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Efficacy and tolerability of ferrous sulfate – oral iron therapy in the management of Iron deficiency anemia during pregnancy – a prospective study

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Abstract
Background: Anemia is the most common medical disorder of pregnancy and carries significant maternal & fetal morbidity. Iron deficiency anemia is the commonest cause for this potentially preventable and treatable condition. A significant number of pregnant women need IV iron or blood transfusion during their late pregnancy despite having regular follow up and iron & folic acid supplementation. GI intolerance with oral iron therapy and subsequent poor drug compliance is the leading cause for this. This study designed to assess the efficacy of ferrous sulfate therapy, prevalence of GI intolerance and non – compliance with the treatment in a tertiary care Obstetrics Institute.
Methods: It is a prospective observational study. Eighty pregnant women with diagnosis of Iron deficiency anemia were included in this study. Ferrous sulfate 200mg with folic acid 500 μgm tablets twice daily was given over 12 weeks. Parameters Hb, Hematocrit, Ferritin at baseline, at 6th week and 12th week measured. Six had lost follow up and seventy four women completed the study. Questionnaire to find out drug non – adherence applied. Adverse drug reactions noted. Rescue therapy in the form of IV iron or blood transfusion given whenever needed.
Results: Ferrous sulfate therapy significantly improved hemoglobin in 58% patients who compliant with the therapy. Eighty percent of patients experience GI intolerance. 42% of study population became non - compliant with drug and showed poor response to therapy. The difference in the hemoglobin improvement between compliant and non - compliant group was statistically significant ($p < 0.001$). Twenty five patients (34%) who received IV iron all from non – compliant group.
Conclusion: Oral iron in the form of ferrous sulfate is effective in the treatment of iron deficiency anemia during pregnancy. Newer formulations of oral iron with less GI side effects may be a better option in people experiencing gastro intestinal side effects to avoid IV iron or blood transfusion during pregnancy.

Keywords: Pregnancy, iron deficiency anemia, ferrous sulfate, non – compliance

Introduction
Anaemia is a global public health problem affecting 1.62 billion people which corresponds to 25% of the population worldwide. It is estimated by the WHO that 47.4% of pregnant women are anaemic. According to the recent data of National Family Health Survey (NFHS-4), the prevalence of anemia in India is estimated to be 50.3% [1]. Nutritional iron-deficiency anaemia (IDA) is the commonest cause of anemia during pregnancy. A recent study from India reported 58.7% prevalence of anemia in pregnancy. Another study from north India in 3000 pregnant patients reported anemia in 86.6% pregnant females.
Anaemia is responsible for nearly 40% of maternal deaths in developing countries. Iron deficiency anaemia (IDA) which is associated with increased risk for poor maternal and fetal outcome [2]. The clinical consequences of iron deficiency anemia include preterm delivery, perinatal mortality, and postpartum depression. It also causes indirect effects such as predisposition to cardiac failure, hemorrhage, infection and pre-eclampsia [3]. Fetal and neonatal consequences include low birth weight and poor cognitive function and psychomotor performance [4].
Although oral iron supplementation is widely used for the treatment of IDA, not all patients respond adequately to oral iron therapy. This is due to several factors including the side effects of oral iron which lead to poor compliance and lack of efficacy. The side effects, predominantly gastrointestinal discomfort, occur in a large cohort of patients taking oral iron preparations. Non-compliance to iron therapy is associated with increasing prevalence of anemia in later half of

pregnancy and makes them to require intra venous iron or blood transfusion to avoid anemia related complications. Conventional form of intravenous iron also associated with undesirable and sometimes serious side effects and therefore should be used judiciously [5].

This study aimed at analyzing the efficacy and tolerability of conventional oral Iron, ferrous sulfate in the treatment of Iron Deficiency Anemia during pregnancy. We also studied the prevalence of Non – compliance with the therapy and its consequences.

