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A randomised placebo-controlled trial to determine the effect of iron supplementation on pregnancy outcome in pregnant women with haemoglobin ≥ 13.2 g/dl

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Objective To study the effect of iron supplementation on pregnancy outcome in pregnant women with haemoglobin (Hb) ≥13.2 g/dl.

Design A randomised, double-blind, placebo-controlled trial.

Setting Routine health services.

Population Seven hundred and twenty-seven pregnant women with Hb ≥13.2 g/dl in the early stage of the second trimester.

Methods Each woman took one tablet of 50 mg of ferrous sulphate daily in the case group (n = 370) or placebo in the control group (n = 357) throughout pregnancy.

Main outcome measures Pregnancy outcome.

Results While there were no significant differences in demographic and obstetric characteristics between the two groups before any intervention, small-for-gestational-age birth rate and the number of women with hypertension disorder increased significantly in the case group in comparison with the control group (57 [15.7%] versus 36 [10.3%], P = 0.035, 10 [2.7%] versus 3 [8%], P = 0.05, respectively).

Conclusions Our finding proves that routine iron supplementation in nonanaemic women is not rational and may be harmful.

Keywords Iron supplementation, nonanaemic women, pregnancy outcome.

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Introduction

Routine iron prophylaxis is commonly recommended for pregnant women. Arguments used in support of this practice have included decreasing haemoglobin (Hb) values ameliorated by iron, calculations of the extra iron needed for the growth of the fetus and placenta, and surveys in the 1950s and 1960s that indicated correlations between a mother's anaemia and/or low serum iron and small size and mortality of the infant.[1–3]

However, pregnancy induces haemodilution, and iron-induced Hb increase may reflect a pharmacological rather than physiological effect. In addition, calculations of the extra need for iron during pregnancy usually have not considered decreased iron loss as a result of missed menstruation and increased iron absorption during pregnancy. In several studies, either a U-shaped or negative correlation between Hb level and infant problems has been observed.[4–8] Possible drawbacks of iron supplementation include increased blood viscosity with impaired placental circulation, possibility of adverse effect caused by oxidative damage, a negative influence on the absorption of other minerals, and subjective adverse effects. Also, special interest was on the following diseases of infants hypothesised to be caused or facilitated by iron: convulsions, malformations, cancer, and infectious diseases.[9]

For these reasons, the rationale of routine iron supplementation in nonanaemic women needs to be re-examined. We have therefore performed a clinical trial in a group of nonanaemic women to elucidate the relationship between iron supplementation and pregnancy outcome in this group.

Material and methods

This was a multicentric clinical trial made within routine health services with the help of community midwives. Prior to our study, iron prophylaxis was routinely recommended in the area; permissions for the trial were obtained from ethics committee. As there was no information in the literature in this regard, a pilot study was conducted. Then with $\alpha = 0.05$ and $\beta = 0.1$ to detect a 7% difference between ferrous sulphate and placebo in the rate of small-for-gestational-age (SGA; below the tenth percentile) birth as the primary outcome, a sample size of 360 women for each group was calculated. To allow for loss to follow up, 750 women were enrolled and randomised. The method of simple randomisation was used employing the ordinary tables of random numbers. The 125 random numbers were allocated to each of six clinical centres. First 63 random numbers between 1 and 125 determined the case group whose women were to receive iron supplementation .The remaining 62 random numbers between 1 and 125 determined the placebo group.

The participants were the pregnant women with Hb ≥ 13.2 g/dl in the early stage of the second trimester with the following characteristics: 1) body mass index (BMI) between 19.8 and 26 kg/m^2, 2) single pregnancy, 3) age between 17 and 35 years, 4) nonsmoking, 5) no diseases related to polycythemia like asthma and chronic hypertension, and 6) no history of threatened abortion in the present pregnancy. Both ferrous sulphate and placebo were packed in similar wrapping containing a code which was known only to the principle investigator. The study was double-blind, and the contents were known neither to the women nor to the health centre which administered them. Each woman took one ferrous sulphate tablet (150-mg tablet, containing 50 mg of elemental iron) or placebo per day throughout pregnancy. All participants were followed up for evaluation of pregnancy outcome during pregnancy and until 6 weeks after delivery. The participants received only 1 mg of folic acid daily, and they were not permitted to consume other preparations with vitamins and other minerals. All pregnant women were also taught about their suitable diet by midwives, who attended to women's diet programme.

Cell blood count was controlled in 24–28 and also in 32–36 gestational weeks, and if Hb decreased to less than 10.5 g/dl in the second trimester or 11 g/dl in the third trimester, the women were excluded from the study because of the anaemia.

