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KEY PRACTICE POINTS 2024
INDIAN PERSPECTIVE

Prepartum anemia and risk of postpartum hemorrhage: Improved anemia correction strategies

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PREPARTUM ANEMIA AND RISK OF POSTPARTUM HEMORRHAGE: IMPROVED ANEMIA CORRECTION STRATEGIES

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Background

Anemia is a major public health concern pregnant women in India, affecting 45.7% in urban areas and 52.1% in rural areas, with hemoglobin (Hb) levels below 11 g/dL.[1] Iron deficiency (ID) is the leading cause, responsible for approximately 50% of cases.[1] Anemia during pregnancy has been linked to an increased risk of postpartum hemorrhage (PPH), suggesting that antepartum anemia may play a role in PPH development. Though the underlying pathophysiology regarding the influence of anemia on PPH is not completely understood, recent evidence suggests that red blood cells may play an essential role in hemostasis.[2] The incidence of PPH in India is reported to be 2%–4% following vaginal delivery and 6% following cesarean section.[3] PPH accounts for 38% of maternal deaths in India which is exacerbated by the widespread prevalence of anemia among pregnant women.[4] It is typically defined as a blood loss of 500 mL or more within 24 hours after childbirth, or any amount of blood loss that makes the woman hemodynamically unstable. Severe PPH, characterized by a blood loss of 1000 mL or more within the same timeframe, poses significant risks.[4] Uterine atony is the primary cause of PPH, but other factors such as genital tract trauma (e.g., vaginal or cervical lacerations), uterine rupture, placental abruptions, placenta previa, pregnancy-induced hypertension, anemia, retained placental tissue, or maternal coagulation disorders can also contribute to PPH.[4] Multiparity and multiple gestation are also associated with an increased risk of postpartum bleeding. PPH may be aggravated by pre-

existing anemia and, in such instances, the loss of a smaller volume of blood may still result in adverse clinical sequelae. Moreover, the patient blood management (PBM) approach is effective in addressing severe PPH, but it is difficult to access in India.[5] Therefore, addressing anemia during pregnancy is essential for reducing the severity of PPH complications.[4]

Iron deficiency anemia (IDA) can be diagnosed using laboratory tests. The findings will include a decrease in the Hb level, CBC (MCV/PCV), serum iron concentration, serum transferrin saturation, and serum ferritin level, along with an increase in total iron-binding capacity.[6]

Scope

The aim of key practice points is to develop a validated treatment approach to prevent prepartum anemia and avoid the risk of PPH, suitable for daily clinical practice.

Methodology

The task force comprised 10 experts in the field of Obstetrics and Gynaecology. The task force reviewed the existing literature and developed a consensus statement based on published literature, their individual clinical experience, and focused discussions 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 task force were presented to larger group consisting of 39 experts in the field of Obstetrics and Gynecology. Each consensus point was deliberated upon 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 1. 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

Patient Blood Management Programs for post-partum hemorrhage

Patient blood management (PBM) is a multidisciplinary, evidence-based, and patient-centric approach to maintaining an optimal Hb level, optimize hemostasis, minimise blood loss, and limit blood transfusions aiming to improve patient outcomes.[8] PPH management often requires a multidisciplinary team involving obstetricians, hematologists, anesthesiologists, and other healthcare professionals to ensure comprehensive care.[9] Despite its proven benefits, PBM implementation in obstetrics remains limited in many hospitals. However, given the high prevalence of ID and anemia in pregnancy and the risk of peripartum hemorrhage for every woman, integrating PBM into obstetric care is promising.[9]

PBM in obstetrics, especially for PPH, revolves around anemia and relies on three fundamental principles: (1) Identifying, addressing, and managing preoperative/prepartum anemia; (2) Minimizing and managing perioperative/peripartum red blood cell (RBC) loss; and (3) Enhancing postoperative/postpartum anemia treatment, with an emphasis on judicious red blood cell transfusion practices.[8]

Screening for ID during pregnancy

Recommendation as per different international guidelines

Guidelines from various organizations recommend routine blood tests during pregnancy to detect and manage anemia. The NICE (The English National Institute for Health and Care Excellence) guideline suggests screenings at the beginning of pregnancy and at 28 weeks[8], the UK and ACOG guidelines recommend screenings at initial visit and during the third trimester. Similarly, the FIGO committee advises screenings at initial visit and during the third trimester.[10]

