A prospective, partially randomized study of pregnancy outcomes and hematologic responses to oral and intramuscular iron treatment in moderately anemic pregnant women1–3

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ABSTRACT

Background: Daily oral iron supplementation during pregnancy fails to reduce the prevalence of anemia. However, 2 or 3 intramuscular doses of iron given at monthly intervals were recently found to be effective.

Objective: We compared the safety and efficacy in treating pregnancy anemia of 3 intramuscular doses of iron given at monthly intervals with those of daily oral iron supplementation.

Design: In a prospective, partially randomized study, 148 pregnant women received daily oral doses of 100 mg elemental Fe and 500 μg folic acid, and 106 pregnant women received 3 intramuscular doses of 250 mg elemental Fe as iron dextran at 1-mo intervals and oral doses of 5 mg folic acid twice weekly. One hundred women in each group completed the study. Changes in hemoglobin, iron indicators, pregnancy outcomes, and birth weight were compared between the 2 groups.

Results: Hemoglobin and iron indicators improved significantly with both treatments. The increase in serum ferritin concentration after parenteral iron treatment was significantly higher than that after oral iron treatment. No significant differences between the 2 groups in pregnancy outcomes and birth weight were observed. Systemic side effects were more common in the parenteral iron group, whereas gastrointestinal side effects were more common in the oral iron group.

Conclusions: The intramuscular administration of 3 doses of 250 mg Fe at monthly intervals appears to have good compliance and efficacy and may be used in women who cannot tolerate oral administration of iron. However, intramuscular administration of iron is appropriate only in hospital settings well equipped to treat anaphylactic crises.


KEY WORDS Anemia, pregnancy, blood indexes, iron supplementation, intramuscular administration of iron

INTRODUCTION

Anemia is a common medical disorder that contributes significantly to maternal morbidity and mortality, intrauterine growth retardation, preterm delivery, and perinatal morbidity and mortality (1–9). In India >90% of anemia cases are estimated to be due to iron deficiency, because high iron requirements during pregnancy are not easily fulfilled by dietary intake, especially when iron bioavailability is poor (10–14). Because of religious reasons, poverty, or both, the Indian population observes dietary patterns that are largely vegetarian (15). Diet alone cannot supply the 30–40 mg Fe that is required for absorption of the 4–6 mg Fe/d needed during the latter stages of pregnancy. Iron supplementation is strongly recommended for all pregnant women in developing countries (15–17). Oral iron intake is the treatment of choice, and almost all women can be treated effectively with oral preparations.

However, parenteral administration of iron is necessary under certain circumstances and may be suitable under the following situations: inability to tolerate the side effects of orally administered iron, inflammatory bowel disease, peptic ulcer, noncompliance with oral regimens, documented iron malabsorption, and pregnancies near term (18). In theory, parenteral administration of iron provides quick and certain correction of the total iron deficit because it not only corrects the anemia but also builds up iron stores. Parenteral administration of iron can be achieved by either an intramuscular or an intravenous route. Intravenously administered iron can cause anaphylactic shock, and all safeguards, such as hospital admission with resuscitation equipment available by the bedside, the use of correct techniques, and correct infusion rate as advised by the manufacturer, should be followed (18, 19).

Intramuscular administration of iron is usually achieved by repeated injections of small doses of iron (20). Jenkinson (21) found that for anemia prevention in pregnant, urban, Zambian women, a single intramuscular dose of iron dextran along with oral administration of iron produced a greater increase in hemoglobin concentration than did oral administration of iron alone. For better compliance and adequate results, Bhatt (22) from India has recommended that 2 intramuscular injections of...
iron dextran (250 mg each) be given at a 4-wk interval along with a tetanus toxoid injection.

In the present study, we tested the hypothesis that intramuscular and oral iron therapies during pregnancy are equally effective in improving various iron variables. The objective of the present study was to compare the efficacy of 3 intramuscular doses (250 mg each) of iron dextran with that of 100 consecutive days of 100 mg Fe given orally in treating pregnancy anemia. In addition, the study attempted to assess the safety and compliance of the 2 treatments.

SUBJECTS AND METHODS

The study was carried out from January 2001 to December 2001 with pregnant women attending the antenatal clinic of Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi.

