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Cohort Study on Benefit of Martial Supplementation with EDTA Sodium Iron in Management of Gravidic Anemia at the University Clinics of Kinshasa

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Abstract

Background: Anemia is mainly attributed to nutritional deficiency, especially iron deficiency, which predominates during pregnancy, and is associated with parasitic diseases such as malaria and intestinal parasitosis, acute or chronic diseases such as sickle cell disease, tuberculosis, HIV infection and various micronutrients disorders. It is associated with an increased risk of low birth weight and prematurity and can contribute to impaired cognitive development in early childhood, as well as to maternal mortality. The impact on the fetus is even greater if maternal anemia onset is at an early stage, or prior to pregnancy. Iron salts, such as sulfate or fumarate, are widely used in the treatment of gravidic anemia, but due to various gastrointestinal side effects, many pregnant women are not compliant with treatment. Sodium iron EDTA, on the other hand, is highly absorbable and bioavailable. The latter improves hematological values and appears to be free from the usual iron-related side effects, hence compliance with this supplementation. **Objectives**: To evaluate the evolution of hemoglobin levels after sodium iron EDTA supplementation at the university Clinics of Kinshasa, to determine the frequency of gravidic anemia, the dose-dependent benefit of sodium iron EDTA supplementation in pregnant women and to identify factors associated with insufficient hemoglobin gain after supplementation. **Methods**: This longitudinal cohort will take place in the gynecology department of the University Clinics of Kinshasa from September 2022 to August 2023 and will include at least 54 pregnant women with anemia. **Conclusion**: The study will enable us to better assess the benefits of sodium iron EDTA in improving hematological

values, as well as its tolerability in pregnant women suffering from anemia during pregnancy in our environment.

Keywords

Anemia, Pregnancy, EDTA Sodium Iron, Martial Supplementation

1. Introduction

Anemia is a condition characterized by a reduction in the number of red blood cells or a drop in hemoglobin levels, which prevents oxygen from being carried to organs and tissues. 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] [2] [3]. Around one in four women conceives with insufficient or absent iron stores, with serum ferritin levels below 30 mg/l. These levels are insufficient to meet increased iron requirements during pregnancy, childbirth and the postpartum period [4]. The global prevalence of anemia is 24.4%, and an estimated 2 billion people suffer from anemia [3] [5]. According to the World Health Organization (WHO), the prevalence of anemia among women of childbearing age in sub-Saharan Africa is 57.1%, but this varies from region to region, with the highest level recorded in Central and West Africa (61%) and the lowest in Southern Africa (34%) in 2011. Although the authors report a downward trend from 1995 to 2011, the anemia is found in 38% of pregnancies (32.4 million) worldwide [6], with a prevalence of 14% in developed countries and 51% in developing countries [7] [8]. This prevalence is more marked in sub-Saharan Africa, due to a lower intake of iron and other micronutrients before and during pregnancy [9]. In the DRC, especially at the University Clinics of Kinshasa, the reported frequency of anemia during pregnancy has varied from 52.2% to 53.4% [10] [11]. Anemia is a public health problem mainly affecting developing countries [12]. Anemia can be attributed mainly to nutritional deficiency, particularly iron deficiency, which predominates during pregnancy, and is associated with parasitic diseases such as malaria and intestinal parasitosis, acute or chronic diseases such as sickle cell disease, tuberculosis, HIV infection and various micronutrient disorders [13] [14] [15] [16]. Anemia contributes to 23% of maternal mortality (MM) worldwide and is directly responsible for more than 3% of severe MM in Africa [17] [18] [19]. Maternal anemia during pregnancy, particularly from the second trimester onwards, influences the infant's postnatal growth and is associated with an increased risk of low birth weight, prematurity and may contribute to impaired cognitive development in early childhood. The impact on the fetus is even greater when maternal anemia onset is at an early stage, or even prior to pregnancy [20] [21]. Management of anemia during pregnancy is twofold: preventive, involving exclusively exogenous iron supplementation combined with blood and intestinal cleansing; and curative, involving either oral iron in the form of iron

