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KEY PRACTICE POINTS 2024

INDIAN PERSPECTIVE

Optimizing maternal and neonatal outcomes in pregnancy with IDA

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OPTIMIZING MATERNAL AND NEONATAL OUTCOMES IN PREGNANCY WITH IDA

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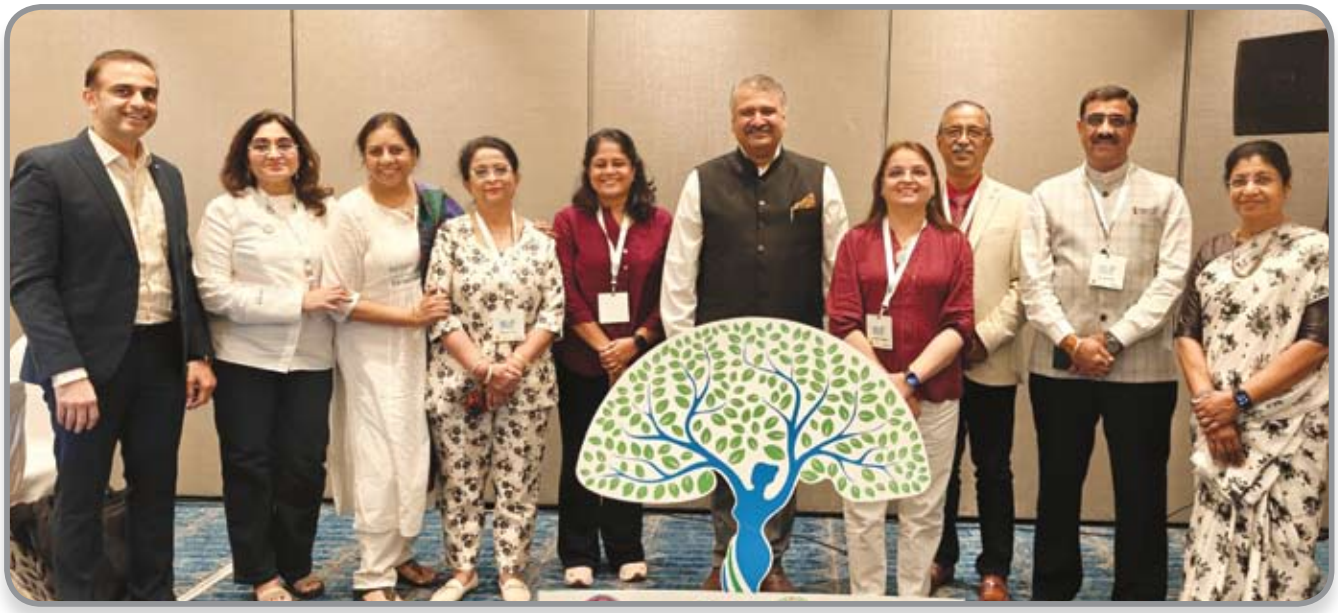

From left to right: Dr. Kunal Doshi, Dr. Girija Wagh, Dr. Krishna Kumari, Dr. Rajul Tyagi, Dr. Charmila Ayyavoo, Dr. Jaydeep Tank, Dr. Sunita Chandra, Dr. Arun Madhab Boruah, Dr. Ajay Mane, Dr. Y Savitha Devi

Background

Anemia during pregnancy is a global health problem. The National Family Health Survey 2019-21 (NFHS-5) showed increased prevalence of anemia compared to previous NFHS-4 survey.[1] Severe anemia leads to unfavourable pregnancy outcomes including increased maternal morbidity and mortality.[2–5]

Treatment for iron deficiency anemia (IDA) involves oral or intravenous (IV) iron supplementation. Oral iron supplementation is a common therapy for IDA in pregnancy, but frequent gastrointestinal (GI) side effects significantly affect patients' adherence and efficacy of therapy.[5] Oral preparations are insufficient in moderate-to-severe anemia where a rapid improvement in hemoglobin (Hb) levels and iron stores is essential. Hence, parenteral iron preparations are primary mode of treatment for moderate-to-severe anemia.[6]

Scope

This consensus meeting aims to formulate validated key practice points to optimize maternal and neonatal outcomes after treatment of IDA in pregnancy.

