Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Oral Ferric Pyrophosphate Formulation Utilization Surveillance Study to Assess Clinical Impact on Hemoglobin levels: Maxiim-Hemoglobin Study

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Abstract

After hemorrhage, anemia is the most common cause of maternal mortality and leading cause of maternal morbidity in India. The prevalence rates of anemia in pregnancy in India is estimated to be >50%. Iron deficiency anemia (IDA) is the most common type of anemia in pregnancy in India, which I can be as high as 80–90%.

Aims and Objectives: The present survey was initiated in pursuit of analyzing the effectiveness and safety of oral ferric pyrophosphate (FPP) formulation given once to twice daily for treatment and prophylaxis of IDA in pregnancy.

Materials and Methods: This was a questionnaire-based retrospective survey. Each gynecologist was given this survey booklet containing questionnaire. Clinical response was assessed by measuring rise in mean hemoglobin (Hb) levels at baseline, week 4, and week 8, after giving oral FPP formulation for 8 weeks.

Results: A total of 60 gynecologists participated and completed the survey, which involved 1073 pregnant subjects and patients suffering from IDA (864 patients, i.e., 80%). Mean Hb level at baseline was found to be 8.98 g/dl, 10.03 at week 4, and 10.99 at week 8. Thus, rise of Hb from baseline to week 8 was found to be 2.01 g/dl. Adverse events were reported in only 10 patients (<0.09%), none requiring discontinuation of therapy. 98% of the participants agreed good acceptability of oral FPP formulation.

Conclusion: Findings of the present survey suggests that oral FPP formulation therapy can serve as potent choice of therapy for IDA in pregnancy, both therapeutically and prophylactically.

Key words: Ferric pyrophosphate, Gynecologists, Hemoglobin, Iron deficiency anemia, Oral ferric pyrophosphate formulation, Pregnancy, Survey

INTRODUCTION

Pregnancy is a unique experience in every women life. Unfortunately, pregnancy is engrossed with significant morbidity and mortality, especially in developing countries like India.[1] Anemia is one of the most common cause of maternal mortality and leading cause of maternal morbidity in India.[2] The estimated number of sufferers from anemia in pregnancy is around 2 million, on a global scale.[1] The prevalence rates of anemia in pregnancy in India are estimated to be >50%, as per the World Health Organization (WHO) and National Family Health Survey.[3,4]

Anemia in pregnancy is defined statistically as condition, characterized by decreased hemoglobin (Hb) which is less than two standard deviations of the median range of matched age, trimester of pregnancy in normal subjects.[5] Plethora of standard health and research organizations such as the WHO, Centre for Disease Control (CDC), and Indian Council of Medical Research (ICMR) has defined anemia in pregnancy as Hb <11 g/dl in all the three trimesters, except for CDC which has laid down cutoff for the second trimester as <10.5 and <11 for the rest and hematocrit <33%.[5-8] ICMR has further categorized anemia in pregnancy into mild, moderate, and severe categories with Hb 10–10.9, 7–10, and <7, respectively.[6]

Access this article online

www.ijss-sn.com

Month of Submission : 11-2018
Month of Peer Review : 12-2018
Month of Acceptance : 12-2018
Month of Publishing : 01-2019

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Iron deficiency anemia (IDA) is the most common type of anemia in pregnancy in India, which is estimated to be as high as 80–90%.[9-11] Pathophysiologically, IDA is characterized by depletion of iron stores in the body, which ultimately results in an absolute deficiency of iron in the body and tissues are deprived of iron. Biochemical parameters suggestive of IDA are derangements in serum levels of ferritin, erythrocyte protoporphyrin, transferrin saturation, and total iron-binding capacity.[12] IDA evolves through three stages:

- Stage 1 - reduction of iron stores
- Stage 2 - iron-deficient erythropoiesis
- Stage 3 - absolute depletion of iron stores/overt iron deficiency/IDA.[13,14]

The most common cause of IDA in pregnancy is nutritional deficiency, i.e., poor intake of iron in diet.[15] Although IDA is slow to develop in non-pregnant population, it develops faster in pregnancy since physiological hemodilution is usually present in pregnancy.[12] There are numerous evidences in literature that suggest linkage of IDA in pregnancy and increased rates of spontaneous abortion, prematurity, low birth weight, fetal growth retardation, and even fetal death in very severe cases.[16,17] It was found in a clinical study that perinatal mortality was increased 3 times when maternal Hb was <8 g/dl as compared to Hb level of 11 g/dl.[18] Therefore, numerous guidelines advocate iron supplementation in pregnancy and this has become a routine part clinical care of pregnant women, irrespective of the presence of IDA.[6,7]

