Research Article

Comparative Effectiveness of Oral Iron Medications and Patient Preference in Anemia during Pregnancy

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ABSTRACT:

Objectives: This study was design to compare the efficacy and patient preference of three different marketed formulations as folic acid plus ferrous fumarate, or carbonyl iron oramino acidplus chelated iron in the treatment of anemia during pregnancy. **Materials and methods:** The study was multi-centric, randomized and controlled. Patients with 15-25 weeks of pregnancy with hemoglobin between 6 to 10 g/dl were included in this study. The enrolled 156patients were randomly allocated to received folic acid plusferrous fumarate, or carbonyl iron or amino acid pluschelated iron, once daily for a period of 12 weeks. Hemoglobin was estimated at baseline, 6 weeks and at the 12 weeks of the treatment. **Results:** At the end of treatment the hemoglobin of the patients in the folic acidplus ferrous fumarate group achieved the WHO target, 11.2 ± 1.7 as compared to the carbonyl iron group 9.93 ± 0.82 and the amino acid pluschelated iron group 9.82 ± 0.65 ($p>0.05$).The serum ferritin level at the end of treatment in the ferrous fumarate plus folic acid group were reached 25.65 ± 4.61 whereas the patients in the carbonyl iron group reached 22.20 ± 1.7 and in the amino acid plus chelated iron group reached up to 21.36 ± 0.98 ($p>0.05$). More adverse effects occur in the carbonyl iron group patients. **Conclusion**: Folic acidplus ferrous fumarateis superior in efficacy, safe in pregnancy and better preferred as compare tocarbonyl iron or amino acid pluschelated iron and gives a good hematological response with minimal adverse effects.

Key words: Iron deficiency anemia, pregnant women, folic acid, ferrous fumarate, carbonyl iron and amino acid

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INTRODUCTION

Anemia, the most common hematologic abnormality, is a reduction in the concentration of erythrocytes or hemoglobin in blood. Anemias are a group of diseases characterized by a decrease in hemoglobin or red blood cells (RBCs), resulting in decreased oxygen carrying capacity of blood [1]. World Health Organization recommends a hemoglobin concentration value of a minimum 11.0 gm% during pregnancy. However in India and most of the other countries the lower limit is often accepted as 10 gm% [2,3].

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. 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 [4-6].

Iron Deficiency Anemia in pregnancy is present in very high percentage of pregnant

women in India. According to WHO, the prevalence of anemia in pregnancy is about 30 %, and in developing countries and India, incidence is around 40–80% of women suffering from [7].

Iron requirement needed during pregnancy, early pregnancy- 2.5 mg/day, 20 to 32 weeks- 5.5 mg/day, 32 to 40 weeks- 6.8 mg/day.

Iron transported into cells through attachment of transferring to specific membrane bound receptors. The complex is engulfed releases iron intra cellularly and returns to the cell surface to carry fresh loads. In iron deficiency and hemolytic states, transferrin receptors in erythropoietic cells increase in number, this does not occur in other cells. Thus, the erythron becomes selectively more efficient in trapping iron. Iron is transported in blood in combination with a glycoprotein transferring, it binds ferric iron. The total plasma content of iron is ~3 mg. This is recycled 10 times every day (turnover of iron is 30 mg/day) [8-12].

Oral iron preparations are safe, inexpensive and effective way to administer iron. Oral route should be the route of choice in routine cases. If all pregnant women receive routine iron and folic acid, it is possible to prevent nutritional anemia in pregnant women. National nutritional anemia prophylaxis program advices 60 mg elemental iron and 500 μg of folic acid daily for 100 days to all pregnant women. The higher dose in Indian women is required as they start pregnancy with low or absent iron stores due to poor nutrition. Nowadays various oral iron preparations are available in to the market for the correction of iron deficiency includes iron salts, iron chelates and ferric hydroxide complexes. Oral iron must be continued for 3-6 months after haemoglobin has come to normal levels, this helps in building iron stores [13,14].

Moreover, the bioavailability of iron preparation increases with the increasing dose, with ferrous fumarate having high bioavailability [15]. However, adverse events such as nausea, vomiting, epigastric pain and constipation, diarrhea are commonly associated with iron salts. Some food and/or 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 correctionas well as serum ferritin level during anemia in pregnancy.

A newer formulation of iron called carbonyl iron and amino acid and chelated iron combination has been introduced into the market with good bioavailability. Additionally, folic acid plus ferrous fumarate as iron in pregnant women is reported to be safe with nosignificant adverse events [18,19].

Therefore, the present study was conducted to compare the efficacy and safety of a preparation containing ferrous fumarate plus folic acid versus acarbonyl iron versus amino acid plus chelated iron in the treatment of anemia during pregnancy.

Objective of the study

To compare the efficacy and tolerability of three different marketed formulations like, a folic acid plus ferrous fumarate versus carbonyl iron versus amino acid plus chelated iron in the treatment of iron deficiency anemia during pregnancy.