Methodology

The task force comprised of nine experts in the field of Obstetrics and Gynecology. The task force reviewed the literature and developed the consensus statement based on published literature, their individual clinical experience, and focused discussion within the task force. The task force members followed a well-defined grading system (Table 1) for the critical appraisal of evidence and grading strength of consensus statements. The consensus statements developed by the task force were presented to a larger group consisting of 39 experts in the field of Obstetrics and Gynecology. There was deliberation on each consensus point and later accepted, modified, or deleted. Thus, this

document provides much-required insights and useful, practical, and accurate feasible guidance that aids a practicing clinician across the country.

Table 2. Level of evidence and grading strength of recommendations

Grades of recommendation	Level of evidence	Type of Study
A	1a	Systematic review of (homogenous) randomized controlled trials
A	1b	Individual randomized controlled trials (with narrow confidence intervals)
B	2a	Systematic review of (homogenous) cohort studies of "exposed" and "unexposed" subjects
B	2b	Individual cohort study/low-quality randomized control studies
B	3a	Systematic review of (homogenous) case-control studies
B	3b	Individual case-control studies
C	4	Case series, low-quality cohort, or case-control studies
D	5	Expert opinions based on non-systematic reviews of results or mechanistic studies

Maternal outcomes of anemia during pregnancy

Anemia in pregnancy increases rates of severe maternal morbidity and mortality.[7]

Association of anemia and PTB

Severity of anemia is linked to increased risk of preterm delivery and stillbirth.[8,9] A meta-analysis comprising 18 studies (n= 932,090) revealed a significant link between maternal anemia and preterm birth (PTB) (RR: 1.56, 95% CI: 1.25–1.95). Maternal anemia in the first trimester was linked to an increased risk of PTB (RR: 1.65, 95% CI: 1.31–2.08).[10] A population-based cohort study has shown that iron therapy significantly reduced the odds of PTB.[11]

Association of anemia with pre-eclampsia

Anemia and hypertensive disorders (HDP) are a significant risk factor for adverse maternal and neonatal outcomes.[11] The Community Level Interventions for Pre-eclampsia (CLIP) cluster-randomized controlled trial (RCT) reported increased maternal morbidity in all anemic pregnant women.[12]

Association of severe anemia with PPH

Nair et al. found that severe anemia increased the odds of postpartum hemorrhage (PPH) by nine times than those with mild anemia (adjusted odds ratio (aOR) 9.45; 95% CI: 2.62 – 34.05).[13] A systematic review and meta-analysis has reported that severe anemia during the pre-conceptional period is a significant predictive factor for PPH.[14,15]

PRACTICE POINT

For anemia during pregnancy associated with preterm birth

Maternal anemia is a risk factor for preterm birth. (Grade A/Level I)

WHO PPH guidelines recommendes screening for anemia in pregnancy as it increases the risk of blood loss during delivery and PPH.[16]

Neonatal adverse effects of maternal anemia

Lower Hb levels in the mother restricts the oxygen supply to the fetus resulting in alterations in placental angiogenesis, potentially leading to impaired intrauterine growth and low birth weight (LBW).[17] In a systematic meta-analysis of 68 studies, it was reported that maternal anemia was associated with LBW with an adjusted OR: 1.23 (95% CI: 1.06–1.43) and I^2 (heterogeneity index): 58%.[18] Anemic mothers deliver infants with low Apgar scores.[19-21] An observational study of women in third trimester diagnosed with severe anemia (Hb <70 g/L) demonstrated increased risk of LBW with an adjusted relative risk (RR) of 7.47 (95% CI: 2.53, 22.08).[22]

