Original Article

Effect of Directly Observed Oral Iron Supplementation During Pregnancy on Iron Status in a Rural Population in Haryana: A Randomized Controlled Trial

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Abstract

Background: In India, more than half of the pregnant women suffer from anemia. Low compliance to iron supplementation is one of the important reasons. **Objectives:** The objective of the study is to estimate the reduction in the prevalence of anemia, improvement in iron status, and to compare the compliance to oral iron supplementation during pregnancy between directly observed iron-folic acid (IFA) supplementation group and control group. **Methods:** This was a community-based open labeled parallel block-randomized controlled trial including 400 pregnant women in a rural setting of north India. In the intervention group, the first dose of IFA every week was supervised by ASHA and women were instructed to take the remaining tablets during the week as per the prescription. In control group, IFA tablets were supplemented without direct supervision. **Results:** After 100 days of IFA supplementation, the reduction in anemia in the intervention group was 6% higher as compared to control group ($P = 0.219$). The increase in the mean hemoglobin level over and above control group was 0.52 g/dl in intervention group ($P < 0.001$). However, the mean increase in serum ferritin level in the intervention group was similar to the control group. The mean percentage compliance in the intervention group was almost 9% higher than that of control group ($P = 0.001$). **Conclusion:** Directly supervised oral iron (IFA) supplementation improves compliance to oral iron (IFA) supplementation and also improves hemoglobin status among pregnant women. However, the mean increase in serum ferritin and reduction in the prevalence of anemia in the intervention group were not higher than the control group.

Key words: Anemia prevalence, compliance, directly observed, iron-folic acid, oral iron supplementation, pregnant women

Introduction

Anemia is one of the most common public health problems in the world affecting more than 1.6 billion people.[1] Globally, reproductive age group women are most at risk of anemia and anemia contributes to high number of maternal and perinatal deaths globally every year.[1,2]

In India, almost 50% of pregnant women suffer from anemia.[3] Anemia leads to loss of productivity and causes a substantial economic burden.[4,5] The National Iron Plus initiative guideline recommends one iron-folic acid (IFA) tablet containing 100 mg elemental iron and 0.5 mg folic acid for nonanemic women and two IFA tablets daily for anemic women for 100 days.[6] Despite the proven efficacy of oral iron supplementation, the existing anemia control program in India has not been effective in controlling high prevalence of anemia.[3]

Poor compliance to IFA consumption is one of the important reasons behind the continued high prevalence of anemia among pregnant women in India.[7-10] Supervision and direct observation of treatment in patients with tuberculosis, asthma, and HIV infection have been shown to be highly effective in improving treatment compliance.[11-13] Directly observed

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iron supplementation in pregnant women could, therefore, be expected to increase compliance to IFA tablet supplementation which would ultimately improve hemoglobin level and iron status among pregnant women.[14] Feasibility of supervised oral iron therapy over large geographic area is already documented by the successful implementation of adolescent anemia control program globally as well as in India.[15-17]

Hence, a community-based randomized controlled trial was undertaken to estimate the reduction in the prevalence of anemia, improvement in iron status, and to compare the compliance of oral iron supplementation during pregnancy between directly observed group and control group.

Materials and Methods

An open-label randomized controlled trial of directly observed IFA supplementation among pregnant women (12–16 weeks of gestation) was undertaken. The study period was from January to December 2014.

Study setting

Seventeen villages under the Primary Health Center Dayalpur, Ballabgarh, Faridabad, Haryana.

Sample size

Assuming a difference in reduction of the prevalence of anemia between intervention and control groups of 15%, power of 80%, significance level of 5%, and attrition rate of 10%, the required sample size was 200 pregnant women in each group. Assuming 1.0 g/dl difference in increase in mean hemoglobin level between two groups, pooled standard deviation (SD) of 1.1, for 90% power and significance level of 5%, and attrition rate of 10%, the required sample size was 30 in each group. Similarly, assuming a difference in compliance to IFA of 15% between two groups, power of 80%, significance level of 5%, and attrition rate of 10%, the required sample size was 90 in each group.

