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The Efficacy of Daily Versus Weekly Ferrous Sulfate in Maintaining Normal Serum Ferritin Levels During Pregnancy: A Randomized Controlled Trial

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ABSTRACT

Background: Serum ferritin is the most reliable indication of stored iron in pregnancy, offering a noninvasive way to detect iron deficiency anemia before it occurs. Therefore, this study aimed to determine serum ferritin levels among women receiving daily versus weekly iron supplementation, with a secondary focus on comparing the proportion developing iron deficiency anemia and compliance rates between the two groups.

Methods: This non-blinded randomized control trial involved non-anaemic pregnant women attending antenatal clinics at two Teaching Hospitals in Osun State. One hundred twenty-five subjects were recruited to receive 65mg in the control group, while another 125 subjects in the active group received three tablets (195mg) of ferrous sulfate (Fesulf) once weekly for 17 weeks from the 20th to 37th weeks of gestation. The primary outcome measure was comparing mean serum ferritin levels in both groups at 37 weeks.

Results: Among the 240 subjects analyzed, the 37-week serum ferritin level was higher in the daily group (73.26±26.67µg/L) compared to the weekly group (63.04±30.71 µg/L), p value=0.006. Four (3.36%) and 10 (8.26%) of our subjects had Iron deficiency anaemia. Nine subjects (3.75%) reported dyspepsia as a side effect. Daily 65 mg of Felsulf proved more effective than weekly 195mg in maintaining normal blood ferritin levels during pregnancy.

Conclusions: Daily iron supplementation with 65mg ferrous sulfate was more effective at maintaining adequate maternal iron concentration in this group of non-anaemic pregnant women. This dosage is recommended for routine iron supplementation in our environment.

Key words: Serum ferritin, Ferrous sulfate, Iron supplements, Pregnancy, Anaemia, Nigeria.

1. INTRODUCTION

Anemia in pregnancy is a significant contributor to maternal mortality as it increases a parturient risk of poor obstetric outcomes. This is mainly due to obstetric hemorrhage, which is a significant cause of maternal mortality. Unfortunately, anaemia remains prevalent in developing nations like Nigeria.

Anaemia affects over 40% of pregnant women worldwide, and more than half of these cases occur in Africa[1]. In Nigeria, the prevalence of pregnancy-related anaemia vary, reportedly as 61.8% in Oyo, 62.6% in Port Harcourt, 46.0% in Enugu, 44.0% in Lagos, and 17.0% in Kano [2–6]. While the etiology is often multi-factorial, iron and folate deficiencies are significant contributors, with up to two billion people globally experiencing iron deficiency anemia, including fifty-six million pregnant women [1].

Plasma ferritin levels correlate with body iron stores and serve as a diagnostic test for iron deficiency anaemia [7]. It acts as a buffer, releasing needed iron in a regulated manner, thus playing a crucial role in iron metabolism [8]. Serum ferritin is identified as the single best indicator of iron storage in pregnancy [9,10]. It offers a non-invasive option to predict iron deficiency anaemia before it becomes evident[7].

The recommended iron supplementation in pregnancy varies. Ogunbode et al. recommended a dosage of 180 mg of elemental iron in three divided doses daily from the second trimester onwards in non-anemic pregnant women based on a landmark clinic-based study carried out in Ibadan, which

showed a significant level of iron deficiency (ID) in pregnant women[11]. However, this approach may carry potential risks, including iron overload and an increased risk of malaria infestation and eclampsia in the third trimester. [12,13,14] Compliance is also influenced by dosage, as higher doses may lead to side effects like nausea and constipation[15]. This and the need to promote adherence prompted the calls for a change to intermittent supplementation [16]. The World Health Organization (WHO) recommends weekly intermittent 200mg elemental iron in non-anemic pregnant women to ensure an optimal outcome [17].

Studies in this environment have predominantly focused on daily supplementation and its impact on pregnancy outcomes [8,18]. Routine iron supplementation is recommended in developing countries due to the relatively iron-deficient states in which women often get pregnant [11]. However, despite interventions, anaemia in pregnancy persists, raising concerns about utilization and compliance [19,20]. Compliance is reportedly improved if iron supplements are free, administered less frequently, and women are educated on their necessity [20.21]. .Despite findings suggesting an equivalence between twice-weekly and weekly regimens, compliance remains a concern. Hence, this prompted us to investigate whether the once-weekly regimen improved compliance compared to the daily regimen. This study aims to compare the mean serum ferritin levels between the daily and weekly groups with a secondary focus on assessing compliance.