Ideal diagnostic work up

- Complete blood count (CBC) in the first trimester.
- If IDA is suspected, ferritin level of <30 ng/ml is diagnostic.[22,23] A normal/borderline ferritin level do not exclude IDA as it is an acute phase reactant.[22]

PRACTICE POINT

For anemia during pregnancy associated with pre-eclampsia

Severity of anemia during pregnancy increases risks of pre-eclampsia. (Grade A/Level I)

PRACTICE POINT

For maternal anemia associated with neonatal outcomes

Untreated maternal anemia can adversely affect the neonatal outcome, including, LBW, **NICU admissions, and congenital malformation. (Grade A/Level I)**

Oral Iron

Oral iron therapy is the widely prescribed for IDA, and ferrous iron is more effective than ferric compounds. Ferrous ascorbate is widely prescribed and has a bioavailability of up to 67%.[26]

Disadvantages

- Presence of GI diseases affect the absorption of iron minimizing the effectiveness of therapy.[26]
- Absorption can be reduced due to the presence of certain foods or mucosal luminal damage.[27]

Hence, parenteral iron has emerged as an alternative in managing IDA.[28,29]

Intravenous iron preparation

Advantages

Parenteral iron helps in restoring iron stores faster and more effectively than oral iron without GI side effects.[28] IV iron administration benefits several patient populations (those with inflammation, intolerant, and noncompliant with oral iron therapy).[30, 31]

Indications for parenteral iron[32,33]

- Failure/non-compliance or intolerance to oral iron
- Second trimester of pregnancy if Hb <10.0 g/dL
- Late second or third trimester with moderate to severe IDA
- Rapid correction of anemia and iron stores
- Malabsorption (e.g., surgery or diseases)
- Bleeding diathesis
- Comorbid inflammatory condition and IBD
- After gastric bypass or chronic renal disease

Dose

The recommended cumulative replacement dose for IV iron is 1000 mg of iron.[34] The iron requirement can be calculated using Ganzoni's formula which is body weight in kg x 2.4x [expected Hb-patient's Hb g/L] + 500 mg for stores.[34]

Iron sucrose

Iron sucrose has a short half-life of 5.3±6 hours, causing increased serum ferritin and transferrin saturation (TSAT) within 24 hours and 1 week, both returning to baseline within 3-4 weeks.[35] The maximal single dose per day is 200 mg, but its use is limited due to **multiple infusions**.[35]

Ferric carboxymaltose

Ferric carboxymaltose (FCM) is a macromolecular ferric hydroxide carbohydrate complex with a ferric hydroxide core stabilized by a carbohydrate shell.[36] In the bloodstream, the iron from the iron-carbohydrate complex is released and is either taken by ferritin or serum transferrin. This iron-transferrin complex binds to receptors on erythroblasts situated in the bone marrow providing essential iron for Hb synthesis. Thus, FCM is rapidly cleared from plasma and largely distributed to bone marrow.[37] Infusion of FCM can correct IDA in second and third trimester of pregnancy.[38] It is administered intravenously, as a single dose of 500 mg diluted in 100 ml normal saline over 6 minutes or 1000 mg diluted in 250 ml normal saline over 15 minutes. The dose should not exceed 1000 mg/week and must be diluted only in sterile 0.9% saline.[39]

Table 2. Treating IDA in pregnant Indian women

Severity	Hemoglobin levels	Serum Ferritin levels	Therapy
Mild	10–10.9 g/dL	≤30 mcg/L (IDA)	Oral iron, 100 mg elemental iron and 500 µg of folic acid[24]
Moderate	9.9–7 g/dL	≤30 mcg/L (IDA)	Oral iron 100 mg/day If rapid Hb rise is needed: Parenteral iron can be calculated based on pre-pregnancy weight, aiming for a target Hb of 11g/dl using the following Ganzoni formula: Required iron dose (mg) = {2.4 × (target Hb-actual Hb) × pre-pregnancy weight (kg)} + 1000 mg for replenishment of stores[25] Iron injection 1500–2000 mg (in divided doses) depending upon the body weight and Hb level
Severe	6.9–4		Parenteral IV Iron
Very severe	<4		Hospitalization and blood transfusion
Post-partum anemia	Parenteral intravenous (Iron sucrose/ ferric carboxymaltose (FCM) FCM has an advantage of administration as a bolus dose in the postpartum period for correction of anemia and restoration of iron stores.[24]		

