The effect of iron supplementation on birth outcome in mothers with high hemoglobin: a randomized double-blind clinical trial study

Leila Alizadeh

Islamic Azad University Ardabil Branch

Leili Salehi (✉ leilisalehi@abzums.ac.ir)

Alborz University of Medical Sciences <https://orcid.org/0000-0001-8459-7702>

Mostafa Ashrafi Osalou

Islamic Azad University Ardabil Branch

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Abstract

Background: Although Iron supplementation is a chief component of prenatal care to prevent anemia in pregnant women, Extreme maternal iron status may adversely affect pregnancy outcome. The aim of this study was to examine the effect of iron supplementation on birth outcomes among pregnant women with high hemoglobin. **Methods:** In a randomized, double-blind, placebo-controlled trial, 189 women who had a hemoglobin concentration more than 13.2 g/dl and a serum Ferritin level higher than 15 µg/l between the 16th and 20th weeks of pregnancy took either one 50 mg tablet of ferrous sulfate daily or placebo during their pregnancies. The data obtained from 13 pregnant women were not used in final analysis for different reasons. After birth, the birth weight, head circumference and birth height in each group were measured and compared, and also two groups compared due to risk of neonatal jaundice. **Results:** The mean of maternal age and pre-pregnancy BMI was 26.11 ± 5.13 , 23.9 ± 2.32 , respectively. There were no statistically significant differences between the two groups with respect to birth weight and height, but the difference in head circumference was significant ($P=0.003$). Also, the risk of neonatal jaundice in intervention group was more than that in control ($P=0.005$). **Conclusion:** Iron supplementation in mothers with high hemoglobin did not increase the risk of maternal anemia or low birth weight, but the supplementation increased the risk of jaundice in newborns. It was an interesting finding that the birth head circumference was larger in the non-supplement group than that in the intervention group. **Key words:** Pregnancy, ferrous sulfate, Birth Weight, Head Circumference, Neonatal jaundice. Clinical trial registration: IRCT2013020612383N1, Registered 27.06.2014

Background

Although blood volume increases in pregnancy, the increase in plasma volume is greater than that in red cell volume; therefore, the physiologic hemodilution and reduction of hemoglobin occur [1]. This change is obviously detected in 25-30 weeks of pregnancy when the hemoglobin level falls to 2 g/dl [2, 3]. Therefore, iron supplementation is a chief component of prenatal care to prevent anemia.

In the recently published guidelines by the World Health Organization (WHO), 30-60 mg of iron supplementation is advised for all pregnant women [4].

Extreme maternal iron intake may increase Hb level and blood viscosity [4-9], So it causes to poor placental transfusion and adverse prenatal outcomes, such as preterm delivery, low birth weight (LBW), low APGAR score, intrauterine growth retardation (IUGR), preeclampsia, maternal hypertension, neurological and skeletal abnormalities in fetus [5,6,7,9,10,11,12,13,14]

At the same time, there is still a lot of conflicting information about iron supplementation in pregnancy [14]; however, iron consumption is routinely advised for all pregnant women.

This study aimed to examine the effect of iron supplementation on birth outcome among mothers with high hemoglobin.

Methods

Design

This randomized double-blind, placebo-controlled clinical study was conducted from February 2016 to June 2018 on 189 healthy pregnant women who received prenatal care at four major prenatal clinics in Ardabil, North West of Iran.

Sample size

The samples were selected from these centers using convenience sampling method based on $\alpha = 0.05$, $P_1=5$, $P_2= 7$, and $d = 10$ (Equation 1) [15]

Equation 1. Sample size formula

$$n = \frac{(Z_{(1-\alpha/2)} + Z_{(1-\beta)})^2 (p_1(1-p_1) + p_2(1-p_2))}{d^2}$$

We used the prevalence of low birth weight in mothers with normal Hb and mothers with higher than 13.2 hemoglobin as chief criteria for sampling.

Laboratory procedures

Hb concentration and serum ferritin levels were measured twice during the study: before the intervention (16-20 weeks) and at the end of pregnancy (37-39 weeks). To increase the reliability of laboratory results, all the blood samples were evaluated in a specific laboratory by a trainer where the laboratory equipment was calibrated. A complete blood count (CBC) was measured with an automated cell counter (Hycell, France) and serum ferritin was measured by the enzyme-linked immune absorbent assay (ELISA)

(ORG5Fe, Bngomtak, Germany). Neonatal bilirubin level was measured by the photometric method (BT 3500, Italy)

Inclusion criteria

The study inclusion criteria were as follows: maternal age of 18–35 years, not having a medical disease (healthy pregnant women), having a normal body mass index (BMI =19.8 - 26 kg/m²), Hb level more than 13.2 g/dl and ferritin level more than 15 µg/L and having a singleton pregnancy with 16 -20 weeks of gestational age.

Exclusion criteria

The study exclusion criteria were as follows: smoking, diabetes mellitus, having a disease related to polycythemia (such as asthma or chronic hypertension), renal disease, malignancy, known blood disorder and having a history of vaginal bleeding in the present pregnancy.