Inclusion and exclusion criteria

Pregnant women, who were registered for antenatal care at subcenter during the first trimester of pregnancy, were eligible for enrollment. Pregnant women, who were willing to stay at their current address till completion of the second trimester of pregnancy, were enrolled in the study. Exclusion criteria included severe anemia, diagnosed case of malabsorption syndrome, diagnosed psychiatric illness, history of severe bleeding (within last 1 month), and those who took iron supplements for more than 1 week in the past 1 month.

According to the World Health Organization (2011) anemia in pregnancy is defined as hemoglobin level <11.0 g/dl.[18] Serum ferritin level <15 µg/L and soluble transferrin receptor (sTfR) level <5.0 mg/L were considered as iron deficiency status.[19,20] These cutoff values were used uniformly for all trimesters of pregnancy to define anemia or iron deficiency.

Randomization

Block randomization was done to allocate enrolled pregnant women to intervention or control group (ten pregnant women per block). Random sequences were generated per ASHA and pregnant women were recruited based on the random sequence into control and intervention groups.

Intervention

We selected 40 ASHAs from villages of PHC Dayalpur. Each ASHA was allotted 10 pregnant women (five in control group and five in intervention group) for follow-up. After filling pretested interview schedule, at baseline 5 ml blood sample was drawn from antecubital vein of pregnant women for measuring blood hemoglobin and serum ferritin. Serum samples were stored at −20° C temperature locally and transferred in batches to the hematology laboratory at All India Institute of Medical Sciences (AIIMS), New Delhi. The laboratory personnel were blinded to the group allocation of women. One senior faculty member of the department of hematology supervised the laboratory procedures.

In both groups, ASHAs were given IFA tablets for a month for each randomly allocated pregnant woman. The IFA supplementation was started from the 12th week of gestation. Women were prescribed either two tablets or one tablet of IFA per day as per the national guidelines.[6] In the intervention group, the first dose of IFA every week was supervised by ASHA and women were instructed to take the remaining tablets during the week as per the prescription. Empty blisters were collected at the end of every week to assess compliance. In case of noncompliance, ASHA worker informed the importance of IFA tablets during pregnancy and motivated her for continuous consumption of IFA.

In control group, ASHAs did not undertake the direct observation of IFA consumption of pregnant women. The IFA blister packs for 1 month were handed over by ASHA to pregnant women at the start of the month. Empty blisters packs were collected and replenishment for next month was provided at the end of every month. In both groups, the reasons for noncompliance were recorded by the investigator on monthly basis. Pregnant women were followed up for 100 days of IFA supplementation. After completion of 100 days, 5 ml of venous blood was collected to measure hemoglobin, serum ferritin level, and sTfR. Due to resource constraints, 100 samples each from control group and intervention group were chosen at random for sTfR using computer-generated random number (at baseline and endline).

Each IFA tablet used in the study contained 100 mg elemental iron and 0.5 mg folic acid. Each blister packet contained 10 IFA tablets.

Compliance is defined as the extent to which a patient's behavior coincides with medical advice.[21] Following definitions were used for compliance.

$$\text{Compliance rate} = \left(\frac{\text{number of tablets consumed}}{\text{number of tablets prescribed}}\right) \times 100$$

(expressed as a percentage)

Compliant = Compliance rate >80%

Laboratory procedure

Blood hemoglobin, and serum ferritin estimation was done using auto-analyzer, and ELISA Organtech Ferritin Kit manufactured by ORGENTEC, Germany (least count was 10 µg/L), respectively. Serum transferrin receptor estimation was done using Human sTfR Quantikine IVD ELISA kit (manufactured by R and D systems a bio-techne brand, USA).

Blood samples used for ferritin and sTfR estimation were collected in plastic serum separation tube vacutainer. Sera were separated on the same day. Separated serum samples were stored at −20°C in cryovials at the laboratory of Sub District Hospital Ballabgarh (CRHSP Ballabgarh). Serum samples were transported to Hematology laboratory, AIIMS, New Delhi, at monthly interval for further analysis.