Subjects

The subjects were 254 pregnant women who had moderate anemia (hemoglobin concentration by cyanomethemoglobin method between 80 and 109 g/L) and singleton pregnancies between 16 and 24 wk of gestation. The inclusion criteria were as follows: permanent residence in Delhi, age between 18 and 40 y, gestation between 16 and 24 wk, and willingness to participate. The exclusion criteria were as follows: multifetal pregnancy, hemoglobin concentration <80 or >110 g/L, pre-existing illness of mother, history of late miscarriage or stillbirth, unwillingness to participate in the study, and intolerance to intramuscular administration of iron at the first 0.5-mL test dose (for the parenteral iron group).

Most of the women who attended the antenatal clinic of the hospital and were suitable for inclusion into the study were approached to participate in the study. Of the 600 women approached, 400 fulfilled the criteria (another 200 had exclusion criteria). Of those 400, 254 (63.5%) consented to participate in the trial. Of the remaining 146 (36.5%) women, 80 (20%) declined because of inability to come for follow-up, 20 (5%) declined because of fear of needles, 36 (9%) declined because of side effects of oral iron therapy in the past, and 5 (1.25%) declined because of worries about the new research; 5 women had a reaction to the intramuscular test dose of iron. All the women who did not participate in the study were given a prescription for orally administered iron according to the hospital’s protocol. The study protocol was approved by the ethical committee and the review board of Maulana Azad Medical College. Informed consent was obtained verbally from each subject after the study protocol was explained in detail in the regional language. All the women in the study were given a course of anthelmintic treatment with 100 mg mebendazole (Wormin; Cadila Pharmaceuticals Ltd, Ahmadabad, India) twice daily for 3 d because previous research in the same institute showed that the prevalence of worm infestation was very high (23).

Methods

The expected change in serum ferritin was the basis for calculating sample size. The pilot studies carried out in the same institute with 25 women showed an increase of nearly 4 μg/L in the oral iron group between recruitment and completion of pregnancy compared with an increase of nearly 18 μg/L in the parenteral iron group. Thus, to detect a statistically significant difference of nearly 15 μg/L in the change in serum ferritin concentration between the above 2 groups with a power of 90% and a chance probability level of 5%, a sample size of nearly 80 subjects in each group was necessary. We decided to enroll 100 women in each group. Because the loss to follow-up was very high in the oral iron group relative to that in the parenteral iron group, more women were enrolled until the time of the second blood sample so that pregnancy outcomes were achieved in 100 women in each of the groups. Thus, 148 and 106 women had to be enrolled in the oral iron and parenteral iron groups, respectively, and the 2 groups had study completion rates of 67.5% and 94.3%, respectively. The higher loss to follow-up in the oral iron group was not fully explored but could have been due to gastrointestinal side effects in the oral iron group. In our experience, Indian women prefer to have injections of iron because they believe that the efficacy of parenteral treatment for other diseases also is better than that of oral treatment. This preference may have been responsible for the higher rate of follow-up in the parenteral iron group.

Characteristics such as age, parity, weeks of gestation, and literacy did not differ between the oral iron and parenteral iron groups or between the women who completed the study and those who dropped out of the study.

Two hundred fifty-four subjects were assigned to 1 of the 2 groups. The subjects were assigned in a balanced, one-for-one manner in the early part of the study but were then assigned exclusively to the oral iron group once complete evaluations were made for 100 subjects in the parenteral iron group. The women in the oral iron group were given daily oral doses of 100 mg elemental Fe (ferrous sulfate) and 500 μg folic acid (Folifer; Ministry of Health, Government of India, New Delhi). Tablets were provided every month, and the women were asked to take 100 such tablets during the entire pregnancy. They had to bring back empty packs and were also asked about the intake of their tablets and the color of their stools to ensure that they had consumed the tablets. The women in the parenteral iron group were given 3 intramuscular injections of 250 mg elemental Fe as iron dextran in an injection volume of 5 mL (Imferon; Rallis India Ltd, Mumbai, India) at 1-mo intervals. Initially, 0.5 mL (25 mg) of a test dose was given; if no adverse reaction to the test dose was documented, then a full dose was given after 0.5 h. Precautions consisted of having injectable adrenaline and hydrocortisone, intravenous fluids, and inhalant oxygen at the ready in the eventuality of any anaphylactic reaction. The injection was given in the gluteal region via a deep intramuscular route and use of the Z-technique. As stated above, 5 women had a reaction and did not participate further in the study. All the women in the parenteral iron group were prescribed an oral dosage of 5 mg folic acid twice weekly because, at the time of study, this was the only oral dosage available.

