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Effect of Ferric Sodium EDTA in Combination with Vitamin C, Folic Acid, Copper, Zinc, and Selenium, for Prevention of Iron Deficiency Anemia during Pregnancy

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Abstract

During pregnancy iron requirement increases for meet the needs of mother and fetus development and growth. Often iron stores of pregnant women are not sufficient, inducing a major risk of occurrence of iron deficiency (ID) and iron deficiency anemia (IDA), that have been associated with major risk of adverse pregnancy outcomes. The aim of this study was to verify the effect of the administration of 1 tablet a day of Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®), on the hematological status of pregnant women, with reference to the prevention of IDA in pregnancy. Pregnant non-anemic women (N=100) were enrolled and randomized to treatment with Ferric Sodium EDTA combination (Group A, N=50) or with folic acid (Group B, N=50). Blood parameters of hemoglobin (Hb), total number of red blood cells (RBCs), ferritin, and transferrin were evaluated at T0: before starting therapy (<12th week), T1 at 20-24 weeks, T2 at 30-32 weeks, and T3 at 36 weeks. Degree of tolerability in treatment group and adverse events eventually reported were added as evaluation of safety. Results showed that Group A maintained almost unchanged blood parameters evaluated and the therapy was effective to prevent IDA onset. Group B results showed a worsening statistically significant ($P < 0.001$) of all parameters evaluated. In Group A most women reported that treatment was safe and well tolerated. In conclusion, this study confirmed the efficacy and safety of supplementation with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate, and selenomethionine (Ferachel Forte®), for preventing anemia in pregnant women.

Keywords: Pregnancy; Iron deficiency anemia; Ferric Sodium EDTA; Folic acid; Iron supplementation; Safety; Tolerability

Introduction

During pregnancy iron requirement increases for several reasons, including the dilation of red blood cell mass, and iron needs for placenta function and for fetus development and growth. Plasma and blood volumes increase in physiological pregnancies in order to assure proper circulation and oxygen delivery to both maternal body and placenta [1-2]. The World Health Organization (WHO) defines anemia in pregnant women as hemoglobin (Hb) levels less than 11 g/dL, recognizing that the Hb levels in second trimester reach their lowest point [3]. Additionally, the American College of Obstetricians and Gynecologists (ACOG) differentiated by trimester the anemia in pregnancy setting the Hb level of <11.0 g/dL in the first and third trimesters and Hb level of <10.5 g/dL in the second trimester of pregnancy [4].

It has been estimated that the iron amount needed for a normal pregnancy is from 1000 to 1200 mg [1-5]. However, often iron stores of pregnant women are not sufficient to supply these increased requirements and iron absorption from diet can be inadequate, inducing pregnant women to a major risk of occurrence of iron deficiency (ID) and iron deficiency anemia (IDA) [2-5]. In turn, ID and IDA during pregnancy have been associated with major risk of adverse pregnancy outcomes, including preterm delivery, low birth weight, small gestational age (SGA) live birth, preeclampsia, cesarean delivery, maternal and perinatal death [4-6].

Latest estimates showed that anemia affect about 38% of pregnant women globally, with the highest prevalence in South-East Asia regions (48.7%) and Africa (46.3%), followed by Eastern Mediterranean regions (38.9%) and with the lowest incidence in Western Pacific regions (24.3%), the Americas (24.9%) and Europe (25.8%). Therefore, the percentage of anemic pregnant women is still too high, even if several strategies have been applied to stem this disease and global nutrition targets have been defined for improving maternal, infant, and young child nutrition and health [7-8].

For these reasons, WHO guidelines regarding antenatal care for a positive pregnancy experience, issued in 2016 recommend daily supplementation with oral iron (in the dosage from 30 mg to 60 mg of elemental iron) and folic acid (at dosage of 400 μg) for pregnant women to prevent maternal anemia, puerperal sepsis, low birth weight, and preterm birth [7]. In April 2019, the Executive Guideline Steering Group (GSG) updated these guidelines in response to new evidence on two interventions, namely: multiple micronutrient supplements (MMS) and United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP), by issuing following recommendation: Antenatal multiple micronutrient supplements that include iron and folic acid are recommended in the context of rigorous research [9]. These guidelines confirm the recommendation for pregnant women

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that should be supported and encouraged to receive adequate nutrition, achieved through consumption of a healthy and balanced diet [9].