2. METHODOLOGY

2.1 Study Design

This study was a non-blinded randomized controlled trial (RCT) conducted among 250 non-anaemic pregnant women recruited at 20 weeks gestation at the antenatal clinics of the selected hospitals.

2.2 Study Subjects

The participants of this study were pregnant women attending antenatal clinics at two teaching hospitals in Osun State, southwest Nigeria: the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC) in Ile-Ife, and the UNIOSUN Teaching Hospital, Osogbo, from January 2017 to March 2018.

2.3 Inclusion Criteria

Non-anaemic pregnant women with packed cell volume (PCV) greater than or equal to 30% (according to WHO guidelines) and aged between 18 and 40. All subjects were recruited at 20 weeks gestation, and only subjects with singleton pregnancies were recruited.

2.4 Exclusion Criteria:

Subjects with ongoing infections, such as ongoing or previous urinary tract infections (UTI) in the index pregnancy, and haemoglobinopathy, such as haemoglobin SS or SC, were excluded. Additionally, women with medical conditions such as hypertension and diabetes mellitus in pregnancy were excluded.

2.5 Sample Size

Sample size calculation was based on the formula for the comparison of means [22]. Sample size N was calculated assuming the minimum difference between the mean serum ferritin of both groups we set out to detect was ± 3ug/L (minimum detectable difference) [13], 95% confidence interval, precision of 0.05, and power (1-β) of 80%. The minimum effect size was based on a prospective observational study by Lao et al.[13], who reported a mean serum ferritin level of 34.5 µg/L ± 5.3 in the third trimester. The N was 226, and a 10% attrition rate was provided to account for loss to follow-up; the total sample size was N=249, rounded to 250.

Therefore, 125 subjects were recruited for each arm of this study.

2.6 Interventions

The standard of care/control group received daily administration of 65mg of elemental iron (one tablet of Fesulf 200mg by Therapeutic Pharmaceuticals, Lagos). In contrast, the intervention group received three tablets of ferrous sulfate (Fesulf® 200mg BP) equivalent to 195mg of elemental iron once a week. Subjects were allocated to either arm of the study at booking using a simple random sampling technique in the ratio of 1:1, as prepared by a Statistician. Participants were allocated even or odd numbers generated by the computer consecutively. Participants allocated odd numbers were in the control group, while those allocated even numbers were in the intervention group. The PI was blinded to this process to reduce selection and allocation bias.

Participants were then sent to the Principal Investigator (PI) for blood sample collection. 5mls of venous blood was collected in K-EDTA bottles and sent to the laboratory where the PCV was analyzed, and serum separated for serum ferritin test. The drug dispensation (Fesulf tablets) was done by a Pharmacy technician, according to the group allocation.

Participants in both arms were also instructed to take iron tablets with 100mg of vitamin C. They were also advised to avoid drinking milk or antacids with their iron tablets or within 30 minutes of taking the medication.

2.7 Outcome Measures:

The primary outcome in both groups was the mean change in serum ferritin concentration between 20 and 37 weeks of gestation. The secondary outcomes included the proportion of women in both groups who had iron deficiency and iron deficiency anemia, the change in packed cell volume (PCV) between 20 and 37 weeks, the mean birth weight, and the occurrence of side effects.

2.8 Methods of Measurement

A 5ml blood sample was collected in a plain universal bottle for serum ferritin estimation using the Accu-Bind ELISA Microwells Ferritin Test System with Product code 2825-300, manufactured by Monobind® Inc., USA. The capillary tube blood sampling technique was used for PCV estimation. Both tests were conducted at the 20th and 37th weeks of pregnancy.

Baseline ferritin levels were categorized as low (<30µg/L), normal (31-130µg/L), and high (>130)(23). Anaemia was diagnosed in the second and third trimesters in subjects with PCV < 30%, iron deficiency (ID) in subjects with PCV >30% but serum ferritin < 30 µg/L, while iron deficiency anemia was diagnosed in subjects with PCV < 30% and serum ferritin < 30 µg/L [23,24]. Inquiries were made about side effects, including dyspepsia, nausea, and constipation, at every clinic visit.

