

Benefit of Iron Supplementation with Ferric Sodium EDTA (NaFe³⁺-EDTA) in the Treatment of Anemia during Pregnancy in Democratic Republic of Congo (FERARI Study)

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Abstract

Background: Oral iron supplements, usually in the form of ferrous salts, are associated with gastric side effects, poor compliance and failure of anemia treatment. To make iron more bioavailable, reduce the gastric side effects and increase the patient compliance, newer iron form, Ferric Sodium EDTA, has become available on the market. **Objective:** To assess the change in hemoglobin level after iron supplementation with Ferric Sodium EDTA during pregnancy. **Materials and Methods:** This is a longitudinal study concerning 337 women attending antenatal care in maternity hospitals in the Democratic Republic of Congo from May to December 2020. The study included sociodemographic and anthropometric variables along with type of feed, hemoglobin level at recruitment and after three weeks of taking iron supplement with Ferric Sodium EDTA (Hemoforce Plus Zinc[®] syrup). For statistical analysis, we used t-test or ANOVA and chi-square test, the significance being stated at $p < 0.05$. **Results:** The frequency of pregnancy anemia was 51.4%. The mean hemoglobin value of the overall study group was 8.7 ± 0.5 g/dL. The mean maternal age and weight were 28.9 ± 6.2 years and 65.3 ± 11.7 kg, respectively. Most pregnant women (83.1%) had a diet consisting of food of plant and animal origin in equal proportions. Mean of Body Mass Index (BMI) was 24.6 ± 4.6 Kg/m² and 44.3% were overweight and obese. The co-morbidities associated were malaria and intestinal parasitosis found in 45% and 5.9% of cases, respectively. After iron treatment with Ferric Sodium EDTA, the average he-

hemoglobin level increased to 11.2 g/dL with mean gain of 2.5 g/dL ($p < 0.001$). Pregnant women with excess weight (≥ 90 kg) and malaria as a comorbidity achieved a significantly lower mean hemoglobin gain ($p = 0.014$ and $p = 0.022$, respectively). Majority of women (91.2%) had not experienced the metallic taste of the syrup. **Conclusion:** Ferric Sodium EDTA as a novel iron formulation (Hemoforce Plus Zinc[®]) has shown a rapid increase in hemoglobin levels in pregnant women suffering from anemia. The speedy rise in hemoglobin is related to the property of Ferric Sodium EDTA to enhance the iron absorption by inhibiting the dietary iron inhibitors. Thus, Ferric Sodium EDTA should be used as an effective and promising iron supplement in pregnant women with iron deficiency anemia.

Keywords

Iron Supplementation, Ferric Sodium EDTA, NaFe^{3+} -EDTA, Anemia, Pregnancy

1. Background

Anemia is a condition of the red blood cells that are insufficiently supplied to meet the body's physiological needs. According to the World Health Organization (WHO), the hemoglobin (Hb) threshold for anemia is below 11 g/dl for pregnant women in developed countries and below 10 g/dl in developing countries [1].

Anemia is a global public health problem that mostly affects low- and middle-income countries (LMICs) [2]. Anemia affects 38% (32.4 million) of pregnant women globally with highest prevalence in the WHO regions of South-East Asia (48.7%) and Africa (46.3%) [3]. Evidence from various low- and middle-income countries suggests that anemia is disproportionately concentrated in the low socioeconomic group [4] with poorest, ethnically disadvantaged, and least educated at the greatest risk.

The WHO has estimated prevalence of anemia in developed and developing countries among pregnant women at 14% and 51%, respectively [5]. In the Democratic Republic of the Congo, in particular in the university clinics of Kinshasa, the frequency of anemia during pregnancy has varied, in the last decade, from 52.2% to 53.4% [6] [7].

Anemia during pregnancy poses a greater risk for low birth weight, preterm birth, and perinatal and neonatal mortality [6] [8] [9]. Besides, the severity of anemia is associated with higher rates of maternal mortality [10].