Methods

It is a prospective observational study conducted at a tertiary care Obstetrics Institute, south India. All the pregnant women attending our ante natal clinic during February 2019 to December 2019 with gestational age of 12 and 24 weeks were screened for Anemia. Pregnant women with diagnosis of Iron Deficiency Anemia were enrolled in this study. Informed and written consent was obtained. Women with severe and symptomatic anemia, anemia of other than iron deficiency were excluded from the study. Persons who were already on iron supplements also not included in this trial.

Baseline clinical and lab parameters (Hb, Hematocrit and Ferritin) were measured. Ferrous sulfate 200mg with folic acid 0.5mg tablets twice daily was prescribed for12 weeks. At the first follow up visit (6^{th} week) and the second follow up visit (12^{th} week) clinical and lab parameters reviewed. Questionnaire for non – compliance of therapy was noted. Rescue therapy in the form of conventional intra venous Iron or blood transfusion given whenever needed.

At the end of 12^{th} week patients were divided in to two groups; group A – Poor drug compliance and group B – Good drug compliance. Changes in Hb, Hematocrit and Ferritin between the two groups measured. GI intolerance and need for IV iron therapy among the groups compared. Appropriate statistical tests applied.

Results

Eighty eligible women were enrolled in the study. Six women lost to follow up and the remaining seventy-four patients completed study. Mean age of the women was 24.71 ± 2.88 years. Thirty-one (41.9%) women were primi and forty-four (58.1%) were multiparous women. Mean gestational age was 17.79 ± 2.86 weeks ranges from 12 weeks to 22 weeks. Mean hemoglobin and hematocrit at baseline were 8.72 ± 0.71 g/dl and 25.48 ± 2.52 respectively. Ferritin level at baseline was 3.90ng/ml. No women had peptic ulcer disease or any other GI symptoms at starting of the study.

Table 1: Baseline parameters

Baseline parameters	
Age	24.71 ± 2.88 years
Parity	Primi 31 women & Multipara 44
Gestational age	17.79 ± 2.86 weeks
Hemoglobin	8.72 ± 0.71 g/dl
Hematocrit	25.48 ± 2.52
Ferritin	3.90 ng/ml
GI symptoms	Nil

Hemoglobin at 6^{th} week and 12^{th} week was 9.32 ± 0.81 g/dl and 9.64 ± 1.09 g/dl respectively. Hematocrit at 6^{th} week and 12^{th} week was 27.61 ± 2.89 and 28.64 ± 3.54 respectively. Ferritin at 6^{th} week and 12^{th} week was 13.80ng/ml and 24.45ng/ml respectively.

Table 2: Hb

Hb	g/dl	
	N	Mean±SD
Baseline Hb	74	8.72±0.71
6 weeks Hb	74	9.32±0.81
12 weeks Hb	74	9.64±1.09

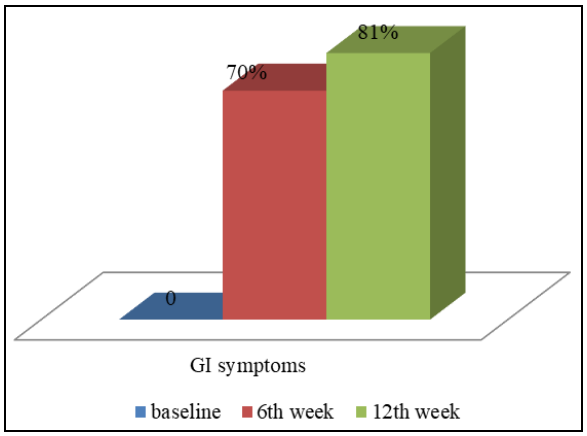
Table 3: PCV

PCV	%	
	N	Mean±SD
Baseline PCV	74	25.48±2.52
6 weeks PCV	74	27.61±2.89
12 weeks PCV	74	28.64±3.54

