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DIFFERENT REGIMENS OF IRON SUPPLEMENTATION ON MATERNAL IRON STATUS AND PREGNANCY OUTCOME: RANDOMIZED CONTROL TRIAL

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Abstract:

Background: In non-anemic pregnant women recommended a daily intake of iron supplementation. This study aimed to determine the effects of daily iron supplementation versus twice a week in non-anemic pregnant women on pregnancy outcome.

Material and method:: In this double- blind randomized clinical trial study 508 pregnant women with Hb> 11mg/dl and serum ferritin 10-300 ng/dl in first half of pregnancy were randomly divided to receive either of 1 table/day [50 mg elemental] ferrous sulphate[n=254], or two tablet per weeks[n=254]. Haemoglobin, ferritin and glucose challenge test were measured in the 24-28th weeks and at the end of pregnancy. Patient information was recorded and analysed for haemoglobin, insulin, and ferritin. Data were analysed using independent-t test, ANOVA, and Chi square tests.

Results: The risk of preeclampsia and low birth weight significantly increased in the groups with daily intake of iron supplements. In addition, the levels of FBS, insulin and blood-pressure rise significantly in the second trimester. We should also note that the mean ferritin levels were significantly higher in cases with low birth weight and pre-eclampsia.

Conclusion: The daily supplementation of iron significantly increased preeclampsia and low birth weight in non-anaemic pregnant women which is associated with high level of ferritin in patient

Keywords: *Low Birth weight, Ferritin, Iron, dietary supplement, gestational diabetes*

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INTRODUCTION:

The need for iron during pregnancy to increase the mass of red blood cells, the blood supply to the developing fetus and placenta is necessary [1] Iron deficiency can be associated with morbidity and preterm delivery [2]. WHO recommended iron supplement in pregnancy [3], the prevalence of iron deficiency anaemia in pregnant women in Iran, according to WHO definitions are between 3.4-5.21% [4] According to Iranian health ministry protocol, pregnant women from 12-17 weeks till 3 months after delivery should intake 30 mg elemental iron tablets [5]. Recently, studies in relation to the daily consumption of iron supplementation in Non-anaemic pregnant women and its complications, questioned daily consumption of iron supplementation.

New evidence has shown the effects of iron supplements on production of free radical and oxidative stress [6-7].some studies show that increased ferritin and iron levels are associated with gestational diabetes, low birth weight and increased risks of pregnancy [9-11].In some countries using iron supplementation is not routine [8] Thus, according to available reports, the aim of this clinical trial was to assess the effects of daily iron supplements versus 2 times a week in Non-anaemic pregnant women on pregnancy and perinatal outcome.

MATERIALS AND METHODS:

This study was a randomized, double-blind clinical trial that has been done on singleton pregnancy .women attending in prenatal clinic of Yas Hospital during the years 2009-2010. Inclusion criteria were: Non-smoking, No history of (asthma, chronic hypertension leads to polycythaemia, gestational diabetes, preeclampsia and overt diabetes), No use of glucocorticoid and sympathomimetic drugs. After confirming the research in the ethics committee of Tehran University of Medical Sciences with the code; 2400 the project was explained to each individual and written consent obtained. Eligible individuals were randomly divided into two groups. Random method was so that according to entering the hospital and after being qualified for inclusion, individuals were randomly assigned to groups A and B, this process continued until the completion of the sample. Ferrous sulphate supplements from doctor Abidi pharmaceutical company was prepared and delivered to the individual. Haemoglobin test was done using Sian Matt haemoglobin and a Coulter Counter (Model 2001 - Made in America).The definition of variables in this study were as follows: Diagnosis of gestational diabetes - At gestational age of 24-28 weeks GCT (testing glucose 1 hour after intake of 50 grams edible Glucose), was done and if GCT was equal or higher of 130 mg per/dl, the GTT Test was done (4 times blood sugar test were done in which including fasting plasma glucose, and 1, 2 and 3 hours after consumption of 100 grams of glucose) if 2 items of measurement were abnormal (FBS ≥95, 1h≥180, 2h≥155, 3h≥140) diagnosis of gestational diabetes was confirmed. Preeclampsia was a checked at 24-28 and 32-36weeks for patients with blood pressure and random urine protein. If there was a blood pressure equal to or higher than 140/90 mm Hg and urine protein+1 or higher, preeclampsia was approved. Low birth weight- In all patients after delivery, birth weight of 2500 grams or less weight, was confirmed as low birth weight.

