European Review for Medical and Pharmacological Sciences 2018; 22: 3602-3608

Effects of micronised dispersible ferric pyrophosphate combined with alpha-lactalbumin in pregnant women affected by iron deficiency anemia: results from a prospective, double-blind, randomized controlled trial

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Abstract. – OBJECTIVE: This study aimed at evaluating the effects obtained by administering 30 mg of micronised dispersible ferric pyrophosphate plus 300 mg of alpha-lactalbumin (MDFP-AL) compared to 80 mg of ferrous gluconate (FG) in pregnant women affected by iron-deficiency anemia (IDA).

PATIENTS AND METHODS: We considered eligible all second-trimester singleton pregnancies in women affected by IDA. We excluded any other disease, twin pregnancies, any other pharmacologic/nutraceutical treatments (besides folic acid) before/during pregnancy. We randomized patients in two groups: one underwent treatment with 1 tablet of MDFP-AL/day, the other one with 1 tablet of FG/day, for 30 days. We evaluated hemoglobin (Hb), ferritin, red blood cells (RBCs), serum iron, hematocrit (Hct), and side effects at baseline (T0), after 15 days (T1) and 30 days (T2).

RESULTS: 50 women met the inclusion/exclusion criteria. We did not observe significant differences between the two groups for mean age, gestational age at the enrollment and parity. In MDFP-AL group, after 15 days (T1) Hb, ferritin, serum iron and Hct and were significantly improved respect to baseline (T0); after 30 days (T2), all the parameters, including RBCs, were significantly improved respect to baseline (T0). Similarly, in FG group the investigated parameters were improved both after 15 (T1) and 30 days (T2) respect to baseline (T0), although less in percentage terms respect to MDFP-AL group. The side effects rate was 24% in FG group, whereas MDFP-AL group did not show any significant side effect.

CONCLUSIONS: Overall, MDFP-AL is more effective and safe than FG for the treatment of IDA in pregnant women.

Key Words:
Micronised dispersible ferric pyrophosphate, Alpha-lactalbumin, Ferrous gluconate, Iron-deficiency anemia, Iron supplementation, Pregnancy.

Introduction

Iron deficiency is the most common cause of anemia in the world and represents a major challenge in healthcare policy[1]. In particular, iron deficiency anemia (IDA) is the leading cause of anemia-related disability[2], especially in reproductive aged women[3]. The total prevalence of iron deficiency even in the absence of anemia is estimated to be between 30% and 60%[4]. Nevertheless, continuous iron deficiency during the time causes unavoidably anemia, since erythropoiesis consumes the iron body store, which gradually becomes depleted[5].

Anemia is particularly frequent during pregnancy: recent data reported an estimated prevalence of 38%, equivalent to 32 million women worldwide[6]. In addition, accumulating evidence suggests that IDA affects a quarter of pregnant women in Europe[7]. These data are of paramount importance, considering that both anemic and

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non-anemic iron deficiencies in pregnancy may have severe consequences on maternal-fetal outcomes[8]. Indeed, accumulating evidence suggests that IDA can be associated with increased preterm labor, preeclampsia, maternal sepsis[9], fetal loss or even perinatal death[10]. Furthermore, a large cohort analysis found long-term impairments in cognitive development and growth in babies exposed to IDA *in utero*[11]. In most of the cases, IDA during pregnancy is caused by suboptimal iron content in mother's diet and insufficient iron stores during the reproductive years[12].

For all these reasons, prevention and treatment of IDA during pregnancy represent high priority targets in order to prevent adverse maternal-fetal outcomes. According to recent guidelines and recommendations[13], during pregnancy the total demand for iron is about 1240 mg. Although intravenous iron administration seems to be very effective for the treatment of IDA during pregnancy[14,15], to date oral iron supplementation is preferred whenever it is possible for its feasibility and better compliance. The major problem with oral iron therapy in its classic ferrous form is poor tolerability and gastrointestinal side effects such as abdominal pain, diarrhea and constipation (up to 40% of patients)[16]. Currently, the oral preparations of micronized dispersible ferric pyrophosphate (MDFP, SunActive® Fe) and alpha-lactalbumin (AL) opened a new scenario: on the one hand, this type of micro-coated iron shows similar bioavailability compared to ferrous sulfate when added to a wheat-milk infant cereal and a yogurt drink[17]; on the other hand, AL was found to play a positive role on gut microbiota[18], likely increasing the iron absorption.

Despite these promising results, data about MDFP in pregnant women are still insufficient and do not allow to draw firm conclusions. Considering this point, the aim of our study was to evaluate the effects of MDFP combined with AL (MDFP-AL) respect to ferrous gluconate (FG) in pregnant women affected by IDA.