Primary outcome variables

(1) Difference in change in prevalence of anemia in directly observed and control group from baseline to end line; (2) difference in change in mean hemoglobin level, serum ferritin, and serum transferrin receptor in two groups from baseline to end line; and (3) difference in compliance level in two groups.

Statistical analysis

Per-protocol (PP) and intention to treat (ITT) analysis was done. Baseline socio-demographic characteristics were analyzed for all 400 pregnant women. Independent *t*-test and Mann–Whitney U-test were used to compare the mean changes in hemoglobin, serum ferritin, and serum transferrin receptor in two groups. "*P*" < 0.05 was considered as statistically significant. Data were analyzed using IBM SPSS for Windows, Version 22.0. (Armonk, NY: IBM Corp.).

Ethical clearance

Written informed consent was obtained from pregnant women for participating in the study. Ethical approval was obtained from the Institute Ethics Committee of the AIIMS, New Delhi. The trial was registered in clinical trials registry – India (Trial registration number: CTRI/2015/06/005920).

Results

A total of 400 pregnant women were randomly allocated, 200 of them were randomized to control group, and 200 to intervention group. Four pregnant women were excluded from the study during enrollment because of severe anemia (one in control group and three in intervention group). Twenty-six (6.5%, 26/400) pregnant women had an abortion during the study (15 in control group and 11 in intervention group), and six were lost to follow-up (1 in control group and 5 in intervention group) after random allocation in control and intervention group. Thus, 184 pregnant women in each completed the study with attrition rate being 8% [Figure 1]. Mean (SD) age of pregnant women (n = 400) was 22.9 (2.7) years, with mean age of control group and intervention group being similar (P = 0.921). Most of the pregnant women (n = 400) were Hindu (96%) by religion, 33.6% belonged to schedule caste, 49.5% to other backward classes, and 16.9% to other castes, there being no statistically significant difference between control and intervention group (P = 0.609) [Table 1].

There was no statistically significant difference in baseline mean hemoglobin level between control group (n = 184) and intervention group (n = 184) (P = 0.694). The prevalence of anemia at baseline was 91.8% in control group (n = 184) and 92.9% in the intervention group (n = 184) (P = 0.712) [Table 2].

After 100 days of follow-up, the prevalence of anemia decreased from 91.8% to 84.8% in control group (difference of 7.0%, P < 0.001), and from 92.9% to 79.9% in the intervention group (difference of 13%, P < 0.001). Thus, in comparison to baseline, reduction in the prevalence of anemia was 6% higher in intervention group than in control group (P = 0.219). In control group, mean (SD) hemoglobin level increased from 9.49 (1.0) to 9.95 (1.15) g/dl (mean difference, 0.46 g/dl; P < 0.001). In intervention group, mean (SD) hemoglobin increased from 9.38 (0.97) g/dl to 10.36 (0.98) g/dl (mean difference, 0.98 g/dl; P < 0.001). Hence, an additional increase in mean hemoglobin level in intervention group, over and above the control group was 0.52 g/dl (P < 0.001) [Table 3]. In intervention group, higher level of increase in hemoglobin was observed both in mild and moderate anemia category (categorized as per baseline hemoglobin) than control group after 100 days of IFA supplementation [Table 4].

At baseline, mean serum ferritin was 25.2 µg/L and 21.8 µg/L in control and intervention group, respectively (P = 0.120). After 100 days of IFA tablets supplementation, serum ferritin increased to 37.3 µg/L in control group and 34.6 µg/L in intervention group. Mean difference in serum ferritin in control group was 12.1 µg/L and in intervention group was 12.8 µg/L (P = 0.198). Mean difference in serum transferrin receptor, after 100 days of follow-up was (−) 0.56 mg/L in control group, and (−) 0.50 mg/L in intervention group (P = 0.873) [Table 3].

Compliance in the control group was 60.4% whereas it was 69.1% in the intervention group (P = 0.001). Forgetfulness (39.3%) and side-effects (30%) were the most common causes of low compliance in intervention and control group, respectively. In control group, nausea/vomiting (36.5%), upper abdominal pain (17.4%), and constipation/diarrhea (9.5%) were the common side effects. In intervention group, nausea/vomiting (57.6%), upper abdominal pain (38.5%), and constipation/diarrhea (7.7%) were the common side effects. No other intervention like intravenous iron sucrose was given to those who experienced side effects.