In Gestational age of less than 18 weeks, , 508 patients were selected and divided into 2 groups, early CBC and serum ferritin levels have been checked and individuals with Hb 11 -13 g /dl and serum ferritin level of 10 -300 ng / ml interred the study. Group (A) were given daily one 50 mg elemental ferrous sulphate tablet from week of 20, and group (B) received 2 tablets elemental ferrous sulphate a week. In the gestational age of 24-28weeks, CBC and serum ferritin, blood pressure, glucose tolerance test (GCT) and random urine protein were checked and if GCT≥ 130 mg / dl, GTT was done. At the gestational age of 32-36weeks the CBC and serum ferritin level were checked again. All patients have been checked for birth weight at delivery.

RESULTS:

Our results showed that among all 72 patients with GDM, 55 patients (76%) were in the A group and 17 patients (24%) in the B group $p< 0.001$ (Table 1). In total, those 69 patients with preeclampsia, 53 patients (77%) placed in the group A and 16 patients (23%) in the group B $p< 0.001$ (Table 1). Ferritin level is significantly higher in patients with pre-eclampsia (Table 2). Ferritin in the first, second and third trimester in the women with low birth weight infants was significantly higher (Table 3).

Table 1:Variables and iron status in the study groups

	Fe		Odds Ratio	95% Confidence Interval		P value
	daily	Two in week		lower	Upper	
Preeclampsia	*53*	*16*	*0.255*	*0.141*	*0.46*	*0.001*
	76.80%	*23.20%*				
low Birth weight=<2500 gr	*43*	*11*	*0.222*	*0.112*	*0.442*	*0.001*
	79.60%	*20.40%*				
Serum insulin level in second trimester > 20	*55*	*17*	*0.258*	*0.145*	*0.46*	*0.001*
	76.40%	*23.60%*				
Abnormal GTT	*49*	*17*	*0.3*	*0.168*	*0.537*	*0.001*
	74.20%	*25.80%*				
Serum ferritin level ≥300 ng/ml	*40*	*10*	*0.202*	*0.099*	*0.415*	*0.001*
	80.00%	*20.00%*				

Table 2:Variables and iron status in the study groups in at women with preeclampsia

	daily	two in weeks	
	Mean	Mean	p value
Hb[g/dl] [under 20 weeks]	12.8±.60	12.7±.14	0.178
Fri[Ng/ml][under 20 weeks]	135.6±52.7	120.3±43.1	0.0001
Hb[g/dl] [24-28 Weeks]	12.5±.60	12.4±.70	0.799
Fri [Ng/ml][24-28 Weeks]	273.8±91.0	287.7±69.2	0.0001
insulin [mg/dl][24-28 Weeks]	15.3±6.9	13.0±3.4	0.001
GCT[mg/dl][24-28 Weeks]	110.7±15.3	107.8±12.2	0.007
Hb [g/dl][32-36 Weeks]	12.7±.4	12.6±.3	0.78
Fri[Ng/ml] [32-36 Weeks]	278.4±102.1	280.2±109.5	0.0001
birth weight[gr]	2798.2±945.6	2952.6±832.0	0.0001

Table 3: Variables and iron status in the study groups at women with LBW

	daily	two in weeks	p value
	Mean	Mean	
Hb[g/dl] [under 20 weeks]	12.7±.5	12.8±.5	0.295
Fri[Ng/ml][under 20 weeks]	94.7±43.9	125.3±77.1	0.0001
Hb[g/dl] [24-28 Weeks]	12.5±.5	12.6±.6	0.343
Fri [Ng/ml][24-28 Weeks]	180.9±115.8	192.4±128.24	0.0001
Insulin [mg/dl][24-28 Weeks]	15.5±7.0	13.6±2.5	0.008
GCT[mg/dl][24-28 Weeks]	108.9± 12.6	108.1±19.6	0.009
Hb [g/dl][32-36 Weeks]	12.8±.5	12.6±.5	0.78
Fri[Ng/ml] [32-36 Weeks]	153.2±103.2	245.0±192.4	0.0001
Birth weight[gr]	1779.2±606.7	1683.0±553.2	0.0001

DISCUSSION:

