ORIGINAL ARTICLE

Effect of iron therapy on fatigue symptoms in non-anaemic iron deficient women of reproductive age- A Randomized Controlled Trial

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Abstract

Objective: To assess the effect of iron therapy on fatigue symptoms in non-anaemic iron-deficient women of reproductive age.

Method: The double-blind placebo-controlled randomised trial was conducted at the department of Obstetrics & Gynaecology Central Park Teaching Hospital, Lahore from March 2023 to February 2024 and comprised women aged 18-45 years who were non-anaemic, had haemoglobin level >11g/dl a fatigue score of at least 36, and a low serum ferritin level. Socio-demographic data was recorded. The subjects were randomised into Group 1 receiving iron therapy and group 2 receiving placebo. After 2 months of intervention, the fatigue scores, haemoglobin and serum ferritin levels were assessed again, and compared with baseline values. Data was analysed using SPSS 26.

Results: Of the 164 subjects, 86(52.4%) were in Group 1 with mean age 30.70±18.123 years, and 78(47.6%) were in Group 2 with mean age 29.46±7.99 years (p=0.325). In Group 1, significant decrease in fatigue score and significant increase in ferritin and haemoglobin levels were noted post-intervention (p=0.05).

Conclusion: Iron supplementation alleviated fatigue and enhanced serum ferritin concentration in non-anaemic, iron-deficient women of childbearing age.

RCT No: (NCT06596161).

Keywords: Fatigue, Iron deficiency, Reproductive age, Haemoglobin, Iron therapy.

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Introduction

Fatigue is a subjective complaint manifesting as extreme tiredness, lack of energy and decreased motivation. It is the most common presenting complaint at primary care level with a prevalence of 41%, reported more commonly in women of childbearing age than men.[1,2] Women of childbearing age experience different challenges, including entering into new phase of life, household responsibilities, childbirth, parenting and many more. Fatigue may hamper women's general health, impair cognitive functions, reduce mother-infant bonding and results in a poor quality of life.[3] Fatigue is seen in many chronic medical conditions, such as anaemia, diabetes, thyroid disorders and autoimmune conditions.[4,5] Unexplained fatigue, in the absence of any identified organic disease, can lead to more severe impairment in the quality of life than explained fatigue.[6]

Anaemia is the most prevalent global condition presenting with fatigue symptoms.[7,8] While association of iron deficiency anaemia and fatigue symptoms is well established, there is little evidence to suggest that iron deficiency and fatigue are related in the absence of anaemia. Iron is involved in oxygen transport, energy metabolism and synthesis of neurotransmitter, making it vital in any cellular and physiological process.[9] Again, fatigue can emerge from the disruption of these processes regardless of whether or not the patient has iron-deficiency anaemia. Women of this age group undergo hormonal changes that may lead to menstrual blood loss, and pregnancy and lactation are other vital reasons for the repeated attack of iron deficiency.[9] Fatigue on the other hand is another multi-factorial state where both physical and cognitive functions may be either influenced by changes in hormonal levels, psychological state and other factors present in a woman's life.[6] Although non-anaemic iron deficiency is considered to be a severe problem in terms of health, the effects of iron deficiency on women's fatigue symptoms in particular have become a focus of attention only recently. Awareness of the possibility of alleviating such symptoms by iron supplementation and improvement of reproductive health of these women are likely to enable better functioning of daily life routine. The current study was planned to assess the effect of iron therapy on fatigue symptoms in non-anaemic iron-deficient women of reproductive age.

