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Original Research Article

Retrospective observational study to assess clinical impact of ferric pyrophosphate supplementation in antenatal settings of India (FEMINA study)

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ABSTRACT

Background: Globally, anemia during pregnancy is a major public health concern. Conventional iron supplements limit their effectiveness due to poor absorption, water solubility and untoward GI side effects. This study assessed the clinical impact and safety of Micronized Microencapsulated Ferric Pyrophosphate (MMFP) supplementation in an antenatal setting of India.
Methods: Real world, cross-sectional, single-arm, observational study in 814 patients from 122 clinics across India. Study done with central IEC approval in accordance with ICH-GCP and Helsinki Declaration. Descriptive and analytical statistics applied for study endpoints using SPSS ver. 29.0.1.0(171).
Results: 814 pregnant women data was analysed with a mean age (29.39±3.98 years) and weight (59.48±8.14 kg). 61.79% patients were multiparous. 50.12% women were in their second trimester of pregnancy. Thyroid diseases were commonest comorbidity (21.25%). Mild anemia (37.35%) and moderate anemia (50.49%) were more prevalent. Hemoglobin levels showed significant improvement from 9.46±1.27 g/dl to 10.95±1.47 g/dl at 12 weeks ($p<0.0001$). Mean corpuscular volume (MCV) and serum ferritin also showed significant improvement from 85.31±9.49 fl to 90.93±8.51 fl and from 103.06±61.91 ng/ml to 164.42±79.61 ng/ml at 12 weeks ($p<0.0001$) respectively. Consistent improvement seen in three parameters irrespective of diet patterns or anemia severity at baseline. 12 weeks MMFP supplementation showed significant surge in patients having Hb (>11 g/dl) to 62.03% from 9.58% at baseline. Furthermore, MMFP demonstrated favourable safety profile, with only five mild adverse events observed, unrelated to the treatment.
Conclusions: MMFP supplementation is a valuable therapeutic option for managing iron deficiency anemia in pregnant women.

Keywords: Hemoglobin, Iron-deficiency anemia, Micronized ferric pyrophosphate, Pregnancy, Real-world study

INTRODUCTION

Iron deficiency anemia (IDA) is a type of microcytic anemia, defined by a decreased mean red cell volume (MCV) due to reduced hemoglobin (Hb) production.[1] IDA is typically caused by inadequate intake of iron, chronic blood loss, or a combination of both.[2] The presentation of anemia, symptomatic or otherwise, depends on its

etiology, the acuity of onset, and the presence of comorbidities, particularly cardiovascular disease. Common symptoms of anemia include chronic fatigue, impaired cognitive function, and diminished well-being.[1]

Iron deficiency (ID), with or without anemia, constitutes a significant global health challenge, impacting over 2 billion individuals worldwide.[3] Statistics indicates that 56% of pregnant women in low- and middle-income countries suffer from anemia.[4] The prevalence of iron deficiency among pregnant women in India is among the highest globally. Untreated ID can lead to severe adverse consequences for both the foetus and the mother.[5] It is estimated that approximately 20% of maternal deaths are directly attributable to anemia, while an additional 50% of maternal deaths are associated with this condition.[6] To prevent anemia during pregnancy and mitigate its adverse effects, strategies include treating underlying conditions, providing iron and folate supplementation to all menstruating women, including adolescents, as well as daily supplementation during pregnancy and the postpartum period.[7] Oral iron supplementation is recommended for mild to moderate IDA. Insufficient dietary intake can result in deficiencies of cobalamin (vitamin B12) and folate, with folate deficiency being more prevalent. These vitamins are crucial for embryogenesis, and any deficiencies can lead to congenital abnormalities.[8] Administering low-dose oral iron supplements from the first trimester and throughout pregnancy can prevent the occurrence of IDA.[9] The Indian Council of Medical Research (ICMR) recommends a daily iron intake of 27 mg/day for pregnant women and 23 mg/day for lactating women during pregnancy and lactation period.[10]

IDA treatment includes oral and intravenous (IV) iron replacement. As oral iron is convenient and inexpensive it remains the mainstay of treatment for stable patients. Conventional iron salts, such as ferrous fumarate, gluconate, sulfate etc. are commonly used in clinical practice. However, they are often associated with taste changes and various gastrointestinal side effects, including nausea, vomiting, abdominal pain, constipation, diarrhoea, and dyspepsia. These adverse effects have driven the development of newer iron salts.[11] A micronized dispersible form of ferric pyrophosphate microencapsulated with an emulsifier coating has been developed to enhance the bioavailability and solubility of ferric pyrophosphate.[12-14]