The intervention group had iron tablets on their antenatal clinic day to enhance compliance.

The clinic visits were monthly until 28 weeks, fortnightly until 36 weeks, and weekly until delivery. The Pharmacy administered the exact number of pills needed at each visit. A pill count was conducted at each visit, and all subjects were contacted by telephone at fortnightly intervals to remind them to take their iron tablets. The pills were also given to all participants at no cost.

In this study, the subject in either group was considered compliant if she took at least 85% of her medications within the specified

prescription period, as assessed by the pill count and leftovers at each clinic visit.

2.9 Statistical Analysis

Our primary data analysis used an intention-to-treat analysis. The characteristics of each group were described using frequency descriptions and measures of central tendency and dispersion. An independent t-test was used for continuous variables. A p-value less than 0.05 was considered statistically significant. All analyses were conducted using IBM SPSS Statistics Version 21.0.

2.10 Ethical Approval

Research approval was obtained from the Obafemi Awolowo University Teaching Hospital's Ethics and Research Committee (ERC/2015/09/05), and consent forms were duly filled for each subject.

2.11 Data Availability

The data for this study is available on Zenodo at https://zenodo.org/records/13128548

3. RESULT

Two hundred fifty subjects were recruited, and ten were lost to follow-up. Therefore, 240 subjects were analyzed: 119 in the daily arm (control) versus 121 in the weekly (intervention) arm. All 121 subjects received the intended intervention. None of the participants disengaged from the study due to side effects or changed from the weekly to the daily group due to anemia in pregnancy. In the daily arm, 11(9.2%) had a primary level of education versus 5 (4.1%) in the weekly group. The majority had secondary and tertiary levels of education (108(90.8%) vs (116(95.8%)), (daily versus weekly) a p-value of 0.118.

Table 1 shows participants' characteristics, including mean ages, parity, GA at delivery, and birth weight. These parameters were comparable between the two groups.

Furthermore, twenty-five (6.25%) of the 240 subjects had iron deficiency (serum ferritin level < 30ug/L) at recruitment (20 weeks), despite having a PCV ≥30%.

Table 2 shows, the baseline mean serum ferritin (ug/L) at 20 weeks and the serum ferritin level at GA of 37 weeks in the daily versus weekly groups (73.26±26.67 ug/L versus 63.04±30.71ug/L, p-value= 0.006). The mean difference in serum ferritin in the daily group is 14.70±2.43ug/L versus 1.12±0.26ug/L in the weekly group, with a p-value = 0.001; this was statistically significant.

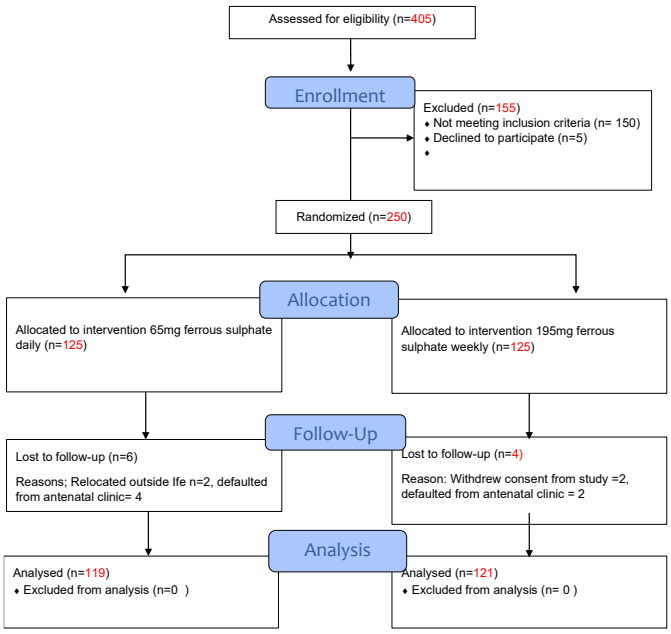

Figure 1: Consort Flow Diagram of Daily Versus Weekly Iron Supplementation

Table 1: Comparison of Subject Characteristics Between Daily and Weekly Supplementation Groups

Variable	Daily Mean ±SD	Weekly Mean ±SD	P value
Age	28.97±5.06	28.73±5.38	0.720
Parity	2.19±1.05	2.28±1.22	0.534
Birth Weight	2.99±0.37	2.93±0.29	0.135
EGA At Delivery	38.43±2.65	38.55±1.70	0.664

EGA: estimated gestational age

Table 3 shows the distribution of iron deficiency and iron deficiency anaemia in the daily and weekly groups. IDA was diagnosed in 4 (3.36%) of the daily group and (10)8.26% of the weekly group.