However, the routinely iron supplementation during pregnancy is not always recognized and applied, mainly for the poor tolerability of traditional oral iron therapies that often can cause gastrointestinal side effects and lack of adherence to therapy, and for concerns about safety among women with an adequate iron intake, and about risk of iron overload [10]. A recent Cochrane review evaluated the use of intermittent iron supplementation during pregnancy (two or three times per week) in clinical trials, concluding that this approach is as effective as daily supplementation, decreasing side effects, and probably resulting in higher compliance [10].

New iron sources have been placed on the market with improved efficacy and tolerability, including Ferric Sodium EDTA, consisting of a complex between ferric ion and ethylenediaminetetraacetate (EDTA) representing a highly bioavailable and stable source of iron. The complex between iron and EDTA (NaFeEDTA) is a stable chelate in acid pH conditions and is not being bonded to inhibitors of iron absorption from diet, such as phytic acid or phenolic compounds. The water-soluble chelate once arrived in duodenal tract releases ferric ion, with change of pH, and allows iron to be adsorbed once reduced to ferrous ion trough a duodenum-specific cytochrome b–like protein, Dcytb, a reductase present at the apical surface of enterocytes, as occurs to non-heme iron ingested with diet [11-12].

Ferric Sodium EDTA has been evaluated for treatment of ID and IDA in several studies that was conducted also in pregnant women, children, and adolescents [13-23]. In some study this iron source was added as fortification in whole wheat flour or soy sauce and this measure showed an improvement of hematological and iron status of enrolled subjects [14-20].

Along with iron needs during pregnancy other nutritional deficiencies can occur, like for vitamin C that showed decreased levels in pregnant women, both for increased requirement of mother, that active transfers it to fetus, and for hemodilution. Vitamin C deficiency can be associated with increased risk of infections, premature rupture of membranes, and pre-eclampsia [24]. Also, the role of folic acid supplementation is well recognized, both 2-3 months before and during pregnancy, for the correlation between folate deficiency and neural tube defects (NTD) [24]. Consequently, folic acid supplementation at dosage of 400 µg/day is recommended by WHO guidelines [7].

Other micronutrient's deficiencies can be harmful during pregnancy, for example, zinc deficiency has been associated with the appearance of pre-eclampsia, postpartum hemorrhage, and even spontaneous abortions, as well as selenium deficiency has been associated with increased risk of miscarriage [24]. For these reasons it is important to have a food supplement that allows to integrate more active ingredients at the same time. One example of Italian product in market is a food supplement based on the association of Ferric Sodium EDTA with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine, named Ferachel Forte®, where the new iron source has been associated with the other active ingredients to improve iron absorption and erythropoiesis. This product has been already evaluated in several studies and showed efficacy in improvement of hematological status of IDA patients and high tolerability [25-32].

The aim of this study was to verify the effect of the administration of 1 tablet a day of Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®), on the hematological status of pregnant women, with reference to the prevention of anemia and iron deficiency in pregnancy.

Materials and Methods

This is a prospective, randomized, open-labelled study conducted on 100 pregnant women visiting the pregnancy clinic of the "Centro Salute Donna", AUSL Ferrara, of Ferrara city, Italy.

Pregnant women during the first routine visit with over 18 years of age, gestation time <12 weeks, without laboratory indication of anemia (Hb >11.0 g/dL on week 12) were recruited. Exclusion criteria were: pregnant women with microcythemia, thalassaemias or other hemoglobin alterations (e.g. sickle cell anemia), pregnant women already with an anemic condition with any etiology, with particular eating habits (like vegetarian - vegan) or with malabsorption (e.g. due to bariatric surgery, celiac disease etc.), women with a history of coagulation disorders.

All enrolled women were randomly allocated to one of following oral treatment groups during entire pregnancy:

- Group A (N=50) treated with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®, AQMA Italia S.p.A, Milan, Italy) 1 tab/day, containing 30 mg of ferric ion, as treatment group

- Group B (N=50) treated with folic acid 1 tab/day, containing 400 mcg of folic acid, as control group.