The above-mentioned recommendations are likely intended to diagnose anemia due to hemodilution during pregnancy and to correct it before the birthing process. Considering the high prevalence of anemia in women in India and the associated perinatal adverse outcomes, screening for anemia should be done in the first trimester and, if possible before conception and should be proactively corrected through therapeutic interventions as discussed below.[11,12]

Hemoglobin cut off in pregnancy anemia (WHO)[13]

Pregnancy state	Normal (g/dL)	Mild (g/dL)	Moderate (g/dL)	Severe (g/dL)
First trimester	11 or higher	10–10.9	7–9.9	Lower than 7
Second trimester	10.5 or higher	9.5–10.4	7–9.4	Lower than 7
Third trimester	11 or higher	10–10.9	7–9.9	Lower than 7

Hemoglobin cut off for anemia as per ICMR[14]

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

Treatment of antenatal anemia to prevent the risk of PPH

Preventing PPH by addressing prepartum anemia requires a comprehensive strategy. Treatment should be tailored based on factors such as time to delivery, anemia severity, and risks of complications such as preterm labour and maternal health conditions.[15]

Steps to take into consideration for therapy of anemia and ID in pregnancy[15]

1. Screening for anemia during every trimester of pregnancy and definitely at the first visit.
2. Diagnosis: Confirm the diagnosis of IDA through laboratory tests.
3. Treatment according to trimester and severity
   - » If IDA is diagnosed in the first- or second-trimester, initiate oral iron supplementation. Consider the use of intravenous (IV) iron therapy, if oral supplementation is ineffective or poorly tolerated.
   - » For severe ID in the second trimester and any ID in the third trimester, consider the use of IV iron supplementation.

Recommended treatment options for IDA in pregnancy

IDA should be treated by replenishing iron stores through either oral or IV administration of iron, depending on the severity of the anemia and the urgency of correction.[16]

Indications for IV Iron supplementation[9]

The IV iron is recommended in the following situations:

- Intolerance to oral iron preparations due to gastrointestinal side effects.
- Inadequate increase in Hb levels due to impaired intestinal absorption or poor compliance (failure in the rise of Hb by at least 1 g in 2 weeks).
- Severe, advanced, or progressive anemia (Hb ≤ 9 g/dL).
- When rapid treatment for anemia is required due to advanced gestational age.

A systematic review and meta-analysis examining the efficacy of IV iron versus oral iron during pregnancy concluded that IV iron is superior for managing. Pregnant women who received IV iron achieved desired Hb levels compared to those who took oral iron over a 4-week treatment period. The IV iron treated pregnant women experienced fewer adverse events, mainly lesser incidence of gastrointestinal side effects, than those treated with oral iron.[17] Another systematic review and meta-analysis examining the advantages of IV iron for the treatment of postpartum anemia similarly determined that women administered IV iron exhibited elevated Hb and ferritin levels at postpartum weeks 1, 2, 3, 4, and 6 compared to those receiving oral iron supplementation.[18]

PRACTICE POINTS

For IV iron therapy

- Based on efficacy and side effect profile for use in pregnancy after the first trimester parenteral iron may be considered for those who cannot tolerate or do not respond to oral iron or for those with severe ID in second half of pregnancy and any ID anemia nearer term (Grade A, level 1a)
- During pregnancy and postpartum period, IV iron administration for IDA is deemed superior to oral supplementation in terms of both efficacy and treatment duration. (Grade A, level 1a)

Parenteral Ferric Carboxymaltose for IDA in pregnancy

There are number of parenteral iron preparations with different dosing regimen.[9] The IV iron formulations consist of ferric iron, which may be more or less tightly bound.[16] First-generation formulations include low molecular weight iron dextran and iron sorbitol citrate. While these formulations allow for higher doses, they are associated with anaphylactic reactions. Second-generation compounds like iron sucrose require multiple injections to deliver 1000 mg of iron. Ferric carboxy maltose (FCM), a third-generation parenteral iron formulation, offers rapid iron stores replenishment and can be administered in a single dose of up to 1000 mg IV over 15 minutes.[16] **IV FCM offers several advantages such as lower rates of hypersensitivity reactions, single dose administration and reduced frequency of hospital visits.[10,19]**

