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Side Effect Profile of Hematinics in Pregnancy in Jos Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Anemia in pregnancy is common especially in developing countries and iron supplementation is routinely given to pregnant women to mitigate the impacts of anemia in pregnancy.
Objective: This study aimed at determining the side effect profiles of twice weekly and daily iron supplementation in a group of healthy pregnant women in our clinic setting.
Patients and Methods: This was a longitudinal prospective study involving 120 pregnant women who received either daily or twice weekly iron supplementation. Their blood samples were assessed by determining hemoglobin concentration by an auto analyzer (Mindray) and a structured questionnaire was used at each follow up visit to assess the side effects they experienced from the booking visit at 16-24 weeks of gestation and follow up visits at 4, 8 and 14 weeks. All data was analyzed using EPI info computer software version 3.5.2 and level of significance was set at *P<0.05.*
Results: Over three-quarter (77.1%) of women in the twice weekly supplementation group had hemoglobin concentration greater than 10g/dl at the 14th week follow up visit, while that of the daily arm supplementation was 48.6% and was *P=0.031*. The gastrointestinal side effects were more

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exaggerated and of clinical importance 35% experienced heart burns in the daily arm as against 20.9% in the twice weekly arm (*P=0.06*).
Conclusion: The side effects of routine hematinic are commoner among daily supplementation group and heartburn is the commonest side effects among the pregnant women therefore for non-anemic pregnant women who cannot tolerate the daily iron regimens, twice weekly dosing may suffice.

Keywords: Hematinic; side effects; anemia.

1. INTRODUCTION

Despite widespread preventive measures, iron deficiency anemia during pregnancy is still prevalent and is associated with adverse pregnancy outcomes for both mother and newborn [1,2]. Poor compliance with national protocols because of side effects especially gastrointestinal (GT) complications such as nausea, vomiting and constipation is suggested as one of the main reasons for the inefficiency of these programs [3]. Several studies indicate that iron absorption could improve if iron supplementation is given intermittently, matched with the epithelial regeneration time of the intestinal mucosa, which in turn diminishes side effects and enhance compliance rates [4].

Interaction of iron with other micronutrients especially zinc, and the postulated relationship between high-dose iron supplementation and pregnancy complications including gestational diabetes, preterm labor and low birth weight, suggest that the amount of iron recommended in the current protocol is too high [4,5].

Very high hemoglobin (Hb) concentration causes high blood viscosity, which results in both compromised oxygen delivery to tissues and cerebrovascular complications. Epidemiologic studies have found an association between high maternal Hb concentrations and an increased risk of poor pregnancy outcomes. Available evidences do not support that this association is causal, it could rather be attributed to hypertensive disorders of pregnancy and preeclampsia [5,6].

A Meta-analysis comparing the two dose frequencies concluded that although a daily regimen was better than a weekly dosing; both were efficacious in preventing a fall in hemoglobin concentration during pregnancy [6].

A randomized longitudinal study conducted in Pakistan on the effectiveness of weekly iron supplementation on anemia in pregnancy, a total of 110 pregnant anemic women attending the antenatal clinic were randomized into receiving 200mg ferrous sulfate daily or weekly. Hb concentration, Serum ferritin, red cell count, red cell indices and reticulocyte count were assessed to compare the effectiveness of the regimens. The result was that Hb% ($P<0.05$), red cell counts ($P<0.01$) and reticulocyte count ($P<0.05$) were significantly increased in the weekly group when compared with the daily group, while serum ferritin values increased non-significantly in daily group when compared with weekly group, hence weekly supplementation of iron is equally effective in controlling iron deficiency anemia (IDA) as is daily iron supplementation [7].

WHO for more than 20years, published recommendations on the design of large-scale iron supplementation programs with the aim of reducing the prevalence of iron deficiency anemia in populations of developing countries [8]. Two decades later, little has changed in the situation of iron deficiency anemia.

Compliance is of importance in combating iron deficiency anemia, as non-compliance reduces treatment benefits and is associated with poorer prognosis. A study carried out in India on compliance of antenatal women to iron supplementation in routine antenatal clinic at a tertiary health care center, 860 women at 16-30 weeks pregnancy prescribed daily tablets of iron supplementation observed compliance in 80.47% and non-compliance in 19.53%.The reasons for non-compliance were; side effects(29.03%), suffering from pregnancy complications and taking multiple drug supplements(22.58%), long term taking of iron tablets (19.35%),dislike for pharmaceutical preparations(16.94%),forgetfulness (9.68%)and perceived poor quality of iron tablets supplied by government (2.42%) [9].

