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Original Article

Pregnancy induced iron deficiency and the evaluation and comparison of the efficacy and safety of ferrous fumarate and carbonyl iron in its treatment - PERFECT trial

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Key words: ferrous fumarate, carbonyl iron, iron deficiency anemia, pregnancy

Introduction

Iron deficiency anemia is the commonest medical disorder to occur in pregnant women affecting around 80% of the pregnant females [1], its incidence being particularly high in many underdeveloped tropical countries where it remains a major contributing factor to maternal morbidity and mortality and also high perinatal mortality [2]. The requirements of iron increase during pregnancy, as in the third trimester, a pregnant woman needs six times more iron than a nonpregnant woman [3]. World Health Organization recommends a hemoglobin concentration value of a minimum 11.0 gm% during pregnancy [4].

The major concern about the adverse effects of anemia on pregnant women is the belief that this population is at greater risk of perinatal mortality [5,6]. There is a substantial amount of evidence showing that maternal iron deficiency anemia early in pregnancy can result in low birth weight subsequent to preterm delivery [7,8]. An association between maternal anemia and lower infant apgar score was reported in some studies [9-11]. Iron supplements improve the iron status of the mother during pregnancy and during the postpartum period, even in women who become pregnant with reasonable iron stores [12].

The amount of iron absorbed from the diet is not sufficient to meet the requirements during pregnancy, when physiological iron requirements are the highest. Iron supplementation is necessary to control iron deficiency anemia. Folic acid is added to iron since the combination gives an enhanced hematological response [13].

Oral iron preparations for the correction of iron deficiency include iron salts, iron chelates and ferric hydroxide complexes. Iron salts like ferrous sulphate, ferrous fumarate and ferrous gluconate are extensively prescribed for the prevention and treatment of iron deficiency. Relatively high concentrations of elemental iron are present in ferrous fumarate, with each 183 mg of ferrous fumarate containing 60 mg of elemental iron, whereas the same amount of elemental iron is present in 300 mg of carbonyl iron [14].

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Moreover, the bioavailability of iron preparation increases with the increasing dose, with ferrous fumarate having high bioavailability [15]. However, gastrointestinal symptoms such as nausea, epigastric pain and constipation are commonly associated with iron salts. Food and / or chelating drugs in the gastrointestinal tract may interfere with absorption and decrease the concentration of the bioavailable iron [16,17]. This leads to variability in the Hb correction during anemia in pregnancy.

A newer formulation of iron called carbonyl iron has been introduced into the market with claims of higher bioavailability and safety. However, there have been reports of low bioavailability of carbonyl iron [18]. Additionally, ferrous fumarate as iron prophylaxis in pregnant women is reported to be safe with no significant gastrointestinal side effects [19].

Therefore, the present study was conducted to compare the efficacy and tolerability of a preparation containing ferrous fumarate and folic acid versus a preparation containing carbonyl iron and folic acid in the treatment of anemia of pregnancy.

Objective of the study

To compare the efficacy and tolerability of a marketed formulation containing ferrous fumarate with a marketed formulation containing carbonyl iron in the treatment of anemia of pregnancy.

Materials and methods

The study was multi-centric, observer-blind, randomized and controlled. Randomization was done for each center. A total of 150 pregnant females with >14 weeks of amenorrhea and pregnancy confirmed by the presence of β-HCG in urine with hemoglobin between 7 to 10 g/dl were included in the study after obtaining informed written consent.

Patients with known hypersensitivity to iron preparations, with associated diabetes mellitus and/ or hypertension, a history of eclampsia, preeclampsia or pregnancy induced hypertension (PIH) during the previous pregnancy and patients with known hyperthyroidism or hypothyroidism were excluded. Also those patients with severe concurrent illness (cardiovascular, renal, hepatic), and in any other condition that in the opinion of the investigator did not justify the inclusion of the subject in the study were excluded from the study.

On screening the patients were assigned a serial number as per the chronological order. After the patient was found to be eligible and satisfying inclusion/exclusion criteria, the sealed study medication pack was opened to reveal the study medication.

The enrolled patients were randomly allocated to received formulation A (ferrous fumarate 152 mg (app. 50 mg elemental iron), folic acid 750 mcg and zinc sulphate 61.8 mg), twice daily or formulation B (carbonyl iron (app. 100 mg elemental iron), folic acid 1500 mcg, vitamin B12 10 mcg and zinc sulphate 61.8mg) once daily with a glass of water for a period of 12 weeks.

The patients were not allowed to take iron and folic acid in any other pharmaceutical formulation. They were allowed to take calcium and multivitamin preparations.

Efficacy Evaluation

Hemoglobin was estimated at baseline, 2 weeks, 4 weeks, 8 weeks and 12 weeks of the treatment.

Primary efficacy variable – Rise in hemoglobin levels at the end of the therapy, analyzed on coulter cell counter

Secondary efficacy variables – Percentage change in hemoglobin from the baseline values.

Safety Evaluation

Clinical safety was evaluated based upon the nature and severity of adverse effects if any, recorded at 2 weeks, 4 weeks, 8 weeks and 12 weeks of treatment. The response and tolerability to therapy was recorded on a scale called global assessment of response to therapy (PGART) on a 5-point rating scale of "1-Excellent, 2=Good, 3=Average, 4=Poor and 5=Very Poor" at the end of study period. This rating was done independently by the patients and the physicians with respect to efficacy and tolerability.