MATERIALS AND METHODS

The study was scheduled conducted in outpatient department of 'Vidya Nursing Home' and New Atrik Hospital, Bilimora, Gujarat, India. The study was prospective, randomized, single blind and multi-centric comparative study. Randomization was done for each center. The study was carry out in the 15 to 25 weeks of the gestation period in the pregnant women confirmed by the presence of β-HCG in urine with hemoglobin between 6 to 10 g/dl were included with iron deficiency anemia. Written informed consent was obtained from all patients before including in the study.

Patients with known either of the following clinical conditions like diabetes mellitus, asthma, thyroid diseases, severe concurrent illness like cardiovascular, renal, and hepatic, infection, inflammation, malignancy, urinary tract infection, abortion, twins or premature baby born were excluded from the entire study. In any other condition patients who are taking medications like quinolones, tetracycline,

antacids, chloremphenicol, levodopa, penicillamine, thyroid hormones, amino acid and anticonvalescent and in the opinion of the investigator did not justify 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 marketed formulation A (folic acid 1.5 mg plus ferrous fumarate 300 mg (app. 98.6 mg elemental iron) once daily or B (carbonyl iron 250 mg (app. 100 mg elemental iron) once daily or C (amino acid 250 mg plus chelated iron 125 µg (app. 100 mg elemental iron) once daily with a glass of water for a period of 12 weeks (up to end of study period/treatment).

The patients were not allowed to take iron or folic acid in any other pharmaceutical formulation. They were allowed to take calcium or multivitamin preparations as well as iron rich food.

Patient Preference and Efficacy Evaluation

Hemoglobin was estimated at baseline, 6 weeks and at 12 weeks of the treatment. Primary efficacy variable – rise in the hemoglobin levels at the end of the therapy, analyzed on coulter cell counter, rise in serum ferritin level at the end of 12 weeks, analyzed by turbidimetric immunoassay method.

Secondary efficacy variable – the response to therapy was recorded on a scale called Physicians 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 physicians with respect to efficacy.

Safety Evaluation

Clinical safety was evaluated based upon the nature and severity of adverse events if any, recorded by patients at each visits to the hospital at baseline, 6 weeks and at 12 weeks of the treatment. The tolerability to therapy was recorded on a scale called Patients 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 with respect to 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 Tukey: all pairs column comparison. Proportions were analyzed using the chi square test. Level of significance: 'p' <0.05 at 95% C.I. (2 sided).

RESULTS

A total of 156 patients (52 folic acid plus ferrous fumarate, 52 carbonyl iron and 52 amino acid plus chelated iron) were completed the study as per protocol.

During the entire study; three patients in folic acid plus ferrous fumarate group developed moderate degree of constipation and abdominal pain at first follow-up before 6 weeks of treatment. Four patients reported moderate nausea and vomiting at 3rd weeks of treatment period and another 2 patients reported diarrhea associated with abdominal pain after first follow-up at 9th weeks of treatment in carbonyl iron group and all 5 patients in amino acid plus chelated iron group developed moderate degree of constipation associated with abdominal pain as well as nausea and vomiting at first follow-up after 6 weeks of treatment. Not a single patient reported any serious adverse events during the study period.

The demographic characteristics and/or values of the patients did not differ significantly in either of the groups [**Table 1**].

As shown in [**Table 2**] as well as [**Fig. 1a and 1b**] represent the mean ± SD in Hb (gm%) of the patients at baseline (beginning of study) and during the study period in the three treatment groups. As depicted in [**Table 2**] as well as [**Fig. 1**], baseline hemoglobin values did not differ significantly at the beginning of the study in either of the treatment groups.

Table 1: Demographic data (mean ± SD) in all the treatment groups

Variables	Folic acid plusferrous fumarate (n=52)	Carbonyl iron (n=52)	Amino acid pluschelated iron (n=52)	*p* Value
(Hospital Base) VNH / Atrik	25 / 27	21 / 29	27 / 27	
Age (yr)	24 ± 0.12	24.02 ± 0.17	23.88 ± 0.11	0.491
Gestational Age (weeks)	20.6 ± 0.48	19.64 ± 0.12	19.41 ± 0.59	0.376
BMI	25.41 ± 0.59	26.58 ± 0.005	26.59 ± 0.59	0.560
(Diet Status) Veg./Non-Veg.	32/20	28/24	29/23	

Values for variables are mean ± S.D.

Table 2: Hemoglobin level (Hbgm %) of the patients at entire study period in all treatment groups

Hb (gm %)	Folic acid plusferrous fumarate (n=52)	Carbonyl iron (n=52)	Amino acid plus chelated iron (n=52)	*p* Value
Baseline	8.8 ± 0.92	8.77 ± 0.5	8.90 ± 0.36	*NS*
6 weeks	10.1 ± 0.78*	9.47 ± 0.33*	9.40 ± 0.3*	0.04
12 weeks	11.2 ± 1.7*	9.93 ± 0.82*	9.82 ± 0.65*	0.008

Values for variables are mean ± SD (Standard Deviation)
* $p < 0.0001$, statistically significant as compared to baseline (One-way ANOVA)

The rise in hemoglobin in the patients receiving a folic acid plus ferrous fumarate preparation was significantly better than that seen in other patients receiving a carbonyl iron as well as amino acid plus chelated iron preparation at the end of six weeks [10.1 (0.78) vs9.47 (0.33) vs 9.40 (0.3) (p=0.04)] and at end of treatment 12 weeks of treatment [11.2 (1.7) vs 9.93 (0.82)vs 9.82 (0.65) (p<0.01)].

