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Impact of Twice Weekly Hematinics on Hematological Parameters in Pregnancy

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Authors' contributions

This work was carried out with the collaboration of all authors. Author GDM lead author, designed the study, wrote the introduction, materials and methods and discussion. Authors PHD and SAA supervised the work and proofread the manuscript. Author DD coordinated the hematological assay and proofread the work. Author IL was involved in sample size calculation, statistics and conducted the serum ferritin. All authors read and approved the final manuscript.

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ABSTRACT

Background: Anemia is prevalent in our setting for myriads of reasons hence iron supplementation has become a routine in the antenatal clinics; other regimens are practiced in other climes.
Aims: This study aimed at comparing the efficiency of the twice-weekly as against the daily iron supplementation on hematologic indices in healthy pregnant women.
Study design: This was a longitudinal prospective study
Place and duration of study: this study was carried out at antenatal clinic at the Jos university teaching hospital Jos plateau state of Nigeria over a period of 14 weeks.
Methodology: A total of 120 pregnant women were assigned by simple random sampling to receive either daily or twice weekly iron supplementation. Their blood samples were assessed by

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determining hemoglobin concentration, mean corpuscular volume and serum ferritin as baseline at booking visit from 16-24 weeks of gestation and follow up at 4, 8 and 14 weeks. All data generated was analyzed using EPI info computer software version 3.5.2. The level of statistical significance was set at P<0.05.

Results: The twice weekly supplementation showed similar effects with the daily regimen with regards to the trends in Hb and serum ferritin. More women (77.1%) on twice weekly regimen had Hb>10g/dl at the 14 week visit compared with daily regime and this was statistically significant *P*=0.031.

Conclusion: These findings suggest that both regimens have about the same effect on hematological parameters during pregnancy. Therefore, in non-anemic pregnant women twice weekly iron supplementation may be used.

Keywords: Anemia; Iron supplementation; pregnancy; Nigeria.

1. INTRODUCTION

Anemia is a critical health concern at it adversely affects growth and energy levels, afflicting about two billion people worldwide. Although iron is the most abundant element on the earth crust, iron lack in the body has been identified as the commonest cause of anemia worldwide [1].

Anemia which compromises the immune mechanisms is associated with increased morbidity and is regarded as a major risk factor for unfavorable pregnancy outcomes including preterm labour, low birth weight, maternal and perinatal morbidity and mortality [2-3].

The definition of anemia can be based on either hemoglobin (Hb) or hematocrit (Hct) concentration [4]. Hb has the physiological function of carrying oxygen from the lungs to the different organs, and accordingly, environmental oxygen tension can affect Hb concentration in the blood [5]. Environmental oxygen declines gradually with increasing altitude, while Hb increases with increasing altitude, especially when the altitude is greater than 1000m above sea level [5-6].

In 1993, the World Bank ranked anemia as the 8th leading cause of disease in girls and women in the developing world [6]. The most affected groups in descending order are pregnant women, the elderly, school children and adult males the least [7].

In developing countries, prevalence rates of anemia range between 20-60% (in pregnant women 40 – 60%, Non-pregnant women and school aged children 20-40%, and 20% of adult Males) [7].

Nutritional deficiencies are responsible for most cases of anemia, especially in the developing countries, typified by Damulak et al. 2012 where 33.3% of anemia in the Plateau state specialist hospital was due to nutritional anaemia [8].

A study done on the incidence of anemia in 735 normal singleton pregnant patients at booking in the UCH Ibadan, between 1st June, 2000 and 31st May 2001 reported a prevalence of 15% [9].

The 2012 WHO Guidelines estimated that 41.8% of pregnant women worldwide are anemic, with at least half of this assumed to be due to iron deficiency [10]. The rest of cases of anemia are due to other conditions such as folate, vitamin B12 or vitamin A deficiencies, chronic inflammation, parasitic infections and inherited disorders [11].

