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A Comparison of the Efficacy, Tolerability and Compliance of Ferrous Ascorbate and Carbonyl Iron With Ferrous Fumarate in Pregnant Women

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ABSTRACT:

Background: Iron insufficiency is the most prevalent single dietary deficiency in the world,1 impacting over one-third (over 2 billion) of the global population. 2 Pregnant women are particularly susceptible to iron shortage and iron-deficiency anaemia due to their increased iron requirements. In impoverished countries, the prevalence of iron-deficiency anaemia in pregnant women is reported to range from 35 to 75% (mean: 56%), but in affluent nations, the prevalence averages 18%. 3, 4 The frequency is extremely high in Central Asia, with India reporting a rate of 87%. An estimated 90 percent of anaemia occurrences in India are attributed to iron deficiency. **Aim's & Objectives:** To study and compare the effect of different iron preparations on hemoglobin and serum ferritin levels in pregnant women attending antenatal clinic. **Methods & Materials:** The protocol for the study was submitted to the Institutional Ethics Committee (I.E.C.) and approval was sought. After getting approval from concerned authorities, the study was conducted over 120 pregnant women in age group of 18-35 years, attending the antenatal clinic of the Department of Obstetrics and Gynecology, Santosh Medical College and Hospital, Ghaziabad. The study was conducted over a period of one year, from 11 Aug to 12 July. **Results:** A significantly higher compliance of 73% was reported with Ferrous ascorbate when compared with that of 61.7% with Ferrous fumarate and 55.4% with Carbonyl iron. The overall incidence of adverse effect with use of oral iron preparations was 54.4%. The maximum incidence was observed in Carbonyl iron group (61.5%) followed by 57.6% in Ferrous fumarate group and 45.2% in Ferrous ascorbate group and these differences were statistically significant. **Conclusion:** The current study was undertaken to assess efficacy, tolerability and compliance of three iron preparations, Ferrous fumarate, Ferrous ascorbate and Carbonyl iron. Ferrous fumarate is a conventional and inexpensive iron preparation. Ferrous ascorbate and Carbonyl iron are two newer preparations, claimed to be more efficacious and having superior tolerability profile as compared to conventional iron preparations, Ferrous sulphate and Ferrous fumarate.

Keywords*:* Pregnancy, Physiologic, Adaptation, Hematopoietic

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INTRODUCTION:

Iron deficiency is the most common single nutritional deficiency in the world,[1] affecting approximately one third (over 2 billion) of the world's population.[2] Pregnant women are particularly at high risk for iron deficiency and iron-deficiency anemia because of increased iron needs during pregnancy. The prevalence of iron-deficiency anemia in pregnant women is estimated to be between 35 and 75% (average 56%) in developing countries whereas in industrialized countries the average prevalence is 18%.3, 4 The prevalence is very high in Central Asia, reported as being 87% in India. In India, about 90% of anemia cases are estimated to be due to iron deficiency.[5,6]

Women in India and other developing countries are always in a state of precarious iron balance during their reproductive years. Their iron stores are not well developed because of poor nutritional intake, food habits, recurrent infections, menstrual blood loss and repeated pregnancies. Thus the average Indian woman enters her reproductive years, and particularly pregnancy, with iron and folate deficiency.[7-11] Pregnancy is a time in which the risk for developing iron deficiency anemia is highest, because iron requirements are substantially greater than average absorbable iron intake. The fact that iron deficiency anemia frequently develops in pregnancy indicates that the physiologic adaptations are often insufficient to meet the increased requirements and the iron stores are inadequate to meet the increased iron needs required for red blood cell mass expansion in the mother as well as for the development of the fetus and the placenta.[12-14]