Iron supplementation in pregnancy can be given orally and parenterally, but oral supplements are preferred over the later, although parenteral being more efficacious. This is due to better feasibility and patient compliance.[19,20] Plethora of oral iron salts is available for this purpose, which includes ferrous sulfate, ferrous fumarate, and ferric citrate.[21] Globally, ferrous sulfate is most commonly prescribed iron salt for prophylaxis and treatment of IDA in pregnancy.[22,23] Although efficacy of these conventional iron salts is well established, the gastrointestinal intolerance caused by them offsets their use. These adverse effects are comprised diarrhea, dyspepsia, nausea, vomiting, constipation, abdominal pain, and blackish discoloration of stools. Moreover, absorption of conventional iron salts is hampered by the presence of phytates, calcium, and tannins in the food by converting absorbable ferrous form to comparatively less absorbable ferric form through oxidation reaction.[24] In pursuit of overcoming these shortcomings, newer iron salts such as ferrous ascorbate, iron polymaltose complex, and ferric pyrophosphate were introduced,[25] of which ferric pyrophosphate is the recent one and has shown promising results in clinical studies.[26]

The present survey was initiated in pursuit of analyzing the effectiveness and safety of oral ferric pyrophosphate (FPP) formulation given once to twice daily in the treatment and prophylaxis of IDA in pregnancy. To the best of our knowledge, the present survey is the first of its kind to analyze the effectiveness and safety of FPP alone in pregnant women with large sample size.

MATERIALS AND METHODS

The present survey was conducted using a prevalidated questionnaire, which was structured to analyze the effectiveness and safety of FPP in the treatment and prophylaxis of IDA in pregnancy. Survey was of 10-month duration, from January 2018 to October 2018. Gynecologists involved in the treatment and prophylaxis of IDA in pregnancy were identified through "Scrip" intelligence database. Among these, 60 gynecologists were selected across four directional zones of the country to ensure uniform sampling. These gynecologists were selected on the grounds of maintaining complete patient records.

Each gynecologist was given the survey questionnaire in the form of survey booklet. At the end of survey period, these questionnaires booklets were analyzed, to assess the effectiveness and safety of oral FPP formulation in IDA of pregnancy.

Effectiveness Evaluation

Effectiveness evaluation was done by analyzing Hb levels at baseline, week 4, and week 8. Mean Hb was calculated for each visit and rise of Hb from baseline to week 4, week 4–8, and baseline to week 8 was calculated after giving FPP for 8 weeks.

Safety Evaluation

All the adverse events (AEs), mainly gastrointestinal intolerance, were analyzed for severity and their association with FPP, at each visit. The AE which occurred numerously in same patient was counted as one AE only.

Apart from this, patient acceptability of oral FPP was measured on a scale, where responses ranged from strongly agree to strongly disagree.

Statistical Analysis

Hb values were expressed as mean. Student's *t*-test was applied to compare these mean values at baseline, week 4, and week 8. $P < 0.05$ was set as cutoff for statistical significance [Figure 1].

RESULTS

Of a total of 1300 pregnant participants, 1073 were finally included for analysis, of which 864 (80%) had IDA. Mean

age of study participants was 28.6 years. Mean height and weight were 155.9 cm and 56 kg, respectively [Table 1].

The mean Hb at baseline was found to be 8.98 g/dl. This rose to 10.03 at the second visit/week 4 and 10.99 g/dl at the third visit, i.e., week 8 [Table 2].

On analyzing the rise in mean Hb, it was found that there was a rise of 1.05 g/dl in week 4 as compared to baseline, 0.96 in week 8 as compared to week 8, and 2.01 in week 8 as compared to baseline [Table 3 and Figure 2].

Only 10 participants of 1073 (<0.09%) reported AEs, which were mild and transient. None of the study participants discontinued FPP therapy. Bloating and constipation were most commonly reported, only in two patients each. Other AEs reported were mild belching, nausea, vomiting, and abdominal pain in one patient each [Table 4].