A pregnant woman is said to be anemic if her Hb concentration during the 1st and 3rd trimesters of gestation is lower than 11g/dl, at sea level; in the second trimester of pregnancy, the hemoglobin concentration usually decreases by approximately 0.5g/dl [12]. Authorities in Nigeria have adopted the cutoff of Hb<10g/dl for anemia in pregnancy because in many developing countries, the vast majority of women with Hb around 10g/dl are apparently healthy and symptom free with perinatal mortality rates not different from among pregnant women with higher Hb level. Only Hb< 10g/dl is likely to reflect inadequate maternal nutritional status with respect to iron, folic acid and other nutrients [13].

Low Hb concentration during pregnancy have been associated with an increased risk of premature delivery, maternal and child mortality, and infectious diseases, [14] fetal growth and development may also be affected, both in utero and in the long term [15]. Conversely, Hb concentration greater than 13g/dl at sea level

may also be associated with negative pregnancy outcomes such as premature delivery and low birth weight [10].

Various interventions have been put forward for the prevention of iron deficiency anemia in pregnancy including iron supplementation, iron staple food fortification, health and nutrition education, control of parasitic infections, and improvement in sanitation and clean water supply [10]. Delayed umbilical cord clamping is also effective in preventing iron deficiency among infants and young children [16].

During pregnancy there is increased maternal iron demand to meet both maternal and fetal needs [7]. Most pregnant women require additional iron intake to ensure sufficient iron stores at conception, during pregnancy and the post natal period to prevent IDA [7]. The use of daily iron and folic acid supplements throughout pregnancy has been the standard approach to cover this gap in preventing and treating iron deficiency anemia. Despite the proven efficacy, the use of daily iron supplementation has been limited in program settings possibly due to lack of compliance because of common side effects (e.g. nausea, constipation, dark stools or metallic taste) [10]. Intermittent use of oral iron supplements (i.e. once, twice or three times a week on non-consecutive days) has been proposed as an effective alternative to daily iron supplementation for prevention of anemia in women of reproductive age, including those who are pregnant [10]. The rationale behind this intervention has traditionally been that intestinal cells turn over every 5 – 6 days and have limited iron absorptive capacity. Thus intermittent provision of iron would expose only the new intestinal epithelial cells to this nutrient, which in theory, should improve its absorption [11,17] intermittent supplementation also reduces oxidative stress and other side effects of daily supplementation [16,18-19] and may minimize blockage of absorption of other minerals due to the high iron levels in the gut lumen and in the intestinal epithelial cells [20]. It has therefore been suggested that intermittent regimens may be more accepted by women, which may result in increased adherence to supplementation programs [20].

Iron supplementation with or without folic acid supplementation has been used in a variety of doses, and regimens. The current recommendations for pregnant women include the provision of a standard daily dose of 60mg of elemental iron and 400ug (0.4mg) of folic acid [21]. However this study aimed at ascertaining the effects of twice weekly Iron supplementation compared to daily Iron supplementation on hematological parameters among pregnant women in our clinical setting. This study may add to the body of knowledge for a paradigm shift from the traditional (daily) to intermittent (twice weekly) hematinic supplementation model in non-anemic pregnant women as there are efforts at different levels to shift away from the traditional to focused antenatal care model that is evidence based, goal directed, woman centered care that emphasizes quality rather than frequency of visits.

2. MATERIALS AND METHODS

This was a longitudinal prospective study of women on twice weekly iron supplementation as cases and those on daily supplementation as controls, carried out at the antenatal clinic of the Jos university teaching hospital, JUTH, a tertiary hospital situated in the North Central Zone of Nigeria. The hospital serves as a referral Centre for neighboring States of Benue, Kogi, Nasarawa, Taraba, Adamawa, parts of Southern Kaduna, Bauchi and Gombe and the Federal Capital Territory Abuja, between September 2014 and January 2015. The women were those who booked for antenatal care between 16-24 weeks of gestation with hematological parameters (packed cell volume and hemoglobin concentration,>=30% and 10g/dl respectively) with in normal range, singleton, without comorbidities and consented for the study were included whereas pregnant women with multiple gestations, those already on hematinic, and those with other comorbidities such as sickle cell disease, anemia, HIV and those who had early vaginal bleeds were excluded following history taking, examination and investigations at the booking clinic.

