

The effect of supplemental iron elimination on pregnancy outcome

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ABSTRACT

Objective: To assess the effect of eliminating supplemental iron on pregnancy outcome.

Methodology: A clinical trial was conducted at Alzahra hospital from 2007 to 2009. Nine hundred sixty healthy women at first trimester of pregnancy with Hb>12 gr/dl and BP<140/90 mmHg were randomized into receiving daily one multivitamin+30 mg elemental iron or multivitamin + placebo tablet from 13 weeks of pregnancy. Iron parameters were analyzed at the 1st trimester and before delivery by using ELISA. Monthly Hb and Hct checkup was performed for placebo group and whom with Hb < 10.5 gr/dl at the end of 2nd trimester or Hb < 11 at 3rd trimester, excluded from the study. Finally 410 women in iron group and 372 in placebo group accomplished the study.

Results: The mean weight gain of mothers in iron group was significantly greater than placebo group. (11.57kg vs. 11.09kg, p=0.018). Iron parameters at delivery time decreased, in two groups and were meaningful in placebo group. Neonatal complications were not significantly different between groups. The rate of preterm labor, IUGR, PROM, placental abruption, gestational diabetes and preeclampsia were not significantly different between groups except for pregnancy induced hypertension (6.7 % in iron group vs. 3.4 in placebo group , p=0.04).

Conclusions: Considering iron is a possible source of producing free radicals which has ability of oxidative damage, it is recommended that in iron-replete non anemic women at beginning of pregnancy especially who are at high risk for hypertension, iron should not be prescribed until Hb falls below normal level.

KEY WORDS: Iron supplement, Pregnancy, Outcome.

Pak J Med Sci April - June 2011 (Part-II) Vol. 27 No. 3 641-645

How to cite this article:

Ouladsahebmadarek E, Sayyah-Melli M, Taghavi S, Abbasalizadeh S, Seyedhejazie M. The effect of supplemental iron elimination on pregnancy outcome. Pak J Med Sci 2011;27(3):641-645

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* Received for Publication: December 7, 2010

* Accepted: April 4, 2011

INTRODUCTION

The total demand to iron in a normal pregnancy is approximately 1000mg. About 300mg is actively transported to placenta and fetus and 200mg is excreted from the body. The mean corpuscular volume is increased about 450ml in pregnancy which needs 500mg iron. Actually the whole iron for this purpose is used during second half of pregnancy so, the demand for iron is greater in 2nd half of pregnancy and reaches to 6-7mg per day. Since this much of iron is not available in most of women from the iron stores so, adequate intake of hexogen iron is needed for appropriate rising of maternal erythrocytes and hemoglobin.

In the absence of supplemental iron, production of Hb in fetus is not affected because placenta takes enough iron from mother to fetus until stabilize the Hb in a normal level even though the mother is in severe iron deficiency.¹ Serum ferritin level is a useful index of iron stores situation.² Lao's study on 488 pregnant women with Hb >10 gr/dl at 28-30 weeks of pregnancy showed that high level of ferritin has been associated with poor pregnancy outcome so, he recommended the routine prescription of iron in pregnancy be reevaluated.³ The higher level of ferritin has been reported with greater risk of preterm delivery, preeclampsia, PROM, chorioamnionitis, low birth weight, neonatal asphyxia and hospitalization duration in NICU.^{3,4}

According to Rayman serum iron and ferritin concentrations were remarkably higher in preeclamptic women than control group.⁵ In another study Xlao found that probability of preterm delivery before 34 weeks of gestation was 2.7 times in women with ferritin > 96 ng/ml compared with whom had ferritin < 26 ng/ml.⁶ Although iron deficiency anemia is one of the common causes of maternal anemia and supplemental iron is a method to reduce the maternal anemia and it has been a standard recommendation in developing countries during the past three decades, the results of Solan's study revealed that supplemental iron causes the increase in hemoglobin level.⁷ It has claimed that iron has a role in increasing the oxidative reactions particularly in preeclampsia.⁸ Considering the previous studies, this study was conducted to survey the role of supplemental iron elimination on pregnancy outcome.