The major concern about anemia in pregnancy is the possible adverse effects on both the mother and the fetus. With increasing severity of anemia maternal morbidity and mortality progressively increases. In India, 20% of all the maternal deaths are attributed to anemia during pregnancy and in another 20% of maternal deaths, anemia is a contributory factor.[17-19] Anemia is estimated to contribute to nine times higher risk of perinatal mortality.[16] Iron deficiency anaemia during pregnancy has been associated with Increased risk for low birth weight, preterm delivery, and perinatal mortality. [15]

WHO recommends routine oral supplementation of 60mg elemental iron plus 400µg folic acid daily for 6 months during pregnancy in areas where the prevalence of anemia in pregnancy is <40%. In areas where the prevalence of anemia in pregnancy is ≥40%, it recommends the same dosages for 6 months and continuing for 3 months postpartum. 9 In some developing countries, however, oral iron doses as high as 240mg daily have been used 15 while in many industrialized countries 30 mg elemental iron is recommended daily.

However, patients do not always respond adequately to oral iron therapy because of noncompliance due to side effects. Gastrointestinal disturbances characterized by colicky pain, nausea, vomiting, diarrhea, and gastric distress occur in about 6%–12% of patients taking iron preparations.[24] Therefore, the present study was conducted to compare the efficacy, tolerability and compliance of newer iron preparations (ferrous ascorbate and carbonyl iron) with a conventional iron preparation (ferrous sulfate or fumarate) in pregnant

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women. Since ferrous sulfate tablets containing 50 mg or 100 mg of elemental iron are not available in India, the tablet containing 60 mg of elemental iron had to be given twice daily to compare the efficacy with other iron preparations, but twice daily dosing would itself be a factor responsible for poor compliance, therefore ferrous sulfate was not included in the study. Hence, Ferrous fumarate, which is almost similar in efficacy and side effect profile to ferrous sulfate, was included in the study to compare with some newer oral iron preparations.

METHODS & MATERIALS:

The protocol for the study was submitted to the Institutional Ethics Committee (I.E.C.) and approval was sought. After getting approval from concerned authorities, the study was conducted over 120 pregnant women in age group of 18-35 years, attending the antenatal clinic of the Department of Obstetrics and Gynecology, Santosh Medical College and Hospital, Ghaziabad. The study was conducted over a period of one year, from Aug 11 to July12. It was a prospective, open label, randomized, parallel group, single-center, 12-week study. The subjects were randomly divided into subgroups in accordance with iron preparations prescribed to them. The total duration of the study was 12 weeks.

Written informed consent was sought from all the patients included in the study, prior to enrolment and screening. Detailed history was taken and physical examination was carried out in conformity to pretested format prepared for the purpose.

All eligible women who gave informed consent were consecutively enrolled and randomly assigned to three groups (A, B & C), using the random table. Group A was given Ferrous fumarate, 300mg tablet, containing 100mg elemental iron (Tab. Steadifer, Steadfast Pharma; 1 tablet orally once daily), Group B was given [24].Ferrous ascorbate, 100mg elemental iron (Tab. Ferricip-XT, Cipla Pharma; 1 tablet orally once daily), Group C was given Carbonyl Iron, 100mg elemental iron (Cap. Carbol-FZ, Gopal Pharma; 1 capsule orally once daily).

Quantitative data was analyzed using one-way ANOVA with post-hoc Student-Newman-Keuls Multiple comparison for within the group analysis and student's two-tailed Paired t-test for between the group comparisons. p-value < 0.05 was considered significant. Mean, SD and SE were calculated wherever applicable. The parameters were described in terms of Mean ± SD and/or percentages.

OBSERVATIONS & RESULTS:

The present study was conducted over 120 pregnant women, attending the antenatal clinic of the Department of Obstetrics and Gynecology, Santosh Medical College and Hospital, Ghaziabad. Out of 120 subjects enrolled for the study, 30 left the study at the beginning and were excluded from the study. Out of 90 subjects, 74 (82%) completed the 12 weeks of study and 16 (18%) were lost to follow up after end of 6 weeks.

