015 (195)	121	IV-FC : efficacy & safety	IV-FC	-	↑ in Hb & ADR	• Mean↑ Hb: 2.7 patients with b • patients report (1); rash/urtica • **IV-FC was eff patients & wa**

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 (196). The recent Royal College of Obstetricians and Gynaecologists (RCOG) blood transfusion guideline recommendsblood transfusion in labor or immediate postpartum

period if the Hb< 7 g/dL(197).The indications for blood transfusion are presented in Table 11.

Table 11Indications of blood transfusion in pregnancy(197, 198, 199)

Antepartum Period
1. Pregnancy <34 weeks
a. Hb <5 g/dL with or without signs of cardiac failure or hypoxia b. Hb 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 <7g% (postpartum): Decision of blood transfusion depends on medical history or symptoms

Deworming

The prevalence data on soil-transmitted helminthiasis is not uniformly available in India, but clinical experience shows thehighburden of worm infestationin the community. Intestinal helminthiasis and Hb concentrations are known to have aninverse relationship (200); hence, administration of anthelmintic agents has been recommended as an additional intervention to reduce anemia. A systematic review of RCTs evaluating theeffect of anthelmintic drugs on Hb demonstrated mean Hb increase of 1.71 g/dL (201).

A recent Cochrane review found insufficient evidence to recommend deworming in pregnancy (202),though there is a demonstrable benefit of deworming in endemic areas (203). In hookworm-endemic areas, WHO risk–benefit analysisconfirmed the benefits of deworming in endemic areas – this is evidenced by improved infant birth weight and survival (204) and reduced maternal anemia (205).For soil-transmitted helminthiasis, WHO recommendofferingalbendazole or mebendazole to pregnant women in the second

andthirdtrimesters of pregnancy and to lactating women as a preventive therapeuticinterventions inareas where the prevalence of any soil-transmitted helminth infection (hookworm infection, ascariasis, and trichuriasis) exceeds 20%(206). The national guidelines for deworming in pregnancy by the MoHFW, Government of India, recommend a single dose of 400 mg of albendazoletablet after the first trimester, preferably inthe secondtrimester(207).

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 (208). The report finds approximately80% of these cases in African countries and 13% in South East Asia Region (SEAR) countries(208), of this, India contributes to 61% of malaria cases and 41%deaths due to malaria (209). The reported prevalence of malaria in pregnancy varies from 46-51% in India(210-214). Malaria increases the risk of maternal anemia, placental parasitaemia, stillbirth, spontaneous abortion, LBW and neonatal deaths (131, 215,).

The WHO recommends a three-pronged approach to the prevention and management of malaria during pregnancy, which includes: insecticide-treated nets (ITNs), intermittent preventive treatment (IPT), and effective care management of malarial illness (216). The IPT with at least 2 doses of sulphodoxine pyrimethamine (SP) has been found to reduce the prevalence of maternal anemia and placental parasitemia; and the incidence of LBW in the second and third trimesters of pregnancy in several studies conducted in Africa(217-220-). Furthermore, 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 (221). However, we could not find the evidence on IPT 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 firsttrimester and artemisinin combination therapy in the second and third trimesters of pregnancy (222).Co-supplementation with other micronutrients

Folic acid or folate insufficiency during pregnancy is directly associated with adverse pregnancy complications and poor birth outcomes. These includes the risk of preterm birth, LBW, intrauterine growth restriction (IUGR) and neural tube defect (NTD) in the neonates (223). Folate supplementation and fortified food can reduce the incidence of NTD by 46%

and neonatal death by 13% (224). Therefore, theadditionof 500µg of folic acid or folate during antenatal period is necessary to avoid the maternal and perinatal complications.

Maternal Vitamin B_{12}deficiency is directly associated with adverse pregnancy complications and poor birth outcomes, e.g. LBW (225), IUGR (226), & NTD (227). A 2.6 µg & 2.8 µg of Vitamin B_{12} daily during pregnancy and lactation, respectively, need to be added to avoid the maternal and neonatal complications (228).

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 (229). 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 (68). 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 (230). Vitamin C usage other than enhancing the absorption of iron, its routine supplementation in IDA is not advised.

A systemic review of 13 RCTs shows no advantage in reducing maternal mortality with vit-A compared with placebo or when added to iron supplements (231). A prophylactic vit-A supplementation to prevent maternal and infant morbidity and mortality is not recommended (232).

Appendix I.Iron rich food, iron (mg/100g)(233)

1. **Cereal grains and products**
   Whole wheat flour (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 gram, whole (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

CBC	complete blood count
DALYs	disability-adjusted life in years
DFS	double fortified salt
EPP	erythrocyte protoporphyrin
FOGSI	Federation of Obstetric and Gynecological Societies of India
GCPR	Good Clinical Practice Recommendations
GDP	gross domestic product
GI	gastro intestinal
Hb	hemoglobin
ID	iron deficiency
IDA	iron deficiency anemia
IFA	iron and folic acid
IM	intramuscular
IPT	intermittent preventive treatment
ITNs	insecticide-treated nets
IUGR	intrauterine growth restriction
IV	intravenous
LBW	low birth weight
MCH	mean corpuscular hemoglobin
MCHC	mean cell hemoglobin concentration
MCV	mean corpuscular volume
MoHFW	Ministry of Health and Family Welfare
NaFeEDTA	sodium iron ethylene diamine tetra acetic acid
NE	nutrition education
NFHS	National Family Health Survey
NTD	neural tube defect
PGART	patient global assessment of response to therapy
PGATT	patient global assessment of tolerability to therapy
RBCs	red blood cells
RCOG	Royal College of Obstetricians and Gynaecologists
RCTs	randomized clinical trials
RDA	recommended dietary allowance
RDW	red cell distribution width
SEAR	South East Asia Region
SP	sulphodoxine pyrimethamine
sTfR	soluble serum transferrin receptor
sTfR-F	soluble transferrin receptor-log [ferritin]
TIBC	total iron binding capacity
WHO	World health organization
ZPP	zinc protoporphyrin

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