METHODOLOGY

A double-blind-randomized clinical trial study was carried out at Alzahra University dependent hospital from 2007 to 2009. Eligible participants included the women who 1) were at first trimester of pregnancy with single fetus 2) had Hb > 12 gm/dl and had not taken iron containing supplements in the last month 3) BP < 140/90 mmHg and 4) planned to go for all their prenatal care to the prenatal clinic at Alzahra Hospital.

Exclusion criteria included: Hb < 10.5 gm/dl and < 11 gm/dl at the end of 2nd and 3rd trimesters respectively, miscarriage of current pregnancy, abnormality of the fetus and loss to follow-up. The purpose and design of the study were explained to eligible participants by a research assistant. From 2000 eligible women after taking written informed consent 960 participants were randomized into two groups. Iron group received one tablet daily from 13

weeks of pregnancy contained 30 mg elemental iron and multivitamin. Placebo group took one placebo + multivitamin tablet daily (Figure-1).

Iron parameters including Hb, Hct, serum iron, ferritin and TIBC were analyzed at the first trimester and before delivery by using ELISA. Hb and Hct were checked monthly in both groups after first trimester and if the Hb decreased below 10.5 gr/dl at the end of 2nd trimester and <11 gr/dl at the end of 3rd trimester they would exclude from the study and receive appropriate dose of iron.

The sample size calculated by

$$n = \frac{t^2 pq}{d^2} = \frac{(2.58)^2 \times 0.5 \times 0.5}{(0.05)^2} = 660$$

Due to follow up failure and exclusion from the study 410 participants in iron group and 372 in placebo group completed the study. The outcome of pregnancy was recorded on a questionnaire. Data were analysed using SPSS 15 software and statistical t-test, Uman Withny, Fisher exact and k² tests.

RESULTS

Both groups were matched as for as mothers' age, BMI, parity, previous obstetric history and iron parameters at the entry to the study. The basic characteristics of studied women has been shown in Table-I. There was significant difference between the mean weight gains of mothers in groups. (11.57 kg in iron group vs. 11.09 kg in placebo group, p=0.018).

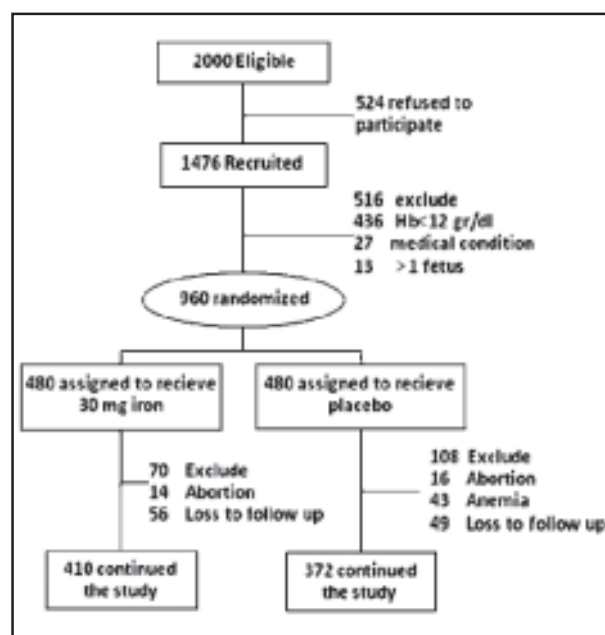


Figure-1: Flow of the patients.

No meaningful differences were found between the means of neonatal age, weight, Apgar scores and complications included hyaline membrane disease, asphyxia, convulsion and septicemia in two groups. Although the average weight of neonates in iron group was 43.22 gr heavier than placebo group, it wasn't significant (3260 gr vs 3216.78 gr, $p=0.28$).