Simple randomization was performed by using excel random function by matching every numerical ID patient to one of treatment groups. One ID was assigned to every consecutive patient visited in the pregnancy clinic and enrolled in the study. The supplements were administrated every day in the morning. All patients were informed of the study procedures and provided written informed consent. Local ethic boards approved the protocol. The study was conducted in accordance with the Declaration of Helsinki guidelines regarding ethical principles for medical research involving human subjects. Control of blood parameters of Hb, total number of red blood cells (RBCs), ferritin, transferrin was performed at following timepoints: T0 before starting therapy, within the first trimester of pregnancy (<12th week), T1 in the second trimester (20-24 weeks), T2 in the third trimester (30-32 weeks), and T3 at 36 weeks. Blood samples were collected in the morning after an overnight rest, by antecubital venous puncture. Plasma and serum samples were obtained by centrifugation and frozen at −70°C until further laboratory analysis. All blood parameters were measured using standard automated laboratory methods on Cobas 6000 (Roche, Rotkreuz, Switzerland), by using the relative kits, according to the manufacturer's instructions. At visit T3 (36 weeks) medication adherence was recorded, expressed as degree of tolerability in treatment group, and evaluated by assigning a score of 0=suspension, 1=poor, 2=fair, 3=good, 4=excellent, according to women judgment regarding the easiness of taking the therapy and any discomfort deriving from taking the tablet. Adverse events eventually reported were added as evaluation of safety. In both groups (Group A as treatment and Group B as control) in case of occurrence of iron deficiency anemia, defined as Hb < 10.5 g/dL in the second trimester and Hb < 11g/dL in the first and third trimester according to national and international guidelines, due to the necessity to consider other iron therapies, the patients dropped out of the study. At the end of the study percentage of patients with IDA was considered as primary outcome. The secondary outcome was the degree of tolerability and safety

profile of the oral therapy in Group A patients. This endpoint was not evaluated in Group B women since folic acid treatment was considered safe by investigators. Statistical analysis was performed using Paired T-test with Microsoft excel analysis program for Windows 11 Pro, by comparing all blood parameters collected at T0 and T3. The differences were considered significant when $P<0.05$.

Results

In this study 100 pregnant women were enrolled and randomized to Group A (treatment group) treated with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®) or Group B (control group), treated only with folic acid. Figure 1 shows the flow diagram for the patients enrolled in the study. Enrolled women were 31.7 ± 5.18 years old, at week of gestation < 12, without laboratory indication of IDA. Blood parameters of Hb, RBCs, ferritin, and transferrin were evaluated in 2 Groups of patients and reported in Table 1. Group A did not show statistically significant changes of Hb and transferrin parameters evaluated between T0 and T3. Group A results indicated that pregnant women in treatment with oral iron association maintained almost unchanged blood parameters and the therapy was effective to prevent IDA onset. Group B results showed a worsening statistically significant ($P < 0.001$) of all parameters evaluated. Blood parameters results reflect the percentage of women developing IDA during the study, according to international ACOG guidelines defining anemia in pregnancy when Hb level is <11.0 g/dL in the first and third trimesters and Hb level is <10.5 g/dL in the second trimester. Table 2 shows the percentage of anemic women in both groups. In Group B 84% of women (N=42) became anemic, in comparison to Group A where only 12% of women (N=6) showed IDA.

Regarding the secondary outcome, consisting of the evaluation of tolerability degree of treatment in Group A pregnant women, data are reported in Table 3 showing that the majority of pregnant women (86%, N=43) considered as good or excellent treatment with Ferric Sodium EDTA association. Overall, about safety outcome the treatment with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate, and selenomethionine was safe and well tolerated, since only 2 women (4%) reported mild adverse events (AEs). These women reported nausea, resolved by assuming treatment after meal. No pregnant woman has discontinued therapy.

Discussion

This was a preliminary comparative study conducted on 100 pregnant women treated with the new oral iron source Ferric Sodium EDTA, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate, and selenomethionine (Group A) or only with folic acid (Group B), in order to evaluate treatment effect on the hematological status of women and on the prevention of anemia and ID in pregnancy. During pregnancy, ID and IDA can increase the risk of adverse pregnancy outcomes like preterm delivery, low birth weight, SGA live birth, preeclampsia, cesarean delivery, maternal and perinatal death [4-6]. More in details several studies reported that moderate and severe anemia was associated with higher rates of preterm and SGA live births, along with placental-related morbidity such as preeclampsia,