Eligible pregnant women who consented to participate in the study were grouped into two cohorts, the twice weekly iron supplementation and the daily iron supplementation group using simple random sampling. There were sixty pregnant women in each group.

Blood sample was drawn before the commencement of hematinic and sent to the hematology laboratory for analysis by automation (bt prosel, Mindray) and also chemical pathology laboratory for serum ferritin assay by ELISA method (STAT FAX 4200 microplate reader).

About 5 ml of blood taken from each subject from the antecubital or dorsal vein of the hand then 2.5 ml was put into dipotassium EDTA anticoagulant tube for complete blood count analysis while 2.5ml into a plain bottle for serum ferritin assay, these were sent to the hematological and Chemical Pathology laboratories respectively for baseline Hb, MCV and serum ferritin. These women were then placed on hematinic, 200mg of ferrous sulfate (65 mg elemental iron) and 5mg of folic acid, those on twice weekly were instructed to take on Monday and Thursday's. The age of each pregnant woman, gestational age, parity, educational, socio-economic status, baseline anthropometric data – (weight, height and body mass index) were estimated.

Hematological estimation (Hb, MCV) was carried out during antenatal care at 4 and 8 weeks follow up periods while Hb, MCV and serum ferritin levels at 14 weeks respectively

Data collection was through the assistance of the midwives at the antenatal clinic as well as the laboratory staff. All data generated from the questioner was collated into Microsoft excel and analyzed using EPI info computer software version 3.5.2. The level of statistical significance was set at $P<0.05$. Student t-test was done to determine the difference in the hematological parameters of women taking twice weekly hematinic supplementation compared to those on daily, chi square and Fischer exact test were adopted where applicable at 95% confidence interval.

3. RESULTS

The Socio-demographic and reproductive characteristics of the studied women are shown in Table 1 below. The women in the two groups differed significantly in age ($P<0.05$) but were marched in terms of educational Status, occupation, Husband educational status, Parity and Body mass index (BMI) ($P>0.05$). Most of the women studied (47.6%) were within the Age range of 25-30 years, of the 105 subjects studied (15 patients were lost to follow up, 8 from the cases while 7 from the controls with response rate of 87.5%). 51.4 % were Housewives while 48.6% were employed.

Table 2 below, shows the anthropometric characteristics of the study population, 25.8± 6.1Kg/m2 in the twice weekly group, and 25.5± 3.7 Kg/m2 in the daily iron supplementation group, this difference was not statistically significant ($P>0.05$).

The hematological characteristics of the women at booking and follow up visit using the independent t test shown on Table 3 below shows Hb concentration and MCV levels dropped at 4 and 8 weeks visit in both groups and started rising at 14th week visit, serum ferritin dropped slightly from 31.4± 25.4µg/l to 30.1± 25.2µg/l in the twice weekly arm while a deeper drop from 27.7±22.4µg/l to 23.9 ±19.3µg/l in the daily arm at the 14th week visit. There was no statistically significant differences in the initial and follow up Hb, MCV, and Serum Ferritin level between the two groups ($P>0.05$).

Table 4 below showed the pattern of anemia, using Hb< 10g/dl cut off At the booking clinic, all the patients enrolled had Hb > 10g/dl representing 100%. The percentage of women with Hb <10 g/dl increased to 50.5% at the 8th week visit and reduced to 41% at the 14th week visit. Its worthy to note that more women (77.1%) had Hb > 10g/dl in the twice weekly group at 14 week visit, this was statistically significant ($P<0.05$).

Table 5, show Serum Ferritin concentration pattern according to the booking and 14th week visits. At booking 80% of women had ferritin levels >12µg/l while 20% had hypoferritemia (serum ferritin levels < 12µg/l). There was a non-statically significant change at 14th week with 76.2% and 23.8% for ferritin levels of >12µg/l and <12µg/l respectively ($P>0.05$).