The level of iron parameters (Hb, Hct, serum iron and ferritin) at delivery time significantly decreased in placebo group (Table-II). There wasn't remarkable difference between studied groups in the mode of delivery [(48.8% NVD & 51.2% CS) in iron group vs. (54.2% NVD & 45.8% CS), in placebo group respectively, $p=0.09$]. The outcomes of pregnancy were not significantly different between two groups except for pregnancy induced hypertension (6.7% in iron group vs. 3.4% in placebo group, $p=0.04$) (Table-III).

DISCUSSION

The present study was designed to explore if non iron-deficient, non anemic women need iron supplementation during pregnancy and does it affect the outcome of pregnancy. According to this study, giving 30 mg supplemental iron to non anemic (Hb >12 gr/dl) women with appropriate iron stores (ferritin >20 µg/l) from 13 weeks of pregnancy resulted in significant improvement of iron status at 3rd trimester of pregnancy and rising about 43gm in average neonatal birth weight, but it wasn't significant.

Recent studies couldn't show the causal link between prenatal iron supplementation and increase in birth weight whereas Siega-Riz and Cogswell reported significant effect of iron on 100-200gr increase in birth weight ($p=0.03$).^{9,10} In 1995, Steer in a study of birth weight in more than 115 thousand women stated that Hb >11 gr/dl has been associated with lower birth weight.¹¹ Little's study on more than 200 thousand women revealed that perinatal mortality has significantly been higher with Hb >12 gr/dl.¹²

In 2007, Ziaei reported 15.4% SGA in prenatal iron supplement group vs. 10.1% in control group.¹³ The

Table-I: Basic characteristics of participants.

Characteristics	Iron (n=410)	Placebo (n=372)
Age (y)	26.28±(5.25)	25.48±(4.96)
Weight at entry to study (kg)	66.55±(10.89)	64.46±(11.67)
Weight at delivery (kg)	78.12±(10.88)	75.55±(11.37)
Parity	0.53±(0.03)*	0.41±(0.03)*
Live child	0.43±(0.03)*	0.34±(0.02)*
Hb (g/dl)	13.83±(0.78)	13.26±(0.78)
Hct (%)	41.48±(3.60)	41.22±(3.33)
Ferritin (µg/l)	41.05±(2.16)*	35.008±(1.86)*
TIBC (µg/dl)	359.69±(67.64)	354.61±(64.86)
Serum Iron (µg/dl)	89.73±(33.50)	86.76±(41.06)

Data are given as mean±SD or mean±SEM

* SEM= Standard Error of Mean = $\frac{SD}{\sqrt{n}}$

results of a recent study showed no difference in preterm labor and less than 100gm difference between birth weights at term but preterm neonates born from non-supplemented mothers were 200gr heavier.¹⁴ The mean weight of participants in two groups did not differ at entry to our study (66.55kg in iron group vs. 64.46kg in placebo group, $p=0.055$) but was significantly higher in iron group at delivery (78.12kg vs. 75.55kg, $p=0.018$).

As birth weight is affected by mother's weight so, higher neonatal weight in iron group seems to be related to higher mother weight gain in this group. Previous studies have stated that iron supplementation raises the concentration of Hb and ferritin but Cochrane systematic reviews have not found any evidence of a measurable improvement in any other outcome in women who are not anemic at the beginning of pregnancy.

Another study in Hong Kong showed that adverse effects such as an increased risk of preterm labor,

Table-II: Iron parameters status at delivery.

Characteristics	Iron (n=410)	Placebo (n=372)	Pvalue
Hb (g/dl)	13.46±(0.75)	12.48±(0.91)	0.03
Hct (%)	41.48±(2.62)	37.36±(3.99)	0.01
Serum Iron (µg/dl)	84.38±(40.41)	51.43±(29.03)	<0.001
Ferritin (µg/dl)	26.91±(2.11)*	9.26±(0.62)*	0.048
TIBC (µg/dl)	453.55±(123.21)	540.7±(125.11)	<0.001

Data are given as mean±SD or mean±SEM

* SEM= $\frac{SD}{\sqrt{n}}$

LBW and neonatal asphyxia have been associated with hemoglobin rise in supplemented nonanemic mothers.³ High hemoglobin concentration results in increased blood viscosity and thereby reducing placental circulation.