The mean hemoglobin increase in the ferrous fumarate group was 2.4gm% at the end of 12 weeks as compared with the carbonyl iron group, which recorded a mean increase in hemoglobin by 1.16 gm% and 0.92 gm% respectively.

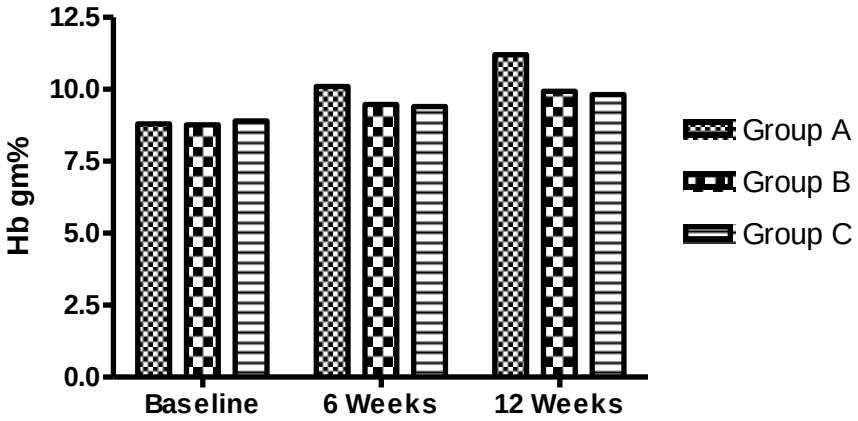

Figure 1(a): Hb level (gm%) of the patients

When the final values in all the treatment groups were compared with the respective baseline values, the improvement in Hb (gm%) was significant in all the groups

p<0.05 for folic acid plusferrous fumarate treatment group, carbonyl iron treatment group, and amino acid plus chelated iron treatment group.

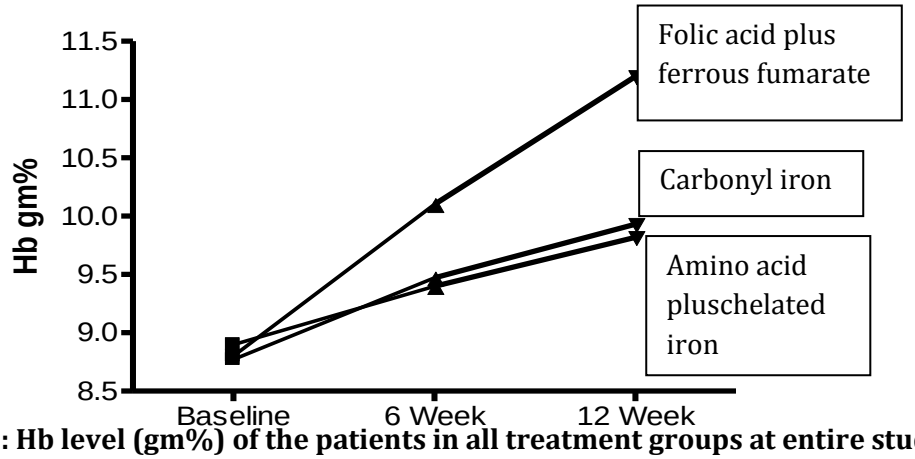

Figure 1(b): Hb level (gm%) of the patients in all treatment groups at entire study

As shown in [**Table 3**] as well as [**Fig. 2a and 2b**] represent the mean ± SD in serum ferritin level (µg/L) of the patients at baseline (beginning of study) and during the study period in the three treatment groups. As depicted in [**Table 3**] as well as [**Fig. 2**], baseline hemoglobin values did not differ significantly at the beginning of the study in either of the treatment groups.

Table 3: Serum ferritin level (µg/L) of the patients at entire study period in all treatment groups

Serum ferritin (µg/L)	Folic acid plus ferrous fumarate (n=52)	Carbonyl iron (n=52)	Amino acid pluschelated iron (n=52)	*p* Value
Baseline	19.13 ± 3.03	19.80 ± 1.14	19.98 ± 0.61	*NS*
6 weeks	23.42 ± 1.58*	21.41 ± 0.56*	20.84 ± 0.37*	*NS*
12 weeks	25.65 ± 4.61*	22.20 ± 1.7*	21.36 ± 0.98*	*NS*

Values for variables are mean ± SD (Standard Deviation)
* $p < 0.0001$, statistically significant as compared to baseline (One-way ANOVA)

The rise in ferritin level in the patients receiving a folic acid plus ferrous fumarate preparation was significantly better than that seen in other patients receiving a carbonyl iron as well as amino acid plus chelated iron preparation at the end of six weeks [23.42 (1.58) vs21.41 (0.56) vs20.84 (0.37) (p>0.05)] and at end of treatment 12 weeks [25.65 (4.61) vs22.20 (1.7) vs21.36 (0.98) (p>0.05)]. The mean ferritin level increase in the ferrous fumarate group was 6.52 µg/L at the end of 12 weeks as compared with the carbonyl iron group, which recorded a mean increase in hemoglobin by 2.4µg/L and 1.38µg/L respectively.

