Do We have a Magic Bullet to Treat Moderate and Severe Anemia in Pregnant Women?

Shashi Kant
Professor and Head, Centre for Community Medicine, AIIMS, New Delhi, India

Summary

A desperate situation may evoke a fundamental question or suggestion of a radical solution. Hence, let us first examine whether the current situation of maternal anemia in India is really desperate and therefore merits a search for a “magic bullet” as a cure.

Key words: Anemia, pregnancy, treatment

Policy Initiatives

Anemia is one of the most common micronutrient deficiency disorders on this earth, ironically caused by the deficiency of the most abundant mineral on earth, i.e., iron. The initial effort to address anemia among pregnant women in India was made in 1970 under the National Nutritional Anemia Prophylaxis Program.[1,2] The strategy was rather conservative with one tablet daily of iron folic acid (IFA) containing 60 mg of elemental iron and 500 µg of folic acid given for 100 days as a supplement. An evaluation of this program in 1987 concluded that the program was performing very poorly.[3-5] Based on the Indian Council of Medical Research study, the dose of elemental iron in IFA tablet was increased from 60 to 100 mg.[6] A more aggressive strategy of test, detect, and treat anemia in all settings was adopted, and the program was renamed as National Anemia Control Program in 1991. In 2013, under the National Iron Plus Initiative, the strategy was further modified wherein IFA supplementation throughout the life cycle was adopted. Pregnant women were given IFA containing 100 mg of elemental iron and 500 mcg of folic acid for 100 days if they were not anemic. For mild and moderately anemic pregnant women, the therapeutic dose was two tablets per day. For the first time, parenteral iron in the form of intramuscular (IM) iron preparation was proposed to treat severe anemia.[7] The highest level of political commitment to control anemia was displayed in 2018 when the Honorable Prime Minister of India launched the Anemia Mukt Bharat (AMB) (Anemia-Free India) program. Under this program, an ambitious target of annual reduction in the prevalence of anemia by 3% from the National Family Health Survey (NFHS)-4 level has been set.[8] To achieve this target, annual allocation of Indian Rupee (INR) 19 million/district has been made.[9] Thus, there is evidence that the Government of India has tried to address maternal anemia by periodically fine-tuning its public health response.

Results

The NFHS-2 done in 1998–1999 revealed that the prevalence of any anemia in pregnant women was 49.7%.[10] It remained unchanged at 50.3% when the latest round of survey (NFHS-4) was done in 2015–2016.[8] Thus, despite repeated tweaking of the national program, there has been no decline in the prevalence of anemia among pregnant women in India in the past two decades. The prevalence of anemia in pregnant women in India is not only among the highest in the world but also the worst even when compared to the neighboring countries.[11] It would, therefore, be reasonable to conclude that the situation of maternal anemia in India is indeed desperate.

Suggestion of a Radical Solution

The question that should exercise our minds is whether deploying the same old tool, i.e., IFA tablets to all pregnant women is adequate. It is time to re-look at alternative ways of treatment such as blood transfusion. It is probably time to bullet-proof anemia in India.
women, whether as a supplement or in therapeutic dose, would deliver a different result this time? The answer to this question is nuanced. IFA tablet may still be the first choice as supplement to the nonanemic pregnant women and as a therapy for mildly anemic pregnant women who collectively constitute three-quarters of all pregnant women. However, for moderate and severely anemic pregnant women, a different strategy is required. IM iron which contains dextran can cause local pain, skin discoloration, abscess formation, allergic reaction, fever, lymphadenopathy, and rarely anaphylaxis. Because of these reasons, the use of IM iron for the treatment of iron deficiency anemia has been almost discontinued. Moreover, the proportion of pregnant women who have severe anemia is very small (1.3%). Therefore, even if we were to treat the severely anemic pregnant women with IM iron, it would not make any difference to the overall prevalence of maternal anemia. We now have dextran-free parenteral iron formulations, for example, iron sucrose (IS) and ferric carboxymaltose (FCM) which are administered by intravenous (IV) route. IV iron bypasses the gastrointestinal regulatory mechanism. This allows the delivery of nonprotein-bound iron directly to the red blood cells. FCM and IS have improved safety profile, are easy to administer, and are more effective in rapid restoration of hemoglobin (Hb) level and body iron reserve.

**Should We Have a Different Treatment Strategy for Moderate and Severe Anemia in Pregnant Women?**

Much of the adverse consequences of maternal anemia on mother and her unborn child (e.g., poor pregnancy outcome, delayed cognitive and motor development, poor educational performance, and substantial impairment of work capacity) have already been documented in the published literature and need no repetition.