Recent publications in BJOG suggest that routine supplementation of nonanemic women increases the risk of preeclampsia and infection including malaria.¹⁵⁻¹⁷ Although the rate of preterm labor in present inquiry was lower than reported rates in other studies, it wasn't affected by iron supplementation (3.9% in iron group vs. 4.8% in placebo group, $p=0.6$)

The studies of Scholl in 2000 and 2005 and Lindsay in 2001 have noted increased risk of preterm labor associated with iron deficiency anemia in early pregnancy¹⁸⁻²⁰ but clinical trials carried out in Nepal and the USA couldn't find any effect on preterm labor incidence with iron supplementation from the initiation of pregnancy.¹⁹ On the other hand increased levels of Hb, Hct and ferritin were observed with higher risk of IUGR, preterm labor, preeclampsia and gestational diabetes.¹⁹

In current study IUGR, PROM, preeclampsia, gestational diabetes, oligohydramnios and placental abruption have not increased with iron supplementation, but pregnancy induced hypertension in supplemented mothers was higher (6.7% vs 3.4%, $p=0.04$). Rayman in an investigation of iron parameters in preeclampsia (2002) explored that serum iron concentration and ferritin were higher in preeclamptic patients so, he recommended in the absence of

iron deficiency anemia, iron supplements should not be given to pregnant women at higher risk for preeclampsia.⁵

Scholl (2000) showed that Hct >40% before 20 weeks of pregnancy and between 31-34 gestational weeks has remarkably noted with risk of preterm labor (OR>2), also ferritin greater than 40 ng/l at 3rd trimester considered as a marker for increased risk of preterm labor.¹⁸ Iron is a probable source for producing free radicals and has the ability of oxidative damage to protein and lipids DNA.²⁰ Iron overload and oxidative stress increase the risk of type 2 diabetes, preeclampsia and preterm labor.¹⁹

Chan in 2009 in a randomized placebo-controlled trial on 1164 pregnant women couldn't show the relationship between gestational diabetes and prenatal iron supplementation.¹⁴ According to our results it might be recommended that iron-replete, non anemic women at 1st trimester of pregnancy particularly whom are at higher risk for hypertension, not be supplemented by iron until Hb falls below normal level. We suggest further investigation with larger sample size in women with Hb >14 gr/dl be conducted.

ACKNOWLEDGEMENTS

We acknowledge Dr. M. Ghojzadeh for cooperation on statistical analysis. The study was funded by Vice-Chancellor for Research, Tabriz University of Medical Sciences.

Table-III: Outcome of pregnancy in study groups.

Characteristics	Iron (n=410)	Placebo (n=372)	Pvalue
Birth weight (g)	3260 ± 395.97	3216.78 ± 430.72	0.28
Gestational age at birth (w)	39 ± 1.10	38.96 ± 1.33	0.74
Preterm labor*	16 (3.9)	18 (4.8)	0.6
IUGR**	58 (14.1)	65 (17.5)	0.23
1 st minute Apgar score	8.89 ± 0.7	8.93 ± 0.4	0.5
5 th min Apgar score	9.96 ± 0.3	9.99 ± 0.07	0.11
Admission duration in NICU (min)	165.15±148.36	132 ± 100.76	0.12
PROM	20 (4.9)	23 (6.2)	0.43
Placental abruption	6 (1.5)	3 (0.8)	0.51
PIH	25 (6.7)	14 (3.4)	0.04
Preeclampsia	16 (3.9)	10(2.7)	0.42
Gestational diabetes	2 (0.5)	3 (0.8)	0.67
IUFD	2 (0.5)	3 (0.8)	0.67
Oligohydramnios	0 (0)	3 (0.8)	0.1

