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Efficacy and safety of ferrous asparto glycinate in the management of iron deficiency anaemia in pregnant women

S. P. Kamdi & P. J. Palkar

Department of Medical Services and Clinical Research, Akumentis Healthcare Ltd, Kasarvadavali, Near Hyper City, Maharashtra, India

The aim of the present investigation was to compare the efficacy and safety of oral ferrous asparto glycinate and ferrous ascorbate in the pregnant women with iron deficiency anaemia (IDA). We performed a double blind, prospective, randomised, multicentric, parallel group comparative clinical study at three different centres in India. A total of 73 pregnant women at 12–26 weeks' gestation were divided into two arms. While one group received ferrous ascorbate, another group was administered with ferrous asparto glycinate for a period of 28 days. The mean rise in haemoglobin and ferritin levels on day 14 and 28 was evaluated. At both time points, significantly higher levels of haemoglobin and ferritin were noticed with ferrous asparto glycinate treatment as compared with ferrous ascorbate. Our results showed that ferrous asparto glycinate is an effective iron–amino acid chelate in the management of IDA in pregnant women as compared with ferrous ascorbate. Nevertheless, additional large scale prospective, randomised trials are warranted to confirm the findings of the present efficacy trial, and also to find out the anaemia eradication rate.

Keywords: General gynaecology, general obstetrics, maternal medicine

Introduction

Iron deficiency anaemia (IDA) is the most common nutritional disorder worldwide, which is accountable for approximately one-half of anaemia cases (Short and Domagalski 2013). According to the World Health Organization (WHO), IDA with haemoglobin levels ≤ 11 g/dl, is one of the world's leading causes of disability (UNICEF/UNU/WHO 2001). In India, the prevalence of IDA during pregnancy is estimated to be more than 80% (Kalaivani 2009). IDA is the devastating blood condition for pregnant women and their offspring. It is considered as the major underlying cause for low birth weight ($< 2{,}500$ g), premature births (< 37 weeks' gestation), fetal loss or abortion, prenatal deaths, stillbirths and neonatal deaths within 6 months (Allen 2000; Ezzati et al. 2002; Akhter et al. 2010). In late pregnancy, IDA attributes to the poor fetal iron stores (Rao and Georgieff 2007), which irreversibly alters the iron and neurotransmitters levels in the brain during fetal and postnatal life (Agarwal 2001; Kapur et al. 2002). In spite of several steps being undertaken to combat IDA during pregnancy, it continues to remain a most important public health issue. This suggests that the measures so far taken have largely been inadequate. Since no food in itself contains enough iron, oral iron supplementation has been recommended to treat IDA.

Since folate deficiency is implicated in the aetiology of anaemia and pregnancy complications, folic acid is used as an integral component of the iron preparations (Greenberg et al. 2011). In fact, WHO recommends a daily supplement of oral iron and folic acid as a part of the antenatal care to reduce the risk of maternal anaemia and low birth weight (WHO 2012). It is, however, noteworthy that about 40–60% of the population has genetic polymorphisms that impair the conversion of supplemental folic acid to its active form, L-methylfolate (Greenberg and Bell 2011; Miller 2008). The Indian population is also unable to convert conventional folic acid into L-methylfolate due to methylenetetrahydrofolate reductase (MTHFR) polymorphism (Mukherjee et al. 2002). In addition to this, cyanocobalamin deficiency is highly prevalent in India (Bhate et al. 2008). Methylcobalamin, an active form of cyanocobalamin, is normally supplemented in multivitamin healthcare products, with a view to augment the erythrocytes maturation. In spite of this information, appropriate measures have not been yet taken to correct the deficiencies of L -methylfolate and cyanocobalamin.

Among the various oral iron supplements available on the market, ferrous ascorbate showed high iron bioavailability, and therefore emerged as one of the highly prescribed iron preparations. Incorporation of ascorbic acid helps to convert ferric into easily absorbable ferrous form in the duodenum (Plug et al. 1984). Several studies have reported the efficacy of ferrous ascorbate in the treatment of anaemia in adults (Agarwal and Rathi 2006), children (Ganguly et al. 2012) and pregnant women (Fadnavis et al. 2011). Despite good efficacy, incomplete absorption and gastrointestinal (GI) consequences raise concern during ferrous ascorbate therapy. While only 40% of the ferrous can be absorbed (Mendoza et al. 1998), the remaining 60% of the unabsorbed iron may increase free radicals to a level that could cause mucosal cell damage, leading to serious GI adverse effects (Lund et al. 1999). Indeed, in $> 8\%$ of cases, the incidences of GI intolerability are reported with ferrous ascorbate administration (Fadnavis et al. 2011). In general, none of the iron preparations in the market is free of GI side-effects.