**Pregnant Women**

A meta-analysis has shown that for each 1 g/dL increase in mean Hb level, the risk of maternal death falls by 25%. The decreased risk of maternal mortality is continuous over the full range of Hb level between 5 and 12 g/dL. However, this relationship is not linear. The decrease in the risk of maternal mortality is greater at lower Hb concentrations. Therefore, more health benefits would accrue if we adopt an aggressive approach for the treatment of moderate and severe anemia among pregnant women.

**Child**

A double-blind randomized controlled trial that included >17,000 pregnant Chinese women found that low maternal Hb level at 24–28 weeks was a risk for anemia in the infant at age 5–7 months (adjusted odds ratio 1.95, 95% confidence interval [CI] 1.59–2.40). Another study found that compared to nonanemic mothers, the newborns of anemic Ethiopian mothers had significantly lower levels of serum ferritin and Hb concentration. Thus, the newborns of anemic mothers are not only likely to be anemic but also have lower body iron reserve.

If the Hb level of children was to improve even by 1 g, the risk of death will fall by 24%. The more severe the maternal anemia, more adverse is the consequence for the child. There is usually a 2–3-fold increase in perinatal mortality rate when maternal Hb level falls below 8 g/dL, and this escalates to 8–10-fold increase when the maternal Hb level is <5.0 g/dL.

Thus, the benefits of improvement in maternal Hb level are not only restricted to the mother alone but also accrue to the newborn. This intergenerational benefit is not appreciated often enough. Therefore, more aggressive treatment of moderate and severe anemia in pregnant women is warranted.

The long-term developmental consequences of anemia in infancy have been reported by many studies. Between 30% and 50% of infants aged 6 months have anemia. The anemia worsens during 6–24 months of age. This is precisely the time when neurogenesis and brain differentiation take place. Unfortunately, the damage caused to cognitive status is permanent even if the anemia is corrected at a later stage. Treating maternal anemia improves not only the Hb level but also the body iron reserve of the infants and thereby protects against the cognitive damage. It is reported that for each gram increase in Hb in infants, there would be a gain of 1.73 intelligence quotient points. These facts further justify the robust treatment of moderate and severe anemia in pregnant women.

**Economic Cost**

Cognitive damage in childhood leads to an irreversible loss of productivity in adult life. A recent study from India has estimated that among the birth cohort of 6–59-month-old children with iron deficiency anemia, the lifetime production loss was US$ 24 billion in 2013 (corresponding to 1.3% of gross domestic product). Therefore, no treatment or inadequate treatment is many times more expensive for the nation in the long run compared to the cost of treating moderate and severe anemia in pregnant women adequately.

Currently, two IV iron formulations, i.e., IS and FCM are available in the Indian market. They are potential contenders for the treatment of moderate and severe anemia in pregnant women. We now examine their respective merit to choose one of them, tentatively termed as “Magic Bullet.”

**Iron Sucrose for Treatment of Anemia**

Large amount of published literature, both from India and elsewhere, is available to confirm that the administration of IS to anemic pregnant women leads to an increase in Hb level in the range of 1.6–3.6 g/dL. We also found similar results when we administered a uniform dose of 400 mg of IS divided in four doses on alternate days to moderately and severely anemic pregnant women. The overall mean increase in Hb level was 1.76 g/dL. Severely anemic pregnant women had larger increase...
Anemia in pregnant women

in mean Hb level (2.54 g/dL) when compared with pregnant women with moderate anemia (1.65 g/dL). In another study, we administered the full calculated dose of iron to moderately anemic pregnant women. More than two-thirds of these anemic pregnant women became nonanemic within 4 weeks. The mean increase in Hb was 2.5 g/dL, and their iron store was also replenished (unpublished data). Thus, giving full calculated dose of IS yielded better results compared to the modest uniform dose of 400 mg of IS (irrespective of existing iron deficit). We therefore conclude that administering full calculated dose of IS is an effective and rapidly acting treatment modality for moderate and severe anemia in pregnant women. However, one of the disadvantages of IS is the limited dose per sitting. The maximum permissible dose is 300 mg/sitting or 600 mg/week. This adds to the total cost of therapy as it requires multiple visits.

**Ferric Carboxymaltose for Treatment of Anemia**

FCM is a relatively new molecule for the treatment of iron deficiency anemia. FCM is currently registered in 46 countries and is marketed in 37 countries globally. It is marketed under the brand name of Injectafer in North America and as Ferinject elsewhere. It is licensed for the use in the second and third trimester of pregnancy in the US, the UK, Europe, New Zealand, and Australia. However, Drug Controller General of India is yet to approve the use of FCM in pregnancy.