Statistical analysis

Quantitative data was analyzed using the unpaired 't' test for between the group comparison; one way ANOVA for within the group analysis with post-hoc Bonferroni's multiple comparison. Non-parametric

(ranking) data was analyzed using the Mann-Whitney 'U' test (Between the group analysis). Proportions were analyzed using the chi square test. Level of significance: 'p' <0.05 at 95% C.I. (2 sided).

Results

Out of the 150 enrolled patients, three patients (two ferrous fumarate, 1 carbonyl iron) were lost to follow up after four weeks, and three patients (one ferrous fumarate, two carbonyl iron) withdrew the consent due to side effects. One hundred forty four (72 ferrous fumarate, 72 carbonyl iron) patients completed the study as per the protocol. Three patients reported troublesome side effects leading to withdrawal of the consent. One patient on ferrous fumarate developed moderate degree of diarrhea and abdominal pain at two weeks follow-up.

One patient on carbonyl iron reported moderate diarrhea at eight weeks follow-up period and another reported diarrhea associated with nausea, vomiting and abdominal pain at two weeks of follow-up period. None of the patients reported any serious adverse events during the study period.

Table 2 and Figure 1 represent the mean +/- SD in Hb (gm%) of the patients at baseline (beginning of study) and during the study period in the two treatment groups. As depicted in Table 2 and Figure 1, baseline hemoglobin values did not differ significantly at the beginning of the study in either of the treatment groups.

Table 1. Demographic data and baseline values (mean ± SD) in the treatment groups.

Parameter	Ferrous fumarate (n=72)*	Carbonyl Iron (n=72)*	'P'
Age (Years)	23.12 (3.50)	22.67 (3.01)	0.401
Body weight (kilogram)	42.75 (5.31)	43.33 (6.07)	0.541
Gestation age (weeks.)	16.90 (2.56)	16.37 (2.51)	0.312
Hemoglobin (gm%)	8.45 (0.45)	8.38 (0.42)	0.321
*Mean (S.D.)			

The demographic characteristics and baseline Hb (gm%) values of the patients did not differ significantly in either of the groups (Table 1).

Table 2. Hemoglobin (gm%) of the patients at baseline and during the study period in the treatment groups.

Hb (gm%)	Ferrous fumarate (n=72)*	Carbonyl iron (n=72)*	'p'
Baseline	8.45 (0.45)	8.38 (0.42)	0.321
2 weeks	8.74 (0.48)	8.53 (0.45)	0.007
4 weeks	9.18 (0.54)	8.94 (0.49)	0.006
8 weeks	9.70 (0.55)	9.27 (0.56)	<0.0001
12 weeks	11.45 (0.73)	9.87 (0.58)	<0.0001
One way ANOVA 'p'	<0.0001	<0.0001	-
*Mean (S.D.)			

The rise in hemoglobin in the patients receiving a ferrous fumarate preparation was significantly better than that seen in the patients receiving a carbonyl iron preparation at the end of two weeks [8.74 (0.48) vs 8.53 (0.45) (p=0.007)], four weeks [9.18 (0.54) vs 8.94 (0.49) (P=0.006)], eight weeks [9.70 (0.55) vs 9.27 (0.56) (p<0.0001)], and 12 weeks [11.45 (0.73) vs 9.87 (0.58) (p<0.0001)]. The mean hemoglobin increase in the ferrous fumarate group was 3 gm% at the end of 12 weeks as compared with the carbonyl iron group, which recorded a mean increase in hemoglobin by 1.489 gm% (Table 3).

When the final values in both the treatment groups were compared with the respective baseline values, the improvement in Hb (gm%) was significant in both the groups P<0.001 for both ferrous fumarate and carbonyl iron.

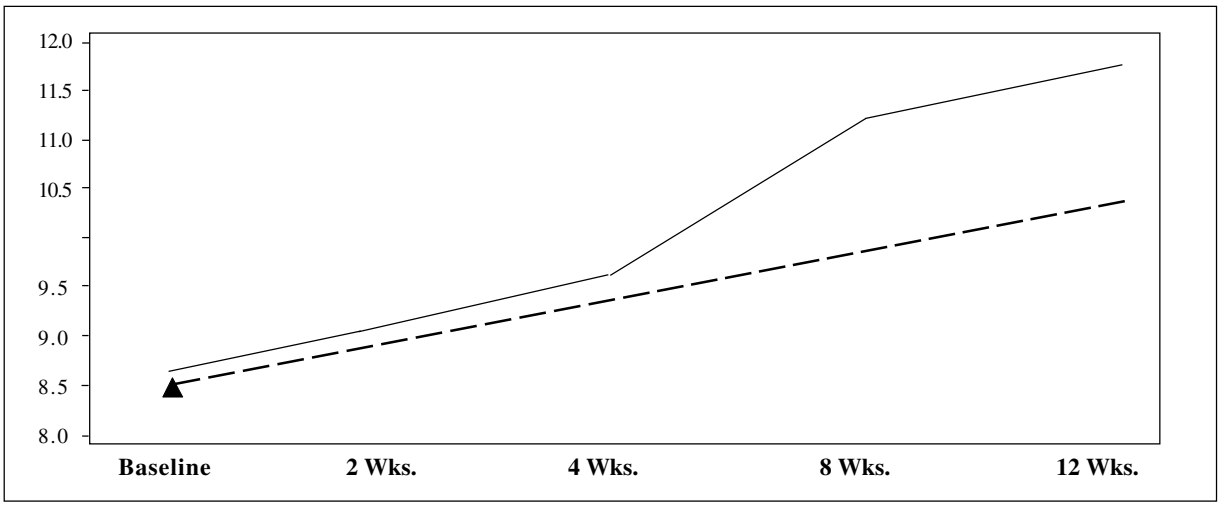

Figure 1. Hb (gm%) of the patients in the two treatment groups at baseline & during the study.