A detailed history was taken from all the women, and a complete physical examination and an obstetric examination were performed at the time of recruitment. At enrollment, ≈8 mL venous blood was taken from each of the patients and divided into 2 aliquots. Three milliliters of blood was transferred to an evacuated tube containing EDTA solution. Peripheral blood smears were performed for estimation of hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. A peripheral
smear was stained with Leishman’s stain to look for the morphology of the blood cells. The other part of the sample was centrifuged for 10 min at 800 × g and 20°C in a REMI refrigerated centrifuge (REMI Instruments Ltd, Delhi, India). The separated serum was then transferred to microcentrifuge tubes, and aliquots were stored at −80°C for later measurement of serum iron, total-iron-binding capacity (TIBC), and serum ferritin in the Department of Biochemistry, Maulana Azad Medical College. Iron and hemoglobin measurements were interpreted according to the Cook and Finch model (24) as the best approach to classifying the distribution of iron status in a population.

Hemoglobin was determined by using the cyanomethemoglobin method (25) and an autoanalyzer (Sysmex F-820; Sysmex, Kobe, Japan). Hematocrit (packed cell volume) and red blood cell count were determined by using automated counters. Blood indexes were calculated. The normal ranges are as follows: mean corpuscular volume, 75–100 fL; mean corpuscular hemoglobin, 24–33 pg; and mean corpuscular hemoglobin concentration, 300–360 g/L. Serum iron and TIBC were determined by using spectrophotometric techniques and iron and TIBC kits (Synermed International Inc, Montreal, Canada) (26). Serum ferritin was measured by using enzyme-linked immunosorbent assays with pathoxyzine ferritin kits (Omega Diagnostic Ltd, Alva, United Kingdom; 27).

All the women were followed up routinely in the prenatal clinic until delivery. All the tests were repeated at term (37–41 wk) or during labor if patients went into preterm labor. Resource constraints precluded more frequent hematologic estimations, which may have been able to detect any differences in the timing of hematologic responses between the 2 treatment groups. However, a woman’s hematologic status at term is more important for pregnancy outcome than her status at other times, especially from the perspective of risks associated with childbirth. Thus, iron indicators were measured at term only. All side effects were noted.

Follow-up and other investigations were performed according to the hospital’s protocol. The mode of delivery, any premature delivery, and the birth weight of the newborn were noted in all cases.

Statistical analysis

Data were analyzed according to an intention-to-treat strategy. Quantitative data were expressed as means ± SDs or as medians. Skewness and kurtosis were determined to test for a normal distribution of the data. If necessary, data were normalized by using a base 10 log transformation. To determine the interaction of time and treatment and the main effects of time and treatment, repeated-measures analysis of variance was performed. Analysis of covariance with the baseline value as the covariate was used when mean baseline values differed significantly. Student’s two-tailed t test was used to compare values between the 2 groups. Qualitative data were analyzed by using the chi-square test (SPSS software, version 10.1; SPSS Inc, Chicago) (28).

RESULTS

The characteristics of the women in the 2 groups are shown in Table 1. There were no significant differences between the 2 groups in age, parity, literacy, socioeconomic status, or gestational age at the start of the study.

Mean values for hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, serum iron, serum TIBC, and serum ferritin in the subjects at recruitment and at term are shown in Table 2. At entry into the study, the 2 groups did not differ significantly in any variable except serum iron. P values for the interaction between time and treatment and the main effects of time and treatment obtained by using repeated-measures analysis of variance and analysis of covariance are shown in Table 2. Serum ferritin was the only variable significantly affected by treatment type. Serum ferritin concentrations increased significantly more in the parenteral iron group than in the oral iron group. Because the patients were enrolled between 16 and 24 wk of pregnancy, the monthly iron injections were completed during weeks 24–32 of pregnancy. Examination of the data showed that none of the women had their second blood sample taken within 1 mo of the last injection, which would preclude any possibility that high ferritin concentrations were due to a short time interval between parenteral iron injection and blood sampling for ferritin measurement. The women in the preterm delivery group had their deliveries between 34 and 37 wk of gestation (mean: 35.2 wk). The women in the term group had their blood test at 39 or 40 wk of gestation or earlier if they went into labor (mean: 39.5 wk). The effect of time was significant for all the variables except serum TIBC. The treatment-by-time interaction was significant for serum ferritin and TIBC.

The distribution of mean hemoglobin concentrations in the 2 groups before and after treatment is shown in Table 3. Twenty-seven percent of the women in the oral iron group and 30% of the women in the parenteral iron group achieved a hemoglobin concentration ≥110 g/L. The difference of 3 percentage points between the 2 groups was not significant.