Patients and Methods

Patients

We developed a prospective, double-blind, randomized controlled trial at the AGUNCO Obstetrics and Gynecology Centre (Rome, Italy), from March 2016 to April 2017. We considered eligible all second-trimester singleton pregnancies in women affected by IDA, according to the Italian Guidelines for physiologic pregnancy and the American College of Obstetricians and Gynecologists guidelines (Hb levels less than 10.5 g/dL, ferritin less than 10-15 mcg/L)[19,20]. Women affected by any other kind of pre-pregnancy or pregnancy-related diseases and twin pregnancies were excluded. Furthermore, also women undergoing any other kind of pharmacologic/nutraceutical treatments (besides folic acid supplementation) before or during pregnancy were not included.

After written informed consent, we enrolled 50 patients between 19 and 21 gestational weeks. Subsequently, we randomized the patients in a non-stratified 1:1 ratio in two groups: the first one orally administered with 30 mg MDFP combined with 300 mg AL (Emogut® Forte, Farmares, Gruppo Lo.Li.Pharma S.r.l., Italy); the second one (controls) with 80 mg FG. Both groups took one daily tablet of for 30 days.

Methods

Allocation of the treatment was concealed in sequentially numbered, opaque, sealed envelopes. The tablets were indistinguishable from each other for size, color, consistency and taste. Patients and investigators were masked to treatment allocation. Any patient taking less than 80% of the prescribed treatment was regarded as noncompliant and excluded from the study. Enrolled patients did not take other drugs that may modify the analyzed parameters during the previous 3 months or during the trial. The study was not advertised and no remuneration was offered to the patients. An independent data safety and monitoring committee evaluated the results.

We evaluated as primary outcomes Hb (g/dL) and ferritin (mcg/L), and as secondary outcomes the number of red blood cells (RBCs x 1000000/mL), serum iron (mcg/dL), hematocrit (Hct, %) levels and side effects. Besides baseline evaluation (T0), follow-up was scheduled at 15 days (T1) and 30 days (T2).

The design, analysis, interpretation of data, drafting and revisions conform the Helsinki Declaration, the Committee on Publication Ethics (COPE) guidelines (http://publicationethics.org/), the CONSORT (CONsolidated Standards of Reporting Trials)[21, 22] and SPIRIT (Standard Protocol Items: Recommendation for Interventional Trials)[23] statements, available through the EQUATOR (enhancing the quality and transparency of health research) network (www.equator-network.org). The study was approved by an independent Institutional Review Board (IRB).

Table I. Characteristics of enrolled patients.

	MDFP-AL	FG	*p*
Age (years)	27.5 ± 6	25.6 ± 6	0.27
Gestational age at enrollment (weeks)	20 ± 3	20 ± 3	1
Parity	1.2 ± 0.5	1.4 ± 0.5	0.16

Data are expressed as means and standard deviations. MDFP-AL: Micronised Dispersible Ferric Pyrophosphate combined with Alpha-Lactalbumin; FG: Ferrous Gluconate.

Statistical Analysis

Statistical analysis was performed using the SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA) software package. The assumption of normal distribution for continuous variables was tested by Kolmogorov-Smirnov test for goodness of fit. Continuous variables were expressed as means and standard deviations (SD), and compared between the two groups using the Student *t*-test. Categorical variables were expressed as percentages and compared between the two groups using the two-tailed x^2-test. A p-value < 0.05 was considered statistically significant.

Results

Based on the inclusion/exclusion criteria, 50 women were enrolled in the trial and randomized in the two groups. All the enrolled patients completed the trial (no drop out). We did not found significant differences between the two groups for mean age (p=0.27), gestational age at enrollment (p=1) and parity (p=0.16) (Table I).

In MDFP-AL group after 15 days (T1) there was a significant increase of Hb (p=0.0001), ferritin (p=0.006), serum iron (p=0.0001) and Hct (p=0.007) (Table II). Similarly, in FG group (Table III) after 15 days (T1) there was a significant increase of Hb (p=0.0009), ferritin (p=0.002), serum iron (p=0.009) and Hct (p=0.005). Nevertheless, the increase of Hb (+11.54% *vs.* +3.88%), ferritin (+65% *vs.* +50%) and serum iron (+55.56% *vs.* +50%) was higher in MDFP-AL group respect to FG group.

In MDFP-AL group after 30 days (T2) all the investigated parameters, including RBCs (p=0.01) were significantly increased respect to baseline (Table IV). Similarly, also in FG group (Table V) after 30 days (T2) all the parame-

Table II. Hematological parameters at baseline (T0) and after 15 days of treatment (T1) with micronised dispersible ferric pyrophosphate combined with alpha-lactalbumin (MDFP-AL).