Table 3. Mean (%) change in hemoglobin (gm%) from baseline of the patients in the treatment groups.

Hb (gm%)	Ferrous fumarate group (n=72)*	Carbonyl iron group (n=72)*	Mean difference	95% Confidence intervals	'p'
2 weeks	0.288 (3.42)	0.148 (1.80)	0.140	-0.010 to 0.154	0.0009
4 weeks	0.733 (8.74)	0.568 (7.79)	0.185	-0.047 to 0.211	0.0107
8 weeks	1.246 (14.85)	0.895 (10.78)	0.351	0.024 to 0.352	<0.0001
12 weeks	3.000 (35.45)	1.489 (17.89)	1.510	-0.088 to 0.327	<0.0001

* Mean (S.D.)

Figure 2 represents the mean percentage increase in the hemoglobin value from the baseline at 2 weeks, 4 weeks, 8 weeks and 12 weeks of treatment. The ferrous fumarate group showed a significantly greater mean percentage increase in the hemoglobin from the baseline in comparison with the carbonyl iron group at all the evaluation points.

In the ferrous fumarate group 90.2% of the patients achieved the WHO target of 11 gm% as compared to just 20.83% of the patients in the carbonyl iron group. At the end of 12 weeks of treatment the mean percentage increase in hemoglobin from the baseline was 35.45% in the ferrous fumarate group and 17.89% for the carbonyl iron group; the resulting difference being highly significant (p<0.001).

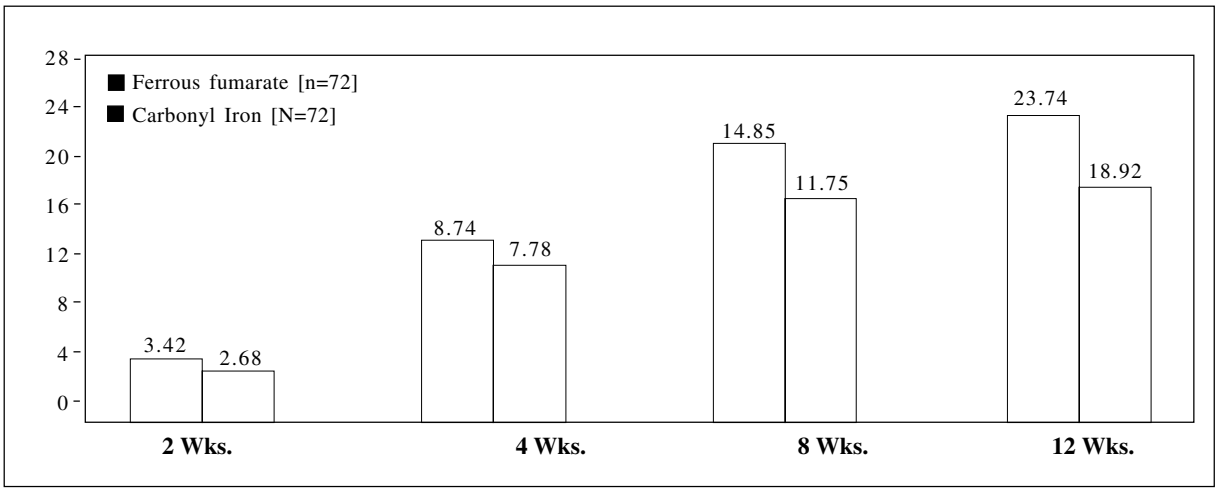

Figure 2. Mean% increase in Hb (gm%) from baseline

Table 4 a. Global assessment of response to therapy (PGART) and tolerability to therapy (PGATT) on a 5-point rating scale of "1=Excellent, 2=Good, 3=Average, 4=Poor and 5=Very Poor" at the end of the study period

(A Lower score corresponding to better outcome)

Global assessment	Ferrous fumarate (n=72)*	Carbonyl iron (n=72)*	Z	'p'
Response to therapy (PGART)	1.416	1.750	-3.570	<0.0001
Tolerability to therapy (PGART)	1.416	1.652	-3.063	0.002

*Mean (S.D.)