Discussion

The distribution of pregnant women by age, religion, and caste was similar in both intervention and control groups. The prevalence of anemia, in our study, was 91.8% in control group and 92.9% in intervention group at baseline. NFHS 4 (2015–2016) had shown a high prevalence of

Table 1: Distribution of pregnant women by demographic characteristics

Characteristics	Control group (*n*=200), *n* (%)	Intervention group (*n*=200), *n* (%)	Total (*n*=400), *n* (%)	*P**
Religion				
Hindu	191 (95.5)	193 (96.5)	384 (96.0)	0.432
Muslim	9 (4.5)	7 (3.5)	16 (4.0)	
Caste				
SC	64 (32.0)	66 (33.0)	130 (32.5)	0.609
OBC	99 (49.5)	102 (51.0)	201 (50.2)	
Others	37 (18.5)	32 (16.0)	69 (17.3)	
Age (SD) (years)	22.9 (2.6)	23 (2.8)	22.9 (2.7)	0.921
Height (SD) (cm)	153.6 (5.6)	153.7 (5.8)	153.7 (5.5)	0.871
Family size				
≤4	44 (22.0)	38 (19.0)	82 (20.5)	0.613
>4	156 (78.0)	162 (81.0)	318 (79.5)	
Occupation				
Housewife	198 (99.0)	195 (97.5)	393 (98.3)	0.127
Others	2 (1.0)	5 (2.5)	7 (1.7)	
Education				
Illiterate	26 (13.0)	17 (8.5)	43 (10.8)	0.339
Primary	37 (18.5)	40 (20.0)	77 (19.2)	
Middle	58 (29.0)	50 (25.0)	108 (27.0)	
High school	40 (20.0)	53 (26.5)	93 (23.2)	
Intermediate	8 (4.0)	8 (4.0)	16 (4.0)	
Graduate and above	31 (15.5)	32 (16.0)	63 (15.8)	
Mean age at menarche (SD) (years)	13.8 (3.3)	13.6 (1.3)	13.7 (2.5)	0.579
Gravida				
≤3	177 (88.5)	170 (85.0)	347 (86.7)	0.637
>3	23 (11.5)	30 (15.0)	53 (13.3)	

*Chi-square test was used for categorical variables. SD: Standard deviation

Table 2: Baseline hemoglobin, serum ferritin, serum transferrin receptor, and anemia prevalence in control and intervention group

Characteristics	Control group (*n*=184)	Intervention group (*n*=184)	Total (*n*=368)	*P*
Baseline mean hemoglobin (g/dl), mean (SD)	9.49 (1.0)	9.38 (1.0)	9.54 (1.0)	0.694
Baseline mean ferritin (µg/L), mean (SD)	25.2 (22.2)	21.6 (16.0)	23.5 (19.0)	0.120
Baseline serum transferrin receptor (µg/L)[#], mean (SD)	2.4 (1.8)	2.5 (1.6)	2.4 (1.6)	0.837
Baseline prevalence of anemia, *n* (%)	169 (91.8)	171 (92.9)	340 (92.4)	0.712

[#]*n*=100. SD: Standard deviation

Table 3: Mean difference in hemoglobin, serum ferritin, and serum transferrin receptor in control and intervention group after 100 days of follow-up

Variable	Control group (*n*=184)	Intervention group			*P*
		PP analysis (*n*=184)	*P*	ITT analysis (*n*=200)	
Mean (SD) difference in hemoglobin (g/dl)	0.46 (0.17)	0.98 (0.19)	0.001	0.95 (0.19)	0.001
Mean (SD) difference in serum ferritin (µg/L)	12.1 (7.1)	12.8 (6.9)	0.198	12.6 (6.8)	0.237
Mean (SD) difference in serum transferrin receptor (µg/L)*	−0.56 (−0.37)	−0.50 (−0.33)	0.873	−0.49 (−0.27)	0.897
Prevalence of anemia (%)	84.8	79.9	0.219	77.9	0.321

**n*=100. SD: Standard deviation, PP: Perprotocol, ITT: Intention to treat

anemia among pregnant women in India (50.3%) as well as in Haryana (55.0%).[3] DLHS-4 reported that almost 73% pregnant women in Faridabad district, Haryana, were anemic.[22] The DLHS-4 had included both urban and rural residents of district Faridabad. Only rural setting in the current study was the possible reason for the observed difference from DLHS-4 figure, and this finding was probably not attributable to measurement error.