Table 3. Cumulative FCM Dose for Iron Repletion[6]

Body Weight	Cumulative FCM Dose	
	Hb <10 g/dL	Hb ≥10 g/dL
35-70kg	1500 mg	1000 mg
>70 kg	2000 mg	1500 mg

The dosage to be given can be calculated using a simple formula based on the body weight and hemoglobin levels.[8]
Notes: Maximum tolerated single dose: 1000 mg of iron (20 mL) per day. 1000 mg of iron (20 mL) not to be administered more than once a week.
Abbreviations: FCM: ferric carboxymaltose; g/dL: grams per deciliter; Hb: hemoglobin; mg: milligram; kg: kilograms

Attributes of FCM

- Type 1 (robust) parenteral iron
- No dextran-induced hypersensitivity
- Can be administered in much higher doses
- Short infusion time
- Iron is released slowly, avoiding toxicity and oxidative stress
- Deposited easily in reticuloendothelial cells
- Test dose is not required
- Low immunogenic potential

Efficacy of FCM

In systematic review of 21 RCT, researchers showed that there was significant improvement in serum ferritin levels and in Hb levels with FCM compared to ferric gluconate, oral iron, and placebo. FCM provided faster correction of Hb and serum ferritin levels compared to other IV iron preparations.[40]

Iron sucrose or FCM

Implementing a single high-dose IV iron approach facilitates efficient replenishment of iron stores, thereby enhancing both subjective and objective outcomes associated with IDA.[41] FCM is a third-generation parenteral iron formulation used for correcting IDA and has been evaluated in many Indian and international, which supports its efficacy and safety in treating IDA in pregnancy. In an RCT, researchers compared IV FCM with iron sucrose complex for treating pregnancy-related IDA. Primary outcome: Hb increase after 12 weeks. Secondary outcomes: RBC indices, serum iron, fatigue scores, visits, perinatal outcomes. FCM showed significantly higher Hb rise (29 g/L vs. 22 g/L; $p < 0.01$), improved fatigue scores, and required fewer visits. FCM rapidly replenished iron stores, with a convenient dosing regimen for better community compliance.[42]

The systematic review aimed to compare the efficacy and safety of IV iron formulations, FCM, and iron sucrose in treating IDA in obstetric and gynecological patients. Results revealed that the FCM group exhibited superior efficacy in raising Hb and ferritin levels, along with a more favorable safety profile, including fewer adverse events, compared to the iron sucrose group.[43]

The IV preparations offer the advantage of delivering a larger supply of iron more rapidly compared to oral iron supplements. Importantly, the IV route of administration bypasses the GI tract, thereby eliminating the risk of GI side effects commonly associated with oral iron supplementation.[7] In a retrospective case-control study, 72 pregnant women who received IV FCM treatment in the third trimester were compared with 72 anemic women (Hb < 10 g/dL) at the time of admission for delivery. The study found that correction of anemia with IV FCM was effective in reducing maternal morbidity, with a mean Hb rise from 8.2 ± 0.8 g/dL to 11.1 ± 1.3 g/dL prior birth.[45] Treatment with FCM led to swift replenishment of iron stores in pregnant women, resulting in a significantly higher rise in Hb levels over a 12-week period. The convenient dosing regimen requiring fewer in clinic visits for completing the treatment is likely to enhance compliance.[44]