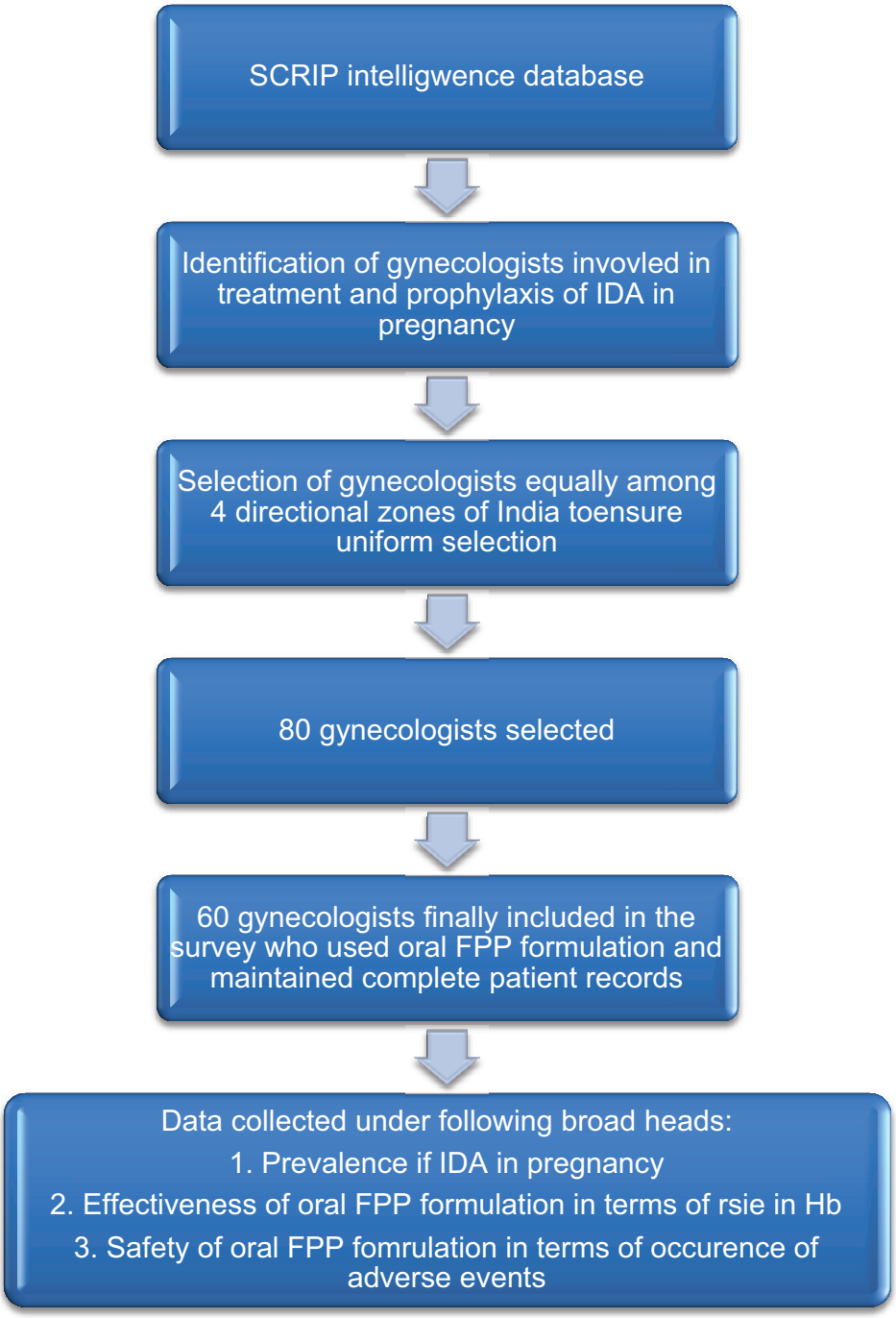

Figure 1: Methodology embraced for the present survey

On analyzing patient acceptability of oral FPP formulation, it was found that majority of the patients agreed that FPP showed good effectiveness in terms of the amelioration of clinical symptoms and tolerability; 1059 (99%) participants agreeing to this effect and only 16 participants disagreeing [Figure 3].