It is reported that the intestinal iron absorption from iron-amino acid chelate is significantly higher compared with inorganic iron salts (Ashmead 2001). Asparagine and glycine not only emerged as the best absorbable amino acids, but are also

Correspondence: S. P. Kamdi, Department of Medical Services and Clinical Research, Akumentis Healthcare Ltd, 504, Fifth floor, G. Corp Tech Park, Kasarvadavali, Near Hyper City, Ghodbunder Road, Thane (W) 400 615, Maharashtra, India. E-mail: sandeshk@myakumentis.com

known to enhance the transport of iron from the duodenum (Christensen et al. 1984). In fact, absorption of iron-asparagine or iron-glycine chelate is more than double that of iron-ascorbate salt (Christensen et al. 1984). Therefore, we assumed that ferrous asparto glycinate (FAG; an iron-amino acid chelate) may exhibit better GI absorption rate of iron than ferrous ascorbate and may produce minimal GI consequences. However, the direct comparison demonstrating the efficacy of ferrous ascorbate and FAG is not yet assessed. With this background in mind, we decided to evaluate and compare the efficacy and safety of two marketed formulations of iron (FAG vs ferrous ascorbate) in pregnant women with IDA.

Materials and methods

Study approvals

Before beginning this study, the clinical protocol, case record forms, etc. were reviewed and approved by the Independent Ethics Committee, SPANDAN, Gujarat state, India. Written permission for carrying out the study was also obtained from the institutional authority at each study centre.

Study site for the intervention study

The intervention study was carried out in the three different centres in India: (1) Bharati Hospital and Research Centre, Pune; (2) Brinda Women's Hospital, Vastrapur Lake, Ahmedabad; and (3) Shardaben Chimanlal Lalbhai General Hospital, Sarsapur, Ahmedabad. The first centre is located in Maharashtra State and other two centres are located in Gujarat State.

Study design

The investigation was a double blind, prospective, randomised, multicentric, parallel grouped comparative clinical study in pregnant women with IDA.

Sample size

The sample size was 30 women at 12–26 weeks' gestation enrolled in each group. The sample size was decided based on previous studies of iron preparations in pregnant (Szarfarc et al. 2001) and postpartum women (Giannoulis et al. 2009).

Screening

The details and potential risks and benefits of the investigation were explained to the woman and family members, and written informed consent was obtained voluntarily before entering into the study. Body weight, haemoglobin and ferritin were measured in 73 women. The criteria for inclusion were: age 18–30 years and body weight 40–55 kg. For haemoglobin, serum levels ≥ 11 g/dl were defined as the safe range, while levels < 11 g/dl were considered as a deficiency (Ma et al. 2004; Zimmermann et al. 2007). For ferritin, serum concentration ≥ 12 µg/l was considered the safe range and levels < 12 µg/l were classified as a deficiency (Goddard et al. 2000; Ma et al. 2004). The patients who willingly complied with the study schedules and procedures were included in the study.

A total of 67 women were eligible for inclusion in the intervention study. Any woman who had anaemia other than IDA, gastric ulcer or erosions, inflammatory bowel diseases, type 1 diabetes mellitus, malignancy, hypersensitivity to iron preparations, received another investigational agent within 4 weeks prior to inclusion, severe concurrent cardiovascular, renal or hepatic illness and any other condition that in the opinion of the investigator did not justify the inclusion of patient, was excluded from the study.

Random assignment of study participants

The women who met the inclusion criteria were stratified according to age and body weight, ensuring that an even number existed in each of the age/strata. At the beginning of the study, each woman was assigned to one of two treatment groups, A or B, by mentioning this on their case report card. Each woman in group A was matched as closely as possible to a woman in group B in terms of age and haemoglobin levels. Summary of the characteristics of the two groups is given in Table I.

The study group randomisation and the process of coding the treatment were completed by a scientist not involved in the study, to ensure the double-blinding of the trial. The codes were kept secure, and the decoding was completed after the analysis of data.