Folic acid is a water-soluble vitamin which is widely utilized for the treatment of macrocytic anemia devoid of neurological complications. It not only improve the deficiencies but also potentially diminishes the occurrence of neural tube defects by 45% in women who maintain a daily intake of 400 micrograms.[15,16] Glycine, a non-essential amino acid, is increasingly recognized for its potential involvement in heme synthesis, as indicated by recent research findings.[17] This real-world, multicentric study was conducted to understand the clinical utility of oral hematinic containing ferric pyrophosphate, folic acid and glycine for anemia management in pregnancy.

METHODS

Ethical conduct of the study

This study was conducted in accordance with principles of the Declaration of Helsinki (Brazil, October 2013), Good Clinical Practices for clinical research in India, 2005, New Drugs and Clinical Trials Rules 2019, The International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use Guideline for Good Clinical Practice E6 (R2), and with Indian Council of Medical Research's national ethical guidelines for biomedical and health research involving human participants, 2017. The study was approved by Sangini Hospital Ethics Committee (EC Registration number: IORG0007258).

Study design and patient population

This study was a real-world, open-label, single-arm, cross-sectional, observational clinical study involving 814 patients, who sought treatment at various outpatient clinics, thereby offering a diverse patient pool from 122 sites across India. From the overall obtained data, patients with missing data for case validation were not considered in the analyses and the final sample size was determined based on the available data (Figure 1).

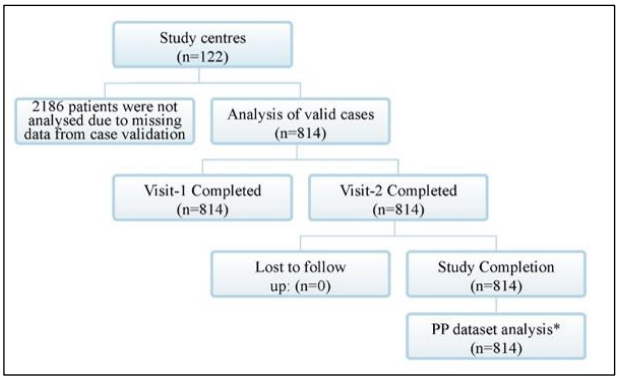

Figure 1: Subject disposition.
*DCF/CRF analyses for drug utilization pattern as specific clinical use, dosage or differential positioning of formulation

Subjects were selected based on inclusion and exclusion criteria. Included were pregnant women with gestational age less than 6 months and pregnant women between aged from 18 to 40 years. Patients having contraindications to treatment ingredients and any other condition or factors as per discretion of treating physician were excluded from participation.

The primary objective of the study included: change in hemoglobin levels from baseline to end of week 4 and week 12. Secondary objectives included change in Serum ferritin, Mean corpuscular volume (MCV) level from

baseline to end of week 4 and week 12 and safety assessment for common and very common adverse events at the end of 3 months ±7 days.

Study procedure

This study involved data collection of three visits: a baseline (day 00) and two follow-ups at week 4 and week 12. Vital signs, medical history, patient examination, and compliance monitoring were assessed as per routine clinical practice. Participants were considered to have completed the study if followed up for 4 and 12 weeks. Study was conducted between January to May 2023. Given the observational nature of this study, obtaining written inform consent from patients was not required.

Data evaluation

Data were recorded on paper Case Report Forms (CRFs) and verified with source documents. After data entry and quality check, an Excel-bases database was transferred to statistical software (SPSS Version. 29.0.1.0(171) for analysis. The full analysis set comprised data from 814 individual, with subgroup analyses performed based on specific demographics and medical history variables. Adherence to the STROBE guidelines has been maintained to ensure transparency and reliability in the presentation of this study results.

Study drug

Ferric pyrophosphate in an extremely micronized bioavailable form (0.3-0.5 microns), encapsulated with emulsifier coating promising excellent M-cell mediated absorption, higher solubility and tolerance of Iron bypassing gut interaction thereby minimizing adverse effects. The composition of the investigational product included elemental iron 30 mg, vitamin C 50 mg, folic acid 250 mcg, vitamin B12 0.75 mcg, glycine 10 mg.