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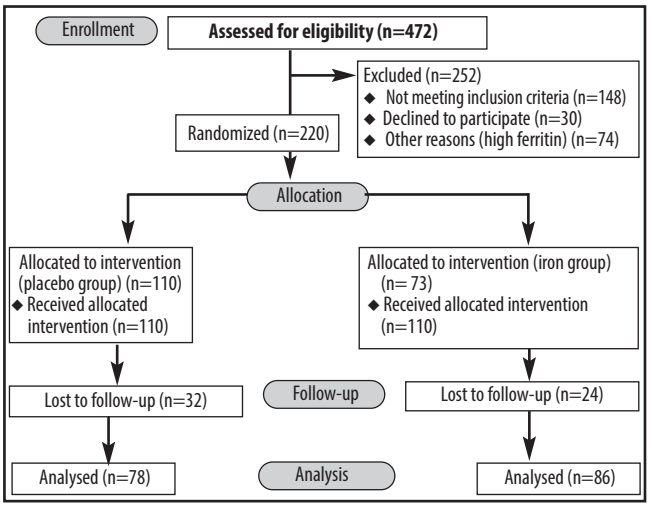

Figure-1: Consolidated Standards of Reporting Trials (CONSORT) diagram of the study

Patients and Methods

The double-blind placebo-controlled randomised controlled trial (RCT) was conducted at the department of Obstetrics & Gynaecology Central Park Teaching Hospital, Lahore from March 2023 to February 2024. The RCT was registered as per Consolidated Standards of Reporting Trials (CONSORT) guidelines with a clinical trial registry (NCT06596161). After approval from the institutional ethics review board, the sample size was calculated using the World Health Organisation (WHO) calculator with confidence level 95%, margin of error 5% and population proportion 15.[10] We employed consecutive sampling technique to all the eligible women aged 18-45 years after taking written informed consent. Women having metabolic disorders and those taking iron or any multivitamins were excluded. The women who were non-anaemic, had haemoglobin (Hb) level >11g/dl, a fatigue score of at least 36, and a low serum ferritin level were randomised 1:1 using a computer-generated, variable-block sequence with concealed allocation into Group 1 receiving iron therapy and group 2 receiving placebo. Neither the subjects nor the investigators were aware of the grouping.

Socio-demographic data, including age, marital status, parity, education, profession, monthly income and body mass index (BMI), was recorded. For the assessment of fatigue levels, the Fatigue Severity Scale (FSS) was employed, and the scores were calculated. FSS is a 10-item questionnaire scored on a Likert scale. A 5cc of blood was collected from the participants for the assessment of Hb and ferritin levels. Once the therapy was started, the participants were told not to take any other supplements during the two months of intervention. Fatigue scores as well as Hb and ferritin levels were measured again post-intervention.

Data was analysed using SPSS 26. Demographic variables were entered as ordinals, while serum iron level and fatigue score before and after supplementation were entered as scales. Data normality was assessed using Shapiro-Wilk test, and paired sample t test or Mann Whitney U test was employed as needed, Paired sample correlation was used to assess the effect of iron therapy. P<0.05 was regarded as significant.

Results

Of the 472 subjects screened, 164(34.7%) were recruited. Of them, 86(52.4%) were in Group 1 with mean age 30.70+18.123 years, and 78(47.6%) were in Group 2 with mean age 29.46+7.99 years (p=0.325).

In group 1, a significant decrease in fatigue scores was noted, from 45.12+6.41 to 30.05+8.93 with mean difference of 15.070 (p=0.0001) (Table 1). Similarly, a significant increase in mean ferritin level was noted in in group 1, from 27.91+13.62 to 67.22+62.36 with mean difference of 39.31 (p=0.001). A significant increase in serum Hb levels was also noted (p=0.034) (Table 1).

In Group 1, a significant correlation was noted in baseline and post-intervention fatigues scores (r=0.139, p=0.002). A strong positive correlation was noted for ferritin levels

Table-1: Comparison of baseline and post-intervention variables in Group 1.

Parameters	Mean±SD		*p*-value
	Pre-Treatment	Post-Treatment	
Fatigue Scores	45.12±6.41	30.05±8.93	0.0001*
Haemoglobin Levels	11.59±0.59	11.86±0.712	0.034*
Serum Ferritin Levels	27.91±13.62	67.22±62.36	0.0001*

SD: Standard deviation

Table-2: Correlation of study variables in Group 1.