Interventions

The treatments consisted of identically appearing tablets labelled A and B that contained FAG equivalent to 100 mg of elemental iron + 300 µg of L-methylfolate + 500 µg of methylcobalamin (Roseus®; Akumentis Healthcare Ltd., Mumbai, India) and ferrous ascorbate equivalent to 100 mg of elemental iron + 1.1 mg of folic acid (Orofer-XT®; Emcure Pharmaceuticals Ltd, Pune, India), respectively. The treatments were administered to each participant daily as a single dose for a duration of 28 days (Pineda and Ashmead 2001; Al et al. 2005).

Data collection

The study period was from 12 March to 15 June 2012. The baseline and final measurements were done for body weight and for biochemical estimation of haemoglobin and ferritin. The weight of the women was measured by using personal weighing scales of 100 g accuracy (seca 813).

Biochemical analysis

Each patient was called at day 14 and day 28 after their first visit for the biochemical analysis of haemoglobin and ferritin. During each visit, the investigator performed the clinical examination of the woman, after which a trained assistant collected 2 ml of blood samples from a dorsal vein in heparinised evacuated tubes for the determination of haemoglobin and ferritin; one sample before iron treatment (baseline), another on day 14 and then day 28. Thus, each woman served as her own control.

Haemoglobin levels were monitored by using the Sysmex KX-21 cell counter and ferritin contents were measured using chemiluminescence immunoassay (CLIA). The study lasted for 28 days. At the end of each visit, the change in haemoglobin and ferritin levels were set as the primary outcome of the study. The secondary outcomes included the incidence of any adverse event. Hence, during the study, all participants were closely evaluated to notice GI or any other type of intolerance to either of the iron treatments.

Table I. Baseline demographic data of enrolled eligible subjects.

Group	A	B
Type of treatment	FAG	Ferrous ascorbate
Participants (*n*)	31	30
Age (years)	23.80 ± 3.90	23.63 ± 4.24
Body weight (kg)	44.54 ± 3.54	44.43 ± 3.71
Initial haemoglobin (g/dl)	8.38 ± 1.41	8.27 ± 1.20
Initial ferritin (ng/ml)	9.86 ± 3.30	10.56 ± 5.53

Data presented as mean ± SD. FAG, ferrous asparto glycinate. Respondents included subjects with a valid plasma ferritin and haemoglobin levels and the differences between FAG and ferrous ascorbate group were determined by using a *t*-test. Significance was defined as $p < 0.05$.

Statistical analysis

Data were entered into Microsoft Excel 2007 (Microsoft Corporation) and analysed with SPSS for windows (version 16.0) to assess the impact of intervention on haemoglobin and ferritin status of women. All the statistically analysed data are presented as mean ± standard deviation (SD) and differences between baseline and post-intervention (at day 14 and day 28) haemoglobin and ferritin values within study groups were tested by means of the paired *t*-tests. The difference in mean haemoglobin and ferritin between two groups at both day 14 and day 28 were tested by means of the unpaired *t*-tests. Differences were considered significant at $p < 0.05$.

Results

Out of the 73 women screened, six were excluded as their haemoglobin levels were > 11 g/dl. While a total of 67 women were thus enrolled in the study, six were randomly excluded in order to have an even number in age stratum. Therefore, 61 participants were randomly divided in two arms, i.e. group A with 31 patients (received FAG) and group B with 30 patients (received ferrous ascorbate). On day 14 of the trial, 27 patients came for the follow-up visit and four patients lost to follow-up from group A. From group B, 25 patients came for the follow-up visit and one patient was lost to follow-up. On day 28 of the study, 26 patients came for the follow-up visit and one patient was lost to follow-up from group A. From group B, 24 patients came for the follow-up visit and one patient was lost to follow-up. The reasons for lost to follow-up in each visit was that patients were not present in town or due to the migration of their families. Figure 1 shows the details of the patients at each stage of the study.