salts, parenteral iron in the form of sugar-bound injectable iron, or blood transfusion, depending on the severity of the anemia [22]. It is well known that iron supplementation in pregnant women improves hematological values and helps prevent complications [23]. The beneficial effect of iron supplementation has been shown to depend on iron dose, duration of use and initial Hb concentration before treatment [24]. Iron salts, such as sulfate or fumarate, have been widely used, but due to gastrointestinal side effects, many patients frequently decide to stop taking them [25]. This is why a multi-component sodium iron EDTA, which allows high absorption and bioavailability, has become available on the Congolese market. It appears to be free from the usual iron-related side effects (metallic taste and gastrointestinal troubles). Several studies have evaluated these beneficial effects, including clinical trials involving pregnant women with iron-deficiency anemia, which demonstrated the superiority of sodium iron EDTA over ferrous sulfate in balancing blood parameters and improving quality of life [26] [27], while a study in India comparing sodium iron EDTA and ferrous fumarate showed that low doses of sodium iron EDTA improved Hb levels without adverse effects, making sodium iron EDTA an effective treatment for anemia in pregnant women [26]. Measurements of serum iron, ferritin and transferrin are the best markers of iron status. In developing countries, on the other hand, where access to healthcare is difficult due to low socio-economic status, Hb measurement is often used [28]. Hemoglobin is an ideal parameter for indirectly identifying iron levels, due to its strong correlation with serum ferritin levels or the presence of genetic alterations in the human hemochromatosis (HFE) protein gene. This paraclinical parameter is relatively fast and easy to perform and is already routinely used in standard clinical practice during pregnancy [25]. In DR Congo, given the poverty of our population, iron supplementation is still the order of the day and occupies a predominant place for pregnant women, compared with other environments where they have found a way of short-circuiting oral iron by administering it parenterally. To avoid treatment discontinuation due to other forms of iron, it is important to know whether sodium iron EDTA can offer particular advantages, as described in the literature, or also in our setting with regard to the characteristics of our population. This is why we initiated the present study.

2. Objectives

This study will evaluate the evolution of hemoglobin levels after supplementation with sodium iron EDTA at the university clinics of de Kinshasa, to determine the frequency of gravidic anemia, the dose-dependent benefit of sodium iron EDTA supplementation in pregnant women, and to identify factors associated with insufficient hemoglobin gain after supplementation.

2.1. Rationale for the Study

To answer the questions of whether martial supplementation with sodium iron EDTA during pregnancy will improve hemoglobin levels, and whether sodium

iron EDTA used as a martial supplement during pregnancy will cause side effects, our study will take place from September 2022 to August 2023 at the university clinics of Kinshasa. Our study population will consist of pregnant women attending antenatal care and giving birth at the university clinics of Kinshasa.

2.2. Study Design and Methods

2.2.1. Overview of the Study

This will be a longitudinal cohort study conducted at the university clinics of Kinshasa (UCK) among pregnant women attending antenatal care at CUK, with a minimum sample size of at least 54 pregnant women, based on a prevalence of 53.4%, calculated according to the formula [10]:

$$n \geq \frac{2\left(Z_{\alpha} + Z_{1-\beta}\right)^2 + p(1-p)}{\left(p_0 - p_1\right)^2}$$

n: is the minimum sample size.

Z_{α}: is the confidence coefficient (1.96).

$Z_{1-\beta}$: corresponds to the test's ability to detect a significant difference (1.645).

p: is the prevalence of anemia in our environment (53.4%).

α: is the type I margin of error (5%).

p_0: is the expected proportion of unsupplemented pregnant women.

p_1: is the expected proportion of pregnancies that have been supplemented and will be able to develop gain after martial supplementation; this proportion of p_1 is estimated by the investigator on the basis of the estimated value of p_0 and the size of the difference between p_0 and p_1 that he thinks it possible and desirable to highlight.

Given that $p_1 = RR \times p_0$ with $RR = 2$ and $\rightarrow \quad p = \frac{p_0 + p_1}{2} \quad \rightarrow \quad 0.534 = \frac{p_0 + 2p_0}{2}$

So $p_0 = 0.36$ and $p_1 = 0.7$.

After incorporating these elements into the formula, our minimum calculated sample size will be at least 54 pregnant women following prenatal consultations at the university Clinics of Kinshasa until delivery. This study is designed and will be financed by our own funds.

2.2.2. Patient Selection

Inclusion criteria:

All pregnant women from 14 weeks following prenatal consultations at the university clinics of Kinshasa, regardless of parity.

Non-inclusion criteria:

- All pregnant women were carriers of any pathology that could have had an adverse effect on the pregnancy.
- All pregnant women having received a transfusion less than three months prior to recruitment

Sampling was carried out consecutively for all pregnant women attending antenatal clinics, taking into account inclusion and non-inclusion criteria.