Pregnancy outcomes in the 2 groups are shown in Table 4. There were no significant differences between the 2 groups in preterm delivery rate or birth weight.

The numbers of women in the 2 groups who experienced side effects are shown in Table 5. Gastrointestinal side effects were observed more frequently in the oral iron group than in the parenteral iron group. Dyspepsia, constipation, diarrhea,
and vomiting were seen in 10%, 5%, 3%, and 2% of the women in the oral iron group, respectively. Dyspepsia was relieved by taking a tablet of ranitidine (Astra Zeneca, Bangalore, India) 2 h before iron therapy. Dyspepsia was generally of mild severity and temporary. Two patients experienced vomiting a few days after starting supplementation. One patient had spontaneous remission, and the other one required tablets of metoclopramide (Perinorm; IPCA, Mumbai, India) to control the vomiting. Rash and itching were more common in the parenteral iron group than in the oral iron group. Although mild pain and mild skin staining were very common with intramuscular administration of iron, severe pain and moderate skin staining were seen in only 4 and 2 subjects, respectively. Systemic side effects, such as fever and ache, were seen more commonly in the parenteral iron group. One woman in the parenteral iron group had a vasovagal attack. She had not eaten breakfast; she was given oral fluids and showed improvement. Four patients in the parenteral iron group required hospital admission; one for systemic reaction and 3 others for severe body ache and arthralgia. The systemic reaction in the patient occurred with the second dose. She had slight dyspnea, a sinking sensation, and generalized rashes. She improved with intravenous hydrocortisone and antihistamines and was discharged the next day. This woman was given the third dose after she was admitted to the hospital under close supervision, fully counseled, and informed that a reaction could happen again and that she could withdraw from the study. She opted to receive the injection along with medication. Women with severe body ache and arthralgia were given an intramuscular dose of diclofenac (Voveran; Novartis, Mumbai, India) and were discharged the next day. As expected, gastrointestinal symptoms were the predominant adverse side effects seen with oral administration of iron, and local symptoms at the site of the injection and systemic and constitutional symptoms were the predominant adverse side effects with intramuscular administration. Moreover, the analysis of symptoms was based on the number of subjects who reported the symptom during the study, and the analysis ignored the frequency with which the symptom occurred within any symptomatic subject. Obviously, in a qualitative sense, the adverse outcomes produced by injected iron dextran can be more debilitating and life threatening than can those produced by iron tablets. Moreover, the expenses per subject treated by the parenteral route are greater in terms of preparation, delivery systems, and hospital facilities usage, and intangible issues such as the risk of wider contamination through improper use and handling of hypodermic needles weigh adversely on the side of the intramuscular choice.

### TABLE 2

| Variable            | Oral iron group (n = 100) | Parenteral iron group (n = 100) | P²  
|---------------------|--------------------------|--------------------------------|------
|                     | Recruitment | Term    | Recruitment | Term    | Treatment | Time | Treatment × time |
| Hemoglobin (g/L)    | 96.3 ± 8.79 | 102.9 ± 10.84 | 94.3 ± 9.47 | 104.2 ± 10.98 | 0.78 | 0.01 | 0.06 |
| Hematocrit, PCV (%) | 31.0 ± 3.51 | 36.3 ± 4.88 | 30.2 ± 3.11 | 35.5 ± 5.47 | 0.09 | 0.01 | 0.94 |
| MCV (fL)            | 84.3 ± 7.24 | 100.9 ± 11.23 | 82.3 ± 7.44 | 98.9 ± 13.77 | 0.09 | 0.01 | 0.99 |
| MCH (pg)            | 27.5 ± 3.36 | 28.6 ± 3.37 | 27.3 ± 3.86 | 28.8 ± 3.68 | 0.98 | 0.01 | 0.27 |
| MCHC (g/L)          | 309.2 ± 32.96 | 282.6 ± 29.17 | 309.9 ± 33.29 | 291.8 ± 30.87 | 0.16 | 0.01 | 0.13 |
| Serum iron (µmol/L) | 34.3 ± 1.50 | 36.5 ± 1.60 | 25.0 ± 1.90 | 27.8 ± 1.70 | 0.53 | 0.01 | 0.48 |
| Serum TIBC (µmol/L) | 113.0 ± 1.52 | 115.4 ± 1.81 | 105.7 ± 1.88 | 98.8 ± 1.68 | 0.15 | 0.79 | 0.01 |
| Serum ferritin (µg/L) | 7.5 ± 1.84 | 12.4 ± 2.02 | 7.0 ± 1.67 | 23.1 ± 2.27 | 0.01 | 0.01 | 0.01 |

¹ Arithmetic mean ± SD for all variables except serum iron, serum total-iron-binding capacity (TIBC), and serum ferritin, for which values are geometric means ± SDs (transformed back to original scale). PCV, packed cell volume; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, MCH concentration. 
² Repeated-measures ANOVA for all variables except serum iron, for which analysis of covariance with baseline serum iron as the covariate was used.