Impact on haemoglobin and ferritin

Administration of FAG significantly increased the blood haemoglobin levels on day 14 ($t = 8.691$, df = 26, $p < 0.0001$) and day 28 ($t = 7.762$, df = 26, $p < 0.0001$) compared with that on day 0. However, ferrous ascorbate treatment raised the haemoglobin to significant levels only on day 28 ($t = 7.488$, df = 24, $p < 0.0001$). Interestingly, when compared with that of ferrous ascorbate treatment, administration of FAG caused a significant increase in

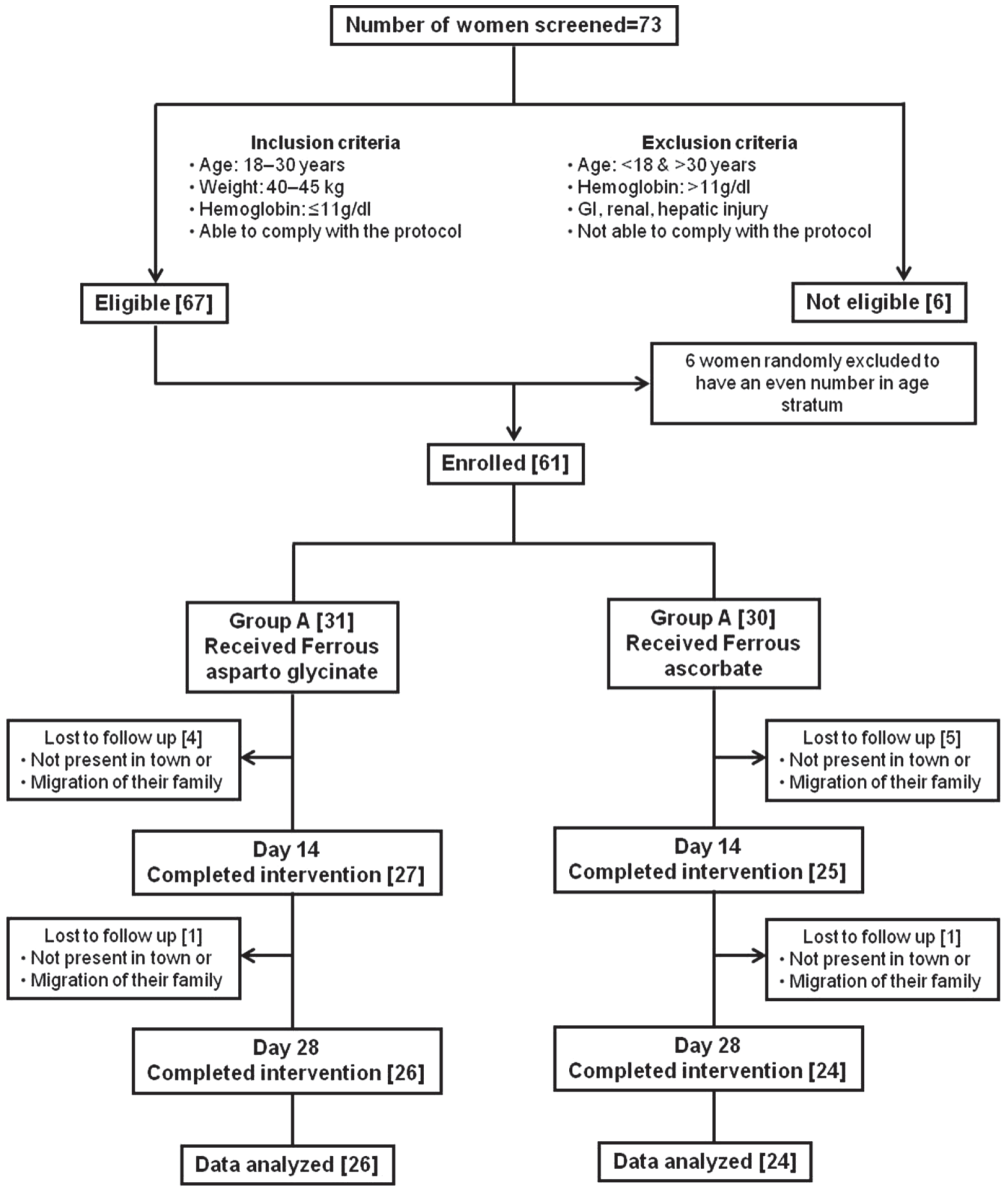

Figure 1. Flowchart showing details at each stage of the study.

Table II. Effect of 14 and 28 day's treatments with FAG and ferrous ascorbate on haemoglobin levels (g/dl).