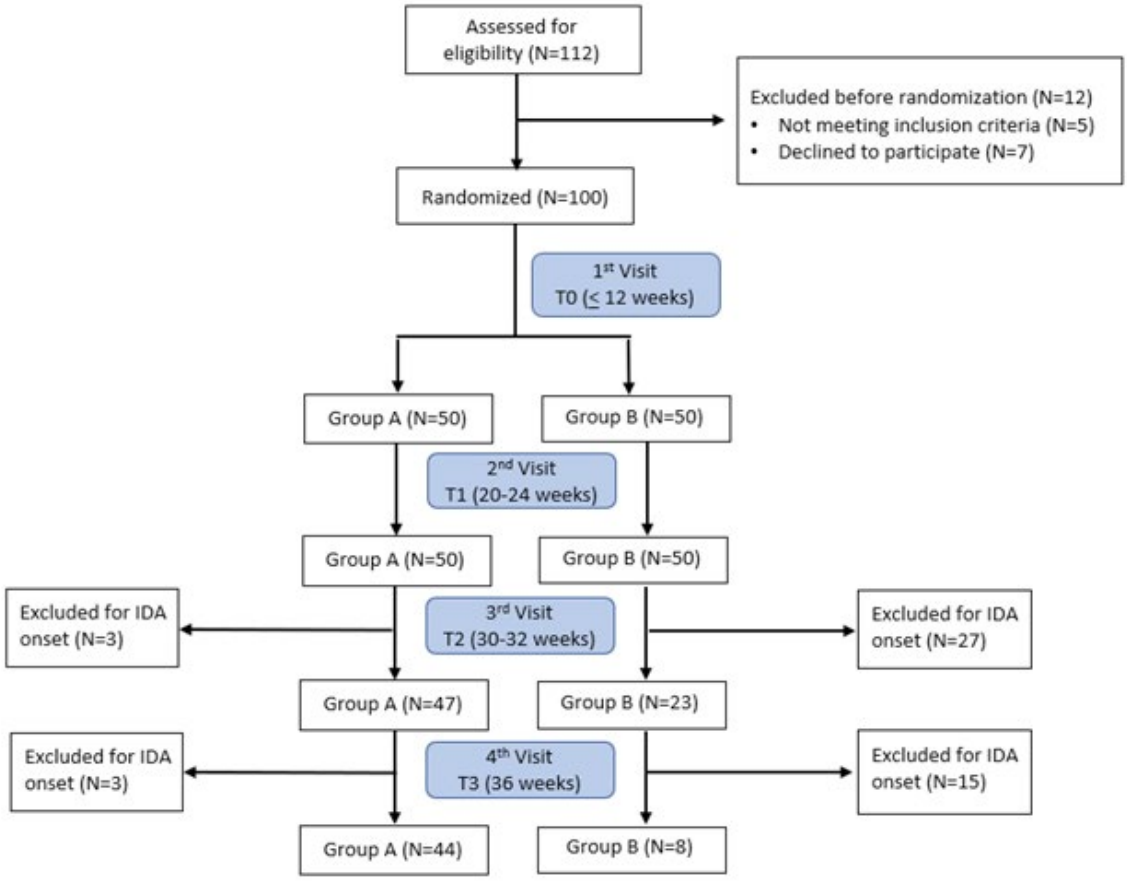

Figure 1: Flow diagram of patients enrolled in the study. Group A: patients (N=50) treated with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate, and selenomethionine; Group B: patients (N=50) treated only with folic acid.

Table 1: Blood parameters of Group A (treated with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate, and selenomethionine) and Group B (treated only with folic acid).

Blood parameters, mean (±SD)	Group A (N=50)					Group B (N=50)				
	T0	T1	T2	T3	P value (T0vsT3)	T0	T1	T2	T3	P value (T0vsT3)
RBCs (millions/μL)	4.16	3.96	3.89	3.95	**< 0.001**	4.25	3.93	3.76	3.58	**< 0.001**
	(0.19)	(0.17)	(0.31)	(0.21)		(0.28)	(0.12)	(0.12)	(0.42)	
Hb (g/dL)	12.15	12.1	12.09	12.04	0.305	12.42	11.55	10.92	10.83	**< 0.001**
	(0.74)	(0.73)	(0.73)	(0.69)		(0.89)	(0.49)	(0.28)	(0.25)	
Ferritin (μg/L)	14.26	13.86	13.66	16.55	**0.013**	14.44	10.95	8.29	7.87	**< 0.001**
	(3.28)	(2.87)	(3.43)	(5.27)		(3.39)	(1.59)	(1.61)	(1.57)	
Transferrin (mg/dL)	293	307.12	307.8	297.79	0.14	287.74	371	390.9	398.48	**< 0.001**
	(23.13)	(33.10)	(34.05)	(23.40)		(26.51)	(29.64)	(24.23)	(18.98)	

Abbreviations: SD: standard deviation; RBCs: total number of red blood cells; Hb: hemoglobin; T0: before starting therapy, within the first trimester of pregnancy (<12th week); T1: 20-24 weeks; T2: 30-32 weeks; T3: 36 weeks.

Table 2: Percentage of anemic pregnant women in Group A (treated with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine) and in Group B (treated only with folic acid).

	Group A (N=50)					Group B (N=50)				
	T0	T1	T2	T3	Total	T0	T1	T2	T3	Total
Anemic patients / total in the group, % (N)	/	0	6 (N=3)	6 (N=3)	12 (N=6)	/	0	54 (N=27)	30 (N=15)	84 (N=42)

Abbreviations: T0: before starting therapy, within the first trimester of pregnancy (<12th week); T1: 20-24 weeks; T2: 30-32 weeks; T3: 36 weeks.