When the final values in all the treatment groups were compared with the respective baseline values, the improvement in serum ferritin level (µg/L) was significant in all the groups p>0.05 for folic acid plus ferrous fumarate, carbonyl iron, and amino acid plus chelated iron treatment group.

As shown in [**Table 4 and Fig. 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 and amino acid plus chelated iron group with respect to response to therapy as well as tolerability.

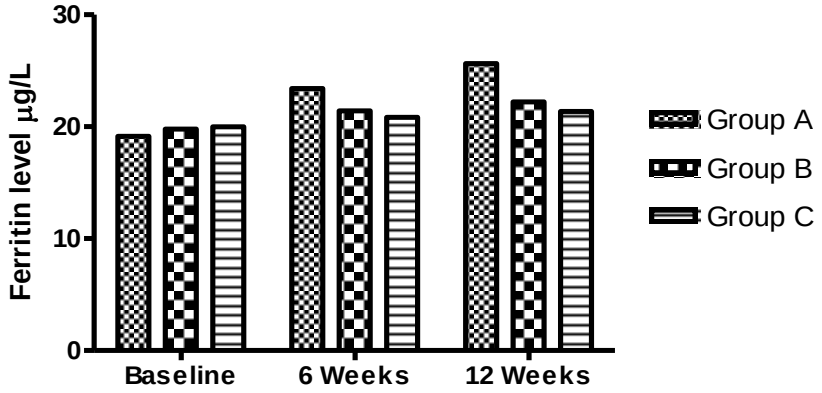

Figure 2(a): Serum ferritin level (µg/L) of the patients in all treatment groups at entire study

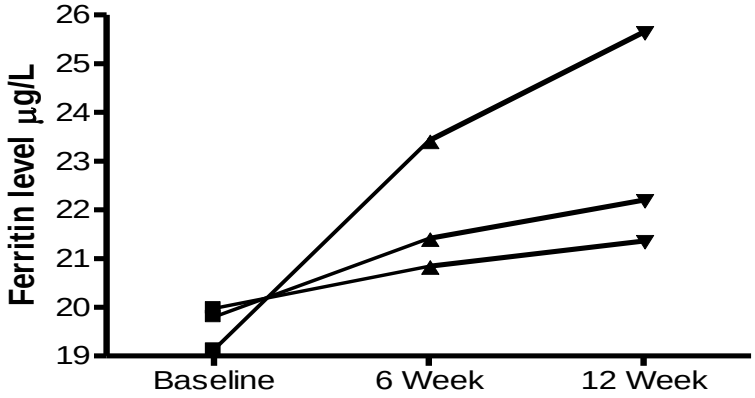

Figure 2(b): Serum ferritin level (µg/L) of the patients in all treatment groups at entire study

Table 4: Patient adherence and preference by 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	Folic acid & Ferrous fumarate (n=52)	Carbonyl iron (n=52)	Amino acid & Chelated iron (n=52)
Physicians Global Assessment of Response to Therapy (PGART)			
Excellent	29 (55.77)	12 (23.08)	10 (19.23)
Good	13 (25)	17 (32.69)	15 (28.85)
Average	8 (15.39)	13 (25)	15 (28.85)
Poor	2 (3.85)	9 (17.31)	9 (17.31)
Very Poor	0 (0.00)	1 (1.92)	3 (5.77)
Patients Global Assessment of Tolerability to Therapy (PGART)			
Excellent	31 (59.62)	24 (46.15)	21 (40.39)
Good	11 (21.15)	12 (23.08)	14 (26.92)
Average	8 (15.39)	10 (19.23)	11 (21.15)
Poor	2 (3.85)	4 (7.69)	5 (9.62)
Very Poor	0 (0.00)	2 (3.85)	1 (1.92)

*Number (Percentage) of Patients

As shown in [**Table 4**] 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 more than half (55.77%) of the cases whereas carbonyl iron and amino acid plus chelated iron were rated as excellent only in 23.08% and 19.23 of the cases respectively [**Fig. 3**].