In a multicenter RCT of women with IDA (n=2045; Hb ≤ 11.0 g/dL) to single dose of FCM (15 mg/kg [maximum 1000 mg]) the mean Hb increase was greater in the FCM than the standard medical care or anemia group. The study concluded that FCM was well tolerated and effective in bring about raise in mean Hb levels in postpartum women or women with heavy menstrual bleeding and IDA.[45] A recent meta-analysis has demonstrated that IV iron treatment is superior to oral iron in terms of improving maternal hematological parameters at delivery.[46] An RCT showed that the primary outcome of increase in Hb by at least 2 g/dL was achieved by 65.8% with FCM vs. 53.6% with iron sucrose (12.2% difference, p=0.004). Achievement of a normal Hb occurred in 72.8% with FCM and 61.8% for iron sucrose (11% difference, p=0.015).[47]

Comparison between iron preparations

Compared with oral ferrous sulfate, IV iron sucrose improved Hb (mean difference 7·17 g/L, 95% CI 2·62–11·73 and IV FCM improved Hb (difference 8·52 g/L, 95% CI 0·51–16·53).[48]

Contraindications[49]

- Iron overload (serum ferritin >150 µg/L)
- Known hypersensitivity
- Liver disorder (jaundice, cirrhosis, or renal failure).
- Acute cardiac failure
- Thalassemia disease, sickle cell anemia disease or hemolytic anemia.

Follow up after IV iron administration

Check Hb level 4 weeks after administration of IV iron. If there is no improvement in Hb level (<1 g/dL) increase the dose after 4 weeks).[49] Iron/folic acid tablets need not be given for 3 months post infusion to those who have received full dose of IV iron.

Advantages of FCM[50]

- FCM is a safe intravenous agent in pregnancy.
- It is superior to iron sucrose for IDA in pregnancy.
- Early rise in Hb level and shorter duration of treatment.
- Patient friendly dosing and better compliance.

Precautions during IV iron therapy

Monitoring for 30–60 minutes post-infusion. A previous hypersensitivity reaction (HSR) to IV iron heightens the risk of an adverse response to subsequent iron infusions.[54] A test dose of IV iron is unnecessary, as it could falsely reassure about the safety of the subsequent therapeutic infusion.[51]

Management of adverse drug reactions

- Mild HSR: stop infusion for ≥ 15 min, monitor pulse BP respiratory rate O_2.
- Moderate HSR: Stop the iron infusion and consider volume load, IV corticosteroids.
- Severe/life threatening HSR: stop iron infusion, Adrenaline IM (5 mg 1/1000) or IV (0.1 mg 1/10000), nebulize β_2 agonist, further isotonic volume load, IV corticosteroid, O_2 face mask, ACLS (if necessary).[51]

PRACTICE POINTS

Parenteral iron therapy for IDA in pregnancy

- Prevention and treatment of anemia by increasing Hb levels is recommended in pregnant and postpartum anemic women to reduce maternal and perinatal morbidity and mortality. (Grade A/Level I)
- Parenteral iron therapy improves the outcome of pregnancies with anemia. (Grade A/Level I)
- Wherever possible, IV iron preparation should be provided due to swift improvement in Hb levels and iron stores. (Grade A/ Level I)
- Corrections of anemia with FCM should be considered due to its efficacy and safety in treating IDA in pregnant women. (Grade A/ Level I)

SUMMARY

- Maternal anemia is a risk factor for preterm birth. (Grade A/Level I)
- Severity of anemia during pregnancy increases risks of pre-eclampsia. (Grade A/Level I)
- There is significant relationship between anemia in pregnancy and risk of PPH. (Grade A/Level I)
- Untreated maternal anemia can adversely affect the neonatal outcome, including, LBW, **NICU admissions, congenital malformation. (Grade A/Level I)**
- Prevention and treatment of anemia by increasing hemoglobin levels is recommended in pregnant and postpartum anemic women to reduce maternal and perinatal morbidity and mortality. (Grade A/Level I)
- Parenteral iron therapy improves the outcome of pregnancies with anemia. (Grade A/Level I)
- Wherever possible, IV iron preparation should be provided due to swift improvement in hemoglobin levels and iron stores. (Grade A/Level I)
- Corrections of anemia with FCM should be considered due to its efficacy and safety in treating IDA in pregnant women. (Grade A/Level I)

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