Day	Group	*n*	Basal	Post-treatment	Change
14	A (FAG)	27	8.38 ± 1.41	9.07 ± 1.26	0.69 ± 0.15*
	B (ferrous ascorbate)	25	8.27 ± 1.20	8.44 ± 1.30	0.17 ± 0.10
28	A (FAG)	26	8.38 ± 1.41	10.81 ± 2.02	2.43 ± 0.61*,†
	B (ferrous ascorbate)	24	8.27 ± 1.20	9.48 ± 1.68	1.21 ± 0.48*

Data presented as mean ± SD. FAG, ferrous asparto glycinate. Respondents included subjects with valid plasma haemoglobin levels and the differences between FAG and ferrous ascorbate group were determined by using a *t*-test. Significance was defined as $p < 0.05$. Haemoglobin values with superscript within a row within both FAG and ferrous ascorbate group on day 14 and day 28 vs respective basal levels are significantly different (*$p < 0.0001$) by paired *t*-test. Haemoglobin values with superscript in FAG vs ferrous ascorbate group on day 28 are significantly different (†$p < 0.01$) by unpaired *t*-test.

the haemoglobin levels on day 28 ($t = 2.677$, df = 50, $p < 0.01$) (Table II).

Changes observed in the haemoglobin levels were entirely reflected on ferritin data. Administration of FAG significantly increased the blood ferritin levels on day 14 ($t = 8.691$, df = 26, $p < 0.0001$) and day 28 ($t = 7.762$, df = 26, $p < 0.0001$) compared with that on day 0. Similarly, ferrous ascorbate treatment raised the ferritin to significant levels on day 14 ($t = 8.691$, df = 26, $p < 0.0001$) and day 28 ($t = 7.488$, df = 24, $p < 0.0001$). However, when compared with that of ferrous ascorbate treatment, administration of FAG caused a significant increase in the ferritin levels on day 14 ($t = 8.691$, df = 26, $p < 0.0001$) and day 28 ($t = 2.677$, df = 50, $p < 0.01$) (Table III).

During the study, out of 24 patients treated with ferrous ascorbate, three participants (~12%) showed GI disturbances, such as mild diarrhoea, nausea/vomiting or constipation. On the other hand, out of 26 women, only one patient (~3%) reported the sign of mild constipation during FAG administration.

Discussion

Anaemia is one of the common blood disorders that may occur during pregnancy. With increasing gestational age, particularly in 12–26 weeks of pregnancy, there is a significant depletion in haemoglobin and ferritin contents (Xiao et al. 2002; Asif et al. 2007). Therefore, most of the women need iron supplementation selectively during pregnancy, with a view to maintaining serum ferritin and haemoglobin levels within the normal ranges (Meier et al. 2003). The present investigation, for the first time, put forward the effectiveness of FAG in the management of IDA in pregnant women. Following 14 and 28 days of treatment with FAG with additional L-methylfolate and methylcobalamin supplements, haemoglobin levels and body iron reserves, as measured by plasma ferritin levels, were significantly increased. The results also indicate a superiority of FAG over ferrous ascorbate in terms of efficiency in the management of IDA. However, 28 days of FAG treatment did not increase haemoglobin levels > 11 g/dl. Therefore, further studies are warranted for the extended 6 months' treatment of the FAG with a view to observe the number of patients turned non-anaemic. Interestingly, FAG administration triggered no GI complication akin to ferrous ascorbate treatment. It seems that significantly more quantity of iron was absorbed from the FAG, an iron-amino acid chelate than from ferrous ascorbate, which, in turn, might contribute for the higher bioavailability for the FAG chelate.

Several studies reported the efficacy of ferrous ascorbate in the treatment of anaemia in adults (Agarwal and Rathi 2006), children (Ganguly et al. 2012) and pregnant women (Fadnavis et al. 2011). After dissociation of ferrous ascorbate in the duodenum, ascorbic acid helps to convert ferric to an easily absorbable ferrous form (Plug et al. 1984). However, we may note that the absorption of iron into intestinal mucosal tissue from iron-amino acid chelate is significantly higher compared with inorganic iron salts (Ashmead 2001). Asparagine and glycine have not only emerged as the best absorbable amino acids, but also are known to enhance the transport of iron from duodenum (Christensen et al. 1984). Christensen et al. (1984) proposed that, preparations containing asparagine and/or glycine with iron may be sufficient to increase iron absorption when compared with other iron complexes. Those investigators noticed 345% iron absorption for asparagine and 309% for glycine compared with that of 54.5% for ascorbic acid. Mendoza and his co-workers (1998) reported only 40% of the ferrous absorption from ferrous ascorbate salt. In support of this, the results of the present study showed that following 14 days of FAG treatment, haemoglobin increased to significant levels, unlike with ferrous ascorbate. Moreover, ferritin contents also rose significantly by FAG treatment within 14 days compared with that of respective ferrous ascorbate administration. On day 28, the increased haemoglobin and ferritin levels following FAG treatment were noticeably higher than that with ferrous ascorbate. Our results are in agreement with earlier studies showing increased haemoglobin and ferritin levels at day 14 and 28 following administration of iron preparations (Pineda and Ashmead 2001; Al et al. 2005). Viewed collectively, it seems that incorporation of asparagine and glycine might enhance absorption and eventually bioavailability of iron from FAG. This in turn may increase the haemoglobin and ferritin levels.