**Structure of Ferric Carboxymaltose**

FCM has an iron core which is enveloped on the outside by carboxymaltose. The bond between iron and carbohydrate is strong, and therefore, their dissolution is low while in the blood stream. The osmolarity of FCM is physiological, and the pH is neutral. These features of FCM result in fewer side effects and also allow administration of high dose of iron (700–1000 mg) per sitting. The serum half-life is 7.4–12.3 h. A repeat dose can be given after 1 week.

**Other Advantages of Ferric Carboxymaltose**

Human model studies have shown that FCM does not cross the placenta. FCM does not affect the placental permeability. Therefore, it can be used during pregnancy. However, as a measure of abundant precaution, its use during the first trimester of pregnancy is contraindicated. Test dose for FCM is not recommended because it has no protective effect. The reported anaphylactoid reactions are rare (≥1/10,000 to <1/1000). FCM can be infused rapidly (within 15 min). This provides added advantage of patient comfort and convenience and lesser staff and institutional resource utilization.

**Guidelines for Use of Ferric Carboxymaltose**

One universal guideline is that FCM should not be used in the first trimester of pregnancy. FCM should be avoided during active systemic infection/bacteremia and when significant hepatic dysfunction is present. A repeat dose of FCM can be given after 1 week. There are variations in guidelines regarding the maximum permissible single dose, which is lower in the USA (750 mg) as compared to Europe, Australia, and New Zealand (1000 mg). IV iron should not be administered to pregnant mothers outside of a hospital setting. In addition, facilities and trained staff should be available to deal with the unlikely event of anaphylaxis. Oral iron should not be prescribed once full calculated dose of iron deficit has been administered.

**Calculation of Body Iron Deficit**

The body iron deficit is calculated by the Ganzoni formula which is as follows:

\[
\text{Total body iron deficit (mg)} = 2.4 \times \text{prepregnancy body weight (kg)} \times (\text{target Hb} - \text{actual Hb in mg/dL}) + \text{iron depot (mg)}
\]

In case the patient is obese, then instead of using prepregnancy body weight, one should use ideal body weight. Conventionally, the allowance for depot iron is 500 mg.

**Effectiveness of Ferric Carboxymaltose in Treating Anemia**

We undertook a meta-analysis of seven studies published from India which had looked at the effectiveness of FCM in correcting maternal anemia. Notwithstanding some methodological deficiencies in individual studies, the summary conclusion was that FCM raised Hb level by approximately 2.5 g/dL (95% CI 2.33, 2.66) (unpublished data).

Most of the studies on the effectiveness of FCM in treating anemia in pregnant women had a follow-up period of 4- or 6-week postinfusion. Therefore, less is known about the impact of FCM on Hb level at the time of delivery. We undertook a study where we measured the Hb and serum ferritin level at 2-week postinfusion and also at the time of delivery. The mean increase in Hb level was rapid (1.9 g/dL at 2 weeks), and it continued to rise till the time of delivery (mean increase of 2.8 g/dL). Thus, most of the women at the time of delivery had become nonanemic (accepted for publication). The baseline serum ferritin level was 6.5 ng/mL, which quickly rose to 269.1 ng/mL at 2-week postinfusion and thereafter declined to 60.1 ng/mL at the time of delivery. The FCM was therefore effective in quick restoration of body iron reserve. The serum ferritin level was within normal range at the time of delivery. Hence, the women were unlikely to become anemic even in postpartum period.

**Effectiveness of Ferric Carboxymaltose versus Iron Sucrose in Treating Moderate and Severe Anemia in Pregnant Women**

Now let us examine the comparative effectiveness of the two contending iron molecules, i.e., FCM and IS in raising the Hb level and replenishing the body iron reserve. Most of the Indian studies found that the mean increase in Hb and serum ferritin
level 4-week postinfusion was better in FCM group compared to IS group. The difference was statistically significant.\(^{[40,45-48]}\) The absolute difference in the increase in Hb level between the two groups was in the range of one g/dL. As stated earlier, every extra 1 g increase in Hb level is of clinical importance. Moreover, the side effects were more in IS group primarily due to the high pH and high osmolarity of IS.