Statistical analysis

Student's *t* test and χ^2 test were used to compare parameters at enrolment in the study and also for analysis of pregnancy outcome. $P \leq 0.05$ was considered as significant.

Results

A total of 7429 pregnant women were enrolled in the prenatal clinics. After screening, 750 eligible women were identified. Twenty-three women were excluded from the study because of loss to follow up, two of them had Hb < 11 g/l in the 32nd gestational week, and the remainder did not return to the clinics. Finally, the analysis was conducted on 370 women in the iron supplement group and 357 women in placebo group (Figure 1). The basic data of 18 excluded women in the control group and five excluded women in the case group were not significantly different to the basic data of the women who completed the study, and we did not expect that these missing data would make the results invalid.

Table 1. Demographic and obstetric characteristics in the two groups before the treatment

Variables	Iron-supplemented group (*n* = 375)	Placebo group (*n* = 375)	*P*
Age (years),* mean ± SD	25.7 ± 4.6	25.7 ± 4.5	NS
Gestational age (weeks),* mean ± SD	13.07 ± 2.02	13.66 ± 3.45	NS
Gravidity,* mean ± SD	1.6 ± 0.9	1.7 ± 0.9	NS
BMI (kg/m^2),* mean ± SD	23.6 ± 2.8	23.8 ± 2.9	NS
Educational levels**			NS
Primary school, *n* (%)	41 (10.9)	26 (6.9)	
High school, *n* (%)	289 (77.1)	312 (83.2)	
University, *n* (%)	45 (12.0)	37 (9.9)	
Occupation**			NS
Employee, *n* (%)	30 (8.0)	38 (10.1)	
Housewife, *n* (%)	345 (92.0)	337 (89.9)	
Hb (g/dl)	13.98 ± 0.56	14.01 ± 0.62	NS

NS, nonsignificant.
**t* Test.
**χ^2 test.

Table 1 shows that there were no significant differences in age, gestational age, gravidity, BMI, socio-economic status, and Hb between the two groups at the onset of the trial.

As shown in Table 2, there were no significant differences in the rate of premature labour, duration of pregnancy, birthweight, weight gain, perinatal mortality rate, number of caesarean deliveries because of obstetric reasons, and low Apgar score in the 10th minute between the two groups. The number of women with hypertensive disorder and SGA birth rate were greater in the case group in comparison with that of the control group (10 [2.7%] versus 3 [8%], $P = 0.05$, 57 [15.7%] versus 36 [10.3%], $P = 0.035$, respectively). Furthermore, Hb in the third trimester was significantly different between the two groups ($P < 0.001$), but this difference was not clinically significant.

Discussion

Observational studies have produced conflicting results concerning the clinical relevance of maternal anaemia during pregnancy. Although several researchers have reported an association between anaemia and low birthweight (LBW), preterm birth, or both, others have not found such an association.[10]

Past studies differ in the criteria used to define anaemia and nonanaemia and in adjustment for factors associated with LBW and preterm birth.[11] Study limitations complicate the interpretation of study results and have led the researchers to question the indications for iron supplementation of pregnant women.[4,5,12,13] A review of clinical trials states that routine iron supplementation had no detectable effect on any substantive measures of either maternal or fetal outcome.[14]

Several studies have found an association between elevated maternal Hb and adverse birth outcome, including LBW, preterm birth, and SGA birth in addition to anaemia.[4–8] However, because a high maternal Hb level is sometimes mistakenly equated with good iron status, its effect on pregnancy outcome has not received the same attention as anaemia.

The mechanism by which expansion of the plasma volume enhances fetal growth is not known, but reduced blood viscosity may favour blood flow in the maternal intervillous space. High Hb values are associated with placental infarction, and pregnancy haemodilution may, by preventing thrombosis in the uteroplacental circulation, promote fetal nourishment and growth.

Therefore, if an elevated Hb concentration reflects maternal iron excess, and is associated with an unfavourable pregnancy outcome, the rationale of routine iron supplementation in nonanaemic mothers should be re-examined.

In our previous study, we examined the relationship between iron supplementation and serum Zn and Cu levels in pregnant women with Hb ≥ 13.2 g/dl. We found that iron supplementation increases the risk of copper and zinc deficiency. Because the deficiency in trace elements may be harmful in pregnancy, we decided to evaluate iron supplementation on pregnancy outcome in women with Hb ≥ 13.2 g/dl in the early stage of the second trimester.[15]

In this study, some of the indicators used to evaluate the pregnancy outcome were similar in the two groups. However, SGA birth rate and the number of women with hypertension disorder were higher in the case group in comparison with those in the control group. Possible explanation for this result may be what Mohamed[14] had reported that iron-induced macrocytosis could increase blood viscosity to a degree that would impair uteroplacental blood flow, decrease placental perfusion, and increase risk of placental infarction.