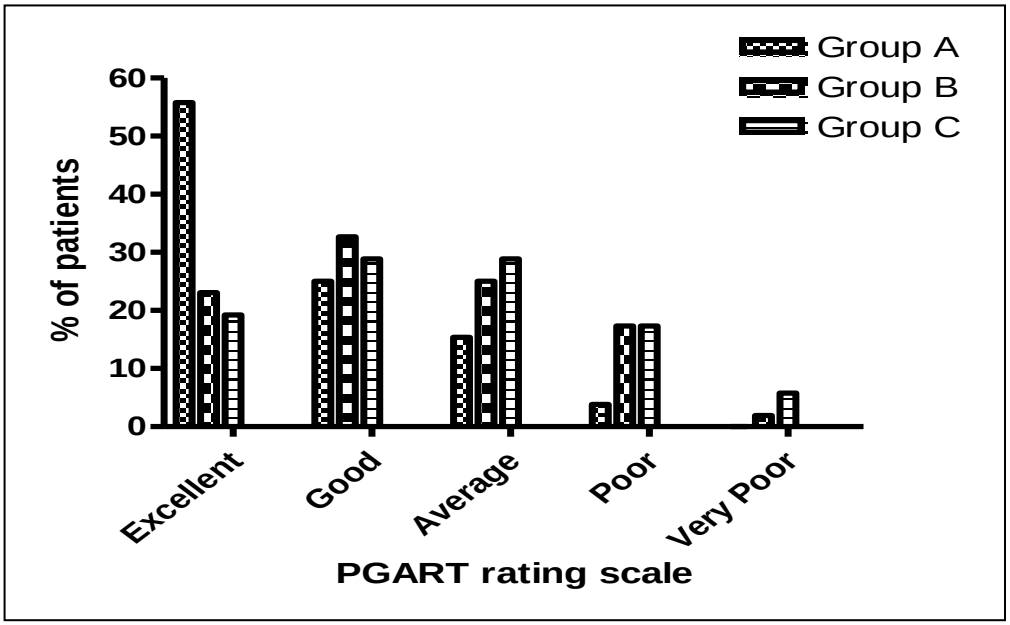

Figure 3: Patient adherence and preference by Physicians Global Assessment of Response to Therapy (PGART) at the end of study period

In the present study 59.62% of the patients in the ferrous fumarate group said that the tolerability to treatment was excellent whereas only half 46.15% and 40.39% of the patients in the carbonyl iron group as well as amino acid and chelated iron group reported the tolerability as excellent respectively. [**Fig. 4**]

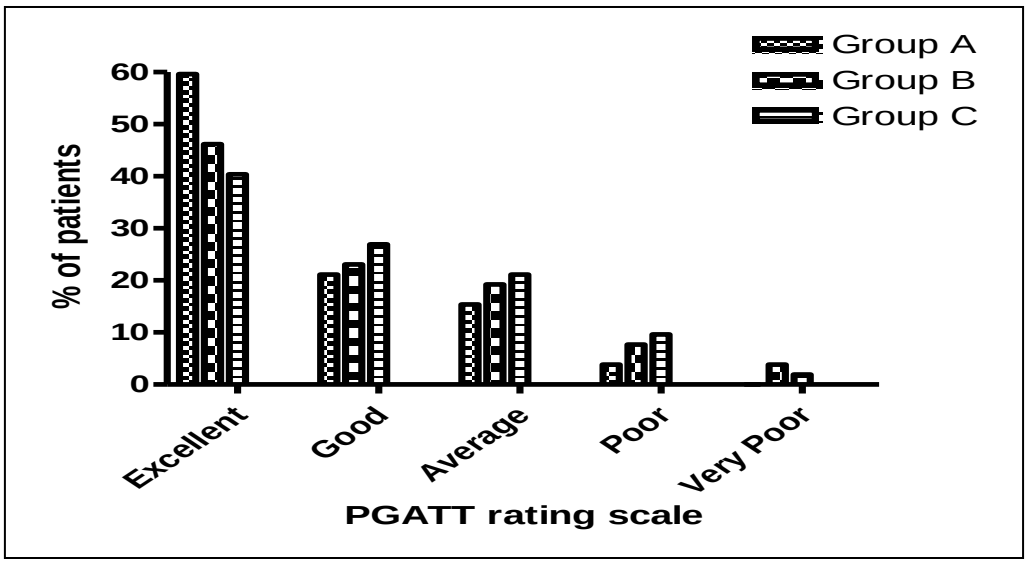

Figure 4: Patient adherence and preference by Patients Global Assessment of Tolerability to Therapy (PGART) at the end of study period

Table 5: Number and Percentage of patients reporting constipation and diarrhea at baseline and entire study period in the treatment groups

	Folic acid plusferrous fumarate (n=52)	Carbonyl iron (n=52)	Amino acid pluschelated iron (n=52)
Constipation			
Baseline	11 (21.16)	12 (23.08)	14 (26.92)
6 weeks	17 (32.69)	18 (34.62)	22 (42.31)
12 weeks	28 (53.85)	26 (50)	26 (50)
Diarrhea			
Baseline	6 (11.54)	6 (11.54)	9 (17.21)
6 weeks	10 (19.23)	13 (25)	16 (30.77)
12 weeks	18 (34.62)	19 (36.54)	21 (40.39)

*Number (Percentage) of Patients

Constipation was the main adverse effect in both the treatment groups throughout the study period. While there was no significant difference in the incidence of constipation between all the groups at baseline, the percentage of patients reporting constipation was significantly lesser in the folic acid plus ferrous fumarate group than the carbonyl iron group as well as amino acid plus chelated iron group throughout the study period ($\chi 2$ test, P=0.002) [**Table 5**].