4. DISCUSSION

Twice weekly Iron supplementation has been shown to be effective in the prevention of Iron deficiency anemia in non-pregnant women, children and adolescent girls [18,22].

The red cell mass expands by about 33% while the plasma volume expands by 50% and this differential increase results in dilutional anemia in pregnancy. Enhanced erythropoiesis of pregnancy increases the utilization of iron which can reach 6-7mg per day in the latter half of pregnancy. The placenta actively transports iron from the mother to the fetus, the fetus generally is not anemic even when the mother is severely iron deficient.

Table 1. Women's Socio-demographics by iron supplementation regimen

Characteristics	Iron Administration		Total	χ2	*P*-value
	Twice Weekly	Daily	n=105(%)		
	n=52(%)	n=53(%)			
Age Group (yrs)				6.473	0.039
<25	14(26.9)	14(26.4)	28(26.7)		
25-30	30(57.7)	20(37.7)	50(47.6)		
>30	8(15.4)	19(35.8)	27 (25.7)		
Education				3.550	0.322
Primary	3(4.0)	4(7.5)	7 (5.7)		
Secondary	27(54.0)	20(37.7)	47 (44.8)		
Tertiary	19(38.0)	24(45.3)	43 (41.0)		
No Formal Education	3(4.0)	5(9.4)	8 (6.7)		
Occupation					
Housewife	29(55.8)	25(47.2)	54 (51.4)	0.777	0.378
Employed	23(44.2)	28(52.8)	51 (48.6)	0.673	0.879
Husbands education					
Primary	3(5.8)	1(1.9)	4(3.8)		
Secondary	14(26.9)	15(28.3)	29 (27.6)		
Tertiary	33(63.5)	35(66.0)	68 (64.8)		
No Formal Education	2(3.8)	2(3.8)	4 (3.8)		
Gravidity				1.468	0.480
1	12(23.1)	13 (24.5)	25(23.8)		
2-4	31(59.6)	27(50.9)	58(55.1)		
≥5	9(17.3)	13(24.5)	22(20.9)		
Gestational age at booking					
<20 weeks	21(40.4)	21(39.6)	42(40)		
20-24 weeks	31(59.6)	32(60.4)	63(60)		

Table 2. Anthropometric characteristics of the pregnant women studied

Characteristics	Iron administration		t-test	P-value
Twice weekly	daily			
BMI (kg/m2)	25.8±6.1	25.5±3.7	0.276	0.783
Height(m)	1.6±0.1	1.6±0.1	0.018	0.985
Weight (kg)	66.2±13.1	64.2±9.2	0.904	0.368

Table 3. Hematological indices of subjects according to regimen of Iron (independent t-test)

	Iron administration		t-test	P-value
Hematological indices				
Twice weekly Daily				
Hemoglobin (g/dL)				
At booking visit	11.3±0.9	11.1±0.9	0.886	0.378
4weeks Follow up visit	10.2±0.8	10.1±0. 9	0.130	0.897
8weeks Follow up visit	9.9±1.3	9.8±1.1	0.448	0.656
14weeks Follow up visit	10.4±0.9	10.1±1.4	1.728	0.088
MCV-mean corpuscular volume (fl)				
At booking visit	88.1±11.8	89.9±10.2	0.785	0.434
4weeks Follow up visit	79.6±5.5	81.0±5.3	1.151	0.253
8weeks Follow up visit	79.0±6.5	81.6±5.7	1.810	0.075
14weeks Follow up visit	79.9±7.3	82.5±5.9	1.644	0.105
Serum ferritin(ug/l)				
At booking	31.4±25.4	27.7±22.4	0.736	0.464
14weeks Follow up visit	30.1±25.2	23.9±19.3	0.622	0.536