There are many Indian clinical studies supporting the efficacy and safety of FCM in treating IDA in pregnancy.[20]

Clinical evidence

A Multicenter retrospective, observational, real-world PROMISE study evaluated the efficacy and safety of IV FCM in Indian pregnant women with IDA over 4 weeks. This analysis of 1191 pregnant women showed that IV FCM resulted in a significant increase in Hb by 2.8 g/dL and serum ferritin by 30 µg/L at 4 weeks ($p < 0.001$ for both). Adverse effects were reported in 8.6% of pregnant women, including headache, mild local reaction, nausea, dizziness, abdominal pain, constipation, and fever and chills. No serious adverse reports were reported. This large real-world study evidence supports clinical use of IV FCM in management of IDA in pregnant women.[20]

A retrospective real-world evidence analysis by Gupte et al. assessed the efficacy and safety of FCM injection in Indian pregnant women with moderate to severe anemia. Data from a cohort of 271 patients was retrieved and analyzed for safety parameters and data of 168 patients was analyzed for efficacy. There was significant increase in Hb levels over 4 weeks (1.25 g/dL; $p < 0.001$). The patients who received FCM in the second trimester noted a significant increase in Hb of 1.74 g/dL ($p < 0.001$). The patients with severe anemia reported an increase in Hb of 4.23 g/dL ($p = 0.01$). Importantly, no adverse fetal or neonatal outcomes were observed. The safety analysis showed that only 4% patients had adverse drug reactions, the most common being itching and rash. These findings confirm the efficacy and safety of FCM in real-world clinical practice.[19]

Similarly, a large real-world retrospective study of 1800 Indian patients with IDA assessed the efficacy and safety of IV FCM in adolescents and adults with IDA revealed 98.3% of the subjects with moderate (77.5%) to severe (20.8%) anemia responded to FCM within 4 weeks. FCM resulted in significant improvements compared to baseline at 4 ± 1 week, including a rise in Hb by 2.76 g/dL, serum ferritin by 35.85 µg/L, red blood cell (RBC) count, hematocrit, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) ($p<0.001$ for all). Safety was reported to be good in 97.2% of subjects. This study contributes to the growing body of evidence that FCM is both safe and effective in correcting moderate to severe anemia within a span of 4 weeks.[21]

A phase IV clinical trial was undertaken to assess the efficacy and safety of IV FCM compared to iron sucrose IS in women diagnosed with IDA. The study findings provided robust evidence supporting the efficacy and safety of IV FCM in correcting anemia and replenishing iron stores during pregnancy. Notably, FCM demonstrated superior effectiveness over iron sucrose, manifesting in elevated Hb levels and faster restoration of iron stores. Moreover, the incidence of adverse drug reactions was minimal with FCM administration, further reinforcing its favourable safety profile.[22]

Dose calculation/total drug infusion for ferric carboxymaltose

The cumulative dose required for Hb restoration and repletion of iron stores is calculated by the following Ganzoni formula:[23]

Cumulative iron deficit (mg) = body weight in kg x (Target Hb - Actual Hb g/dL) × 2.4 + iron storage depot (mg).

PRACTICE POINTS

For IV FCM therapy in pregnancy

- IV FCM is preferred for moderate-to-severe anemia in the second and third trimesters of pregnancy. (Grade A, Level 1b)
- IV iron in mild anemia can be administered during the third trimester when there is inadequate time to correct anemia by oral therapy. (Grade A, Level 1b)

Parenteral Ferric Carboxymaltose for postpartum anemia

IDA is common in postpartum period due to postpartum blood loss. Recent studies suggest that IV iron in the postpartum period is beneficial and more effective than oral iron, particularly in women with moderate or severe anemia.[8]

Clinical evidence

A systematic review by Sultan et al. found that women with PPH had Hb levels nearly 1 g/dL higher at 6 weeks when receiving IV iron compared to oral iron. Given the reassuring safety profile of IV iron, weaker Hb response and higher risk of gastrointestinal side-effects with oral iron use, IV iron can be considered as a viable treatment option for postpartum IDA.[18]