2.2.3. Study Variables and Subject Follow-Up

- **Socio-demographic variables**: age, marital status, weight, height, level of education, occupation, socio-economic level.
- **Clinical variables**: parity, gestational age, abortion, intergenital space, weight, height, BMI, age of pregnancy at recruitment, geophagy, tea intake, coffee intake, alcohol, tobacco, history of anemia, presence, or absence of comorbidities.
- **Neonatal variables**: APGAR, birth weight and route of delivery.
- **Biological parameters**: Hemoglobin and hematocrit will be measured using a Hbmate VERI-Q hemoglobinometer.
- **Treatment-related variables**: dosage, duration of treatment and adverse effects.

2.3. Data Collection Procedure

Our study will take place over 12 months (September 2022 to August 2023) in the Department of Gynaecology and Obstetrics at the University Clinics in Kinshasa, DR Congo. We will recruit pregnant patients of all ages seen in prenatal consultations, and after informed consent, a capillary blood sample will be taken to measure hemoglobin levels. Those with hemoglobin levels below 10 g/dl will benefit from martial supplementation with sodium iron EDTA, the dose of which will depend on the severity of the anemia. These samples will be taken on the initial day (D0) and three weeks (D21) later, to enable us to assess the hemoglobin gain after this supplementation with EDTA sodium iron. All pregnant women will be followed until delivery.

Each 5 ml of component contains 11 mg sodium iron EDTA, 0.5 mg folic acid, 5 mcg cyanocobalamin (vitamin B12), 3.33 mg elemental zinc, 3.25 mcg elemental manganese, 2.54 mcg elemental copper, 20 mg ascorbic acid (vitamin C).

2.4. Expected Results of the Study

In this study, we aim to determine the current frequency of anemia during pregnancy in UCK, describe the socio-demographic and clinical characteristics of pregnant women with anemia in UCK; determine the dose-dependent benefit of sodium iron EDTA supplementation in pregnant women managed for UCK anemia and identify factors associated with insufficient hemoglobin gain after martial supplementation with sodium iron EDTA.

2.5. Statistical Considerations

Data will be entered using Microsoft Excel 2016 and exported to SPSS 22.0 for analysis. For normally distributed parametric data, results will be expressed as a proportion and as mean plus or minus standard deviation. Comparisons of means will be made using Student's t-test or ANOVA, and those of proportions using Pearson's chi-square or Fisher's Exact test. Odds ratios are used to assess the strength of association between variables. The test is considered significant for a p value < 0.05.

2.6. Ethical Considerations

The project was approved by the staff of the Department of Gynecology and Obstetrics of University clinics of Kinshasa, as well as by the Ethics Committee of the School of Public Health at the University of Kinshasa. It should be noted that sampling will be carried out as part of routine pregnancy monitoring. Data from this study will be collected in complete confidentiality and will be treated anonymously.

3. Discussion

Anemia is an important determinant of maternal and child health [7], and to this day constitutes a heavy burden in developing countries [3]. Studies in developed and developing countries have reported frequencies of 39.8%, 83%, 2.49%, 41.6%, 58.8% and 53.4% respectively in Cameroon, India, Portugal, Turkey, Nigeria, and the DRC [11] [29] [30] [31] [32] [33]. Iron salts in the form of ferrous and ferric iron are used in the treatment of anemia of pregnancy. Vijaya *et al.* demonstrated the efficacy of sodium iron EDTA over ferrous fumarate in the treatment of anemia, and the advantage it provides in significantly improving Hb levels with fewer adverse effects than other forms of iron salts [17] while Han *et al.* showed that with medium doses of sodium iron EDTA, pregnant women were less likely to develop oxidative stress during pregnancy than those consuming other forms of salt, and significantly improved hematological parameters [27] [34] [35].

All these aspects will be addressed in our study.

3.1. Strength of the Study

- Our study will be the first in our field to investigate the benefits of martial supplementation with EDTA sodium iron.

3.2. Limitations

- The monocentric nature of the study, carried out in a single healthcare institution, and the small sample size make it impossible to extend the results to the national level.
- Lack of iron status marker assays.

4. Conclusion

The study will enable us to better assess the benefits of sodium iron EDTA in improving hematological values, as well as its tolerability in pregnant women suffering from anemia during pregnancy in our setting.

Authors' Contributions

MMA and LNN are the principal investigators. MMA generated and designed the study. LNN participated in the study design and will be actively involved in data collection. MMA, LMEP, LAJ, MNF, LBJ, LMEP, KNB, NOC and MFM

contributed to the drafting and improvement of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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