Table 4: Mean hemoglobin level at baseline and endline as per hemoglobin level at baseline in both groups

Variable	Mean (SD)				*P*
	Control group		Intervention group		
	Baseline	Endline	Baseline	Endline	
Moderate anemia (Hb-7-9.9 g/dl) Control group (*n*=96) Intervention group (*n*=110)	9.12 (0.59)	9.67 (0.55)	9.02 (0.71)	10.23 (0.43)	<0.001
Mild anemia (Hb-10-10.9 g/dl) Control group (*n*=73) Intervention group (*n*=61)	10.24 (0.26)	10.45 (0.31)	10.27 (0.27)	10.74 (0.38)	<0.001
No anemia (Hb - >11.0 g/dl) Control group (*n*=15) Intervention group (*n*=13)	11.06 (0.12)	11.12 (0.12)	11.02 (0.13)	11.37 (0.18)	0.023

SD: Standard deviation, Hb: Hemoglobin

There was 6% extra reduction in the prevalence of anemia in intervention group as compared to control group. This reduction was significant, from public health point of view, in a country where annual reduction of anemia prevalence is <1% among pregnant women. It has been reported that the major problem in effectiveness of oral iron supplementation is poor compliance. The weekly directly observed oral iron supplementation did increase the compliance rate modestly (69.1%). Thus, even after 100 days of oral iron supplementation, 84.8% in control group and 79.9% in intervention group still remained anemic.

Oral iron supplementation for 100 days is sufficient to meet the additional iron requirement of pregnancy and thus prevent further fall in hemoglobin but insufficient for increasing hemoglobin level. A longer duration of iron supplementation may be required to see improvement in anemia status. In the study, the prevalence of anemia at baseline was very high and mean hemoglobin was in the range of moderate anemia. For significant reduction of the prevalence of anemia, a larger improvement in hemoglobin level was needed. During the whole span of pregnancy, a woman needs an extra 1,000 mg of iron to meet the extra requirement. Iron supplementation for 3–6 months is required to meet this extra iron requirement.[23]

We found higher improvement in hemoglobin level in intervention group in comparison to control group ($P < 0.001$). The reported increase in hemoglobin level after 100 days of oral iron supplementation has ranged from 0.2 gm% to 0.9 gm%.[14,24,25] A study in north India reported higher improvement in hemoglobin level as compared to the present study. This may be due to the difference in inclusion criteria and frequency of observation with the current study.[26] We had not considered other causes of anemia which may have hindered further improvement of hemoglobin level.[27,28] The additional yield of 0.52 g/dl of hemoglobin also justifies the option of using ASHA for weekly directly observed oral iron supplementation.

Serum ferritin level increased by 12 μg/L following IFA administration. However, there was virtually no difference between the two groups as far as mean increase in serum ferritin level or level of serum transferrin receptor. A multicentric study from Myanmar had reported similar serum ferritin improvement after directly observed IFA supplementation.[25] It is known that iron deficiency is associated with only 50% of total anemia cases. Independent effect of folic acid might be one of the reasons for this observation. However, as we have not estimated folic acid in the study, it remained one of the limitations of the study.

Forgetfulness (60%) was the most common contributor to noncompliance to IFA supplementation in the control group. Forgetfulness was low (27%) in the intervention group. Studies have reported forgetfulness as the most common cause of noncompliance to IFA supplementation among pregnant women.[29-31] Earlier studies had reported positive role of directly observed IFA supplementation in improving compliance to IFA tablets[13,22,24] Weekly direct observation of iron supplementation may have improved compliance by reducing forgetfulness among pregnant women.