### DISCUSSION

A significantly greater increase in serum ferritin concentrations with parenteral administration of iron than with oral administration is important for developing nations like India.
TABLE 5
Numbers of women in the 2 groups who experienced side effects from medication

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Oral iron group (n = 100)</th>
<th>Parenteral iron group (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Rash and itching</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Local pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>—</td>
<td>37</td>
</tr>
<tr>
<td>Severe</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>Skin staining</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>—</td>
<td>25</td>
</tr>
<tr>
<td>Moderate</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Systemic ache</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Headache and giddiness</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Malaise</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Vasovagal attack</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Systemic reaction</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Abscess</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Admission required</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

that have a very high prevalence of anemia during pregnancy, which is further complicated by malnutrition and repeated pregnancies separated by short intervals, because serum ferritin is a determinant of iron stores, which are beneficial to women during lactation and subsequent pregnancies (16, 17). The prevalence of anemia in our hospital, which serves poor women in Delhi, was 72.3% in 1999 (29).

The results of the present study showed that the 2 types of iron treatment were equally effective at improving the various iron indicators in the women who completed the study. Hemoglobin concentrations at delivery did not differ significantly between the 2 groups. Apparent gains from intramuscular administration of iron occurred only for serum ferritin, and increased iron stores are important for future iron status. The changes in the iron status achieved with supplementation in both groups were better than those achieved in some other studies, and this difference may have been due to the anthelminthic treatment in the present study. We included women with moderate anemia but not those with severe anemia because, for ethical reasons, the institutional review board decided that patients with severe anemia should get the full treatment with adequate repeated intramuscular injections or blood transfusions according to the hospital’s protocol. Of the 148 women in the present study who were assigned to receive oral iron treatment, only 100 completed the study and came for follow-up for a second blood sample; thus, the rate of successful study termination in this group was 67.5%. In contrast, of the 106 women who were assigned to receive parenteral iron treatment, 100 completed the study; thus, the rate of successful study termination in this group (94.3%) was much higher than that in the oral iron group.

Parenteral administration of iron has been used by many investigators, especially in Asia and Africa, with good results (18, 20, 21). Sood et al (20) observed a greater increase in hemoglobin concentration with intramuscular administration of iron than with oral or intravenous administration. They observed 2 delayed, severe allergic reactions with intramuscular administration of iron. However, the intramuscular dosage required to achieve a given effect was twice the intravenous dosage, and they used between 23 and 34 participants in each test group, which were not enough to draw conclusions about the frequency of rare side effects such as anaphylaxis from iron dextran after either intravenous or intramuscular administration.

In the present study, gastrointestinal side effects were more common in the oral iron group than in the parenteral iron group, whereas systemic side effects were more common in the parenteral iron group. Four patients required hospital admission: 1 for a systemic reaction and 3 others for severe body ache and arthralgia. Toxic reactions to both intramuscular and intravenous administration of iron dextran have been reported, and these reactions ranged from mild reactions, such as joint pains and discoloration at the injection site, to severe reactions, such as allergy, itching, fever, severe joint pains, lymphadenopathy, and anaphylaxis (30–33). The reported incidence of reaction to parenterally administered iron ranged between 0.5% and 30%, with some studies reporting an incidence as high as 30–40% (34). The incidence of reactions was reported to be higher in undernourished subjects than in adequately nourished subjects (35). In a sample of 2099 intravenous iron dextran injections, Hamstra et al (36) reported 3 life-threatening, immediate reactions.

Newer compounds of iron, such as ferric saccharate, may eliminate any risk of anaphylaxis with injectable iron. However, this compound is only available for intravenous usage. In addition, even these compounds seem to present a certain hazard because they increase oxidative stress (37).