In a cross sectional descriptive study in Oyo state of Nigeria, 590 women attending randomly selected PHC centers' were studied on demographic factors determining compliance to

iron supplementation in pregnancy and reported compliance rate was 37.5%. The Hb level was higher among women complying with iron supplements compared with those not complying. The study also concluded that singles, teenage mothers and those aged 35 years and above were less likely to be compliant [10].

At the University Teaching Hospital Port-Harcourt (UPTH), compliance to iron supplementation was 88%, while the side effects of iron and forgetfulness were the main reasons for the observed non-compliance [11].

In Senegal, compliance rate of daily iron supplementation was 69% [12].

A 2012 Cochrane review reported that one to three times a week iron supplementation is as effective for preventing anemia in pregnant women as daily administration, with women experiencing fewer side effects [13].

It is estimated that anemia may be responsible for as much as 20% of all maternal deaths in sub-Saharan Africa through three main mechanisms. First, it predisposes the pregnant woman at risk of hemorrhage by lowering her hematological reserves for blood loss especially at birth, secondly severe anemia increases susceptibility to infection due to lowered resistance to infectious disease, and thirdly, Hb< 4g/dl is associated with high risk of cardiac failure, particularly during delivering or as soon after [14].

According to WHO standards, anemia in pregnancy is present when the Hb concentration in the peripheral blood is less than 11g/dl. 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 [14].

A study carried out at the antenatal clinic of the University of Port Harcourt Teaching Hospital showed a prevalence of 23.2% and 6.7% for Hb< 11g/dl and Hb<10 g/dl respectively [15].

The prevalence of anemia at first antenatal visit in the Jos University Teaching Hospital in a descriptive cross-sectional study was 45.8 %(WHO definition) and 13.8% (Hb<10g/dl) [16].

The WHO also recommended universal supplementation of 60mg elemental iron and 400ug folic acid once or twice daily for 6months in countries where the prevalence of anemia is < 40%, and for an additional 3 months post-partum in countries where the prevalence is >40%. Several studies have shown improved maternal and perinatal outcome following routine iron supplementation during pregnancy [17].

As a result of poor compliance of oral hematinic, studies carried out revealed that weekly or thrice weekly iron supplementation give equally good outcomes as daily dosing with better patient compliance [18].

A review of current knowledge about iron metabolism during pregnancy and the evidence from studies on the effects of iron supplementation in pregnancy on maternal, fetal and infant outcome suggests that the implicit goal of current recommendations regarding iron supplementation may be to achieve the highest Hb concentration possible. This goal is related to improved maternal and infant outcomes in the current pregnancy or to improved maternal iron stores in the long term.

For women in developed countries who are generally clinically healthy and have access to adequate nutrition, the benefits of daily iron supplementation are unclear, thus a better “conservative” approach may be that such women do not require routine (daily) iron supplementation during pregnancy [19].

In well-resourced settings, selective oral iron supplementation based on serum ferritin levels at booking is practiced i.e. for serum ferritin levels >60µg/l, no iron supplementation, while serum ferritin levels 20-60µg/l, iron supplementation is commenced from 20 weeks of gestation, ferritin levels 15-19µg/l, supplementation is commenced from 12 weeks of gestation while serum levels < 15µg/l, the woman is considered a patient and treated [20].

2. MATERIALS AND METHODS

This was a longitudinal prospective study of pregnant 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, Jos 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 Nigeria 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) within normal range. Those with multiple gestations, recurrent abortions those already on hematinic or traditional medications and those with other comorbidities such as sickle cell disease, anemia, PUD, HIV and those who had early vaginal bleeds were excluded.

Eligible pregnant women who consented to participate in the study were grouped into two simple random sampling, the twice weekly iron supplementation and the daily iron supplementation group. 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) also chemical pathology laboratory for serum ferritin assay by ELISA method (STAT FAX 4200 micro plate reader).

About 2.5ml of blood taken from each subject from the antecubital or dorsal vein into dipotassium EDTA anticoagulant tube for complete blood count analysis. These women were then placed on hematinic, 200mg of ferrous sulfate (65mg elemental iron) and 5mg of folic acid. The age of each pregnant woman, gestational age, parity, educational, socio-economic status, baseline anthropometric data – (weight, height and body mass index) were ascertained. A structured proforma was used on each visit to assess side effects of drugs taking, evidenced by presenting an empty plastic envelope signed by the investigator. Hb concentration was carried out during 4, 8 and 14 weeks follow up periods.