It is well known that iron supplementation in pregnant women during pregnancy improves hematological values [11] and helps prevent complications. The beneficial effect of iron supplementation has been demonstrated depending on the iron dose, duration of use and initial Hb concentration before treatment [12].

Hemoglobin is an ideal parameter to indirectly identify iron levels. This is due to its high correlation with either ferritin serum levels or the presence of genetic alterations of human hemochromatosis protein (HFE) gene. These clinical pa-

rameters are relatively quick and easy to perform and are already systematically used in standard clinical practice, during pregnancy and follow-up [13].

Iron salts, such as sulfate or fumarate, have been extensively used, but due to gastrointestinal adverse effects, many patients frequently decide to stop taking them [13]. That's why a multicomponent hematinic combination (Hemoforce Plus Zinc[®]) based on Ferric Sodium EDTA (NaFe³⁺-EDTA or sodium ferredate), which allows higher absorption and superior bioavailability of iron, has become available on the local Democratic Republic of Congo market. This formulation appears to be free of the usual iron-related side effects, such as metallic taste and gastrointestinal problems.

Clinical trials involving pregnant women affected by iron deficiency anemia have demonstrated the superiority of Ferric Sodium EDTA, compared to ferrous sulfate and ferrous fumarate, in normalizing blood parameters and in improving the quality of life [14] [15].

The present study aimed to assess the change in hemoglobin level after iron supplementation with Ferric Sodium EDTA (Hemoforce Plus Zinc[®]) during pregnancy in a population of Congolese pregnant women, while taking into account factors such as diet and factors influencing iron intestinal absorption.

2. Methods

This is a longitudinal study of pregnant women followed in prenatal consultation in maternity hospitals in the city of Kinshasa selected by lot as well as in some maternity hospitals in Kongo Central province, Kwilu province and the Eastern province, in the Democratic Republic of Congo. The following maternities were selected in the city of Kinshasa: in the town of BANDALUNGWA, TSHISWAKA Health Center and HOPE MEDICAL; in the municipality of BARUMBU, MAMAN WA CONFIANCE Medical and Maternity Center, KASAI Medical and Maternity Center and FORCE NAVALE Medical and Surgical Center; in Bumbu Commune, Mother and Child Center, Anamed Bumbu Medical Center and RAPHA Medical Center; in the commune of Gombe, Provincial General Reference Hospital of KINSHASA (Ex Mama Yemo); in the commune of Kalamu, KOS MEDICAL CENTER and PKA Hospital Center; in the commune of Kasa-vubu, SAINTE MARIE Hospital Center, the Maman PAMELA State Hospital Center and LNI Medical-Surgical Center; in the commune of Kimbanseke, COMMUNITY Health Center, TRINITE Hospital Center, HOPE CLINIQUE, KIKIMI Hospital Center, KIMBANGUISTE Hospital and ITM Health Center; in the commune of Kinshasa, KIGOMA Medico-Chirurgical Center, Kinshasa Mother and Child Center and AFRICAN Health and Maternity Center; in the commune of Kisenso, APN Medical Center; in the commune of Lemba, University Clinics of Kinshasa and Reference Hospital Center of Camps KABILA; in the municipality of Limete, BONDEKO YA SIKA Clinic and AMOUR DU PROCHAIN Medical Center in KINGABWA; in Lingwala commune, VIJANA Health and Maternity Center and Central Police Hospital C/LUFUNGULA; in the town