	T0	T1	*p*	Δ (%)
Hb (g/dL)	10.4 ± 0.3	11.6 ± 0.4	0.0001	+11.54%
Ferritin (mcg/L)	10 ± 8	16.5 ± 8	0.006	+65%
RBCs x 1.000.000/mL	3.52 ± 0.3	3.64 ± 0.4	0.24	+3.41%
Serum iron (mcg/dL)	27 ± 15	42 ± 18	0.0001	+55.56%
Hct (%)	34 ± 2	36 ± 3	0.007	+5.88%

Data are expressed as means and standard deviations; Δ represents percent variation between T0 and T1. Hb: hemoglobin; RBCs: Red Blood Cells; Hct: hematocrit.

Table III. Hematological parameters at baseline (T0) and after 15 days of treatment (T1) with Ferrous Gluconate (FG).

	T0	T2	*p*	Δ (%)
Hb (g/dL)	10.3 ± 0.4	10.7 ± 0.4	0.0009	+3.88%
Ferritin (mcg/L)	12 ± 7	18 ± 6	0.002	+50%
RBCs x 1.000.000/mL	3.47 ± 0.3	3.52 ± 0.4	0.6	+1.44%
Serum iron (mcg/dL)	26 ± 18	39 ± 16	0.009	+50%
Hct (%)	33.5 ± 2.5	35.8 ± 3	0.005	+6.87%

Data are expressed as means and standard deviations; Δ represents percent variation between T0 and T1. Hb: hemoglobin; RBCs: Red Blood Cells; Hct: hematocrit.

Table IV. Hematological parameters at baseline (T0) and after 30 days of treatment (T2) with micronised dispersible ferric pyrophosphate combined with Alpha-Lactalbumin (MDFP-AL).

	T0	T2	*p*	Δ (%)
Hb (g/dL)	10.4 ± 0.3	12.1 ± 0.5	0.0001	+16.35%
Ferritin (mcg/L)	10 ± 8	24 ± 9	0.0001	+140%
RBCs x 1.000.000/mL	3.52 ± 0.3	3.78 ± 0.4	0.01	+7.39%
Serum iron (mcg/dL)	27 ± 15	74 ± 22	0.0001	+174.07%
Hct (%)	34 ± 2	37.5 ± 3	0.0001	+10.29%

Data are expressed as means and standard deviations; Δ represents percent variation between T0 and T2. Hb: hemoglobin; RBCs: Red Blood Cells; Hct: hematocrit.

Table V. Hematological parameters at baseline (T0) and after 30 days of treatment (T2) with ferrous gluconate (FG).

	T0	T2	*p*	Δ (%)
Hb (g/dL)	10.3 ± 0.4	11.4 ± 0.4	0.0001	+10.68%
Ferritin (mcg/L)	12 ± 7	22 ± 7	0.0001	+83.33%
RBCs x 1.000.000/mL	3.47 ± 0.3	3.72 ± 0.4	0.01	+7.20%
Serum iron (mcg/dL)	26 ± 18	59 ± 25	0.0001	+126.92%
Hct (%)	33.5 ± 2.5	36.8 ± 3.5	0.0004	+9.85%

Data are expressed as means and standard deviations; Δ represents percent variation between T0 and T2. Hb: hemoglobin; RBCs: Red Blood Cells; Hct: hematocrit.

Table VI. Comparison of percent variations between T0 (baseline) and T2 (30 days of treatment) of hematological parameters in micronised dispersible ferric pyrophosphate combined with alpha-lactalbumin (MDFP-AL) group and ferrous gluconate (FG) group.

	MDFP-AL		FG		
	Mean and SD at T2	T0-T2 Δ (%)	Mean and SD at T2	T0-T2 Δ (%)	*p*
Hb (g/dL)	12.1 ± 0.5	+16.35%	11.4 ± 0.4	+10.68%	<0.0001
Ferritin (mcg/L)	24 ± 9	+140%	22 ± 7	+83.33%	0.38
RBCs x 1000000/mL	3.78 ± 0.4	+7.39%	3.72 ± 0.4	+7.20%	0.60
Serum iron (mcg/dL)	74 ± 22	+174.07%	59 ± 25	+126.92%	0.03
Hct (%)	37.5 ± 3	+10.29%	36.8 ± 3.5	+9.85%	0.45

Data are expressed as means and standard deviations (SD); Δ represents percent variation between T0 and T2. Hb: hemoglobin; RBCs: Red Blood Cells; Hct: hematocrit.

ters were significantly increased. Nevertheless, also for T2 analysis (Table VI) the increase of Hb (+16.35% *vs.* +10.68%), ferritin (+140% *vs.* +83.33%), RBCs (+7.39% *vs.* +7.20%), serum iron (+174.07% *vs.* +126.92%) and Hct (+10.29% *vs.* +9.85%) was higher in in MDFP-AL group respect to FG group. In particular, the comparison between the two groups at T2 showed a significant more marked increase of Hb ($p<0.0001$) and serum iron ($p=0.03$) in MDFP-AL group respect to FG group.