Nine subjects (3.75%) reported side effects, all of whom were in the control group. This is shown in Figure 2, with dyspepsia being the most reported. Furthermore, most respondents (91.7%) complied with using ferrous sulfate as prescribed throughout the study period. Three participants developed pre-eclampsia. Two (1.7%) of the subjects who had daily supplements had pre-eclampsia, while one (0.8%) of those in the weekly group developed the same.

4. DISCUSSION

Maternal serum ferritin is a vital iron store, and low concentration is an early predictor of anemia in pregnancy. In pregnancy, ferritin levels are crucial in the early detection of anemia. It is considered the best test to assess iron deficiency in pregnancy [19,23]. Iron supplementation in pregnancy is vital for both the mother and the fetus. This study showed approximately 6.25% of participants had iron deficiency (low serum ferritin) at recruitment despite having normal PCV. This connotes that significant cases of iron deficiency, which may later progress to iron deficiency anemia, may abound in our antenatal attendees. Pratt reported that a reduction in serum ferritin precedes changes in red cell indices such as hemoglobin concentration in cases of iron deficiency [7]. This proportion is lower than 30-60%, reported by studies of iron status in European women of reproductive age group [10,25,26]. This disparity is probably because these studies used a lower threshold of 15ug/L, which was based on expert consensus and may not be physiological [25,26]. Iron deficiency without anemia is reported to be primarily due to insufficient iron intake or excessive chronic loss which may be more prevalent in LIMCs such as Nigeria[21,24]. It is, therefore, essential to continue to provide antenatal supplementation at the correct dosage due to the inherent benefits [25,26].

A significant improvement in mean serum ferritin level was observed in the daily supplementation group at 37 weeks (p value 0.001) confirming that daily intake of iron supplements is more efficacious than weekly supplementation at preventing Iron Deficiency Anaemia in pregnancy. This concurs with other African studies where iron supplementation significantly improved maternal and perinatal outcomes [18,23]. This contrasts with a study conducted in Vietnam, where there was no difference between the serum ferritin of both groups [28].

We observed a significant reduction in the proportion of women with iron deficiency (ID) at recruitment (20 weeks) compared to 37 weeks in the daily arm of this study (12.6% vs. 3.12%). Notably,

Table 2: Comparison of PCV and Serum Ferritin Concentration Between the Daily and Weekly Supplementation Groups

Variable	Daily Mean ±SD	Weekly Mean ±SD	P value
PCV at 20 wks.	31.76±1.93%	31.24±1.72	0.70
PCV at 37 wks.	32.05±2.16%	30.98±1.79	0.001
Ferritin at 20 wks.	58.56±26.37 ug/L	61.91±31.75ug/L	0.373
Ferritin at 37 wks	73.26±26.67 ug/L	63.04±30.71ug/L	0.006
Postpartum PCV	30.62±2.39%	29.57±2.20	0.001
*Mean Difference In Serum Ferritin	14.70±2.43 ug/L	1.12±0.26ug/L	0.001

20 and 37 weeks refer to estimated gestational age (EGA) at which tests were done.
**The mean difference in serum ferritin is the average of (serum ferritin at 37 weeks and serum ferritin at 20 weeks*

most subjects with both ID and iron deficiency anemia were in the weekly group, suggesting that daily iron supplementation improved serum ferritin levels and iron storage more effectively. This difference may be attributed to cumulative iron absorption over time in the daily group, as research indicates that in non-anemic individuals, absorption at the gastric mucosa rarely exceeds 10% of administered iron [19, 31].