At baseline, 6 and at 12 weeks the percentage of patients reporting constipation in the carbonyl iron group and amino acid plus chelated iron group was more than that reported in the folic acid plus ferrous fumarate group.

As shown in [**Table 5**], the number of patients reporting diarrhea were more in the carbonyl iron as well as amino acid plus chelated iron group than in the folic acid plus ferrous fumarate group.

Table 6: Number and percentage of patients reporting nausea and vomiting at baseline entire study period in the treatment groups

	Folic acid plusferrous fumarate (n=52)	Carbonyl iron (n=52)	Amino acid plus chelated iron (n=52)
Nausea			
Baseline	17 (32.69)	16 (30.77)	19 (36.54)
6 weeks	17 (32.69)	23 (44.23)	22 (42.31)
12 weeks	19 (36.54)	28 (53.85)	26 (50)
Vomiting			
Baseline	11 (21.16)	19 (36.54)	21 (40.39)
6 weeks	14 (26.92)	24 (46.15)	24 (46.15)
12 weeks	18 (34.62)	28 (53.85)	29 (55.77)

*Number (Percentage) of Patients

An increased incidence of nausea as well as vomiting was reported in the 6thweek of the study. The number of patients reporting with nausea was significantly higher in the carbonyl iron group as well as amino acid plus chelated iron group as compared to those in the folic acid plus ferrous fumarate group at 6 and 12 weeks ($p<0.001$, $p=0.005$ and $p=0.001$ respectively), almost double was reported in the carbonyl iron group as well as amino acid plus chelated iron group [**Table 6**].

Table 7: Number and percentage of patients reporting abdominal pain at baseline and entire study period in the treatment groups

	Folic acid plusferrous fumarate (n=52)	Carbonyl iron (n=52)	Amino acid plus chelated iron (n=52)
	Abdominal pain		
Baseline	16 (30.77)	13 (25)	19 (36.54)
6 weeks	19 (36.54)	18 (34.62)	21 (40.39)
12 weeks	19 (36.54)	23 (44.23)	26 (50)

*Number (Percentage) of Patients

At baseline, 6thand 12thweeks the percentage of patients reporting abdominal pain in the carbonyl iron group and amino acid plus chelated iron group was more than that reported in the folic acid plus ferrous fumarate group.

DISCUSSION

Iron deficiency anemia in pregnancy is associated with greater risk of perinatal mortality and morbidity, low birth weight subsequent to preterm deliveryand lower infant APGAR scores[20-22].The requirements of iron increase during pregnancy, as in the third trimester, a pregnant woman needs six times more iron than a non-pregnant woman. Iron requirements during pregnancy are not easily fulfilled through diet alone; thus, many countries recommend that pregnant women take iron supplements [23, 24].

Oral iron supplementation is recommended to prevent and treat deficiency since dietary absorption cannot keep up with the increased iron demands. The higher dose in Indian women is required as they start pregnancy with low or absent iron stores due to poor nutrition and frequent infection like hook worm and malaria [25].

In the present study various patients variables included like age, gestational age, blood group, and diet status of the patient. But these all the variables are not that much of affecting to the present study and not concern with the hematological response of the patients.

We came to know that maximum patients found with 21-26 years of age and due to the hormonal changes in the pregnant lady they are affecting with iron deficiency leading to the anemia. Same way the patients with gestational age from 18-23 weeks of pregnancy suffers from anemia due to the end of the second trimester and starting of third trimester, so the development of the fetus get very fast into the mother uterus. Another reason for suffer is, in concern with Hb concentration plasma volume increases more during the second trimester so the dilution of the Hb in the second trimester decreases the iron status in the body[26].

In the present study, maximum patients with the Rh positive blood factor are more susceptible for iron deficiency anemia. Especially patients having the A^{+ve} and O^{+ve}blood group having iron deficiency anemia. As per the diet status concern more patients having vegetarian food in their diet as compare with non-vegetarian food taken by the patients in their diet, affecting with Iron Deficiency Anemia because non-vegetarian food contain more iron as compare to vegetarian which absorbed more iron into the body.

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. Same as the measurement of serum ferritin level is also very important because of very sensitive and accurate parameter to measure iron store into the body especially in iron deficiency anemia. Iron molecule can found into the hemoglobin structure, so, directly measurement of iron can possible from blood. Other parameters that are used to assess response to therapy include red cell count, serum bilirubin, reticulocyte response [26,27].