of Masina, ESTHER Health Center, MAKENGO Medical Center, the Saint HILAIRE Hospital Center and Saint PAUL Medical Center; in the municipality of Matete, CHRIST ROI Hospital Center; in town of Mont-Ngafula, SUEUR Medical and Maternity Center, MARCELO CENTER, KIMBANGU Clinic and CHRETIEN Medical Center; in the commune of N'djili, LIBIKI Health Center, GRACE DIVINE Medical Center, BOMOI Health Center, Sino-Congolese Friendship Hospital, CHATY Health Center, Medical and Maternity Center TUZOLANU, N'djili General Reference Hospital and MERE THERESIA Medical Center; in the commune of Ngaliema, LUYINDU Medical Center, KINKENDA Hospital Center, SHALOOM MEDICAL Health Center and CELPA Medical Center; in Ngiri-Ngiri commune, State Hospital Center; in the town of N'Sele, CENTENARY Medical Center, JOURDAIN Medical Center, AMED N'SELE, TALANGAI Medical Center and CHARLENE DITONA KABONGO Medical and Maternity Center; in the municipality of Selembao, SANGAMAMBA Reference Health Center. In the Province of Kongo Central, the Polyclinic SANTE POUR TOUS. In Matadi and General Military Hospital in MATADI (CAMP REJAF). In the province of Kwilu, General Referral Hospital of KIKWIT. In the Province of Tshopo, LILEMO Medical Center and University Clinics of Kisangani. The study took place from May to December 2020. Sampling was set up consecutively for all pregnant women attending antenatal care regardless of the age of pregnancy and regardless of age and parity. This study was carried out according to Helsinki's recommendations. Eligible women were recruited after obtaining an informed and written consent to participate in the study.

Study variables and subject monitoring

1) Sociodemographic, anthropometric and clinical variables: age, weight, height, body mass index (BMI) calculated from weight and height, socio-economic level, risk factor for anemia, weakness or feeling of lethargy, history of anemia, presence of co-morbidities (malaria, intestinal parasitosis).

2) Type of feed.

3) Hemoglobin level at recruitment and after three weeks of taking iron supplement with Ferric Sodium EDTA in the form of Hemoforce Plus Zinc[®] in syrup.

4) The parameters related to the iron treatment including the dose used. Pregnant women received doses of 10 to 15 ml of Hemoforce Plus Zinc[®] two or three times a day. Each 5 ml containing Ferric Sodium EDTA 75.85 mg, folic acid 0.5 mg, cyanocobalamin (vitamin B12) 5 mcg, elemental zinc 3.33 mg, elemental manganese 3.25 mcg, elemental copper 2.54 mcg, ascorbic acid (vitamin C) 20 mg.

Information about sociodemographic, anthropometric and clinical variables including type of feed was collected by interview during an antenatal consultation.

Hemoglobin was measured using a hemoglobinometer. By local standards, anemia was defined as hemoglobin < 10 g/dL.

Pregnant women with anemia (Hb < 10 g/dL) received Ferric Sodium EDTA.

Statistical calculations

Data was entered using Microsoft Excel 2007 software and exported to SPSS 21.0 for analysis. For normally distributed parametric data, comparison of means was made using the t-test and comparisons of proportions with the chi-square test. The Pearson correlation test between biological markers was used to look for potential associations with the gain obtained in hemoglobin level after taking Ferric Sodium EDTA. The tests were declared significant at $p < 0.05$.

3. Results

Out of 656 women received for antenatal care in selected maternities during the study period, 337 have presented anemia diagnosed with a hemoglobin level below 10 mg/dl and they fulfilled all the inclusion criteria. The frequency of pregnancy anemia was 51.4%. The mean hemoglobin value of the overall study group was 8.7 ± 0.5 g/dl. Most of pregnant women in our population had a low socio-economic level (69.2%).

Table 1 shows that the mean maternal age was 28.9 ± 6.2 years, the majority of mothers (66.4%) having an age range from 20 to 34 years. Average maternal weight was 65.3 ± 11.7 kg, and 95.8% had less than 90 kg. Most pregnant women in our study (83.1%) had a diet consisting of food of plant and animal origin in equal proportions, while 15.7% had a diet mainly of plant origin; and only 1.2% had a diet mainly of animal origin.

Table 2 shows that the mean parity and gravidity were 3 ± 2 . Multipara and multigravida were 83.1% and 86.9%, respectively. Mean of Body Mass Index (BMI) was 24.6 ± 4.6 Kg/m² and 44.3% were overweight and obese. The co-morbidities associated with pregnancy and anemia in our population were malaria found in 45% of cases and intestinal parasitosis in 5.9% of cases.