Statistical methods

All statistical analyses were performed using Statistical Package for Social Sciences [The International Business Machines Corporation, United States; version 29.0.1.0 (171)]. Analysis was performed for subjects with all valid data. Descriptive statistics was used to analyse quantitative variables like mean, median, standard deviations (SD), change from baseline (CFB), %CFB, minimum and maximum values with 95% confidence interval. Frequency and percentage were reported for qualitative variables. The significance of continuous variables was assessed using the student's paired t-test, employing a two-tailed test and considering a p value <0.05 as statistically significant. For subgroup analysis, a point-biserial coefficient analysis was done using Pearson correlation.

RESULTS

Baseline demographic and patient characteristics

The mean age of the study cohort was 29.39±3.98 years and mean weight was 59.48±8.14 kg. Dietary habits showed a varied distribution, with a significant portion identifying as non-vegetarian (56.14%), while vegetarians made up 43.86% of the population. Parity status of patients were multi-parity (61.79%), followed by null-parity (38.21%). Pregnancy trimester distribution was first trimester in 49.88% and second trimesters in 50.12%. Fatigue (72.11%) emerged as the most common complaint, followed by headache (34.52%). Regarding comorbidities, thyroid diseases (21.25%) stood out as the most prevalent condition, followed by hypertension (7.86%) and type 2 diabetes (5.04%). Anemia grading revealed mild category (10-10.9 g/dl) (37.35%), followed by moderate (7-9.9 g/dl) (50.49%), severe anemia (4-6.9 g/dL) (2.58%) and normal (>11) (9.58%). More details are enlisted in Table 1.

Concomitant medications

At baseline, concomitant medications included calcium supplements (40.54%), folic acid (21.62%), multivitamins (19.41%) and others drugs. At 12 weeks, concomitant medications included calcium supplements (35.26%), multivitamins (12.04%), folic acid (11.55%), protein (6.39%) and others (Table 1).

Table 1: Demographics and baseline characteristics of study population.

Demographic and baseline details of study population		n=814
Demographic data	Age (years) (Mean±SD)	29.39±3.98
	Weight (kg) (Mean±SD)	59.48±8.14
Parity status (%)	Null parity	38.21
	Multi parity	61.79
Diet (%)	Vegetarian	43.86
	Non-vegetarian	56.14
Pregnancy trimester (%)	First	49.88
	Second	50.12
Comorbidities (%)	Thyroid diseases	21.25
	Hypertension	7.86
	Type 2 diabetes	5.04

Continued.

Demographic and baseline details of study population		n=814
	Dyslipidemia	4.55
	Obesity	0.49
	PCOD	0.12
Major complaints (%)	Fatigue	72.11
	Headache	34.52
	Shortness of breath	27.89
	Restless legs	20.64
	Rapid heartbeat	6.88
Anemia grading (%)	Normal (11-14 g/dl)	9.58
	Mild (10.0-10.9 g/dl)	37.35
	Moderate (7.0-9.9 g/dl)	50.49
	Severe (4-7.0 g/dl)	2.58
Baseline concomitant medications (%)	Calcium	40.54
	Folic acid	21.62
	Multivitamin	19.41
	Protein	6.51
	Progesterone	1.47
	Albendazole	0.49
	EPA + DHA supplement	0.49
	Metformin	0.25
	Boric acid	0.25
	Antacid	0.12
	Antiemetics	0.12
Concomitant medications at 4 weeks (%)	Calcium	30.59
	Folic acid	16.83
	Multivitamin	15.72
	Protein	3.44
	Progesterone	2.95
	Metformin	0.25
	Boric acid	0.12
	Antacid	0.12
Concomitant medication at 12 weeks (%)	Calcium	35.26
	Multivitamin	12.04
	Folic Acid	11.55
	Protein	6.39
	EPA + DHA supplement	1.23
	Progesterone	0.61
	Metformin	0.25
	Boric acid	0.12
	Antacid	0.12

n=number of patients, SD= Standard deviation, %=percentage, PCOD=polycystic ovarian disease, OD=once daily, BD= twice daily, EPA= eicosapentaenoic acid, DHA= docosahexaenoic acid

Primary endpoint

Changes in hemoglobin levels

A statistically significant increase in hemoglobin levels (mean±SD) was observed following treatment. At baseline, hemoglobin level was 9.46±1.27 g/dl, which significantly increased to 10.17±1.35 g/dl (7.5% increase, p value <0.0001) after 4 weeks. Subsequently, after 12-week treatment period, hemoglobin levels further increased to 10.95±1.47 g/dl (15.75% increase, p value <0.0001) compared to baseline (Figure 2).