The patients were divided into three groups, A, B & C, using the random table. All the three groups received 100 mg elemental iron in three different formulations, group A was

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supplemented with ferrous fumarate, group B with ferrous ascorbate and group C with Carbonyl iron. All three groups were supplemented with 0.5 mg folic acid per day. A standard diet was advised to all subjects included in the study.

In the present study the Efficacy of different oral iron preparations was compared by analyzing their effect on various hematological parameters, hemoglobin (Hb), red blood cell counts, packed cell volume (PCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), serum ferritin and peripheral blood film. Compliance to oral iron preparations was analyzed by total number of tablets actually consumed out of total number of tablets prescribed and handed over to the subjects. Tolerability to oral iron preparations was analyzed by assessing various adverse effects reported by the subjects. These parameters were recorded at three different intervals, at the start of study (0 week), at 6 weeks and at 12 weeks.

Table 1 : Hematological parameters at different intervals with ferrous fumarate

At 0 week

	Hb (g/dl)	PCV (%)	MCV (fl)	MCH (pg)	MCHC (g/dl)	RBC(million/ mm^3)	Ferritin (µg/l)
Mean	10.07	33.71	75.87	22.7	29.89	4.45	15.92
S.D	1.53	4.38	8.77	3.45	2.28	0.53	7.47
S.E	0.27	0.76	1.53	0.60	0.40	0.09	1.30

At 6 week

	Hb (g/dl)	PCV (%)	MCV (fl)	MCH (pg)	MCHC (g/dl)	RBC (million/mm^3)
Mean	10.53	35.54	78.16	23.15	29.61	4.56
S.D	1.39	3.65	6.66	2.76	2.32	0.38
S.E	0.24	0.64	1.16	0.48	0.40	0.07

At 12 week

	Hb (g/dl)	PCV (%)	MCV (fl)	MCH (pg)	MCHC (g/dl)	RBC(million/ mm^3)	Ferritin (µg/l)
Mean	11.12	37.59	80.46	23.87	29.62	4.68	19.77
S.D	1.26	3.46	6.57	3.12	2.30	0.43	7.88
S.E	0.27	0.64	1.22	0.58	0.43	0.08	1.46

•Ferrous fumarate, 300 mg tablet, containing 100mg elemental iron given orally once a day.

•Hemoglobin, Red blood cell indices studied at the start of study i.e. 0 week, at 6 weeks and at 12weeks.

•Serum ferritin was studied at 0 week and at 12 week.

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Table 2: Effect On Various Hematological Parameters

	MEAN RISE FROM 0 TO 12 WEEKS		p-value
	FERROUS FUMARATE	CARBONYL IRON	
Hemoglobin	1.08 (10.72%)	0.93 (8.87%)	NS
PCV	4.06 (12.04%)	3.21 (9.63%)	NS
MCV	4.26 (5.61%)	4.24 (5.46%)	NS
MCH	1.06 (4.67%)	1.26 (5.29%)	NS
MCHC	-0.28(-0.94%)	-0.11 (-0.36%)	NS
RBC Count	0.25 (5.62%)	0.15 (3.36%)	NS
Ferritin	3.54 (22.24%)	2.70 (13.20%)	NS

DISCUSSION

Iron deficiency continues to be one of the most prevalent nutrient deficiencies in the world. Pregnant women are particularly at high risk for iron deficiency and iron-deficiency anemia because of increased iron needs during pregnancy. With increasing severity of anemia maternal morbidity and mortality progressively increases. Iron deficiency anaemia during pregnancy has been associated with increased risk for low birth weight, preterm delivery, and perinatal mortality.15 Interventions are often designed to prevent the decrease in hemoglobin concentration and in the decline in iron stores associated with pregnancy. Oral iron supplementation is recommended to prevent and treat deficiency since dietary absorption cannot keep up with the increased iron demands.