Table 1: General details of the study participants

Total number of participants	1073
IDA	864
Mean age	28.68
Mean height	155.93
Mean weight	56

IDA: Iron deficiency anemia

Table 2: Mean Hb at baseline and weeks 4 and 8

Visit	Mean Hb (g/dl)
Baseline	8.98
Week 4	10.03
Week 8	10.99

Hb: Hemoglobin

Table 3: Mean Hb at various time points during survey period

Time period	Rise in mean Hb	*P*-value
Baseline to week 4	1.05	<0.05
Week 4–8	0.96	<0.05
Baseline to week	2.01	<0.001

Hb: Hemoglobin

Table 4: AEs reported by study participants

Adverse event	Number of patient
Mild belching	1
Bloating	2
Constipation	2
Gastritis and nausea	1
Vomiting	1
Pain abdomen	1
Nausea	1
Had severe acidity, but after starting with antacid, compliance achieved	1

AEs: Adverse events

DISCUSSION

Anemia in pregnancy is one of the major contributors to maternal morbidity and mortality in India.[27] IDA is the most common anemia encountered in pregnancy.[9] IDA leads to plethora of maternal and fetal complications during and after pregnancy.[28,29] Iron supplements, preferably oral formulations, are used therapeutically and prophylactically for IDA in pregnancy. These iron supplements help to increase Hb levels in blood.[30]

In the present survey, IDA was found in 80% of the pregnant participants. Similar prevalence rate is reported in one study conducted by Narayanan and Bhargava *et al.*[31] There are numerous reasons for such high prevalence of IDA in pregnancy. Lack of optimal nutritional care in pregnancy is still a major issue in India.[32] Furthermore, poor patient compliance is somehow responsible for such high prevalence. This is due to the fact that, even if iron supplements are effective in ameliorating IDA in pregnancy, be it therapeutic or prophylactic use, their gastrointestinal adverse effects offset regular use by therapeutically or prophylactically. All these lead to poor patient compliance which ultimately leads to suboptimal protection against IDA in pregnancy.[33]

One of the most important parameters to assess the efficacy of iron supplements is rise in Hb. Rise in mean Hb in the present survey was 2.01 g/dl at the end of survey period. Singhal *et al.* in their clinical study compared efficacy and safety of various iron salts such as ferrous ascorbate, ferrous fumarate, and ferrous bisglycinate in pregnant patients suffering from IDA. They measured mean Hb at day 30 and day 60 and compared these to baseline values. Maximum rise in Hb was seen with ferrous ascorbate, which was 0.63 g/dl at day 30 and 1.13 g/dl at

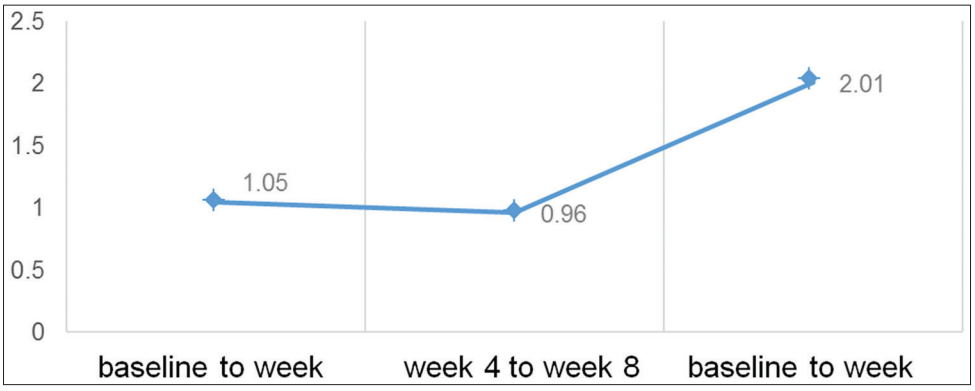

Figure 2: Rise in mean hemoglobin at various time points during the survey period

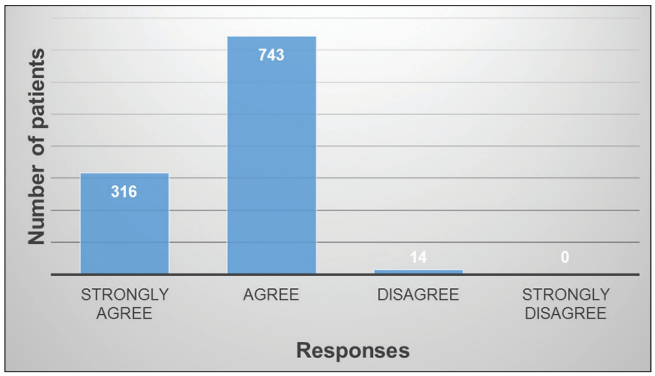

Figure 3: Patient acceptability response to oral ferric pyrophosphate

day 60.[25] Numerous studies have found good efficacy of various iron salts in increasing Hb and the average Hb rise reported with these salts at day 60 was found to be around 1.23 g/dl.[25,26] In a randomized, double-blinded clinical trial by Lagana *et al.*, efficacy and safety of FPP was analyzed in pregnant patients suffering from IDA. The rise in Hb obtained with the regular intake of FPP was somewhat less than that obtained with the present study.[26] Thus, rise in Hb obtained with oral FPP formulation in the present survey is way higher than other iron salts, as seen in various clinical studies.