Secondary endpoint

Changes in s. ferritin levels

S. ferritin (ng/ml) levels at baseline, was recorded at 103.06±61.91 ng/ml which significantly increased to 132.72±67.32 ng/ml (28.77% increase, p value <0.0001) after 4 weeks. By the end of 12-weeks, there was a further improvement in the mean value to 164.42±79.61 ng/ml (59.54% increase, p value <0.0001) compared to baseline (Figure 3).

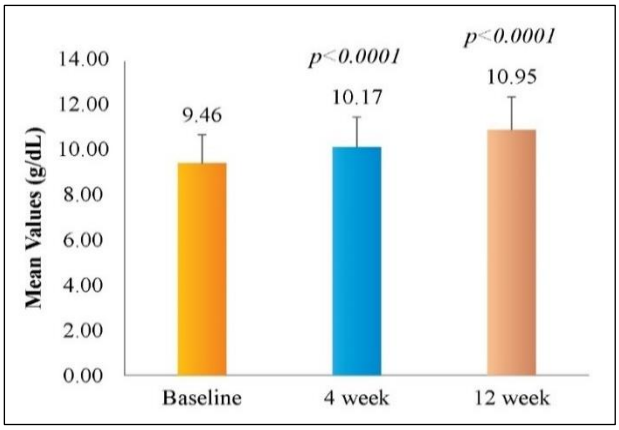

Figure 2: Change in hemoglobin after initiating treatment.

A statistically significant improvement of 1.49 g/dl observed in Hb level at 12 weeks.

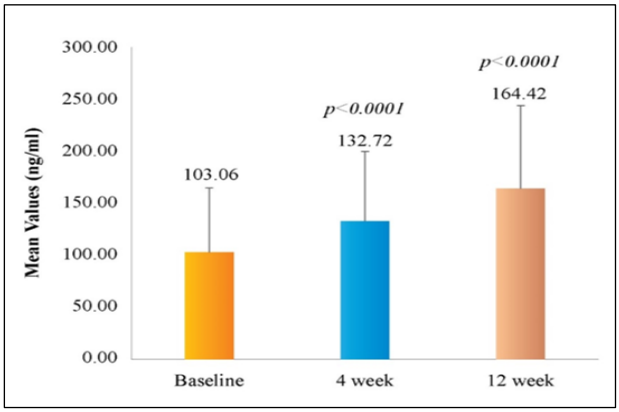

Figure 3: Change in serum ferritin after initiating treatment.

A statistically significant rise of 61.36 ng/ml observed in S. Ferritin level at 12 weeks

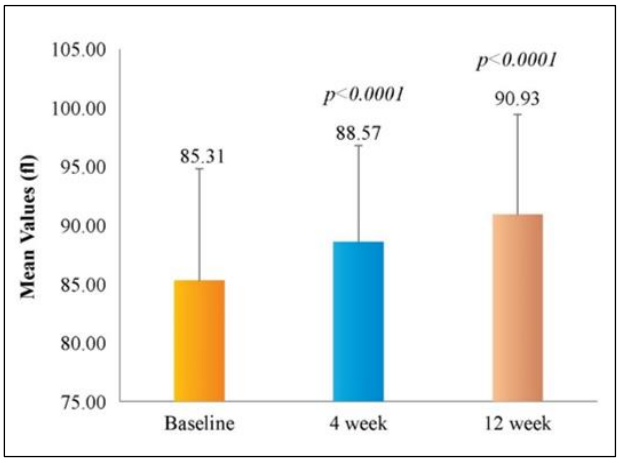

Figure 4: Change in mean corpuscular volume after initiating treatment.

A statistically significant increment of 5.62 fl observed in MCV levels at 12 weeks.