Table 4. Anemia Based on Hemoglobin cut-off of 10 g/dl

Hemoglobin	Iron administration				
	Twice weekly	Daily	Total	χ2	p-value
At booking visit					
≥10g/dl	52	53			
<10					
4wks F. up visit				0.194	0.659
≥10g/dl	30(57.7)	29(54.7)	59(56.2)		
<10	22(42.3)	24(45.3)	46(43.1)		
8wks F. up visit				2.000	0.157
≥10g/dl	29(58.3)	23(43.4)	52(49.5)		
<10	23(41.7)	30(56.6)	53(50.5)		
14wks F. up visit				6.231	0.031
≥10g/dl	36(77.1)	26(49.1)	62(59.0)		
<10	16(22.9)	27(50.9)	43(41.0)		

Table 5. Serum ferritin of the subjects studied

Serum ferritin	Iron administration			χ2	P-value
	Twice weekly	Daily	Total		
At booking visit				0.467	0.495
≥12	43(82.7)	41(77.4)	84(80.0)		
<12	9(17.3)	12(22.6)	21(20.0)		
14wks F. up visit				0.401	0.527
≥12	41(78.8)	39(73.6)	80(76.2)		
<12	11(21.2)	14(26.4)	25(23.8)		

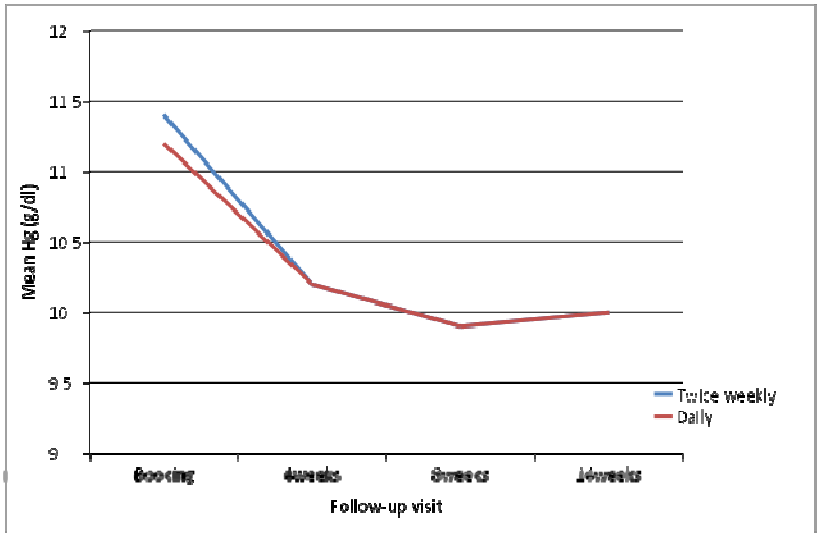

Fig.1. A line graph on trend of mean Hemoglobin concentration

Most women in the study (47.6%) were within the age range of 25-30 years in both groups, which is the similar with studies by Goshtasebi, Farahnaz and Sunil respectively [23-25] and lower than that reported in the study by Erhabor and colleagues in Sokoto with a mean age of 33.2 years [26].

More than half (51.4%) of the subjects studied were House wives, this was slightly more than those who were employed 48.6%. This is less than that found in the study by Goshtasebi and colleagues with 97.5% [23] this wide difference may be attributed to the fact that Jos is a more heterogeneous society than The Islamic

Republic of Iran, where sociocultural and religious practices may have contributed to these wide variations. In our setting women can engage in various types of vocation, menial jobs and petty trading to help their spouses to cater for their families.

Of the studied population, 55.1% were multiparous women while 23.8% were primigravidae and the least (20.9%) were the grand multiparous women.

The mean Body mass index (BMI) in our study was 25.8kg/m2 and 25.5kg/m2 in twice weekly group and daily group respectively, which was slightly higher than those in the study by Goshtasebi et al who had a mean BMI of 23.4kg/m2 and Sunil et al with 20.6kg/m2 23,25.