Data are given as mean±SD The figures in the parentheses represent the percent. * Preterm labor: delivery between 20-38 w of gestation from the date of LMP. ** IUGR: birth weight<10% percentile for gestational age

REFERENCES

1. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY. Maternal physiology, 'Williams Obstetrics' (23rd edition), Mc Graw-Hill company, USA. 2010: 107-135.
2. Kaneshige E. Serum ferritin as an assessment of iron stores and other hematologic parameters during pregnancy. *Obstet Gynecol* 1981;57(2):238-242.
3. Lao TT, Tam KF, Chan LY. Third trimester iron status and pregnancy outcome in non-anaemic women. *Hum Reprod* 2000;15(8):1843-1848.
4. Scholl TO. High third-trimester ferritin concentration: associations with very preterm delivery, infection, and maternal nutritional status. *Obstet Gynecol* 1998;92(2):161-166.
5. Rayman MP, Barlis J, Evans RW, Redman CW, King LJ. Abnormal iron parameters in the pregnancy syndrome preeclampsia. *Am J Obstet Gynecol* 2002;187(2):412-418.
6. Xiao R, Sorensen TK, Frederick IO, El-Bastawissi A, King IB, Leisenring WM, et al. Maternal second trimester serum ferritin concentration a subsequent risk of preterm delivery. *Paediatr Perinat Epidemiol* 2002;16(4):297-304.
7. Sloan NL, Jordan E, Winikoff B. Effects of iron supplementation on maternal hematologic status in pregnancy. *Am J Public Health* 2002;92(2):288-293.
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(1 Suppl):272S-279S.
9. Siega-Riz AM, Hartzema AG, Turnbull C, Thorp J, McDonald T, Cogswell ME. The effects of prophylactic iron given in prenatal supplements on iron status and birth outcomes: a randomized controlled trial. *Am J Obstet Gynecol* 2006;194(2):512-519.
10. 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(4):773-781.
11. Steer P, Alam MA, Wadsworth J, Welch A. Relation between maternal haemoglobin concentration and birth weight in different ethnic groups. *BMJ* 1995;25;310(6978):489-491.
12. Little MP, Brocard P, Elliott P, Steer PJ. Hemoglobin concentration in pregnancy and perinatal mortality: a London-based cohort study. *Am J Obstet Gynecol* 2005;193(1):220-226.
13. Ziaei S, Norrozi M, Faghihzadeh S, Jafarbegloo E. A randomised placebo-controlled trial to determine the effect of iron supplementation on pregnancy outcome in pregnant women with haemoglobin $\geq$ 13.2 g/dl. *BJOG* 2007;114(6):684-688.
14. Chan KK, Chan BC, Lam KF, Tam S, Lao TT. Iron supplement in pregnancy and development of gestational diabetes - a randomised placebo-controlled trial. *BJOG* 2009;116(6):789-797.
15. Smith TG, Robbins PA. Iron, pre-eclampsia and hypoxia-inducible factor. *BJOG* 2007;114(12):1581-1582.
16. Siassakos D, Manley K. Unnecessary iron supplementation in pregnancy can be harmful: intergenerational implications. *BJOG* 2007;114(10):1308.
17. Nweneka CV. Rethinking iron supplementation recommendations in health care. *BJOG* 2007;114(12):1581.
18. Scholl TO, Reilly T. Anemia, iron and pregnancy outcome. *J Nutr* 2000;130(2S Suppl):443S-447S.
19. Scholl TO. Iron status during pregnancy: setting the stage for mother and infant. *Am J Clin Nutr* 2005;81(5):1218S-1222S.
20. Allen LH. Biological mechanisms that might underlie iron's effects on fetal growth and preterm birth. *J Nutr* 2001;131(2S-2):581S-589S.

Authors' contributions:

EO carried out the design and coordinated the study, participated in most of the experiments and prepared the manuscript. MSM, ST, ShA, provided assistance in the design of the study, coordinated and carried out all the experiments. MS participated in manuscript preparation. All authors have read and approved the content of the manuscript.