The aforementioned data emphasise 40% absorption of iron from ferrous ascorbate salt. Eventually, the remaining 60% of the unabsorbed iron may increase free radicals to a level that could cause mucosal cell damage, leading to serious GI side-effects (Lund et al. 1999). Indeed, in > 8% of cases, the incidences of GI intolerability are reported with ferrous ascorbate iron salt administration (Fadnavis et al. 2011). In the present study also, ~12% of the patients treated with ferrous ascorbate showed GI complications, such as mild diarrhoea, nausea/vomiting or constipation. Interestingly, only ~3% of patients reported mild constipation with FAG therapy. Therefore, we suggest that a significantly higher absorption rate of iron from FAG might be attributed to the minimum GI side-effects.

Folic acid and cyanocobalamin are two important vitamins required for the maturation of erythrocytes along with iron (Greenberg et al. 2011). Therefore, these agents are widely used in the management of anaemia along with iron preparations. Study

Table III. Effect of 14 and 28 day's treatments with FAG and ferrous ascorbate on ferritin levels (ng/ml).

Day	Group	*n*	Basal	Post-treatment	Change
14	A (FAG)	27	9.86 ± 3.30	26.70 ± 6.89	16.84 ± 3.59*,†
	B (ferrous ascorbate)	25	10.56 ± 5.53	18.21 ± 8.28	7.65 ± 2.75*
28	A (FAG)	26	9.86 ± 3.30	46.12 ± 10.39	36.26 ± 7.09*,†
	B (ferrous ascorbate)	24	10.56 ± 5.53	36.35 ± 15.51	25.79 ± 9.98*

Data presented as mean ± SD. FAG, ferrous asparto glycinate. Respondents included subjects with valid plasma ferritin levels and the differences between FAG and ferrous ascorbate group were determined by using a *t*-test. Significance was defined as $p < 0.05$. Ferritin values with superscript within a row within both FAG group and ferrous ascorbate group on day 14 and day 28 vs respective baseline levels are significantly different (*$p < 0.0001$) by paired *t*-test. Ferritin values with superscript in FAG row are statistically significant by Unpaired *t*-test in FAG vs ferrous ascorbate group on day 14 (†$p < 0.0001$) and on day 28 (†$p < 0.01$).

preparation, used in the present study contains FAG in combination with L-methylfolate and methylcobalamin. L-methylfolate is the active form of folic acid (Greenberg and Bell 2011), which is highly more bioavailable than conventional folic acid (Willems et al. 2004). It is worth noting that, L-methylfolate is the only active form of folic acid that is involved in the formation erythrocytes. L-methylfolate can cross the blood–brain barrier and therefore can fulfil the requirement of folic acid in fetal development (Greenberg et al. 2011). Based on these reports, it seems that the supplementation of L-methylfolate would be more beneficial than folic acid.

In women, supplements with L-methylfolate and high-dose methylcobalamin may be more effective in maintaining higher haemoglobin levels and reducing the risk of anaemia throughout pregnancy (Bentley et al. 2011). Therefore, we suggest that the supplementation of L-methylfolate and methylcobalamin with FAG may show an additional rise in haemoglobin levels.

In view of these results, FAG with the additional advantages of L-methylfolate and methylcobalamin shows favourable efficacy with a superior rise in haemoglobin and ferritin levels and negligible GI side-effects, compared with ferrous ascorbate. Thus, FAG seems to be an effective oral iron supplement in the management of IDA during pregnancy.

However, the present trial was undertaken for the first time to compare two different iron preparations in a small population of patients. Therefore, further large scale effectiveness trials are warranted to confirm and validate the findings of the present efficacy trial, and also to find out the anaemia eradication rate. Also, community-based intervention studies are needed to assess the efficacy and safety of FAG among other groups, such as preschool children, adolescent girls and lactating mothers.

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