This high rise in Hb with oral FPP formulation in the present survey might be attributed to the combination with other components as well. Folic acid and methylcobalamin in this formulation act as erythropoietic stimulants since they are involved in purine and thymidylate synthesis and thus help in maturation in erythroblasts.[34,35] Deficiency in these components results in apoptosis of erythroblasts and ultimately results in anemia due to inefficient erythropoiesis.[36] Vitamin C present in the oral FPP formulation helps in increasing the absorption of iron form the gut and it does so, by dual action - first, it curbs the materialization of unabsorbed iron compounds, and second, it increases the formation of ferrous form by reduction of ferric form, the earlier one being the preferred form for mucosal uptake in the intestinal cells.[37]

Reduced bioavailability is another major issue surrounding the use of oral iron supplements.[25] Moreover, Indian diet is rich in inhibitors of iron absorption in the gut (phytates, tannins, and calcium).[24] They inhibit the absorption of iron by converting ferrous to unabsorbable ferric form.[24] Moreover, this ferrous form participates in the Fenton reaction and leads to the formation of reactive free radicals, which ultimately results in oxidative damage.[38]

Various manufacturing technologies have been employed in pursuit of increasing the bioavailability of oral iron formulations. Of these, micronization, nanonization, and encapsulation of iron with liposomes have fetched significantly better bioavailability results.[38,39] It is well-known concept that smaller the particle size of drug, better is its absorption. Same principle is applied in nanonization technology, in which particle size of iron is reduced to nanoparticle size (10^{-9}) to aid its absorption in the gut, and was found to increase the bioavailability significantly in a randomized, double-blinded clinical trial on FPP.[39]

Similarly, liposomal encapsulation of iron offers some unique advantages over conventional iron formulations. Liposome-encapsulated iron follows different absorption fate as compared to conventional iron.[38] Since the structure and chemical composition of liposomes is almost similar to that of cell membrane, which allows liposome encapsulated iron to fuse with the cell membrane and enabling direct release of iron into the interior of the cells. It, thus, bypasses the usual protein-mediated iron transport which limits the absorption of iron. Thus, liposome encapsulation increases the absorption of iron which is reflected in a significant increase in Hb, hematocrit, erythrocyte iron, serum iron, and ferritin levels, as found in one study.[38]

Gastrointestinal intolerance-related adverse effects are one of the major setbacks to regular use of conventional iron formulations, which reduce the patient compliance.[30] These AEs were found in <0.09% of the total study participants in the present survey and that too were mild and transient, with none of the patients requiring discontinuation of FPP therapy. These findings are in corroboration with that of clinical trial done by Lagana *et al.* on micronized FPP in pregnant women with IDA.[26] Thus, findings of the present survey suggest that oral FPP formulation with nanonization and liposome encapsulation is effective and safe for treating IDA in pregnancy.

The current survey had certain limitations. First, given the design of the survey chances of bias cannot be ruled out. Second, head-to-head comparison with other iron salts should have been done. Finally, other indicators of IDA should have been evaluated, such as hematocrit, serum ferritin, and serum total iron binding capacity.

CONCLUSION

Oral FPP formulation therapy can serve as potent choice of therapy for IDA in pregnancy, both therapeutically and prophylactically. The oral FPP formulation in the present survey offered numerous advantages such as nanonization and liposomal encapsulation technologies to increase the absorption of FPP and presence of other erythropoietic components such as folic acid and methylcobalamin. Furthermore, the gastrointestinal AEs were very less, thus

making it an attractive choice of the treatment for IDA in pregnancy.

ACKNOWLEDGMENT

Authors would like to thank all the gynecologists who participated in the survey. Authors would like to thank Dr. K. Krishna Prasad and Dr. Payel Bhattacharjee for collating and analyzing data.

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How to cite this article: Parkar V, Mahajan H, Dhoot D, Barkate H. Oral Ferric Pyrophosphate Formulation Utilization Surveillance Study to Assess Clinical Impact on Hemoglobin Levels: MAXIIM-Hemoglobin Study. Int J Sci Stud 2019;6(10):49-54.

Source of Support: Nil, **Conflict of Interest:** None declared.