Table 3: Tolerability degree of treatment reported by pregnant women in Group A (treated with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine), evaluated by assigning a score of 0=suspension, 1=poor, 2=fair, 3=good, 4=excellent, at visit T3.

	Group A (N=50)				
Tolerability degree	0	1	2	3	4
% (N)	0	0	14 (N=7)	48 (N=24)	38 (N=19)

probably caused by placental hypoxia and/or increased oxidative stress. Furtherly, rates of post-partum hemorrhages, of women undergoing hysterectomy and need of Intensive Care Unit admission, were increased in anemic pregnant women. Also, the percentage of blood transfusions, induction of labor, and cesarean delivery was higher in anemic pregnant women. Mild anemia was associated with higher rates of infectious diseases such as bacterial sepsis [4-6]. Starting pregnancy with adequate iron stores becomes of very high importance for avoiding risk of complications for mothers and babies. Unfortunately, the use of iron supplementation for ID and IDA prophylaxis in pregnancy is not fully recognized, mainly for the low compliance to therapy. Concerns about efficacy and safety of oral iron therapy in gynecologist communities are often derived from an history of use of traditional oral iron therapies, mainly based on low bioavailable iron sources, that can be responsible for gastrointestinal adverse events (AEs) in otherwise healthy pregnant women. Gastrointestinal AEs derive from the amount of iron not absorbed that remains at intestinal level. In addition, the low bioavailability of several oral iron sources, like ferrous sulphate, can be responsible for the low efficacy in improving iron blood parameters [5-10]. This study aimed to evaluate a new product based on Ferric Sodium EDTA, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate, and selenomethionine, named Ferachel Forte®, that already showed in previous studies good efficacy and safety profile [25-32], in pregnant non anemic women to prevent anemia occurrence. This product has been designed to provide a new oral iron with high bioavailability and tolerability profile, since both iron source Ferric Sodium EDTA presents the better characteristics of iron absorption and safety and the other active ingredients in the formulation, such as vitamin C, folic acid, copper, zinc, and selenium, improve furtherly iron absorption and erythropoiesis. In antenatal period not only iron but also other micronutrients deficiencies, like previously reported elements, have been associated with pregnancy complications, like pre-eclampsia, abnormal neuronal development, postpartum hemorrhage, and risk of miscarriage [24]. Therefore, the use of one single tablet a day providing all active ingredients, useful for the prevention of such deficiencies and fully tolerated by the patients, can be a valid ally for pregnant women. Results of this study showed that in the Group A women treated with Ferric Sodium EDTA, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate, and selenomethionine, blood parameters evaluated remain almost unchanged during the whole pregnancy. In most cases (88%) women arrived at delivery with good hematological parameters and without tolerability troubles. Conversely, most pregnant women of Group B (84%), treated only with folic acid, showed IDA and consequently were excluded from the study in order to start therapy for IDA. This study represents the first one where the use of this specific Ferric Sodium EDTA combination was evaluated in pregnant women and the challenge derived from the consideration that previous studies conducted on this product showed good efficacy and safety results in several anemic patients type, like elderly, frailty, and nephropathic patients [25-32]. Latest results from Giliberti et al. showed that ferric sodium EDTA in combination with vitamin C, folic acid, copper, zinc, and selenium therapy improved not only blood iron parameters but also the inflammatory status of enrolled patients with chronic kidney disease (CKD) [26]. A previous study showed efficacy and safety of Ferric Sodium EDTA association as oral treatment in non-dialysis-dependent CKD elderly patients with secondary anemia not responders to a previous treatment period based on ferrous sulphate [28]. More recently, another study conducted in real-life settings on IDA patients, confirmed efficacy and safety results of this product [25]. Thanks to high tolerability profile of the product, safety issue in pregnant women was not expected, and therefore this preliminary analysis was performed. Dealing with a small sample size, we cannot generalize the results to the larger population of pregnant women, however results are very comfortable and lead us to consider this supplementation a good candidate to start wide prevention campaigns for reduce the onset of anemia and related risks in pregnant women and newborns. Further evaluations will foresee the use of

this Ferric Sodium EDTA combination in anemic pregnant women, by setting the adequate dosage according to Hb level and, therefore, severity of anemia in such women. In conclusion, this study confirmed the efficacy and safety of supplementation with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate, and selenomethionine (Ferachel Forte®), for preventing anemia in pregnant women.

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