Gestational age (GA) was based on a reliable, self-reported estimate of last menstrual period (LMP) or an ultrasound done early in pregnancy if LMP was forgotten or it was unreliable [1]. BMI is calculated as weight in kilograms divided by the square of height in meters.

To allow for follow up loss, 189 women were enrolled and randomized.

Random allocation

Simple randomization from a table of random numbers was used to assign the women to the iron supplementation group (intervention) or placebo group (control). Random allocation in this study compromised the following steps:

1. Providing a list of subjects' names
2. Assigning each subject to a number
3. Luring all numbers in a box
4. The head of center starting to draw a number randomly
5. The first number allocated to the intervention group and the other one to the control group.

This study was blind to the researcher (first author- LA) and subjects; all the steps have been done by second author (LS).

Intervention

The intervention group received one ferrous sulfate tablet containing 50 mg elemental iron daily, while the control group received a placebo. Because iron supplementation was expected to be necessary after delivery and during the breastfeeding period and to consider ethical concerns in this regard, all women received 50 mg of elemental iron daily for 3 months after delivery.

Ethical Consideration

This study was approved by the Institutional Ethics Committee and registered by Iranian registry of Clinical trial (Code: IRCT2013020612383N1). Written informed consent was obtained from all participants. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The current study adheres to CONSORT guidelines.

Follow Up

All mothers were followed up until delivery. In the cases of diagnosed moderate or severe anemia during pregnancy ($Hb \leq 9$ g/dl) [16], they were excluded from the study, iron supplementation begun and continued until the end of pregnancy.

Outcomes

After delivery, birth weight, head circumferences and birth height were measured and compared. The SECA scale (sensitivity: 10g) was used to determine birth weight. The birth height and head circumference were measured by tape measure. Also, all newborns were exactly examined by a pediatrician. Exclusion criteria were having fetal anomaly, jaundice in first birth day, labor induction with oxytocin and prematurity. All mothers advised to begin breast feeding immediately after birth. The direct and indirect bilirubin levels of newborns were evaluated. The criteria of physiologic jaundice were indirect bilirubin level less than or equal to 12 mg/dl and direct bilirubin level less than or equal to 1 mg/dl [17]. Other types of jaundice were excluded of our study.

Withdrawal

The data obtained from 13 pregnant women were not used in final analysis for different reasons, such as preterm delivery (n=2) vaginal bleeding during pregnancy (n=1) preeclampsia (n=1) gestational diabetes

(n=1), cephal hematoma (n=2), first day jaundice on the first 24h of birth (n=2) labor induction with oxytocin (n=2) and loss to follow up (n=2). At the end, the data of 88 subjects in each group were analyzed and rechecked by two researchers.

Statistical analysis

Normal distribution was checked by Kolmogorov-Smirnov test. 95% CI was considered for data analysis. The control variables were used to check the homogeneity of the groups (Maternal age, BMI, Parity, Hb and ferritin level) by independent t-test. Two groups compared related to birth outcomes by Student's t test. Mean and SD of maternal hemoglobin & ferritin levels were compared between icteric & non icteric newborns.

Results

Demographic Characteristics

The mean of maternal age and pre-pregnancy BMI was 26.11 ± 5.13 and 23.9 ± 2.32 , respectively. In addition, the majority of women were nulliparous [57.81%] and housewife (81.25%). There was no significant difference between the interventional and control groups with respect of maternal age, pre-pregnancy, BMI, parity, Hb and ferritin level (before intervention) (Table1).

We checked of hemoglobin and ferritin levels at the end of pregnancy, there were statistically significant differences between the two groups in Hb ($P = 0.03$) and ferritin ($P = 0.04$) levels, but the incidence of anemia exhibited no difference in either group ($P < 0.001$).

After delivery, birth weight, head circumference and birth height were measured by Seca scale and tape measure. There was no significant difference between the two group in birth weight and newborn height ($P=0.2$), but the difference in head circumference was statistically significant between the two 2 group ($P=0.003$). The results are shown in Table 2.

Bilirubin levels in all newborns in each group were measured and compared. 26 newborns were icteric and 19 of them were born from mothers with iron supplementation. There was a significant difference in neonatal jaundice risk in experimental and control group ($P=0.005$) (Table 3).

Discussion

This study aimed to compare birth outcomes, such as birth weight, head circumference and birth height among pregnant woman with or without iron supplementation. It was conducted on pregnant women who had high Hb and ferritin. Also, bilirubin levels in all newborns were evaluated and compared neonatal jaundice risk in two groups.

Our finding showed there were not significant differences in the birth weight and birth height in the mothers with or without supplementation. Some studies confirm the correlation between maternal Hb and fetal growth. Their study showed low birth weight was more in anemic mothers than others [18- 22]. According their finding, iron supplementation might elevate the Hb level and improve adverse pregnancy outcomes such as LBW, IUGR (intra uterine grow retardation) and maternal mortality rate [23, 24], but their studies were often conducted on mothers who had low or normal hemoglobin in onset of pregnancy. Anemic mothers were often mentioned by researchers and the findings of their studies were highlighted because of high prevalence of maternal anemia worldwide, so mothers with high hemoglobin were often missed and the research recourses about them were restricted.