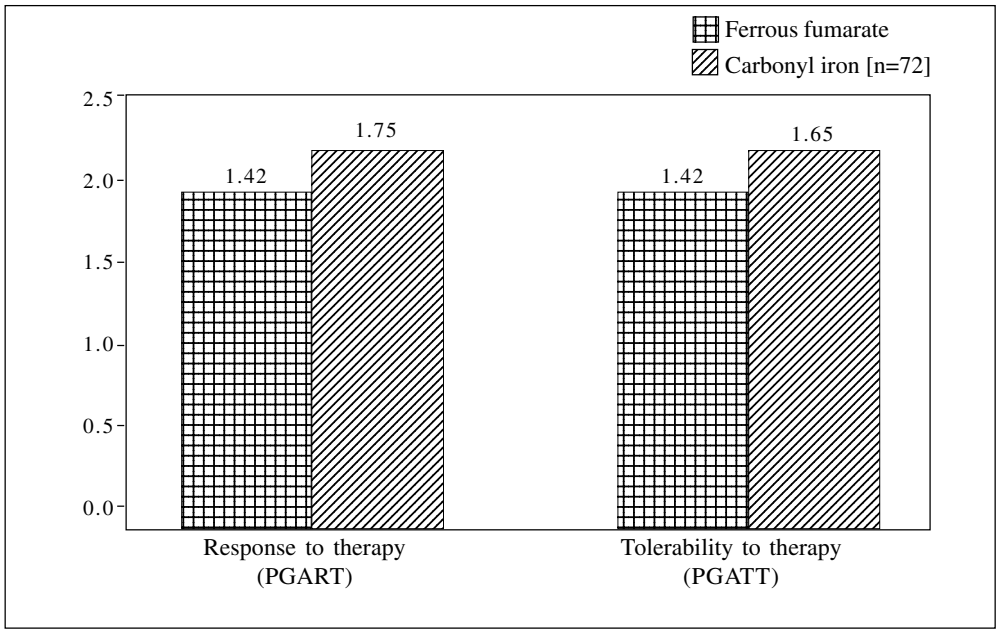

Figure 4. Global assessment of response to therapy (PGART) and tolerability to therapy (PGATT) on a 5-point rating scale of "1=Excellent, 2=Good, 3=Average, 4=Poor and 5=Very Poor" at the end of the study period.

Table 4a and Figure 4 depict the assessment of the response to the therapy and the tolerability of therapy as reported by direct questioning and rated on a 5 point scale with a lower score corresponding to a better outcome. The ferrous fumarate group showed a significantly better outcome than the carbonyl iron group with respect to response to therapy ($p<0.0001$) as well as tolerability ($p=0.002$).

Table 4b. Global assessment of response to therapy (PGART) and tolerability to therapy (PGATT) on a 5 point rating scale of "1=Excellent, 2=Good, 3=Average, 4=Poor and 5=Very Poor" at the end of study period.

Rating	Ferrous fumarate (n=72)*	Carbonyl iron (n=72)*
Physicians Global Assessment of Response to Therapy (PGART)		
• Excellent	49 (68.10)	24 (33.30)
• Good	16 (22.20)	42 (58.30)
• Average	07 (09.70)	06 (08.30)
• Poor	00 (0.00)	00 (0.00)
• Very poor	00 (0.00)	00 (0.00)
Patients Global Assessment of Tolerability to Therapy (PGART)		
• Excellent	47 (65.30)	25 (34.70)
• Good	20 (27.80)	47 (65.30)
• Average	05 (06.90)	00 (0.00)
• Poor	00 (0.00)	00 (0.00)
• Very poor	00 (0.00)	00 (0.00)

*Number (Percentage) of patients

Table 4 b shows the details of the drug rating separately by the physicians (Physicians Global Assessment of Response to Therapy) and patients (Patients Global Assessment of Tolerability to Therapy). The physicians rated the response to ferrous fumarate as excellent in 68% of the cases whereas carbonyl iron was rated as excellent only in 33.3% of the cases (Figure 5a).

Nearly two-thirds (65.3%) of the patients in the ferrous fumarate group said that the tolerability to it was excellent whereas only 34.7% of the patients in the carbonyl iron group reported the tolerability as excellent. (Figure 5b).

Table 5a. No. (%) of patients reporting constipation and diarrhea at baseline and during the study period in the treatment groups.

	Ferrous fumarate (n=72)*	Carbonyl iron (n=72)*	'p', χ^2-test
Constipation			
• Baseline	19 (26.40)	25 (34.70)	0.167
• 2 weeks	20 (27.80)	38 (52.80)	0.002
• 4 weeks	19 (26.40)	39 (54.20)	0.002
• 8 weeks	18 (25.00)	38 (52.80)	0.002
• 12 weeks	18 (25.00)	38 (52.80)	0.002
Diarrhea			
• Baseline	01 (01.40)	00 (00.00)	0.316
• 2 weeks	01 (01.40)	06 (08.30)	0.053
• 4 weeks	00 (00.00)	05 (06.90)	0.075
• 8 weeks	01 (01.40)	05 (06.90)	0.095
• 12 weeks	01 (01.40)	05 (06.90)	0.095

Figure 6 a. No. of patients reporting constipation at baseline and during the study period.