Cogswell *et al.*[16] reported that administration of a daily iron supplement from enrolment to 28th week of gestation to initially nonreplete, nonanaemic pregnant women reduces

Table 2. Comparison of the pregnancy outcome criteria between the two groups after the treatment

Variables	Iron-supplemented group ($n = 370$)	Placebo group ($n = 357$)	*P*
Weight gain (kg),* mean ± SD	12.4 ± 4.9	12.8 ± 5	NS
Hypertension disorder,** *n*(%)	10 (2.7)	3 (0.8)	0.05
Duration of pregnancy (weeks),*mean ± SD	39 ± 2.4	39 ± 1.5	NS
Premature labour,** *n* (%)	17 (4.6)	13 (3.6)	NS
Caesarean for obstetrics reasons,** *n* (%)	96 (25.9)	82 (23.0)	NS
Apgar score at 10 minute*	9.9 ± 0.8	9.8 ± 1.2	NS
Birthweight (kg),* mean ± SD	3.24 ± 0.46	3.23 ± 0.39	NS
SGA,** *n* (%)	57 (15.4)	36 (10.1)	0.035
Perinatal mortality rate,** *n* (%)	3 (0.8)	6 (1.7)	NS
Hb at the third trimester,* mean ± SD	13.75 ± 1.05	12.56 ± 1.24	<0.001

NS, nonsignificant.
**t* Test.
***χ^2* test.

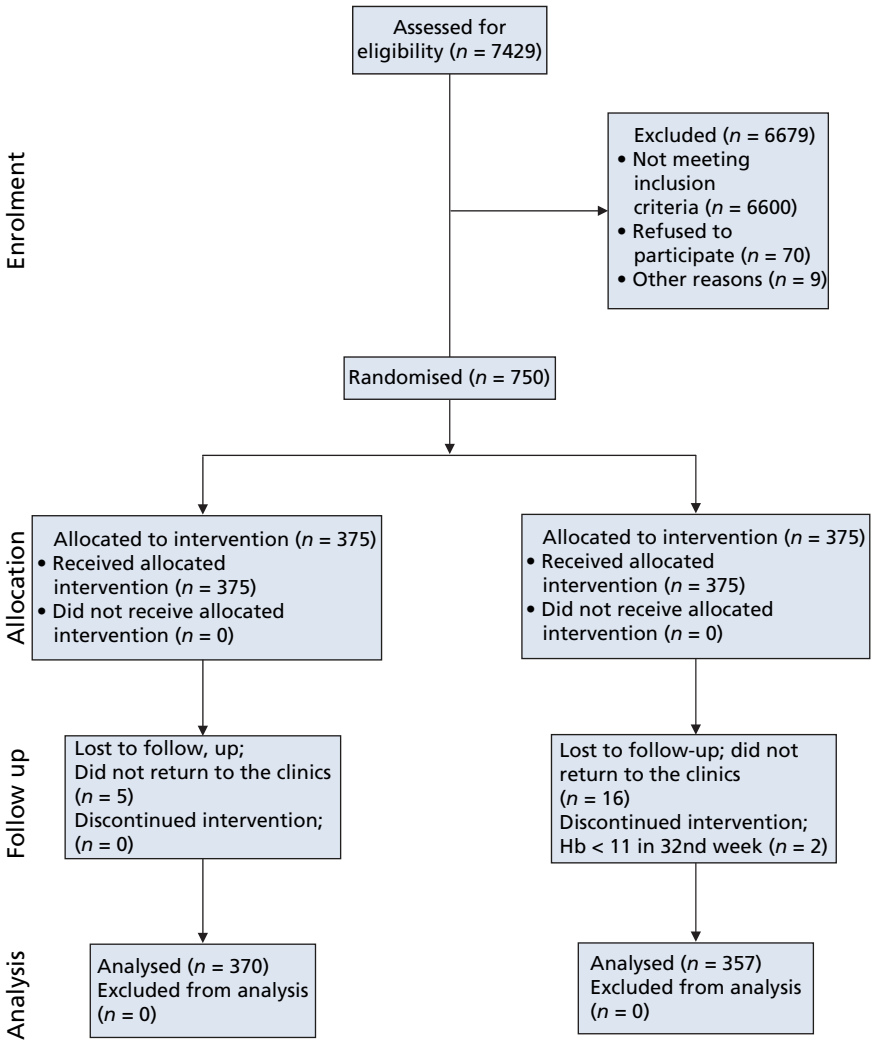

Figure 1. CONSORT statement flow diagram.