Different forms or combinations of iron supplements are available, most are affordable because of their low cost. Ferrous sulfate (32% elemental iron) and ferrous fumarate (33%) elemental iron) are some of the commonly used salts. An iron salt like ferrous fumarate, which is already in the reduced state, does not depend upon gastric acidity for absorption. Ferrous ascorbate is a synthetic molecule of ascorbic acid and iron, hence claimed to have higher absorption than other oral iron preparations. Carbonyl iron is newer iron preparation, which contains uncharged elemental iron micro-particles and is claimed be very effective, with tolerable side effects and very safe even at very high doses. Therefore the current study was undertaken to assess efficacy, tolerability and compliance of three iron preparations, Ferrous fumarate, Ferrous ascorbate and Carbonyl iron.

In the present study, the baseline values of Hemoglobin and other hematological parameters 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. Peripheral smear conversion rate was slightly higher with Carbonyl iron (26.3%) than Ferrous fumarate (21.4%) and the difference between the two was very significant statistically.

ADRs reported by 61.5% pregnant women in Carbonyl iron group, while in Ferrous fumarate group, 57.6% pregnant women reported ADRs and this difference was very significant

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statistically.Therefore, the tolerability was significantly better with Ferrous fumarate, as compared to Carbonyl iron.

Overall compliance with Ferrous fumarate was about 61.8% and with Carbonyl iron, it was about 55% and the difference between the two groups was statistically significant.Thus, overall it can be assumed there is not much difference between Ferrous fumarate & Carbonyl iron in terms of efficacy, but Ferrous fumarate is significantly superior over Carbonyl iron, in terms of compliance as well as tolerability.

These results are in conformity with Bala Suman et al who reported Ferrous fumarate and Carbonyl iron to be equally efficacious in correcting hematological parameters and better tolerated with lesser ADRs with ferrous fumarate when compared to Carbonyl iron. [26]

CONCLUSIONS

Iron deficiency continues to be one of the most prevalent nutrient deficiencies in the world. Pregnant women are particularly at high risk for iron deficiency and iron-deficiency anemia because of increased iron needs during pregnancy. With increasing severity of anemia maternal morbidity and mortality progressively increases. Iron deficiency anaemia during pregnancy has been associated with increased risk for low birth weight, preterm delivery, and perinatal mortality.[14] Interventions are often designed to prevent the decrease in hemoglobin concentration and in the decline in iron stores associated with pregnancy. Routine oral iron supplementation is an essential antenatal protocol followed throughout the world.

Different forms or combinations of iron supplements are available, most are affordable because of their low cost. However, new complexes and fixed dose combinations of iron with vitamins and other micronutrients are being increasingly marketed with claims of superior compliance and hematopoietic response. The current study was undertaken to assess efficacy, tolerability and compliance of three iron preparations, Ferrous fumarate, Ferrous ascorbate and Carbonyl iron. Ferrous fumarate is a conventional and inexpensive iron preparation. Ferrous ascorbate and Carbonyl iron are two newer preparations, claimed to be more efficacious and having superior tolerability profile as compared to conventional iron preparations, Ferrous sulphate and Ferrous fumarate.

Thus from the above discussion, it is obvious that Ferrous ascorbate is more effective in the prevention and treatment of iron deficiency anemia in pregnant women. Ferrous ascorbate is superior over Ferrous fumarate and Carbonyl iron, in terms of efficacy, tolerability and compliance. The superior compliance may be attributed to lower incidence of adverse effects, that is better tolerability of Ferrous ascorbate. The higher efficacy and better hematological response with ferrous ascorbate may be attributed to higher absorption of iron due to presence of ascorbic acid and these observations are in accordance with that mentioned by Kanshansky[26] and Kipps [21]. Whereas they report an enhanced absorption and better hematological response when iron is used in combination with ascorbic acid, they also reported a significant increase in the incidence of adverse effects with increased uptake. Our

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results are at variance with the latter part of the report. In order to further substantiate the higher suitability of ferrous ascorbate for routine antenatal care, further studies with a larger patient population are required to strengthen the results of the present study.

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