Data was collected from questionnaires and the laboratory results. All data generated 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, Chi square and Fischer exact test where applicable was done to determine the difference in the hematological parameters of women taking twice weekly hematinic supplementation compared to those on daily at 95% confidence interval.

3. RESULTS

A total of 120 consenting pregnant women, 60 pregnant women recruited as cases while 60 as controls, eighth women were lost to follow up in the twice weekly group, while seven in the daily group giving a response rate was 87.5%.

The socio-demographic characteristics of the women are shown in table 1 below. The women in the two groups differed significantly in age (P=0.039) but were matched in terms of educational status, occupation, Husband's educational status and Parity.
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.

The pattern of anemia using Hb< 10g/dl cut off at the booking clinic shows that, all the patients enrolled were non anemic, the number of women with Hb<10 g/dl increased steadily to a maximum at the 8^{th} week follow up visit to 50% and reduced to 37% at the 14^{th} weeks follow up visit, is also worthy to note that more women(77.1%) had Hb>10g/dl in the twice weekly group at 14 week visit compared to daily group (*P=0.031*).

For the gastrointestinal side effects associated with the two Iron supplementation regimens, there were more side effects experienced by subjects in the daily group when compared with the twice weekly group, dark stools were seen in 37.5% of the daily arm while 20.9% in the twice weekly group. Of clinical importance heart burns was the most common side effect with 35% as against 20.9% in the twice weekly group, others are nausea, constipation, vomiting and metallic taste. However, the difference was not statistically significant (P=0.06). As seen on Table 3 and bar chart on Fig. 1.

4. DISCUSSION

With advancing gestational age the need for iron is increased due to dilutional anemia which results from differential expansion of red cell mass and the plasma volume, this may reach 6-7mg per day in the second half of pregnancy.

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

Characteristics	Iron administration		Total n=105(%)	χ^2	p-value
	Twice Weekly n=52(%)	Daily n=53(%)			
Age Group (years)				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				0.777	0.378
Housewife	29(55.8)	25(47.2)	54 (51.4)		
Employed	23(44.2)	28(52.8)	51 (48.6)		
Husbands education				0.673	0.879
Primary	2(4.0)	1(1.9)	3 (2.9)		
Secondary	14(28.0)	15(28.3)	29 (27.6)		
Tertiary	33(66.0)	35(66.0)	68 (64.8)		
No Formal Education	1(2.0)	2(3.8)	3 (2.9)		
Gravidity				1.468	0.480
1	12(23.1)	13 (24.5)	25(23.8)		
2-4	31(59.6)	27(50.9)	58(55.2)		
≥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. Anemia based on Hemoglobin cut-off of 10 g/dl

Hemoglobin	Iron administration			χ2	p-value
	Twice weekly	Daily	Total		
At booking visit					
≥10g/dl	52	53			
<10	0	0			
4weeks Follow 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(43.8)		
8weeks Follow up visit				2.000	0.157
≥10g/dl	29(55.8)	23(43.4)	52(49.5)		
<10	23(44.2)	30(56.6)	53(50.5)		
14weeks Follow up visit				6.231	0.031
≥10g/dl	36(69.2)	26(49.1)	62(59.0)		
<10	16(30.8)	27(50.9)	43(40.0)		

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 [21].

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 [22-24] and lower than that reported in the study by Erhabor and colleagues in Sokoto with a mean age of 33.2 years [25].

More than half (51.4%) of the subjects studied were housewives, 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%, [22] this wide difference

may be that Jos is a more heterogeneous society than The Islamic Republic of Iran, where sociocultural and religious belief may have contributed to this wide variation. In our setting women are allowed to engage in any kind of vocation, menial jobs and petty trading to help their spouses to cater for their families.

Of the studied population, 55.8% were multiparous women while 24% were primigravidae and the least (20.2%) were the grand multiparous women.

Table 2, demonstrates 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 48.6% in the daily supplementation group and the difference was statistically significant (P=0.031). Several studies of anemic pregnant

Table 3. Gastrointestinal side effect profile of the different iron supplementation regimens