the prevalence of anaemia at 28th week and the incidence of LBW infants after adjustment for pre-pregnancy weight and initial iron stores. They defined nonreplete, nonanaemic pregnant women as those who had Hb ≥ 11 g/l and ferritin > 20 μg/l. The differences between this report and our study are the following: 1) the difference in the criteria used to define nonanaemic pregnant women. We chose Hb ≥ 13.2 g/l based on the study of Murphy *et al.*,[5] which found that the complication of pregnancy increases at this cutoff point. 2) The dose administered to pregnant women in our study was 50 mg elemental iron, but the dose in the study of Cogswell *et al.* was 30 mg. For the above reasons, although Hb at the third trimester was different between the two groups, this difference was not clinically significant, and only two pregnant women in the placebo group had Hb < 11 g/l in 32nd gestational week, and we were obliged to exclude them from the study. Meanwhile, the study by Cogswell *et al.* found evidence of depleted or absent iron stores in 78% of the women in the placebo group at 28th week. These women were then prescribed supplemental iron for the remainder of their pregnancies.

In conclusion, because routine iron supplementation is common and our trial suggests that administering it even may have some disadvantages in nonanaemic women, further studies are needed to assess these effects on pregnancy outcome until we can select the best iron supplementation programme for pregnant women. ■

References

1 Christian P, Subarna KK, Katz J, Pardhen EK, LeClerq SC, Shrestha SR, *et al*. Effects of alternative maternal micronutrient supplement on low birth weight in rural Nepal: double blind randomized community trial. *BMJ* 2003;326:571.

2 Lindsay HA. Anemia and iron deficiency: effects on pregnancy outcome. *Am J Clin Nutr* 2000;71:1280S–4S.

3 Steer PJ. Maternal hemoglobin concentration and birth weight. *Am J Clin Nutr* 2000;71:1285s–7s.

4 Lao TT, Tam KF, Chan LY. Third trimester iron status and pregnancy outcome in non-anaemic women; pregnancy unfavourably affected by maternal iron excess. *Hum Reprod* 2000;15:1843–8.

5 Murphy JF, O'Riordan J, Newcombe RG, Coles EC. Relation of hemoglobin levels in first and second trimesters to outcome of pregnancy. *Lancet* 1986;1:992–5.

6 Scanlon KS, Yip R, Schieve LA, Cogswell ME. High and low hemoglobin levels during pregnancy: differential risk for preterm birth and small for gestational age. *Obstet Gynecol* 2000;96:741–8.

7 Stephansson O, Dickman PW, Johansson A, Cnattingius S. Maternal hemoglobin concentration during pregnancy and risk of stillbirth. *JAMA* 2000;284:2611–17.

8 Yip R. Significance of an abnormally low or high hemoglobin concentration during pregnancy: special consideration of iron nutrition. *Am J Clin Nutr* 2000;72:272s–9s.

9 Hemminki E, Merilainen J. Long-term follow-up of mother and their infants in a randomized trial on iron prophylaxis during pregnancy. *Am J Obstet Gynecol* 1995;173:205–9.

10 Beaton GH. Iron needs during pregnancy: do we need to rethink our targets? *Am J Clin Nutr* 2000;72:265s–71s.

11 Milman N, Byg KE, Agger AO. Hemoglobin and erythrocyte indices during normal pregnancy and postpartum in 206 women with and without iron supplementation. *Acta Obstet Gynecol Scand* 2000; 79:89–98.

12 Graves BW, Barger K. A conservative approach to iron-supplementation during pregnancy. *J Midwifery Womens Health* 2001;46: 159–66.

13 Hemminki E, Rimpela U. A randomized comparison of routine versus selective iron supplementation during pregnancy. *J Am Coll Nutr* 1991;10:3–10.

14 Mohamed K. Iron supplementation in pregnancy. *Cochrane Database Syst Rev* 2000;CD000117.

15 Janghorban R, Ziaei S, Faghihzadeh S. Evaluation of serum copper level in pregnant women with high hemoglobin. *IJMS* 2006;31: 170–2.

16 Cogswell ME, Parvanta I, Ickes L, Yip R, Brittenham GM. Iron supplementation during pregnancy, anemia, and birth weight: a randomized controlled trial. *Am J Clin Nutr* 2003;78:773–81.