The evidence regarding daily versus weekly iron supplementation during pregnancy remains inconclusive. Although several earlier reports advocate for 200 mg of elemental iron weekly [8, 29, 30], Numerous studies in low-and middle-income countries (LMICs) have demonstrated that daily supplementation is more effective than weekly supplementation [19, 32]. This observation may reflect similarities in socio-cultural factors and economic differences between LMICs and industrialized nations [33].

Our study established that normal packed cell volume (PCV) does not indicate adequate iron storage. Van Den Broek and co-workers also made this conclusion after comparing other invasive and non -invasive serum iron measures [28]. This, among other evidence, formed the basis for the United Kingdom guideline, which recommends iron supplementation when serum ferritin levels fall below 30ug/L in pregnancy to prevent the development of iron deficiency anemia, since routine iron supplementation is not practiced in pregnancy in the UK [9,25, 27]. This test should, therefore, be considered where the laboratory skills and reagents are available to estimate iron stores in pregnancy and probably individualize the need for iron supplementation, especially in low-and middle-income countries.

Side effects were higher in the daily arm compared to the weekly arm of the study even though serum ferritin level did not exceed 150ug/L, which was the upper limit of the normative reference for this study. This agrees with earlier works, which have reported that patients on daily supplements were more likely to report and discontinue iron usage due to the occurrence of side effects compared to women on intermittent doses [12,28]. Side effects were one of the crucial reasons for non-compliance with iron supplementation [21,33]. Dyspepsia was the most common side effect reported. Most other studies reported nausea [32].

Compliance was relatively high in this study. It is comparable to the 92% reported by an Ethiopian study on compliance with iron supplementation[20]. This may be because the drugs were given free of charge, and participants were reminded to take their drugs via telephone. This is in tandem with reports on adherence to iron supplements in pregnant women, where giving the drugs free of charge and adequate health education was shown to enhance adherence and improve utilization[21,33].

Table 3: Comparison of Iron Deficiency and Iron Deficiency Anaemia (IDA) Based on Ferritin Levels Between the Two Groups at Recruitment (20 Weeks) and 37 Weeks.

	Daily (%) N=119	Weekly (%) N=121
20 Weeks (At Recruitment)		
Serum Ferritin Level < 30ug/L and PCV ≥30% at 20 Weeks (ID)	15 (12.61%)	10 (8.26%)
37 Weeks		
Serum Ferritin < 30ug/L and PCV < 30% (IDA)	4 (3.36%)	10 (8.26%)

The perinatal outcome assessed using birth weight was comparable in both arms of the study. This implies that although 195mg of elemental iron weekly may not prevent iron deficiency to the same degree as a 65mg daily dose, it is enough to ensure optimal growth in the fetus. Earlier studies have corroborated this [9,12,20,30].

From the foregoing, daily iron supplements at a dose of 65mg of ferrous sulfate were more beneficial to the parturient in optimizing her iron store. However, the perinatal outcome was similar in both regimens

We reported preeclampsia in three (1.25%) of our subjects. The serum ferritin level in these three women was less than 150ug/dl. Although earlier studies cited a weak link between iron overload and increased risk of preeclampsia[12,13], more recent meta-analyses have failed to establish a link [35].

Limitations

A community-based survey exploring intermittent regimen of varying doses, such as twice or thrice weekly, maybe more informative and generalizable[16,28]. A cost-benefit analysis of both regimens may also be relevant.

4.1 Conclusion

Daily administration of 65mg of ferrous sulfate was more effective at maintaining normal serum ferritin levels in singleton, non-anemic pregnant women. However, daily iron supplementation was associated with a higher side effect profile. The perinatal outcome was comparable in both arms of the study. Due to these results, daily iron supplements with 65mg ferrous sulfate are encouraged.

Conflicts of Interest

The authors declare no conflicts of interest

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Bola-Oyebamiji, SB: Conceptualization, Validation, Format Analysis, Investigation, Resources, Methodology, Data Curation, Visualization, Writing-Original draft, Writing review & editing.

Awowole, IO: Data Curation, Methodology, Writing-review and editing.

Bolarinwa, RA: Methodology. Writing review, editing, and Supervision.

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Kuti O: Methodology. Writing review and editing, and Supervision.

Trial Registration:

This trial was registered at the US National Institute of Health (clinicaltrials.gov) with registration number ISCTRN 77724888.

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