This study compared the efficacy of twice weekly iron supplementation on hematological profile. On Table 3 this regimen showed a similar effect with the daily iron supplementation with respect

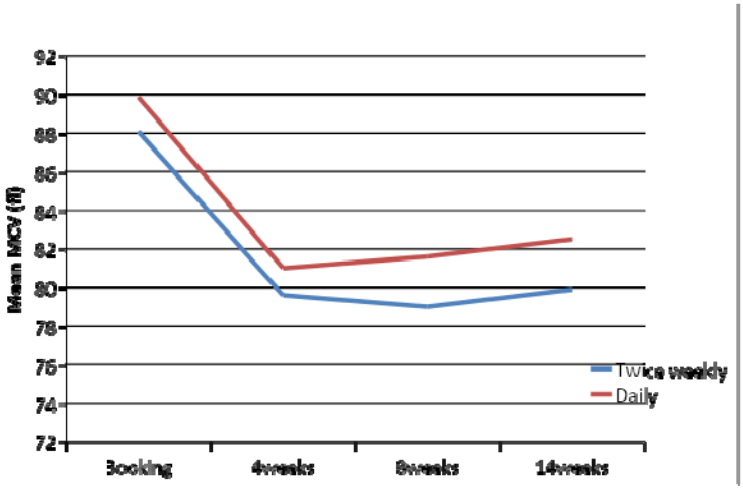

Fig. 2. A Line graph showing the trend in MCV during 14 weeks clinic visits

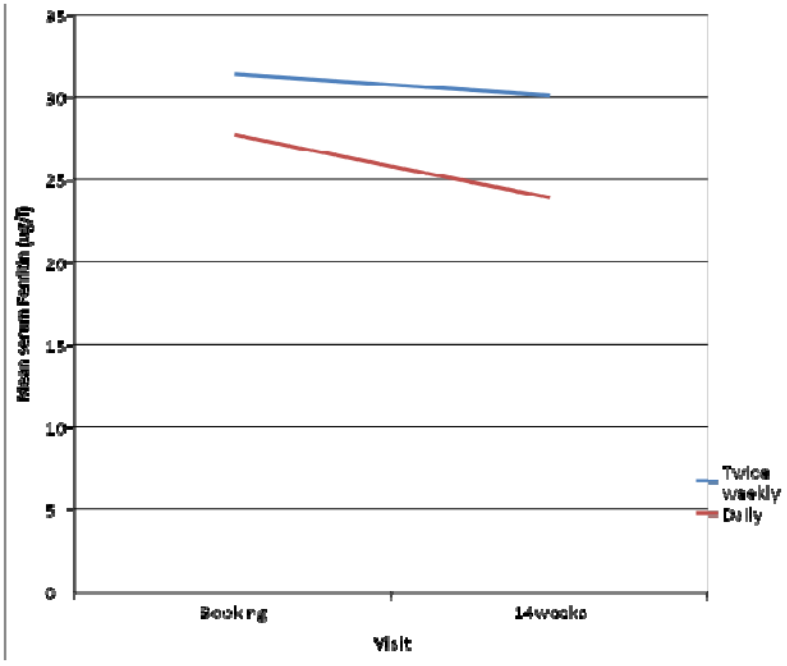

Fig. 3. A line graph showing changes in the mean serum ferritin in the two groups

to maintaining the hemoglobin concentration, the hemoglobin concentration reduces steadily from the initial visit, reaches a nadir at 8 week visit and begins to rise at 14 week visit, though the difference was not statistically significant, this is patterned to the physiological changes that occur in pregnancy. This was similar to the findings by Farahnaz and Bouzari [24,27] but different from a study by Sunil and colleagues which showed a continuous rise in the hemoglobin concentration, which may be due to difference in the elemental Iron used, in our study 200mg (65mg of elemental) iron while 335mg of ferrous sulfate (100mg of element iron) was used [25].