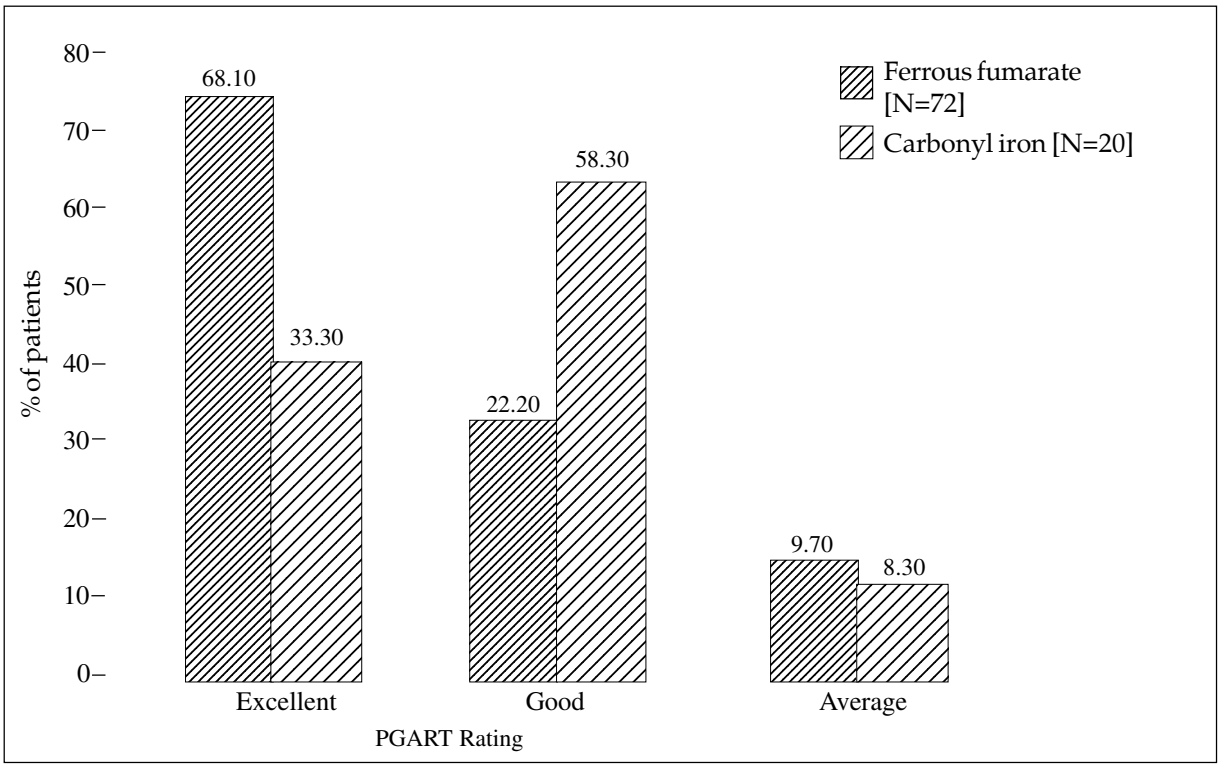

Figure - 5 a: Physicians Global Assessment of Response to Therapy (PGART) att the end of study period.

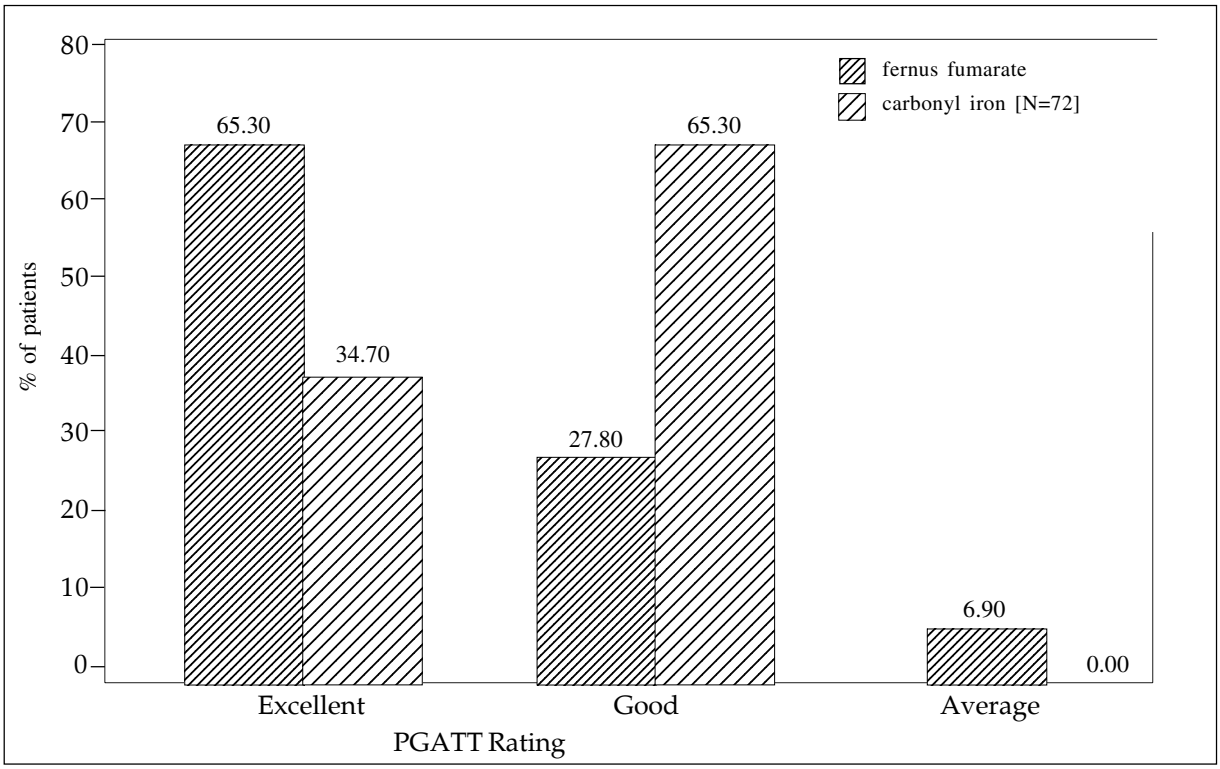

Figure - 5 b: Patients Global Assessment of Tolerability to Therapy (PGATT) at the end of study period.