After iron treatment with Ferric Sodium EDTA, the average hemoglobin level increased to 11.2 g/dL with extremes of 10 and 13 g/dL. The mean gain in hemoglobin obtained after treatment with Ferric Sodium EDTA was 2.5 g/dL

Table 1. Sociodemographic characteristics of the study group.

Age range (years)	n (337)	%	Means \pm SD	Min-Max
≤ 19	27	8		
20 - 34	253	75.1	28.9 ± 6.2 years	16 - 44 years
≥ 35	57	16.9		
Weight (Kg)				
<90	323	95.8	65.3 ± 11.7 Kg	45 - 120 Kg
≥ 90	14	4.2		
Feed type				
Animal feed only	4	1.2		
Plant-based food only	53	15.7		
Both in equal proportion	280	83.1		

*SD: Standard deviation.

Table 2. Clinical characteristics of the study group.

BMI (Kg/m ²)	n (337)	%	Means ± SD	Min-Max
Thinness (<18)	7	2.1		
Normal (18 - 24)	181	53.7	24.6 ± 4.6 Kg/m ²	15 - 49 Kg/m ²
Overweight (25 - 29)	104	30.9		
Obesity (≥30)	45	13.4		
Parity				
Primipara (1)	57	16.9	3 ± 2	1 - 7
Multipara (≥2)	280	83.1		
Gravidity				
Primigravida (1)	44	13.1	3 ± 2	1 - 12
Multigravida (≥2)	293	86.9		
Co-morbidities				
Malaria	152	45.1		
Intestinal parasitosis	20	5.9		

*SD: Standard deviation; BMI: Body Mass Index.

varying between 1 and 5 g/dL. **Table 3** below shows the gain obtained over the dosage used in the treatment of anemia of pregnancy with Ferric Sodium EDTA. **Table 3** also shows the factors associated with a possible insufficiency of the gain in hemoglobin obtained after treatment with ferric sodium EDTA.

The analysis of the gain obtained in hemoglobin level after treatment of anemia in our pregnant women with ferric sodium EDTA showed significant differences by comparing the averages of the gains obtained according to the different dosages applied, according to the weight of the pregnant women and depending on presence of malaria as a co-morbidity. In fact, the gain in hemoglobin level obtained was, on average, significantly higher when the dosage of ferric sodium EDTA administered was 227.55 mg three times a day compared to the other dosages ($p < 0.001$). Pregnant women with excess weight (≥ 90 kg) showed a significantly lower mean hemoglobin gain ($p < 0.02$) compared to pregnant women of with weight < 90 kg. The treatment of anemia with ferric sodium EDTA in pregnant women with malaria, as a co-morbidity, showed that the mean gain in hemoglobin level obtained was significantly lower compared to pregnant women who received the same treatment but in the absence of malaria ($p = 0.022$). Regarding the side effects reported by pregnant women taking ferric sodium EDTA, majority of women (91.2%) had not experienced the metallic taste of the syrup with only 9.8% reported a metallic taste.

4. Discussion

The present study aimed to assess the change in hemoglobin level after iron supplementation with Ferric Sodium EDTA (Hemoforce Plus Zinc[®]) during pregnancy in a population of Congolese pregnant women, while taking into account

Table 3. Benefit of treatment with iron sodium EDTA and factors associated with insufficient gain in hemoglobin level.

Amount of Ferric Sodium EDTA	N	Mean \pm SD Hg gain (g/dl)	Minimum	Maximum	p
151.7 mg twice a day	67	1.8 \pm 0.8	1	3	
151.7 mg three times a day	47	2.3 \pm 1.1	1	5	
227.55 mg twice a day	125	2.5 \pm 0.5	2	3	<0.001
227.55 mg three times a day	98	3.2 \pm 0.4	3	4	
Total	337	2.5 \pm 0.8	1	5	
Weight (Kg)					
<90	323	2.6 \pm 0.8	1	5	<0.02
\geq 90	14	2 \pm 0.9	1	3	
Total	337	2.5 \pm 0.8	1	5	
BMI (Kg/m²)					
Thinness (<18)	7	2.3 \pm 0.8	1	3	
Normal (18 - 24)	181	2.5 \pm 0.8	1	5	0.720
Overweight (25 - 29)	104	2.6 \pm 0.8	1	4	
Obesity (\geq 30)	45	2.6 \pm 0.9	1	4	
Total	337	2.5 \pm 0.8	1	5	
Intestinal parasitosis					
Oui	317	2.5 \pm 0.8	1	5	0.484
Non	20	2.7 \pm 0.8	1	4	
Total	337	2.5 \pm 0.8	1	5	
Malaria					
Oui	185	2.4 \pm 0.8	1	5	0.022
Non	152	2.6 \pm 0.8	1	4	
Total	337	2.5 \pm 0.8	1	5	