Changes in mean corpuscular volume (MCV) levels

At baseline, the average MCV was recorded at 85.31±9.49 fl, which significantly increased to 88.57±8.23 fl (3.82% increase, p value <0.0001) at 4 weeks. By 12-weeks, there was a further improvement observed in the mean MCV to 90.93±8.51 fl (6.59% increase, p value<0.0001) compared to baseline (Figure 4).

Safety analysis

Only five mild adverse events (nausea (3), facial swelling (1) and lachrymation (1)) were reported, but they were not associated with the iron supplementation. All events were mild and transient in nature resolving without any additional intervention.

Subgroup analysis

According to diet

In vegetarian patient's cohort, baseline mean Hb was 9.06 g/dl, which increases to 10.43 g/dl after 12 weeks of treatment. Serum ferritin level at baseline was 171.55 ng/ml, which increased to 208.19 ng/ml at week 12. Mean MCV at baseline was 41.68 fl, which increased to 50.50 fl at week 12 (Figure 5).

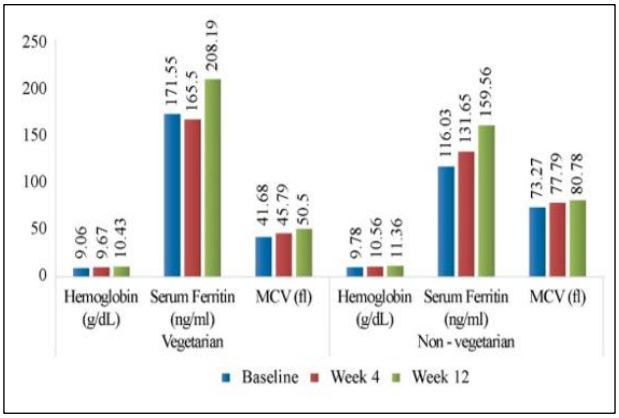

Figure 5: Association of Hb (g/dl), MCV (fl) and s. ferritin (ng/ml) with dietary patterns.

In vegetarian subgroup, 1.37 g/dl rise in mean Hb levels, 36.64 ng/ml in serum ferritin level and 8.82 fl in MCV level was observed after 12 weeks whereas in no-vegetarian subgroup, 1.58 g/dL rise in mean Hb levels, 43.53 ng/ml in serum ferritin level and 7.51 fl in MCV level was observed after 12 weeks.

Among patients following non-vegetarian diet, mean Hb at baseline was 9.78 g/dl, which increased to 11.36 g/dl after 12 weeks of treatment. S. ferritin at baseline was 116.03 ng/ml, which increased to 159.56 ng/ml at week 12. MCV at baseline was 73.27 fl and 80.78 fl at week 12 (Figure 5).

Further stratification of the vegetarians and non-vegetarian patients was done based on the severity of anemia as mild anemia (Hb: 10-10.9 g/dl) and moderate-severe anemia

(Hb: <9.9 g/dl). Initially, both the vegetarian and non-vegetarian groups with moderate to severe anemia had mean Hb values of 8.4 g/dl and 8.75 g/dl, respectively which improved to 9.85 g/dl and 10.67 g/dl, respectively after 12 weeks. The vegetarian and non-vegetarian groups with mild anemia had mean Hb values of 10.25 g/dl and 10.28 g/dl, respectively at baseline. This improved to 11.5 g/dl and 11.76 g/dl, respectively after 12 weeks (Table 2).

Table 2: Visit-wise changes in Hb levels in patients stratified as per diet and Hb levels at baseline.

Distribution of patients based on diet as per Hb levels				
Intervals	**Vegetarian (n=339)**		**Non-vegetarian (n=397)**	
	Moderate-severe anemia (n=238)	**Mild anemia (n=101)**	**Moderate-severe anemia (n=194)**	**Mild anemia (n=203)**
Baseline	8.4	10.25	8.75	10.28
Week 4	9.02	10.86	9.7	11.02
Week 12	9.85	11.5	10.67	11.76

According to anemia severity at baseline

Improvement in Hb based on baseline anemia severity, 37.35% patients had mild anemia (10 to 10.9 g/dl) at baseline, with prevalence further decreasing to 32.80% at week 4 and 16.83% patients at week 12. At baseline, total 50.49% patients had moderate anemia (7 to 9.9 g/dl), which decreased to 30.84% patients at week 4 and 19.29% patients at week 12. At baseline 2.58 % patients had severe anemia (4-6.9 g/dl). Its prevalence further decrease to 2.46% and 2.09% at week 4 and week 12 respectively (Figure 6).