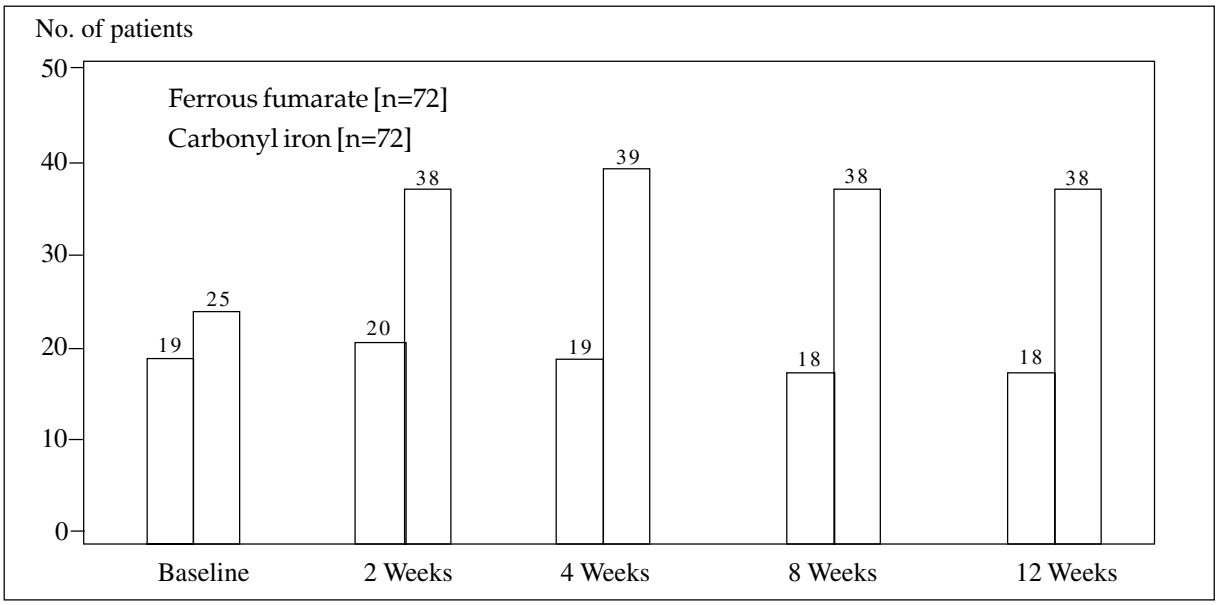

Figure - 6 a: No. of patients reporting constipation at baseline & during the study period.

Constipation was the main ADR in both the treatment groups throughout the study period. While there was no significant difference in the incidence of constipation between the two groups at baseline, the percentage of patients reporting constipation was significantly lesser in the ferrous fumarate group than the carbonyl iron group throughout the study period (χ^2 test, P=0.002) (Table 5a and Figure 6a).

At 2, 4, 8 and 12 weeks the percentage of patients reporting constipation in the carbonyl iron group was almost double than that reported in the ferrous fumarate group.

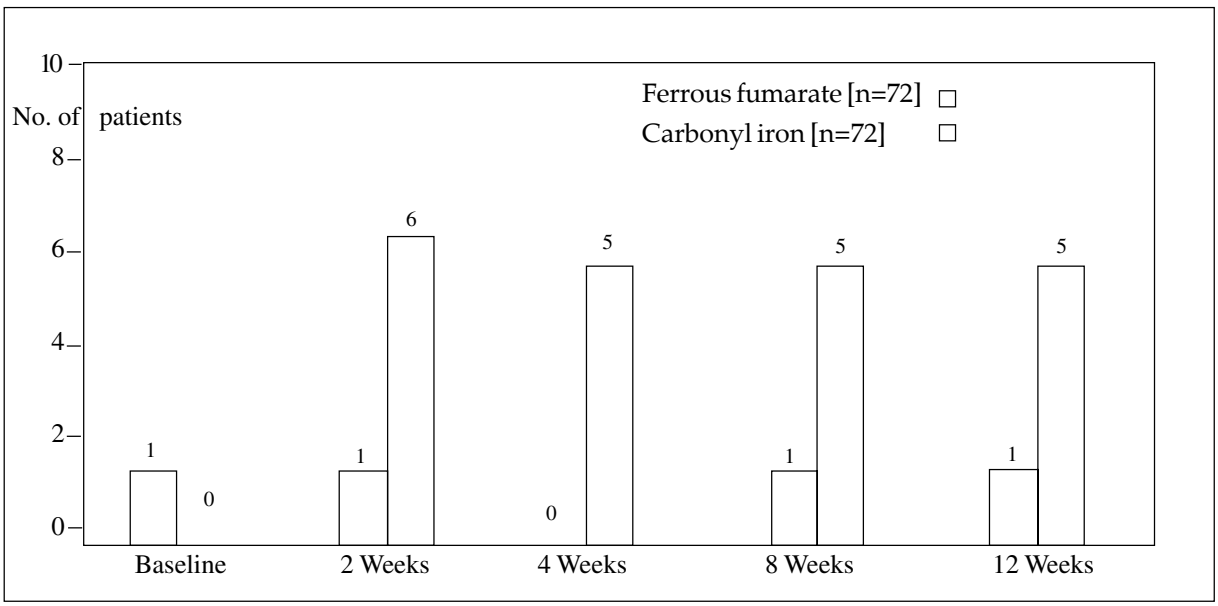

Figure - 6 b: No. of patients reporting diarrhea at baseline and during the study period.

As can be seen from Table 5a and Figure 6b, the number of patients reporting diarrhea were more in the carbonyl iron group than in the ferrous fumarate group.

Table 5b. No. (%) of patients reporting nausea and vomiting at baseline and during the study period in the treatment groups.