A comparative study was conducted at SCB Medical College, Odisha to evaluate and compare the safety and efficacy of FCM, IV iron sucrose and oral iron in the treatment of postpartum anemia. The study demonstrated statistically significant increase in Hb and ferritin levels in FCM group compared to iron sucrose and oral iron. The study concluded FCM restored iron stores faster than IV iron sucrose and oral iron, without any severe adverse reactions.[23] Similarly, a comparative study published in 2021 where total 215 postpartum women with IDA were divided randomly in two groups, iron sucrose and FCM. There was significant rise in Hb with FCM as compared to iron sucrose (4.6 gm/dL versus 3.5 gm/dL respectively) at 6 weeks. The study concluded that FCM is safe and efficient in treatment of IDA in postpartum women as compared to iron sucrose, with lesser adverse effects and better patient compliance.[24]

PRACTICE POINT

For IV FCM therapy in postpartum anemia

FCM should be the choice of iron supplementation in postpartum anemia to rapidly and effectively correct ID, replenish iron stores, and raise Hb to optimal levels. (Grade A, Level 1a)

FCM dosage and dilution

The dose of FCM is calculated based on individual's total iron requirement based on weight and Hb deficit as mentioned in Table 1.[25]

Dosage

Table 1. Determination of the total iron need[25]		
	FCM dose as per patient body weight	
Hb g/dL	35 kg to <70 kg	70 kg and above
<10	1,500 mg	2,000 mg
10 to <14	1,000 mg	1,500 mg

Dilution for intravenous infusion[25]

Volume of FCM required	Equivalent iron dose	Maximum amount of sterile 0.9% m/V sodium chloride solution	Minimum administration time
>4 to 10 ml	>200 to 500 mg	100 ml	6 minutes
>10 to20 ml	>500 to 1000 mg	250 ml	15 minutes

Can be administered in a day-care set up with resuscitation facilities available, if needed.

PRACTICE POINTS

For IV FCM administration[26]

- The dosage of FCM is determined based on the severity of anemia and the patient's weight.
- The maximum FCM dose administered in a single session should not exceed 1000 mg.
- If necessary, the subsequent dose can be repeated after a week.
- In a hospital setting, 1000 mg of FCM should be infused diluted in 250 mL of 0.9% normal saline or 500 mg diluted in 100 mL of 0.9% normal saline over 10–15 minutes, under medical supervision.
- Infusion of 1000 mg dose should be administered in 15 minutes and 500 mg dose should be infused in 6 minutes.