There are other potential problems with parenteral administration of iron. The total cost of 3 injections (750 mg) was Rs 60 (60 rupees; $1.25). The cost of 3 syringes and 6 needles was Rs 27 ($0.5). Thus, the total cost of parenterally administered iron for each patient for all 3 injections was <Rs 50. The cost of taking care of an anaphylactic reaction was Rs 34 ($0.75), and this care was required for only 1 patient. The cost of diclofenac injection was Rs 5.6 ($0.20), and only 3 patients required such an injection (<$1). The cost of iron tablets was Rs 10 ($0.25), and the cost of taking care of their side effects with ranitidine and metoclopramide were only Rs 7 ($0.20) and Rs 8 ($0.20), respectively. Thus, parenteral administration of iron was more expensive than oral administration. However, the cost of orally administered iron can be significant if carbonyl or other slow-release forms of iron are used [Rs 4/tablet, ie, Rs 400 ($8)]. The cost of medical training of doctors and nurses, construction of tertiary care facilities, and resuscitation equipment should also be factored into the cost of parenteral administration. When parenteral iron therapy causes adverse reactions and injection abscesses that result in hospital stays, the cost of parenteral therapy increases significantly. Complete cost accounting as listed above is not included in the present study. Only direct costs were taken into consideration.

The oral iron group received 3.5 mg folic acid/wk, whereas the parenteral iron group received 10 mg/wk. This greater amount of folic acid may have had an influence on hematologic outcomes. Moreover, the high serum ferritin concentrations observed with parenterally administered iron may have been due to the tissue irritant action of the intramuscularly administered iron, because ferritin is an acute phase protein, and
ferritin concentrations may not be a reflection solely of storage iron but may also be due to inflammation. Because of budget constraints, we did not include biomarkers for inflammation (C-reactive protein, α1-glycoprotein), which would have made interpretation of ferritin as a nutritional indicator more reliable.

Maintaining meticulous care standards for intramuscular iron treatment is problematic in countries like India, where standards become lax over time. There is a risk of blood-borne diseases because of the use of recycled syringes and needles, vigilance in ensuring that full resuscitation facilities are available may become compromised, and injected dosage may be reduced if demand exceeds supply; for these reasons, parenteral administration of iron is not a feasible approach at the field level (34).

Despite the efforts of the National Nutritional Anemia Prophylaxis Programme in India since 1970 to provide iron and folic acid supplements to all pregnant women, anemia still continues unabated (38); the number of anemic women is greater than the number targeted, the number of actual beneficiaries is far less than that shown in records, the quality of tablets is poor, and hemoglobin concentrations do not differ between beneficiary and nonbeneficiary groups (38). The main problem with oral iron supplementation is poor compliance because of side effects or other reasons. Alternative strategies, such as weekly or twice weekly iron supplementation, have been developed to improve compliance (39).

However, although the weekly doses are usually high, a patient who fails to take an iron tablet one week should not be expected to still have adequate results. Hallberg (40) assessed the efficacy of weekly iron administration and advocated daily iron administration. Parenteral iron administration has a role in controlling iron deficiency anemia during pregnancy in developing countries. Most women in India consider injection to be superior to oral medication, and the rate of continuation of treatment is better with injectable iron. Bhatt (22) achieved adequate results by giving subjects 2 intramuscular injections of iron dextran (250 mg each) separated by a 4–6-wk interval. However, in a previous study, Bhatt et al (19) reported a high incidence of injection abscesses with intramuscular administration of iron. Many pregnant women in India do not visit antenatal outpatient departments, and many deliver their infants at home. However, most mothers are aware of the advisability of receiving a tetanus toxoid injection during pregnancy and will make at least one clinic visit to receive that service. This visit could be used as an opportunity for intramuscular administration of iron. We admit that the number of women in each group in the present study (ie, 100) was not high enough to establish the safety of intramuscular administration of iron, especially with regard to infrequent, serious side effects.

In conclusion, the administration of 3 intramuscular doses of 250 mg iron dextran at 1-mo intervals is an alternative strategy with good efficacy and compliance for treating pregnancy anemia in women who cannot take iron orally. However, to keep the risk of severe side effects within acceptable limits, parenteral iron injections must be given in hospital settings, where resuscitation facilities are available to deal with any adverse events.

JBS conceptualized the study and wrote the manuscript. SJ recruited the patients, took samples, and wrote clinical details. VM performed all the biochemical tests. TS performed the hematologic tests. AK and RA helped conceptualize the study and write the manuscript. NSM calculated the number of women required for recruitment, performed the statistical analysis, and helped write the manuscript. None of the authors had any conflicts of interest.

REFERENCES

26. Giovannelli TJ, Di Benedetto G, Palmer DW, Peters TJR. Fully and