The rise in hemoglobin was seen in all the groups, as early as six weeks, the difference between all the groups were clinically significant with folic acid plus ferrous fumarate group reaching a hemoglobin level near to the normal value from a baseline value, but the carbonyl iron group not sufficiently increases from their baseline value and same thing for the amino acid plus chelated iron group. When expressed in the form of percentage change in hemoglobin, ferrous fumarate plus folic acid group showed a percentage change of 2.4 whereas carbonyl iron group reached a figure of 1.16 and amino acid plus chelated iron group showed a percentage change of 0.92 at the end of treatment (12 weeks). After the first week, the hemoglobin concentration begins to increase 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 after end (12 weeks) of the treatment where the folic acid plus ferrous fumarate group reached hemoglobin level up to the normal range. Whereas the carbonyl iron group and the amino acid plus chelated iron group not reached up to the normal range.

Significantly from the therapeutic standpoint, the maximum patients in the folic acid plus ferrous fumarate group those achieved the WHO target of 11 gm% Hb was much more than that in the carbonyl iron group and amino acid plus chelated iron group.

In the study we have determine very sensitive test, serum ferritin which show the storage of iron into the body also rise in all the groups, into the first six weeks, the difference between all the groups were non-significant with folic acid plus ferrous fumarate group reaching a ferritin level near up to body requirements (normal range) from a baseline value, where the carbonyl iron group as well as amino acid plus chelated iron group not increases. The difference was more after end (12 weeks) of the treatment where the folic acid plus ferrous fumarate group reached a ferritin level up to the body requirement whereas the carbonyl iron group and amino acid plus chelated iron group cannot reached up to normal value[28,29].

Apart from the hemopoietic response, the most important factor which determines the choice of iron preparation is the tolerability. In the present study oral supplementations are given to the patients because of the parentral supplementation having more as well as frequent adverse effects. Iron salts have been known to cause gastrointestinal disturbances [30,31]. In the present study, constipation was the most common adverse effect in all the treatment groups throughout the study period but; at the end of the treatment very few patients found in folic acid plus ferrous fumarate group, as compare to the patients in carbonyl iron group and the patients in amino acid plus chelated iron group noted with it shown in [**Table 5**].

In the present study, other ADRs also reported in all the treatment groups throughout the study period but at the end of the treatment less number of patients in folic acid plus ferrous fumarate group reported diarrhea and abdominal pain, as compare to the patients in carbonyl iron group and in amino acid plus chelated iron group reported diarrhea and abdominal pain. But in the folic acid plus ferrous fumarate group was significantly lesser than that of the carbonyl iron as well as amino acid plus chelated iron group. [**Table 5 and 6**].

The incidence of nausea and vomiting increased significantly in the carbonyl iron group and amino acid plus chelated iron from the baseline onwards, in comparison with the folic acid plus ferrous fumarate group and remained so thereafter. It was especially high in the 12 weeks (end of the treatment) in the carbonyl iron group as well in amino acid plus chelated iron group shown in [**Table 6 and 7**].

As far as concern with all the treatment groups, only one group which is folic acid plus ferrous fumarate having reported very less adverse effects during their study period; so, it is a safe to use in the pregnancy as compare to other compared combination medication.

Patient adherence and preference with the medication is one of the key factors in the

successful treatment of anemia. This was rated in the present study on the PGART (Physicians Global Assessment of Response to Therapy) and PGATT (Patients Global Assessment of Tolerability to Therapy) on a 5-point rating scale. More than half of the cases were excellent in Folic acid plus ferrous fumarate group far better than cases involve in carbonyl iron group and amino acid plus chelated iron group with respect to response to therapy as well as tolerability to therapy.

As per the present study we came to know, folic acid plus ferrous fumarate group showed a better drug in gastrointestinal tolerability than the carbonyl iron group.

CONCLUSION

According to the results of this prospective randomized, single blind comparative study, we can conclude that daily administration of folic acid plus ferrous fumarate for 12 weeks of pregnancy from baseline of study is superior in efficacy and better tolerated than daily administration of carbonyl iron and amino acid plus chelated iron in patients with complete blood count by measuring the hemoglobin, serum ferritin, and serum bilirubin mainly total, direct and indirect bilirubin. Folic acid plus ferrous fumarate is better combination in gastrointestinal tolerability and safe in pregnancy as compare to both the medication which are carbonyl iron and amino acid plus chelated iron gives a good hematological response as well iron store with minimal adverse effects. As per the present study we came to know, folic acid plus ferrous fumarate group showed a better drug in gastrointestinal tolerability than the carbonyl iron group.