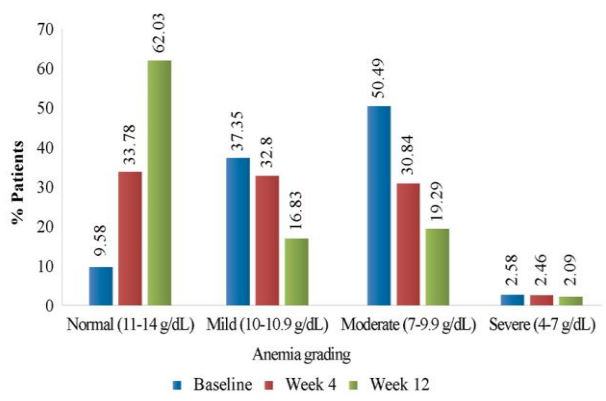

Figure 6: Improvement in Hb according to baseline anemia severity.

At week 12, % of patients with normal Hb levels increased from 9.58% to 62.03%. Conversely, there was a significant decline in the prevalence of anemia, with reductions in the % of patients with mild anemia (37.35% to 16.83%), moderate anemia (50.49% to 19.29%), and severe anemia (2.58% to 2.09%).

Responder rate

Responder rate in entire cohort, 9.58% of patients exhibited Hb levels above 11 g/dl at baseline which surged further to 33.78% at week 4 and further increased to 62.03% at week 12 (Figure 7).

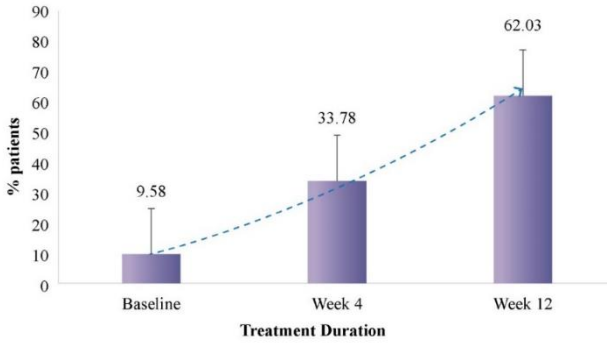

Figure 7: Responder rate for Hb from baseline to week 12.

By week 12, 62.03% of patients achieved the target Hb level of 11 mg/dl or higher.

Correlation between s. ferritin and hemoglobin improvement

A point-biserial coefficient analysis was done using Pearson correlation to determine the relationship between hemoglobin and serum ferritin levels. A positive correlation between s. ferritin levels and increase in hemoglobin levels was observed (r_{pb} = 0.122, p = 0.074). These findings suggest that individual with s. ferritin level <150 ng/mL tend to experience an increase in hemoglobin level (Table 3).

Table 3: Correlation coefficient between serum ferritin level and hemoglobin.

Correlations between s. ferritin level and hemoglobin		
Serum ferritin (ng/ml)	Hb(g/dl): at 12 weeks	
	Pearson correlation	0.122**
	Sig. (2-tailed)	0.074
	N	216

**Correlation is significant at the 0.05 level (2-tailed). 1 = <150 s. ferritin level, 0 = ≥ 150 s. ferritin level

DISCUSSION

Pregnancy is a condition particularly susceptible to the development of IDA due to the increased demand for RBC formation and the requirements for fetal and placental growth.[18] Since dietary intake alone is insufficient to meet the daily required iron during pregnancy, the Centres for Disease Control and Prevention recommends that pregnant women should take a daily supplement of 30 mg of elemental iron as a preventive measure.[19]

Oral iron supplementation is a very successful method for raising hemoglobin levels in patients with IDA. However, low bioavailability, the possibility of adverse gastrointestinal events leading to non-compliance, and inflammation linked to elevated hepcidin levels may limit the effectiveness of most iron salts in replenishing iron stores.[20-23] These factors can also result in impaired iron absorption from the gastrointestinal tract and retention of iron in the reticuloendothelial system.[24]

Compared to non-micronized iron pyrophosphate, which has a greater particle size, and non-encapsulated iron pyrophosphate, MMFP has a higher bioavailability and is soluble in water.[25] The preferential binding of particles up to 10 mm in diameter by M cells and their transfer to immunocompetent cells in underlying mucosal lymphoid tissue provide another explanation for the greater bioavailability of MMFP.[26]

The present study successfully achieved its predetermined primary and secondary objectives, outlining the safety and efficacy of Micronized Microencapsulated Ferric Pyrophosphate (MMFP) supplementation in anaemic pregnant women.