**Cost Considerations**

The choice of IV iron therapy is mainly determined by the cost and convenience of administration.\(^{[49]}\) Hence, let us examine the cost implication of the contending iron molecules. The argument often advanced against widespread use of FCM to treat moderate and severe anemia in pregnant women is that FCM is costlier. There are few published studies that have compared the cost of treating anemia among pregnant women by FCM and IS. These studies have reported lesser cost in FCM group. In a study done in Delhi, the cost of total therapy was INR 6872.4 ± 379.7 and INR 6566.3 ± 449.8, respectively, \((P = 0.0004)\) in FCM group and IS group. This study included only the cost of the drug and the cost of consumables (IV cannula, IV drip set, and normal saline). The cost incurred by the health system was excluded.\(^{[50]}\) Another study among pregnant women done at Muzaffarnagar in Uttar Pradesh found that the cost of treating anemia was cheaper in FCM group (INR 4150) compared to IS group (INR 5460). Authors had included the cost of drug and the travel cost.\(^{[45]}\)

We calculated the upfront cost of competing options based on maximum retail price printed on the product package. The cost of 1000 mg of elemental iron for IS (RoseIron\(^a\)) was INR 2428, whereas for FCM (Orofer\(^b\)), it was INR 5376. It appears that FCM was twice as costly compared to IS when only upfront cost is taken into account. However, we do not know the total cost of the treatment by IS, which would include multiple health facility visits by the recipient, more intense utilization of hospital resources, other opportunity costs, etc. Unfortunately, no study is available that has done comprehensive cost evaluation of FCM and IS in Indian setting. Future studies should include the cost incurred by the health system as well.

The reported cost of treatment of anemia in settings other than pregnant women was also lower for FCM compared to IS group. In a study done among patients with abnormal uterine bleeding, the total per-patient cost which included travel cost and lost wages, incurred over the 12 weeks, were INR 2860.67 ± 491.8 and INR 3298.67 ± 357.13 in the FCM and IS group, respectively. The difference in total costs was statistically significant \((P < 0.001)\).\(^{[51]}\) Thus, most of the available literature from India suggests that the treatment of anemia by FCM is cheaper than IS.

**Enabling Environment**

More than half (58.8%) of all the pregnant women received antenatal care (ANC) by doctors. Most (59%) of the pregnancies were registered in the first trimester itself and only 3.1% in 8 months or later. A vast majority (64.6%) of the pregnant women had three or more ANC visit (NFHS-4). Thus, there is ample opportunity for the skilled care providers to select, counsel, and administer FCM in institutional setting. Sufficient financial resources (INR 19 million/district per year) have been provisioned under AMB program. Therefore, cost should not be a constraint in treating moderate and severe anemia, which occurs in only one-quarter of all pregnant women with FCM.

**Conclusions**

The prevalence of anemia among pregnant women is alarmingly high. Treatment of moderate and severe anemia among pregnant women by oral iron is unlikely to succeed. The consequences of inadequate treatment of moderate and severe anemia in pregnant women are unacceptably high both for the mother and the newborn. We have a proven iron molecule in the form of FCM that is safe, effective, and easy to administer. Sufficient financial resources, trained workforce, and physical infrastructure are available to administer FCM for the treatment of moderate and severe anemia in pregnant women. To my mind, FCM thus qualifies for the moniker of “Magic Bullet.” I therefore propose that FCM should be considered the mainstay treatment for moderate-to-severe iron deficiency anemia in pregnant women.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**


---

Announcement

We are happy to announce that the IPHA Bhaban is now ready for use. Members are welcome to stay at the Bhaban during their official and unofficial visits to Kolkata. The location is very close to the Airport and to the Government and Non Government Offices at Salt lake. It is also away from the traffic snarls and pollution. We request all members to solicit utilization of the Bhaban and spread the message to all concerned.

<table>
<thead>
<tr>
<th>Type of Rooms</th>
<th>For Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>• AC</td>
<td>Rs. 800/- per room</td>
</tr>
<tr>
<td>• AC Seminar/Conference Room</td>
<td>Rs. 6000/- (for 8 hours), Rs.500/- for extra 1 hour.</td>
</tr>
</tbody>
</table>

*Branch will get 30% concession for conducting their official meetings.*

For Booking Rooms/ Seminar Hall Please Contact:-

1. HQ Office: - IPHA Headquarter, 110 Chittaranjan Avenue, Kolkata-700073, Phone-033-2257-3373, email-iphahq@gmail.com, office@iphaonline.org

2. Secretary General: - Dr Sanghamitra Ghosh, email-drsanghamitraghosh@gmail.com, Mob:9830074177

3. Assistant Caretaker: - Mr Rafik Ahmed, Mob:- 8017069719

Sd/- Dr Sanghamitra Ghosh  
Secretary General,  
Indian Public Health Association

Address: IPHA Bhaban, AQ 13/5, Sector-V, Salt lake, Kolkata-700091 (Near 215A Bus-terminal, Mahisbathan Area, Nearest landmark: West Bengal Joint Entrance Board Building, Opposite to Metal House)