Parameters	*r*-value	*p*-value
Pre & Post Fatigue Scores	0.139	0.0374*
Pre & Post Hb Scores	0.266	0.085
Pre & Post Ferritin Scores	0.830	0.002*

Hb: Haemoglobin.

Table-3: Comparison of baseline and post-intervention variables in Group 1.

Parameters	Mean±SD		*p*-value
	Pre-Treatment	Post-Treatment	
Fatigue Scores	43.19±5.24	32.00±7.505	0.0001*
Haemoglobin Levels	11.36±0.60	11.41±0.656	0.776
Serum Ferritin Levels	38.07±7.30	64.10±55.71	0.022*

SD: Standard deviation

Table-4: Correlation of study variables in Group 2.

Parameters	*r*-value	*p*-value
Pre & Post Fatigue Scores	0.502	0.009*
Pre & Post Hb Scores	0.018	0.932
Pre & Post Ferritin Scores	0.258	0.204

Hb: Haemoglobin.

(*r*=0.830, *p*=0.002) (Table 2).

In Group 2, a significant decline in fatigue scores was noted from baseline 43.19+5.24 to baseline and post-intervention 32.00+7.505 with mean difference 11.192 (*p*=0.0001). A significant increase in serum ferritin levels was also noted in Group 2 (*p*=0.022). No significant increase in serum Hb level was noted (Table 3).

In Group 2, a significant correlation of baseline and post-intervention fatigue scores was noted (*r*=0.502, *p*=0.009). No other significant correlation was noted in Group 2 (Table 4).

Discussion

Iron therapy resulted in a reduction of fatigue score, which was in line with earlier studies.[11,12]

The elevation of serum ferritin noted in the current study confirmed that iron augmentation enhanced iron status, and, therefore, reduced the complaints of fatigue. This is in harmony with previous studies.[13,14]

It was rather surprising that in the current study, even the placebo treatment brought about a reduction in the fatigue scores, although it seemed to be less effective than the treatment group. This raises the question of the placebo effect, which is not unusual in clinical trials that are centred on subjective complaints, like fatigue. The effectiveness of placebo is believed to be as a result of participants' belief in a better outcome and effects of being in a clinical trial.[15-17] Again, it is the breakdown between the treatment and placebo groups that render the effect of iron well appreciated on the elimination of fatigue-related symptoms among non-anaemic, iron-deficient women.

Since iron deficiency is very common among women of reproductive age, and fatigue compromises their quality of life and functional capacity, it will be useful to prescribe them iron supplements. Healthcare providers should perform iron status assessment and provide iron treatment for non-anaemic non-pregnant women with fatigue.[16,17]

The current study has limitations as it targetted a particular category of women, and, therefore, the results are not generalisable. Further studies are needed to validate the current findings.

Conclusion

Iron supplementation alleviated fatigue and enhanced serum ferritin concentration in non-anaemic, iron-deficient women of childbearing age.