REFERENCES

1. Joseph T. Dipirio, Barbara G. Wells and et al, Pharmacotherapy, McGraw-Hill Medical Publishing Division; 6th Edition 2006; 322-25.
2. Nutritional anemias. Report of a World Health Organization Group of Experts (Technical Report Series No. 503). Geneva: WHO, 1972.
3. PV Ingle, AG Gandhi, PH Patil, SJ Surana. Iron Deficiency Anemia: Perspectives in Indian Pregnant Women. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2011, July-September, 2 (3):1036-1047.
4. Harsh Mohan and et al; Text book of Pathology; Jaypee Brothers Medical Publishers Pvt. Ltd.; 4th Edition 2002; 200-8.
5. Ingle P. V., Chaudhari S. L. , Dighore P. N., Surana S. J. Sociocultural, Healthy Nutrition & Eating, Exercise Pattern and Use of Ayurvedic Medicines in Pregnancy. Indian Journal of Pharmacy Practice. 2012, Jul - Sep, 5(3):5-12.
6. Beard J.L., Connor J.R., Jones B.C., Brain iron: location and function. Journal of Programme Food Nutrition Sciences 1993; 17;183–221.
7. World Health Organization. The prevalence of anaemia in women: a tabulation of available information. 2nd edition; Geneva: World Health Organization, 1992.
8. Tripathi K.D. and et al; Elements of Medical Pharmacology; Jaypee Brothers Medical Publishers Pvt. Ltd.; 6th Edition, 2008; 581-92.
9. Felt B, Lozoff B. Brain iron and behavior of rats are not normalized by treatment of iron deficiency anemia during early rat development. Journal of Clinical Nutrition 1996; 126: 693–701.
10. Amir Hayat, Dhiren Haria, Moro O Salifu. Erythropoietin stimulating agents in the management of anemia of chronic kidney disease. Patient Preference and Adherence 2008:2 195–200.
11. Chong Gao, Li Li, Baoan Chen, Huihui Song, Jian Cheng, Xiaoping Zhang, Yunyu Sun. Clinical outcomes of transfusion-associated iron overload in patients with refractorychronic anemia. Patient Preference and Adherence 2014:8 513–517.
12. Chengxin Luan, Runzhe Chen, Baoan Chen, Jiahua Ding, Ming Ni. Umbilical cord blood transplantation supplemented with the infusion of mesenchymal stem cell for an adolescent patient with severe aplastic anemia: a case report and review of literature. Patient Preference and Adherence 2015:9 759–765.
13. Frewin R, Henson A and et al; ABC of clinical haematology: Iron deficiency anaemia. BMJ 1997; 314:360-63.
14. Strauss M.B., Anemia of infancy from maternal iron deficiency in pregnancy. Journal of Clinical Investigation 1993; 12:345–53.
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; 37:122-29.
18. Milman N, Byg KE, Bergholt T and et al. Side effects of oral iron prophylaxis in pregnancy – myth or reality? ActaHaematol 2006; 115:53-57.
19. Gaspar M.J., Ortega R.M. and et al, Relationship between iron status in pregnant women and their babies. Journal of Obstetrics and Gynecology 1993; 72:534–37.
20. Rusia U, Madan N, Agarwal N and et al; Effect of maternal iron deficiency anaemia on foetal outcome, Indian Journal of Pathology and Microbiology, 1995; 38:273-79.
21. Greenwood R, Golding J, McCaw-Binns A and et al; "The epidemiology of perinatal death in Jamaica" Paediatric of Perinatal Epidemiology; 1994; 8:143-57.
22. Vidaeff AC, Belfort MA. Critical appraisal of the efficacy, safety, and patient acceptability of hydroxy progesterone caproate injection to reduce the risk of preterm birth. Patient Preference and Adherence. 2013:7 683–691.
23. Galan P, DaoudaH and et al; "Effect of iron supplementation on the status of pregnant women: consequences for newborns" American Journal of Clinical Nutrition, 1997; 66: 1178–82.
24. Maria Makrides, Caroline A Crowther, Robert A Gibson, and et at; "Efficacy and tolerability of low-dose iron supplements during pregnancy: a randomized controlled trial" American Journal of Clinical Nutrition, 2003; 78:145–53.
25. Fleming A.F., Ghatoura G.B.S., Harrison K.A., Briggs N.D., Dunn D.T.; "The prevention of anemia in pregnancy in primigravidae in the guinea savanna of Nigeria". Ann Trop Med Parasitol, 1986; 80:211–33.
26. Ezzati M., Lopus A.D., Dogers A., Vander H.S., Murray C.; "Selected major risk factors and global and regional burden of disease". Lancet 2002; 360: pg. no. 1347-1360.
27. Sagaonkar Smita, Sukhija S., TayalRenu, Sagaonkar P.D.; "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", Journal of Obstetrics and Gynecology India, Vol. 59, No. 6: November/December 2009;552-62
28. Andersson A, Hultberg B and et al; "Decreased serum homocysteine in pregnancy" European Journal of Clinical Chemistry and Clinical Biochemistry, 1992; 30:377–79.
29. Klebanoff M.A., Shiono P.H., Selby J.V., Trachtenberg A.I., Graubard B.I.; Anemia and spontaneous preterm birth; American Journal of Obstetrics and Gynecology, 1991; 164:59–63.
30. Mody R.J., Brown P.I. and Wechsler DS; "Refractory iron deficiency anemia as the primary clinical manifestation of celiac disease";Journal of Pediatric Hematololgy and Oncology;February 2003; 25 (2):169–72.
31. Milman N, Bergholt T and et al; "Side effects of oral iron prophylaxis in pregnancy – myth or reality?" ActaHaematol, 2006; 115:53-57.