	Ferrous fumarate (n=72)*	Carbonyl iron (n=72)*	'p', χ^2-test
Nausea			
Baseline	22 (30.60)	26 (36.10)	0.480
2 weeks	22 (30.60)	34 (47.20)	0.089
4 weeks	17 (23.60)	38 (53.50)	<0.0001
8 weeks	16 (22.20)	32 (44.40)	0.005
12 weeks	14 (19.40)	33 (45.80)	0.001
Vomiting			
Baseline	03 (04.20)	05 (06.94)	0.042
2 weeks	02 (02.80)	04 (05.60)	0.404
4 weeks	01 (01.40)	03 (04.20)	0.684
8 weeks	00 (00.00)	01 (01.40)	0.316
12 weeks	00 (00.00)	02 (02.80)	0.157

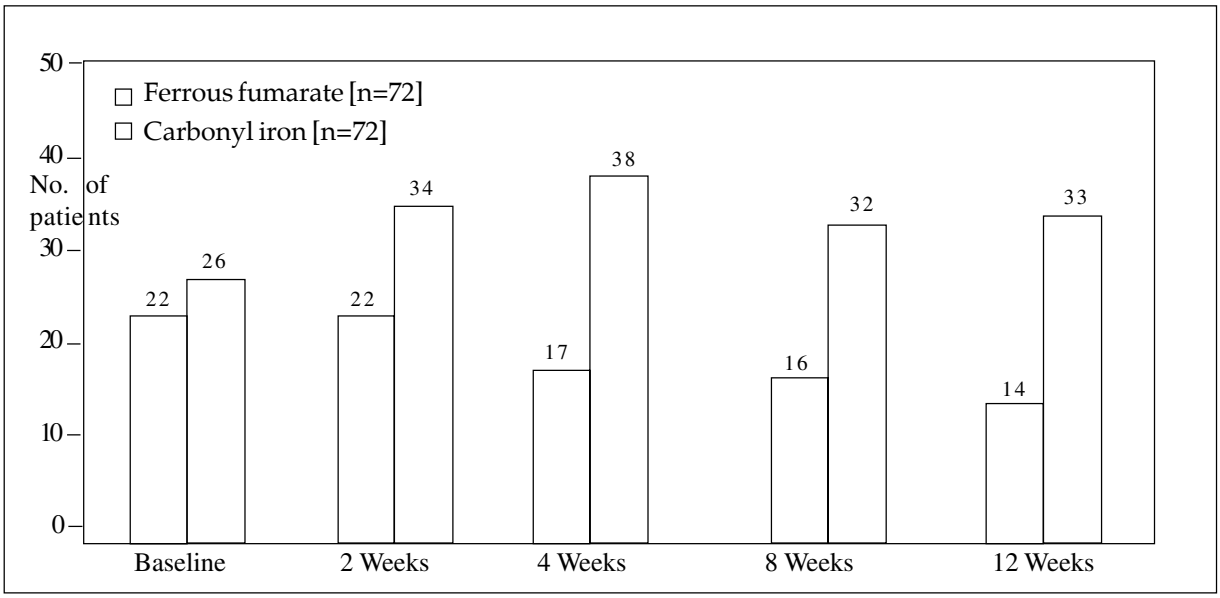

Figure - 6 c: No. of patients reporting nausea at baseline and during the study period.

An increased incidence of nausea was reported in the fourth week of the study. The number of patients reporting with nausea was significantly higher in the carbonyl iron group as compared to those in the ferrous fumarate at 4, 8 and 12 weeks (p<0.001, p=0.005 and p=0.001 respectively), almost double of what was

reported in the ferrous fumarate group (Table 5b and Figure 6c). However, the number of patients reporting with vomiting (Table 5b) or abdominal pain (Table 5c) was not significant in either group.

Table 5c. No. (%) of patients reporting abdominal pain at baseline and during the study period in the treatment groups.

	Ferrous fumarate (n=72)*	Carbonyl iron (n=72)*	'p', χ^2 test
Abdominal pain			
• Baseline	08 (11.10)	08 (11.10)	1.000
• 2 weeks	03 (04.17)	09 (12.70)	0.596
• 4 weeks	02 (02.80)	05 (06.90)	0.245
• 8 weeks	00 (00.00)	03 (04.17)	0.080
• 12 weeks	00 (00.00)	03 (04.17)	0.080

Discussion

Iron deficiency anemia in pregnancy is associated with greater risk of perinatal mortality and morbidity [5,6], low birth weight subsequent to preterm delivery [7] and lower infant apgar scores [9-11].

Oral iron supplementation is recommended to prevent and treat deficiency since dietary absorption cannot keep up with the increased iron demands. Various iron salts are available. Ferrous sulfate (32% elemental iron) ferrous fumarate (33%) elemental iron) and ferrous gluconate (12%) elemental iron) are some of the commonly used salts[20]. An iron salt like ferrous fumarate, which is already in the reduced state, does not depend upon gastric acidity for absorption.

Another form of oral iron is carbonyl iron, which has been mainly used for the fortification of foods. One of the studies revealed that the relative bioavailability of carbonyl iron was unexpectedly low and varied from 5% to 20% [19].

In the present study, the demographic and baseline values of Hb were not significantly different in either of the groups reflecting the lack of bias that might have skewed the results in favor of one of the groups.

Blood hemoglobin level is the most accurate measure of the degree of anemia in iron deficiency [25]. Other parameters that are used to assess response to therapy include red cell count and reticulocyte response.

The rise in hemoglobin was seen in both the groups and even as early as two weeks, the difference between the two groups was significant (p=0.007) with ferrous fumarate group reaching a hemoglobin level of 8.74 gm% from a baseline value of 8.45 gm% and the carbonyl iron group reaching a level of 8.53 gm% from a baseline value of 8.38 gm% (Table 2 and Figure 1). When expressed in the form of percentage change in hemoglobin, ferrous fumarate group showed a percentage change of 3.42 whereas carbonyl iron group reached a figure of 1.80 at the end of two weeks (p=0.0009). The hematological response is in accordance with other reports in literature that state that a mild reticulocytosis usually begins within three to five days after the start of therapy, reaches a maximum within eight to ten days, and declines thereafter. After the first week, the hemoglobin concentration begins to increase[22] and is usually normal within six weeks. Alleviation of iron deficiency symptoms often occurs within the first few days of treatment. The difference was more significant after the 12th week where the ferrous fumarate group reached a hemoglobin level of 11.45 gm% whereas the carbonyl iron group reached a level of 9.87 gm% (p<0.0001).