Side-effects after IFA consumption was less in intervention group (30%) than control group (44%). Studies had found side-effect from IFA supplementation as an important contributor of noncompliance.[30,31] Earlier study has proven that weekly versus daily iron therapy among pregnant women has significant equality and less side effect.[32] Hence, once weekly supervised dose can overcome above-mentioned side-effects and improve compliance of IFA therapy.

Noncompliance has been the Achilles' heel of the oral iron supplementation program in India. One of the essential requirements for scaling up of the directly observed iron supplementation is the availability of community-based functionary who can ensure directly observed supplementation. India has two sets of community-based workers, ASHA, and Anganwadi worker, available in every village. Alternatively, school teachers, traditional birth attendants, community volunteers, and nurses can also be used to ensure directly observed iron supplementation.

Although the directly observed iron supplementation had additional compliance (9%) to oral iron supplementation

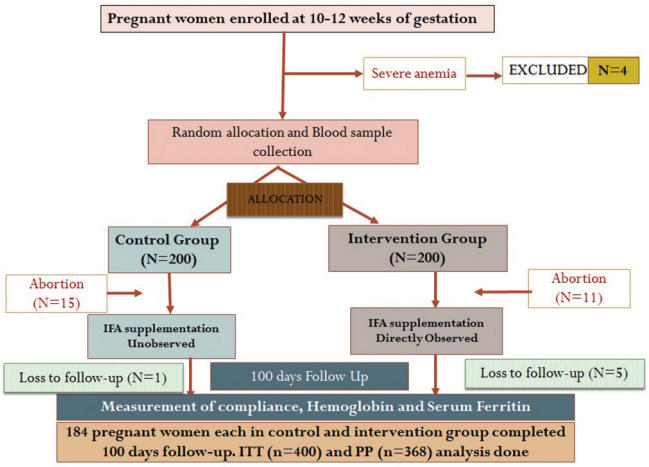

Figure 1: Study flow.

and hemoglobin level (0.52 mg/dl) in intervention group as compared to control group, it was not able to reduce anemia prevalence significantly in intervention group as compared to control group. Hence, alternative route (parenteral) of iron supplementation among pregnant women needs to be evaluated. Studies on effect of low-dose IFA or intermittent IFA therapy could also be evaluated in large-scale community-based study.

The study was a randomized controlled trial that ensured equal distribution of measured and unmeasured confounders. Data were collected by single interviewer, so interobserver variation was minimized. The study was conducted at rural community level and thus could be generalized to other similar setting. Outcome assessment was objective in nature. Laboratory technicians were blinded to intervention status. The number of dropouts from the study was low (8%). The study results are likely to be internally valid and may be extrapolated to other similar population group.

The study was a nonblinded trial at the level of participants and investigators. However, the inherent nature of intervention (directly observed) excluded the possibility of blinding. All ASHA had both groups of pregnant women. Hence, the chance of contamination cannot be ruled out. Serum ferritin is an inflammatory disease marker. Other blood parameter, like C-reactive protein, which indirectly assesses inflammatory condition in body, was not estimated along with serum ferritin. Serum ferritin may not be true reflection of underlying iron status in setting of high acute infection rate. If there was a significant level of inflammatory disease prevalence among pregnant women, then the body iron reserve would have been overestimated. However, we could not assess the infection rate among study participants which added to the limitation of our study. The socioeconomic status of the study participants was not assessed. Dietary iron intake in both groups was also not measured. These two factors added to the limitation of the study. However, study design had addressed the issues to some extent.

Conclusion

Weekly supervision was effective in improving compliance to IFA supplementation and blood hemoglobin level. However, the study did not find any significant effect of weekly supervised IFA supplementation in the reduction of anemia prevalence in comparison to control group. This study provided evidence-base of effective alternative strategy for optimizing compliance of iron therapy to mitigate anemia problem among pregnant women in rural setting. This study demonstrated the feasibility of using ASHA as a conduit for directly observed iron supplementation.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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