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References

1. Libbus K, Baker JL, Osgood JM, Phillips TC, Valentine DM. Persistent fatigue in well women. Women Health 1995;23:57-72. doi: 10.1300/J013v23n01_04.
2. Fuhrer R, Wessely S. The epidemiology of fatigue and depression: a French primary-care study. Psychol Med 1995;25:895-905. doi: 10.1017/s0033291700037387.
3. Baattaiah BA, Alharbi MD, Aldhahi MI, Khan F. Factors associated with postpartum fatigue: an exploration of the moderating role of resilience. Front Public Health 2024;12:e1394380. doi: 10.3389/fpubh.2024.1394380.
4. Goërtz YMJ, Braamse AMJ, Spruit MA, Janssen DJA, Ebadi Z, Van Herck M, et al. Fatigue in patients with chronic disease: results from the population-based Lifelines Cohort Study. Sci Rep 2021;11:20977. doi: 10.1038/s41598-021-00337-z.
5. Bahgat FF, Fetyani IM, Alnasser AH, Alkhalaf AM, Baqais MO, Habib SS. The relationship between fatigue severity and mild cognitive impairment in Saudi patients with type 2 diabetes mellitus. J Pak Med Assoc 2022;72:1255-9. doi: 10.47391/JPMA.656.
6. Yoo EH, Choi ES, Cho SH, Do JH, Lee SJ, Kim JH. Comparison of Fatigue Severity and Quality of Life between Unexplained Fatigue Patients and Explained Fatigue Patients. Korean J Fam Med 2018;39:180-4. doi: 10.4082/kjfm.2018.39.3.180.
7. World Health Organization (WHO). Anaemia. [Online] 2021 [Cited 2021 October 13]. Available from URL: https://www.who.int/health-topics/anaemia#tab=tab_1
8. Din JU, Yousafzai AM, Khan RA, Ullah M, Khan SU, Khan S, et al. Iron deficiency anaemia in school age children of District Tank Khyber Pakhtunkhwa Province, Pakistan. J Pak Med Assoc 2019;69:1543-6.
9. Abbaspour N, Hurrell R, Kelishadi R. Review on iron and its importance for human health. J Res Med Sci 2014;19:164-74
10. Lwanga SK, Lemeshow S. Sample size determination in health studies: a practical manual. Geneva, Switzerland: World Health Organization; ⊠1991⊠. [Online] 1991 [Cited 2025 September 13]. Available from URL: https://apps.who.int/iris/handle/10665/40062
11. Parkin PC, Borkhoff CM, Macarthur C, Abdullah K, Birken CS, Fehlings D, et al. Randomized Trial of Oral Iron and Diet Advice versus Diet Advice Alone in Young Children with Nonanemic Iron Deficiency. J Pediatr 2021;233:233-40.e1. doi: 10.1016/j.jpeds.2021.01.073.
12. Krayenbuehl PA, Battegay E, Breymann C, Furrer J, Schulthess G. Intravenous iron for the treatment of fatigue in nonanemic, premenopausal women with low serum ferritin concentration. Blood 2011;118:3222-7. doi: 10.1182/blood-2011-04-346304.
13. Jyothi GS, Shelatkar R, Kalavathy HR, Vaidya VG, Sisode M, Ganu G. A clinical study evaluating low dose ferrous fumarate vs. standard iron supplements in iron-deficient non-anemic to mild anemic adults. Sci Rep 2024;14:15674. doi: 10.1038/s41598-024-65878-5.
14. Bellad MB, Patted A, Derman RJ. Is It Time to Alter the Standard of Care for Iron Deficiency/Iron Deficiency Anemia in Reproductive-Age Women? Biomedicines 2024;12:278. doi: 10.3390/biomedicines 12020278.

15. Świątczak M, Młodziński K, Sikorska K, Raczak A, Lipiński P, Daniłowicz-Szymanowicz L. Chronic Fatigue Syndrome in Patients with Deteriorated Iron Metabolism. Diagnostics (Basel) 2022;12: 2057. doi: 10.3390/diagnostics12092057

16. Ali SA, Razzaq S, Aziz S, Allana A, Ali AA, Naeem S, et al. Role of iron in the reduction of anemia among women of reproductive age in low-middle income countries: insights from systematic review and meta-analysis. BMC Womens Health 2023;23:184. doi: 10.1186/s 12905-023-02291-6.

17. Mawani M, Ali SA, Bano G, Ali SA. Iron Deficiency Anemia among Women of Reproductive Age, an Important Public Health Problem: Situation Analysis. Reprod Syst Sex Disord 2016;5:1-6. doi:10.4172/ 2161-038X.1000187.

Author Contribution:

NS, FAB & MZS: Concept, data collection, literature search, statistical analysis, drafting, revision and writing.
MMH: Concept, data collection, statistical analysis, drafting and revision.
TM: Concept, statistical analysis, drafting, revision and writing.