Our findings suggest the superiority of the twice weekly iron supplementation with 77.1% of women with hemoglobin concentration greater than 10g/dl at the 14th week follow up visit, as against 49.1% in the daily supplementation group and the difference was statistically significant (P=0.031). Several studies of anemic pregnant women also reported comparable increment of hemoglobin concentration comparing the two supplementation models [23,28-29].

Serum ferritin level is the gold standard for assessing iron deficiency anemia, showed a slight drop from the initial visit compared with that at 14 week follow up visit in both arms. In the twice weekly iron supplementation the drop was from 31.4µg/l to 30.1µg/l while it was 27.7µg/l to 23.9µg/l in the daily group. Though the difference was not statistically significant ($p>0.05$), this is similar to other studies [24-27].

Hypoferritemia (<12µg/l) [26] was observed in 21.2% of subjects in the twice weekly group at 14 week visit as opposed to 26.4% of women in the daily arm. This showed that both regimens did not prevent the percentage of patients with iron deficiency anemia at the end of the study which further buttresses the earlier assertion that iron requirement reaches a crescendo in the last trimester of pregnancy.

The prevalence of iron deficiency anemia among the women studied was 20% at the booking visit and 23.8% at the 14 weeks visits. This is higher than 13.5% in sokoto [26] and higher than the average of 14% in developed countries. The reason for this is not farfetched, nutritional deficiency results from low socioeconomic factors, multiparity, short pregnancy interval, hookworm infestation, malaria parasitization.

The Mean corpuscular volume (MCV) is the measure of the average size of the red blood cell, with a normal range of 80-100fl in pregnancy [30]. MCV less than 80fl indicates microcytic hypochromic anemia and is in keeping with iron deficiency. The twice weekly iron supplementation arm was not sufficient in maintaining normal values as seen in Table 3. MCV was seen to increase significantly in the daily group and non-significantly in the intermittent group in a study by Farahnaz, this difference may be due to exclusion of multiparous women from his study population [24].

5. CONCLUSION

Daily Iron supplementation has been the practice especially in the antenatal clinics in low resource setting like ours for many years due to the high prevalence of nutritional anemia and increased demands for iron in pregnancy and coupled with fact that clients may be on other medications for other health challenges, from the results above reveals that in non-anemic pregnant women twice weekly regimen can be adopted to enhance compliance and reduce pill burden.

6. LIMITATIONS

1. The sample size is small compared to other studies with a lager sample size

2. Due to financial constraint we couldn't do directly observed therapy (DOT) as observed in other studies even though subjects were assessed on follow up visit to ensure they are taking the drugs as expected.

3. Routine Malaria parasite (MPs) and stool microscopy for Hook worm infestation were not done to possibly treat this patients, it may suffice to say that all subjects received Sulphadoxine/ Pyrimethamine, at least 2 doses each, 4 weeks apart as it's the National protocol for IPTp, but routine anti helmintics are not given in our antenatal clinic.

4. The Serum for Ferritin levels was stored in a refrigerator for 14 weeks at a temperature of – 21oC with a fairly stable electricity supply in JUTH, this is due to the high cost and non-availability of the test kits in our environment.

7. RECOMMENDATIONS

1. Improvement in the people's living standards especially the girl child to reduce the incidence of IDA through economic empowerment, advocacy on good and balance diet.
2. Family spacing to allow these women regain their iron stores before they embark on another pregnancy.
3. Malaria Parasite Test (RDT) should be included in our antenatal Investigations for prompt identification and treatment of malaria.
4. Stool microscopy may also be added to the investigations as to identify those women that may require treatment for hook worm infestation.
5. For non-anemic pregnant women, twice weekly supplementation can be adopted..
6. Studies with larger sample size and adoption of DOT may be needed to substantiate the efficacy of the twice weekly iron supplementation regimen as it was seen in our study.

CONSENT AND ETHICAL APPROVAL

Informed consent was obtained from each participant's and non-consenting subjects were excluded without prejudice. The study was approved by the research and ethical committee of the Jos University Teaching Hospital (JUTH/DCS/ADM/127/XIX/5851).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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