References

1. Kaushal S, Priya T, Thakur S, et al. The etiology of anemia among pregnant women in the hill state of Himachal Pradesh in North India: A cross-sectional study. Cureus. 2022;14(1):e21444. **2.** Glonnegger H, Glenzer MM, Lancaster L, et al. Prepartum anemia and risk of postpartum hemorrhage: A meta-analysis and brief review. Clin Appl Thromb Hemost. 2023;29:10760296231214536. **3.** Gora K, Depan A, Yadav K, et al. Causes and management of post-partum haemorrhage at tertiary care center, Rajasthan, India. Int J Reprod Contracept Obstet Gynecol. 2019;8(6):2425–28 **4.** National health Mission. Guidance note on prevention and management of postparum haemorrhage. Available from: https://nhm.gov.in/images/pdf/programmes/maternal-health/guidelines/Guidance_Note_on_Prevention_&_Management_of_Postpartum_Haemorrhage.pdf Accessed on Feb 2, 2024. **5.** Gandhi A, Görlinger K, Nair SC, et al. Patient blood management in India - Review of current practices and feasibility of applying appropriate standard of care guidelines. A position paper by an interdisciplinary expert group. J Anaesthesiol Clin Pharmacol. 2021;37(1):3-13 **6.** Api O, Breyman C, Çetiner M, et al. Diagnosis and treatment of iron deficiency anemia during pregnancy and the postpartum period: Iron deficiency anemia working group consensus report. Turk J Obstet Gynecol. 2015;12(3):173–81 **7.** Stony Brook University, Libraries. Evidence-based medicine. Available from: https://guides.library.stonybrook.edu/evidence-based-medicine/levels_of_evidence . Last updated Jan 25, 2024 4:15 PM. Accessed on 14 March 2024. **8.** Surbek D, Vial Y, Girard T, et al. Patient blood management (PBM) in pregnancy and childbirth: literature review and expert opinion. Arch Gynecol Obstet. 2020;301(2):627–41 **9.** Wiesenack C, Meybohm P, Neef V, et al. Current concepts in preoperative anemia management in obstetrics. Curr Opin Anaesthesiol. 2023; 36(3):255–62 **10.** O'Toole F, Sheane R, Reynaud N, et al. Screening and treatment of iron deficiency anemia in pregnancy: A review and appraisal of current international guidelines. Int J Gynecol Obstet. 2023;00:1–14 **11.** Tandon R, Jain A, Malhotra P. Management of iron deficiency anemia in pregnancy in India. Indian J Hematol Blood Transfus. 2018;34(2):204-215. **12.** Neogi SB, Babre A, Varghese M, et al. Improving the approach to assess impact of anemia control programs during pregnancy in India: A critical analysis. BMC Pregnancy Childbirth. 2022;22(1):966. **13.** Guideline on haemoglobin cutoffs to define anaemia in individuals and populations. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO. **14.** Kriplani, A, Sharma A, Rizvi ZA, et al. FOGSI General Clinical Practice Recommendations Management of Iron Deficiency Anemia in Pregnancy Chairperson. Available from: https://www.researchgate.net/publication/314952524_FOGSI_General_Clinical_Practice_Recommendations_Management_of_Iron_deficency_anemia_in_pregnanacy Accessed on Feb 2, 2024. **15.** Kaserer A, Castellucci C, Henckert D, et al. Patient blood management in pregnancy. Transfus Med Hemother. 2023; 50(3):245–55. **16.** Damineni SC, Thunga S. IV Ferric Carboxymaltose Vs Oral iron in the treatment of post-partum iron deficiency anemia. J Clin Diagn Res. 2016; 10(11):QC08-QC10. **17.** Govindappagari S, Burwick RM. Treatment of iron deficiency anemia in pregnancy with intravenous versus oral iron: Systematic review and meta-analysis. Am J Perinatol. 2019;36(4):366-376 **18.** Sultan P, Bampoe S, Shah R, et al. Oral vs intravenous iron therapy for postpartum anemia: a systematic review and meta-analysis. Am J Obstet Gynecol. 2019;221(1):19-29.e3 **19.** Gupte SA, Venkataraman G, Shah AS, et al. Clinical effects and safety of ferric carboxymaltose in pregnancy: An Indian real-life experience. J Obstet Gynaecol Res. 2021; 47(10):3464–70. **20.** Trivedi P, Chitra S, Natarajan S, et al. Ferric carboxymaltose in the management of iron deficiency anemia in pregnancy: A subgroup analysis of a multicenter real-world study involving 1191 pregnant women. Obstet Gynecol Int. 2022; 2022:5759740. **21.** Charmila A, Natarajan S, Chitra TV, et al. Efficacy and safety of ferric carboxymaltose in managing iron deficiency anemia: A multi-center real-world study from India. J Blood Med. 2022; 13:303–313. **22.** Naqash A, Ara R, Bader GN. Effectiveness and safety of ferric carboxymaltose compared to iron sucrose in women with iron deficiency anemia: phase IV clinical trials. BMC Womens Health. 2018; 18(1):6. **23.** Rathod S, Samal SK, Mahapatra PC, et al. Ferric carboxymaltose: A revolution in the treatment of postpartum anemia in Indian women. Int J Appl Basic Med Res. 2015; 5(1):25–30. **24.** Patel RM, Bhabhor MB, Pahwa NR, et al. Comparative study of efficacy and safety of intravenous ferric carboxy maltose versus iron sucrose in treatment of postpartum iron deficiency anemia. Int J Reprod Contracept Obstet Gynecol. 2021;10(2):707–710 **25.** Ferric carboxymaltose Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/product/5910/smpc/print **26.** Mahapatra PC, Gupte S, Malhotra N, et al. Ferric Carboxymaltose for the treatment of anemia during antenatal and postpartum period: Expert opinion. J South Asian Feder Obst Gynae 2022;14(3):292–301.

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