factors such as diet and factors influencing iron intestinal absorption. Despite anemia being a global concern, women in less developed countries are disproportionately affected. As such, only about 5% of pregnant women in developed countries estimated to be anemic compared to 80% in some developing countries [16] [17].

In the present study, occurrence of pregnancy anemia was 51.4%. The rate of anemic pregnant women found in our study has been quite constant in our setting for years [6] [7], meaning endemicity of anemia among pregnant women in our country. This high rate is common in deprived areas [18] [19] [20], although lower rates have been observed in Tanzania (47%) [21], in Ethiopia (31.7%) [22], and in East Africa (41.82%) [23].

Most of pregnant women in our population had a low socio-economic level (69.2%). Low socioeconomic conditions are to be pointed out as well due to in-

appropriate nutritional intake along with bad hygienic conditions that favour hookworms infestation. This corroborates other studies carried out in similar environments [7] [20] [24] [25] [26] [27] [28]. This situation will thus change only if poverty is reduced and is supportive of routine iron supplementation during pregnancy as well as other preventive measures.

Most pregnant women in our study (83.1%) had a diet consisting of food of plant and animal origin in equal proportions, while 15.7% had a diet mainly of plant origin, and only 1.2% had a diet mainly of animal origin. All plant-derived and animal-derived foods contain nonheme iron, while heme iron mainly found in the foods derived from animals, mainly meat, fish, poultry, and eggs. Heme iron has a higher bioavailability and is absorbed easier without the need for absorption-enhancing cofactors. Nonheme iron, which is the most important dietary source in vegetarians, shows lower bioavailability; its absorption depends on the balance between dietary enhancers and inhibitors and body iron stores. About 25% of dietary heme iron gets absorbed, while only 17% of dietary nonheme iron gets absorbed. Based on the studies, iron bioavailability is estimated to be 14% to 18% for mixed diet consumers and 5% to 12% for vegetarian diet consumers [29]. Therefore, less than one-fifth of the amount of dietary iron gets absorbed by the body.

A number of studies reported that low BMI increases the risk of anemia in pregnancy [17] [30] [31]. In our study, Mean of Body Mass Index (BMI) was 24.6 ± 4.6 Kg/m² and 44.3% were Overweight or obese. The mean hemoglobin value of the overall study group was 8.7 ± 0.5 g/dl. Our results are in contract with those of many authors in the literature who have shown that lower early pregnancy BMI in pre- or early pregnancy is associated with lower hemoglobin levels and higher risk of anemia in pregnancy [30] [31] [32]. Low early pregnancy weight or BMI may be a reflection of poor nutrition intake, including the intake of various micronutrients that are essential for hematopoiesis [4]. Furthermore, low weight or BMI could be a result of chronic illness, such as tuberculosis or parasitic infections, which consequently lead to anemia [17] [33]. These conditions are still the major health problems globally and are often under-diagnosed [20] [34] [35]. What has not been confirmed in this study.

Although anemia in pregnancy is multi-factorial, poor nutrition and infection are also common causes. The co-morbidities associated with pregnancy and anemia in our population were malaria found in 45.1% of cases and intestinal parasitosis in 5.9% of cases. Parasites like the malaria parasites and intestinal parasites have long been recognized as major contributors to reduced hemoglobin levels in endemic countries like Cameroon, thereby causing anemia [36]. Malnutrition or anemia caused by intestinal worms may be worsened during pregnancy and make the pregnancy difficult. Anemia is common in developing countries because of poor nutritional status and highly prevalent parasitic infestation. In Sub-Saharan Africa, soil-transmitted helminths including hookworm, urogenital schistosomiasis, and other parasitic infections such as malaria contribute to the high anemia rates in women and young children [37].