Characteristics	Iron administration			χ^2	p-value
	Twice Weekly n=52(%)	Daily n=53(%)	Total n=105(%)		
Nausea					0.751*
None	47(90.5)	45(85.0)	92(87.8)		
Mild	4(7.1)	7(12.5)	11(9.8)		
Severe	1(2.4)	1(2.5)	2(2.4)		
Vomiting					0.348*
None	51(97.7)	49(92.5)	100(95.2)		
1/day	1(2.3)	4(7.5)	5(4.8)		
Heart burn					0.060*
None	41(79.1)	34(65.0)	75(72.3)		
Mild	11(20.9)	12(22.5)	23(21.7)		
Severe	0(0.0)	7(12.5)	7(6.0)		
Constipation					0.447*
None	48(92.9)	46(87.5)	94(90.2)		
Mild	4(7.1)	7(12.5)	11(9.8)		
Metallic taste					0.849*
None	47(90.7)	48(90.0)	95(90.4)		
Mild	5(9.3)	4(7.5)	9(8.4)		
Severe	0(0)	1(2.5)	1(1.2)		
Dark Stool					0.069*
None	41(79.1)	33(62.5)	74(71.1)		
Sometimes	11(20.9)	15 (27.5)	26(24.1)		
Always	0(0)	5(10.0)	5(4.8)		

**=Fishers exact*

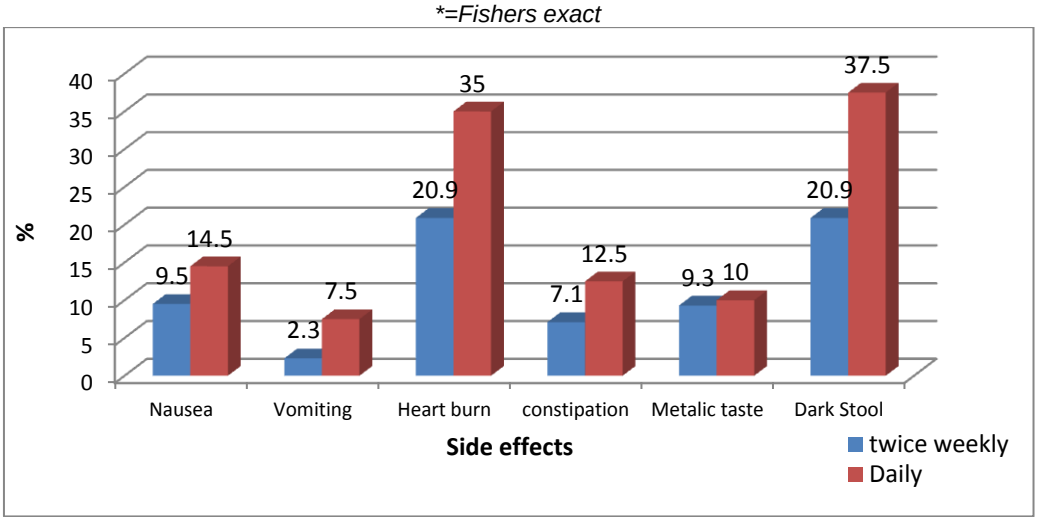

Fig. 1. A Bar chart showing the gastrointestinal side effects profile

women also reported comparable increment of hemoglobin concentration comparing the two supplementation models [22,26,27].

The side effect profile was more in the daily group than the twice weekly regimen. Of clinical importance, heartburn was noted in 35% respondents for daily group while 20.9% respondents in the twice weekly regimen. This was the most common side effect followed by nausea, constipation, metallic taste and the least was vomiting. while dark stools was observed in 37.5% respondents in the daily arm and 20.9% in the twice weekly arm, This is in line with other studies which shows that reducing iron dose or intermittent dosing could decrease these complications and enhance compliance [22,28-31].

The institute of medicine, and the ministry of health in Spain recommended low dose iron supplementation, 30mg/day of iron to all women with risk of IDA and doses like 60-120mg/day for treatment of ferropenic anemia (Hb<10.9g/dl, serum ferritin <12µg/l) [32].

5. CONCLUSION

Pregnant women on daily iron supplementation experienced more side effects compared to those on weekly regime. Though the regiment of daily intake of iron may have a role in reducing IDA in pregnancy, side effects may mitigate its full potential and so for women who cannot tolerate the daily regimen, twice weekly supplementation presents an effective option.

6. LIMITATIONS

1. The sample size may be small compared to other studies
2. Direct observed therapy (DOT) was not done because this will increase financial burden on the clients
3. Routine screening for helminthes and routine anti helminthes are not given at the ANC

7. RECOMMENDATIONS

1. A larger study well-funded is needed to substantiate the findings in this study
2. Routine screening for malaria and helminthes should be introduced in our ANC
3. More emphasis on contraception to reduce incidences of anemia

ETHICAL APPROVAL

The study was approved by the research and ethical committee of the Jos University Teaching Hospital (JUTH/DCS/ADM/127/XIX/5851).

CONSENT

Informed consent was obtained from each participant's and non-consenting patients were excluded without prejudice.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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