Anemia during pregnancy is a major health issue affecting 37.00% of pregnant women and 30.00% of women from age 15 to 49 years globally.[27] In a study conducted on pregnant women with anemia, the mean age was 26.20±4.61 years with majority being vegetarian patients, while in the present study the mean age of patients was slightly higher as 29.39±3.98 years with a majority of patients following non-vegetarian diet. In the same study the most prevalent parity status was “1” followed by “0” and “2” with third trimester being prevalent in 73.25%, followed by second and first trimester in 20.93% and 5.8% respectively.[28] Similarly, in the present study prime “1” parity was the most common parity status followed by “0” and “2” with majority of pregnancies in second trimester in 50.12%.

In a meta-analysis and systematic review including 52 studies and 12,44,747 patients with anemia, based on this review the most prevalent anemia was mild in 70.80% which is similar to the prevalence of the present study also in a study conducted prospectively on pregnant females it was concluded that as the pregnancy progresses the Hb levels decrease reasoning to the physiological changes during pregnancy, which is due to plasma dilution, this might be a reason that in the present study the most prevalent pregnancy duration was second trimester.[29,30]

During the first 2 trimesters of pregnancy, IDA increases the risk for preterm labour, low-birth-weight babies, and infant mortality and predicts iron deficiency in infants after 4 months of age. Additionally, in studies supported by WHO in southeast Asia, iron and folic acid supplementation every week to women of childbearing age improved iron nutrition and reduced IDA.[31] The causes of anemia during pregnancy in developing countries are multifactorial; these include micronutrient deficiencies of iron, folate, and vitamins A and B12 and anemia due to parasitic infections such as malaria and hookworm or chronic infections like TB and HIV.[32]

In a study conducted comparing iron and folic acid supplementation with no treatment or placebo it was recommended that iron and folic acid supplementation was linked to a reduction in anemia by 73%.[33] Additionally, in a study examining the impact of vitamin and mineral supplement, concluded that increased supplementation attributes to the increase in parameters like Hb and MCV.[34] In a meta-analysis, it was found that iron supplementation in anemia during pregnancy results in an increased Hb and ferritin levels.[35]

Subgroup analysis performed in this study according to dietary habits (vegetarian and non-vegetarian patients) showed statistically significant improvement in the levels of Hb, s. ferritin and MCV at 4 and 12 weeks from baseline. These subgroups were further stratified based on severity of anemia as mild anemia and moderate-severe anemia to observe variation of hemoglobin from baseline to 12 weeks of treatment which also mirrored findings of original cohort.

Our study demonstrates that the MMFP is sufficient, not only for efficacy in the second trimester in pregnant women but also is as good, if not better than conventional options, on the basis of literature reports. It totally disproved the main criticism of oral iron, which was that it had unfavorable side effects that prevented people from taking it as prescribed.

Our study's robustness lies in its extensive population size and the representation of pregnant women from various geographical locations. However, it is essential to acknowledge some limitations of our study. Firstly, the study was conducted for a shorter duration of time. Secondly, the study lacked the comparative nature with the placebo or similar active substance. Future well-designed controlled studies with long-term follow-up is required to understand the drug's safety and effectiveness over longer periods for their relative effectiveness in clinical practice.

CONCLUSION

The administration of Micronized Microencapsulated Ferric Pyrophosphate (MMFP) Supplementation resulted

in significant improvements in Hb levels, MCV levels, and S. Ferritin levels after both 4 weeks and 12 weeks. Importantly, these positive outcomes were achieved without the occurrence of any major adverse events. This underlines the effectiveness and safety of the study drug in addressing anemia among pregnant Indian women, which may further contribute to improved maternal and neonatal health outcomes.

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Conflict of interest: Dr. Prajakta Nidhankar, Ashutosh Kakkad, Narendra Chouksey and Dr. Krishnaprasad Korukonda are paid employee of Torrent pharmaceuticals
Ethical approval: The study was approved by the Sangini Hospital Ethics Committee (EC Registration number: IORG0007258)

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