Ferric Sodium EDTA is an iron chelate that has been used successfully as a dietary fortifier in several trials in the developing world [38] [39], as in this form, the iron is protected from inhibitors of iron absorption. It has a bioavailability 2 - 4 times that of ferrous sulfate, especially in meals with high phytate content [40]. Therefore, it is expected to effectively improve both, the iron deficiency and the gastrointestinal side effects in anemic pregnant women. Hemoglobin is an ideal parameter to indirectly identify iron levels. This is due to its high correlation with either ferritin serum levels or the presence of genetic alterations of human hemochromatosis protein (HFE) gene [13] [41].

After iron treatment with Ferric Sodium EDTA 151.7 to 227.55 mg twice or three times a day in our study, the average hemoglobin level increased from 8.7 g/dl to 11.2 g/dL. The mean gain in hemoglobin obtained after treatment with Ferric Sodium EDTA was 2.5 g/dL varying between 1 and 5 g/dL. Our results corroborate a number of studies in the literature, which have reported that Ferric Sodium EDTA might be a better form of iron supplements than electrolytic iron [42]. Iron absorption from Ferric Sodium EDTA might be two to three times higher than from electrolytic iron [43]. Ferric Sodium EDTA increased both Hb concentration and serum ferritin concentration substantially in iron deficient populations [44]. At least 10 mg/day iron as Ferric Sodium EDTA would be necessary to prevent iron deficiency anemia even in populations relying for their subsistence on vegetable food only; although those suffering from severe anemia would require more than 10 mg/day [45], which was also verified in the present study. In our study, the lower daily dose of Ferric Sodium EDTA showed a marginal rise in hemoglobin; however, the gain in hemoglobin level obtained was significantly greater when the dosage of Ferric Sodium EDTA used was 227.55 mg three times a day ($p < 0.001$). Nevertheless, this gain was lower when the pregnant woman had excess body weight (≥ 90 kg) ($p = 0.014$) or had malaria ($p = 0.022$).

Several studies showed that Ferric Sodium EDTA is more suitable than electrolytic iron in the anemia treatment at children and pregnant women [38] [46] [47]. The Xiu *et al.* study showed that iron deficiency among pregnant women untreated in the middle trimester of pregnancy might deteriorate in the third trimester in terms of hematologic status; and moderate iron supplementation has been beneficial in improving iron deficiency, and Ferric Sodium EDTA reported to be superior to ferrous sulfate [39] [48].

Regarding the side effects reported by pregnant women taking Ferric Sodium EDTA, only 9.8% mentioned a metallic taste. The same observation was made in the literature regarding a lower incidence of side effects attributable to Ferric Sodium EDTA [14] [49].

The limitation of the present study is that it could not assess dietary iron intake in pregnant women included in the sample.

5. Conclusion

Ferric Sodium EDTA is a time-tested, oral iron form used for the prevention and

treatment of iron deficiency anemia. Efficacy and safety of Ferric Sodium EDTA have been well reported in literature for various patient populations like pregnant women and children. Ferric Sodium EDTA, as Hemoforce Plus Zinc[®] syrup, has shown a rapid increase in hemoglobin levels in pregnant women suffering from anemia. The speedy rise in hemoglobin is related to the property of Ferric Sodium EDTA to enhance the iron absorption by inhibiting the dietary iron inhibitors. Treatment is well tolerated without clinically significant side effects. Thus, Ferric Sodium EDTA should be used as an effective and promising iron supplement in pregnant women with iron deficiency anemia.

Author's Contributions

MMA is the principal investigator, participated in generated and designing the study and was actively involved in data collection and statistical calculations. He drafted the first manuscript. MDV, MMR, EMJP, LAJ and LNN participated in designing the study and analyzing the results. All authors contributed in preparing the final manuscript.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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