Therefore, in the recently published resources by the WHO, iron supplementation is advised for all pregnant women [4] without attention to primary maternal hemoglobin level.

Our fining showed iron status markers (Hb and ferritin) were more in mothers with high Hb level ($\geq 13/2\text{g/dl}$), but no statistically significant difference was found in the incidence of anemia between the two groups. Achieved similar results were obtained by Ziaei and et al [6]. Anyway, maternal Hb level reflects iron intake, loss of iron and need for the essential element [1].

Our finding showed that the mean of birth head circumference in mothers without iron supplementation was more than that in mothers with supplementation. It is an important finding because, cognitive abilities of children are positively related to head circumference at birth [25].

As previously mentioned, we randomized samples before the intervention; there were no significant differences between the two groups with respect to the factors affecting fetal growth, such as maternal age, pre-pregnancy BMI, parity, the mother's employment status, neonatal maturity, maternal health status and newborns.

Due to the previous limited studies in the mothers with high Hb; we need to investigate its possible cause of relevant studies. According their results, High intakes of supplemental Fe may interfere with zinc (Zn) absorption. Fetal Zn level is directly depended on maternal Zn level [26]. Zn deficiency in pregnant animals may limit fetal growth [27]. According to the results of some studies on human, the supplemental Zn may increase birth weight and head circumference [28, 29].

According to our results, neonatal jaundice was more in mothers with supplementation than that in the other mothers. Previous studies confirmed that fetal Hb and ferritin were correlated with maternal Hb and ferritin in human [30] and rate [31]. Dennergy in his study considered polycythemia as an important factor in neonatal jaundice [18].

More so, and these relationships have been documented by few studies and need more future investigations with large samples. Given that this study was conducted among Iranians pregnant women, the findings of this study might not be generalized to all other pregnant women. These women might differ from others in terms of nutritional pattern.

Conclusions

Our finding confirmed that no iron supplementation in mothers with high Hb did not increase the risk of maternal anemia and low birth weight or height, but they had newborns with larger head circumference than mothers who consumed iron daily. Also, neonatal jaundice was more in mothers with iron supplementation. It therefore likely seems that caution should be advised in iron prescription in these pregnant women.

Abbreviations

LBW: low birth weight, **IUGR:** intrauterine growth retardation, **CDC:** Center for Disease Control, **GA:** Gestational age, **LMP:** last menstrual period, **BMI:** body mass index

Declarations

Ethics approval and consent to participate

The Ethics Committee of Ardabil Branch, Islamic Azad University, Ardabil, Iran approved the study. All participants signed the written consent forms. All participations were assured regarding their privacy.

Consent to publish

Not applicable

Availability of data and materials

All datasets in this study are available in reasonable request.

Competing interests

The authors declare there isn't any competing interest.

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This study was conducted by the funding from the research deputy of Ardabil Branch, Islamic Azad University, and Ardabil, Iran. There is no role for research deputy of Ardabil Branch, Islamic Azad University in my research.

Authors' Contributions

LA as a researcher carried out the study, analyzed the data and involved in drafting the Manuscript. **LS** has supervised the study; contributed to the study design, performed the statistical analysis and gave final Approval for the study to be published. **MA** contributed to the analysis, edited the paper and provided the final version. All authors read and approved the final manuscript.

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Tables

Table 1 . Comparison participants' characteristics between two groups before study

Group	Intervention	Placebo	P value
Variable	(M±SD)	(M±SD)	
Maternal age(year)	26.59 ± 5.26	25.63 ± 5.04	0.71
BMI (kg/m2)	24.12 ± 2.17	23.68 ± 2.47	0.10
Parity	1.68 ± 0.8	1.65 ± 0.7	0.21
Hb level(g/dL)	13.69 ± 0.44	13.57 ± 0.4	0.29
Ferritin level(µg/L)	33.93 ± 13.72	37.05 ± 16.86	0.19

Table 2.Birth outcome comparison between two groups

Variables	Iron Supplementation Group	Placebo Group	P Value
	(M±SD)	(M±SD)	
Birth weight	3319.56±422/43	3314.06±341.3	0.21
Birth height	49.85±1/48	49.34±1.99	0.24
Head circumference	34±1.58	35.14±1.38	0.003

Table 3.Comparison mean and SD maternal hemoglobin & ferritin levels between in icteric & non icteric newborns

Maternal Iron Markers	Time	Icteric newborns	Non icteric Newborns	P value
Hemoglobin	First trimester	13.72±0.48	13.57±0.65	0.09
	Third trimester	12.01±0.8	11.99±0.7	0.38
Ferritin	First trimester	39.96±19.25	32.43±11.23	0.01
	Third trimester	28.86±12.14	27.18±10.66	0.59

Figures

Figure 1

Consort flow diagram of study

Supplementary Files

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- [CONSORT2010Checklist.doc](#)