Significantly from the therapeutic standpoint, the percentage of patients in the ferrous fumarate group who achieved the WHO Hb target of 11 gm% was much more than that in the carbonyl iron group (90.28% vs 20.83%).

Apart from the hemopoietic response, the most important factor which determines the choice of iron preparation is the tolerability. Iron salts have been known to cause gastrointestinal disturbances. Studies

have shown that a supplement of 20-80 mg ferrous iron (as fumarate), taken between meals, has no clinically significant gastrointestinal side effects[19] . In the present study, constipation was the most common ADRs in both the treatment groups throughout the study period but the incidence noted in the ferrous fumarate group was significantly lesser than that of the carbonyl iron group (p, χ^2 test = 0.002) (Table 5a and Figure 6a).

The incidence of nausea increased significantly in the carbonyl iron group from the fourth week onwards, in comparison with the ferrous fumarate group and remained so thereafter. It was especially high in the fourth week with 38 cases in the carbonyl iron group and only 17 cases in the ferrous fumarate group (P<0.0001) (Table 5 and Figure 6c). Even the incidence of diarrhea was more in the carbonyl iron group than in the ferrous fumarate group as compared to baseline values. (Table 5a and Figure 6b).

Patient acceptability of the medication is one of the key factors in the successful correction of anemia. This was rated in the present study on the PGART (Patients Global Assessment of Response to Therapy and PGATT (Patients Global Assessment of Tolerability to Therapy) on a 5-point scale. Ferrous fumarate fared better than carbonyl iron with respect to response to therapy (p<0.0001) as well as tolerability to therapy (p=0.002).

The ferrous fumarate group showed a better gastrointestinal tolerability than the carbonyl iron group.

Conclusion

Ferrous fumarate is not only significantly superior in efficacy but is better tolerated than carbonyl iron. Ferrous fumarate is safe in pregnancy and gives a good hematological response with minimal adverse effects and can be used for the treatment of iron deficiency anemia during pregnancy.

References

1. Mehta BC. Iron deficiency anemia. In, G.S Sainani (ed). API textbook of medicine 6th ed. Mumbai: Association of Physicians of India, 1999;859.
2. Whitfield CR. Blood disorders in pregnancy. In, Whitfield CR (ed). Dewhurst's textbook of obstetrics and gynecology for postgraduates. 5th ed. Carlton, Australia: Blackwell Science, 1995;228-9.
3. India. National Child Survival and Safe Motherhood Programme. Programme interventions. Safe Motherhood newborn care. New Delhi: Ministry of Health and Family Welfare, MCH Division, 1994.
4. Nutritional anemias. Report of a World Health Organization Group of Experts (Technical Report Series No. 503). Geneva: WHO, 1972.
5. Nutritional anemias. Report of a World Health Organization Group of Experts (Technical Report Series No. 405). Geneva: WHO, 1968.
6. Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and prevention. MMWR Recomm Rep 1998;47:1-29.
7. Klebanoff MA, Shiono PH, Selby JV et al. Anemia and spontaneous preterm birth. Am J Obstet Gynecol 1991;164:59-63.
8. Lu ZM, Goldenberg RL, Cliver SP et al. The relationship between maternal hematocrit and pregnancy outcome. Obstet Gynecol 1991;77:190-4.
9. Rusia U, Madan N, Agarwal N et al. Effect of maternal iron deficiency anaemia on foetal outcome. Indian J Pathol Microbiol 1995;38:273-9.
10. Preziosi P, Prual A, Galan P et al. Effect of iron supplementation on the iron status of pregnant women: consequences for newborns. Am J Clin Nutr 1997;66:1178-82.
11. Greenwood R, Golding J, McCaw-Binns A et al. The epidemiology of perinatal death in Jamaica. Paediatr Perinat Epidemiol 1994;8:143-57.
12. Allen LH. Anemia and iron deficiency: effects on pregnancy outcome. Am J Clin Nutr 2000;71:1280-4.
13. Juarez-Vazquez J, Bonizzoni E, Scotti A. Iron plus folate is more effective than iron alone in the treatment of iron deficiency anemia in pregnancy: a randomized, double blind clinical trial. BJOG 2002;109:1009-14.
14. Frewin R, Henson A, Provan D. ABC of clinical haematology: Iron deficiency anaemia. BMJ 1997;314:360-3.
15. Shatrugna V, Raman L, Kailash U et al. Effect of dose and formulation on iron tolerance in pregnancy. Natl Med J India. 1999;12:18-20.
16. Geisser P, Muller A. Pharmacokinetics of iron salts and ferric hydroxide-carbohydrate complexes. Arzneimittelforschung 1987;37:100-4.
17. Kaltwasser JP, Werner E, Niechzial M. Bioavailability and therapeutic efficacy of bivalent and trivalent iron preparations. Arzneimittelforschung. 1987;37:122-9.
18. Hallberg L, Brune M, Rossander L. Low bioavailability of carbonyl iron in main: studies on iron fortification of wheat flour. Am J Clin Nutr 1986;43:59-67.
19. Milman N, Byg KE, Bergholt T et al. Side effects of oral iron prophylaxis in pregnancy – myth or reality? Acta Haematol 2006;115:53-7.
20. Hardman JG, Limbird LE, Gilman AG (eds). Goodman & Gilman's The Pharmacological Basis Of Therapeutics, 10th ed. New York: McGraw-Hill, 2003;1499.