The cumulative side effects rate was 24% in FG group, whereas MDFP-AL group did not show any significant side effect ($p=0.02$).

Discussion

Pregnancy represents a particular condition prone to develop IDA, due to increased request for RBCs formation, fetal and placental growth[24]. Since dietary intake cannot fulfill the daily-required amount of iron (27 mg/day) during pregnancy, the Centers for Disease Control and Prevention recommended that pregnant women should take a daily supplement of 30 mg of elemental iron as a preventive measure[25]. Although in most of the cases IDA becomes overt during the second and third trimesters, the iron supplementation should start before or at the beginning

of pregnancy in order to prevent negative outcomes[26].

Unfortunately, most of the iron supplements are associated usually with constipation, darkened stools, diarrhea, loss of appetite, nausea, stomach cramps, and vomiting[27]. In order to overcome these common and well-known side effects and increase the bioavailability, recent techniques were aimed to emulsify MDFP with maltodextrin and soy lecithin, providing high dispersion stability in aqueous media. In particular, recent *in vitro* experiments suggested that MDFP has better intestinal transport, biokinetics and tissue distribution than ferric pyrophosphate[28].

Despite several promising data in both animal models[29] and humans[17,30], to the best of our knowledge only one previous study investigated the effects of MDFP during pregnancy: Hartman-Craven et al[31] enrolled and randomized 18 healthy pregnant women (24-32 gestational weeks) to receive powdered supplement containing 30 mg of iron as MDFP with an emulsifier coating and 600 μg of folic acid, or tablet containing 27 mg of iron from ferrous fumarate and 1000 μg of folic acid. Nevertheless, the interpretation of this study is extremely limited due to several elements: first, the small sample size; second, the inclusion of investigated iron supplements in two mixtures with many other biologically active nutraceuticals; third, the enrolled women were healthy, not affected by IDA; fourth and most important, the study design aimed to evaluate only the relative bioavailability and absorption kinetics within 8 hours, without any other information about clinical effects in the medium-long term.

Therefore, the current study may be considered the first clinical evaluation of MDFP in pregnant women. Our data analysis showed that the daily supplementation with 30 mg of MDFP combined with 300 mg of AL is able to increase Hb, ferritin, serum iron and Hct in pregnant women more than the daily supplementation with 80 mg of FG, after 15 and 30 days of treatment (at 30 days also RBCs significantly increased). Moreover, women taking MDFP-AL did not report any side effects during the treatment.

The combination of AL with MDFP is likely to have paramount importance for these outcomes: indeed, iron absorption from formulas enriched with bovine AL has been found increased in infant rhesus monkeys[32]; in addition, a recent human-based clinical study found that infants fed with AL-enriched formula showed higher indicators of iron status than infants fed with control formula[33]. Finally, *in vitro* data clearly demonstrated that iron absorption is significantly increased by peptides derived from AL[34].

Besides the effect on iron absorption, AL may play a positive role on gut microbiota: on the one hand, GLF (consisting of Gly-Leu-Phe amino acids) has been shown to be formed during AL digestion in the gastrointestinal tract and to have a powerful immune-stimulating action[35,36]; on the other hand, other antibacterial peptides are formed during AL digestion and lead to a significant reduction of potentially pathogenic bacteria (*Bacteroides, Clostridia, E. coli*) within intestinal microflora[37].

Furthermore, AL shows beneficial anti-inflammatory and anti-nociceptive activity by inhibiting cyclooxygenase-2 (COX-2); in this way, it helps to control and regulate the inflammatory processes during pregnancy[38,39]. Inflammation increases the iron regulatory hormone, hepcidin, that causes iron sequestration in the setting of inflammation, and this element is strongly involved in IDA onset and in its persisting[40,41]. Therefore, the AL anti-inflammatory effect can be effective in improving iron availability and absorption.

Despite our results, several limitations of the research should be taken into account for the data interpretation: we enrolled a small sample size; the results and conclusion are based on a limited period, without any additional information about long-term follow up; we adopted selective inclusion/exclusion criteria, so our research setting does not overlap perfectly the daily practice; the MDFP was combined with AL, but compared with FG alone. Based on the abovementioned elements and lack of other available data, we take the opportunity to suggest future studies. They should be aimed at evaluating our results in larger cohorts and, in addition, at comparing the effects obtained with different doses of MDFP respect to other iron supplementations and/or different administration routes in pregnant women affected by IDA.

Conclusions

In this preliminary trial we demonstrated that MDFP-AL exerts a higher efficacy in improving some pivotal parameters and shows a safer profile than FG for the treatment of IDA in pregnant women.

Conflict of Interest

All authors have no proprietary, financial, professional, or other personal interest of any nature in any product, service, or company. The authors alone are responsible for the content and writing of the paper. No specific funding was obtained.

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