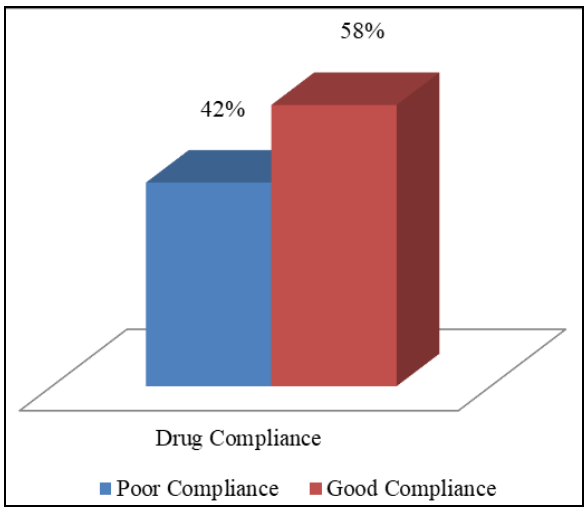
Table 4: Ferritin

Ferritin	ng/ml	
	N	Median
Baseline Ferritin	74	3.90
6 weeks Ferritin	74	13.80
12 weeks Ferritin	74	24.45

70% (52/74) of women at 6^{th} week and 81% (60/74) of women at 12^{th} week experienced GI symptoms. 28% (21/74) of women at 6^{th} week and 42% (31/74) of women at 12^{th} week accepted poor drug compliance. 34% (25/74) of women required IV iron as a rescue measure in view of drug intolerance with persistent anemia. Three women received blood transfusion due to severe anemia.



Graph 1: GI symptoms



Graph 2: Drug Compliance

Hemoglobin, hematocrit and ferritin among patients with good compliance at 12th week were 10.31±0.69 g/dl, 30.77±2.19 % and 26.26±3.25 ng/ml respectively. In patients with poor drug compliance Hb, Hct and ferritin were 8.71±0.84 g/dl, 25.68±2.87 and 13.69±1.86 ng/ml respectively. The difference was statistically significant.

Table 5: Comparison between good compliance and poor compliance

12th week	Good Compliance (n = 43)	Poor Compliance (n = 31)	P value
Mean Hb g/dl	10.31± 0.69	8.71± 0.84	0.001
Mean Hct %	30.77± 2.19	25.68± 2.87	0.001
Mean Ferritin ng/ml	26.26± 3.25	13.69± 1.86	0.001

All of the women who required IV iron had poor compliance and none from the compliant group.

Discussion

Oral iron in the form of ferrous sulfate is cheap and readily available therapy. But a significant proportion of people develops gastro intestinal side effects and tends to discontinue therapy. In our study forty percent of people had non adherence with therapy due to GI intolerance and hence majority of them required IV iron to correct anemia. The remaining sixty percent of people who had good compliant with therapy showed significant improvement in Hb, Hct and Ferritin after 12 weeks.

Newer formulation of iron in a micronized form is the recent approach to improve iron tolerance and absorption [6]. This new, promising strategy for delivering iron orally is associated with greater GI absorption, higher bioavailability with reduced incidence of adverse effects. It is believed that because of no direct contact of iron with intestinal mucosa, it is better absorbed and tolerated.[7] Therefore, supplementing liposomal iron in pregnancy can be helpful to improve tolerability, compliance, and outcomes of the therapy. Also in recent years, newer intra venous type II and III iron complexes have been developed, which offer better compliance as well as high efficacy with a good safety profile. The cost and the availability are the major issues with these therapies in countries like India [8].

And hence, as majority of patients respond to ferrous sulfate without any major complications we can initiate oral ferrous sulfate in all pregnant women with iron deficiency anemia and we can switch over to newer therapy in whom GI intolerance persist.

Conclusion

Oral iron in the form of ferrous sulfate is effective in the treatment of iron deficiency anemia during pregnancy. Because of the significant gastro intestinal side effects nearly one third of our study population had poor compliance and hence required rescue IV iron therapy. So, newer formulations of oral iron with less GI side effects may be a better option in people experiencing gastro intestinal side effects to avoid IV iron or blood transfusion during pregnancy.

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