In this clinical trial, the effect of iron supplementation on preeclampsia and birth weight was studied. Our results showed that daily iron supplementation significantly increased preeclampsia and low birth weight in Non-anaemic women. Iron supplementation in women without iron-deficiency anaemia can increases the risk of pregnancy complication. Our results are in agreement with some other studies which showed that daily iron basis can significantly increase preeclampsia and low birth weight [10-9]

Today, all healthy and iron deficiency anaemia pregnant women are given iron supplements [5].So it seems that Iron supplement in women with iron deficiency has good effect but in women without iron-deficiency anaemia it can increase the risk of pregnancy. This issue in this study is consistent with studies of Scholl in 2005 [12]. As other studies it was indicated that haemoglobin of 13.3 grams per litter could increase blood pressure [13].In another study using130 grams per litter haemoglobin doubled the risk of premature birth and low birth weight [10].

Reports of Siega-Riz in 2006 also argued that Iron supplement was useful for anaemic mothers but could be harmful to healthy women [14]. There are other studies that indicate profits and losses of iron supplements in healthy women leaving to do more research projects [12].According to Jiang in 2004 that was published in JAMA, the high iron stores increased the risk of diabetes in women with no risk factors for diabetes [15].In Goldenberg study, high ferritin at 26 weeks was strongly associated with low birth weight and preterm delivery [9]. Thus, present research studies have confirmed the above results, however some variables are slightly different.

Need to iron in the first and second trimester is 8 mg / day and in the third trimester 6 mg / day [16], Normal levels of haemoglobin are 11.7 -13.7g / dl and normal haematocrit values are 33-38% in pregnant women [17]. Luzm and Murphy have questioned about using iron supplement in low-risk women [18, 13]. Some studies have investigated the effects of an increase in haemoglobin on pregnancy outcome. This studies showed the risk of hypertension in pregnancy, intrauterine growth restriction, low birth weight, premature birth and gestational diabetes with high levels of haemoglobin [23-19].

The novelty of this study, along with other research is that ferritin and not hemoglobin incensement were assayed.

In 2000 Lao showed that the amount of ferritin has an inverse correlation with the fetus weight, the mean of fetus weight was significantly lower in the group with daily iron intake than the control group, our studies also confirms Lao's results[1].

Ziaei recognized that the intake of iron causes blood pressure in pregnant women [24] iron supplements have been linked to increased oxidative stress during pregnancy[12]. In consonance with this study related high ferritin with preeclampsia. According to the previous researches and the present results, we do not recommend a daily dose of iron. There are some debates between the related articles on the pregnancy outcome. For example in Yongh et al. Studies [25] on anaemic women and Casanveva et al. studies on no anaemic women [26] weekly regimes are considerd superior to daily ones.In the findings of Pena-Rosas et al in review article show, [11] the daily supplementation of iron plus folic acid produces similar primary infant outcomes as the intermittent iron plus folic acid regimens (Outcomes such as, low birth weight (average risk ratio (RR) 0.96; 95% confidence interval (CI) 0.61 to 1.52, seven studies), infant birth weight (mean difference MD -8.62 g; 95% CI -52.76 g to 35.52 g, eight studies), premature birth (average RR 1.82; 95% CI 0.75 to 4.40, four studies). On the other hand, the intermittent regimens are associated with fewer side effects for the mothers, namely the average RR and the risk of developing high HB concentrations during the second or third trimester of pregnancy. They also note that those who took daily supplements of iron plus folic acid had increased risk of high levels of HB in mid and late pregnancy but were less likely to show mild anemia near term. Therefore it's been suggested that intermittent regimen may be a practical alternative to daily iron supplementation among those pregnant women whom are not anemic and have sufficient antenatal care. Whereas, in our studies we observed that Groups on a daily iron had a significantly higher risk of pre-eclampsia and low birth weight. Also notable is the remarkably higher FBS, insulin and high blood pressure in pregnant women in their second trimester. In addition, ferritin in the second and third trimester was notably greater in low birth weight. Mean ferritin levels were significantly higher in patients with preeclampsia[27]in 2015 a trial by alizade.L etal was conducted on 86 non anemic pregnant women (an experimental group with daily 50mg iron tablet and control group with placebo) to compared incidence of anemia and LBW as a pregnancy outcome. They showed that iron supplementation is not necessary in non anemic pregnant women during their pregnancy[28]. However in our study a larger sample size of non-anemic pregnant women was investigated and the result showed there is statistically significant difference on pregnancy outcomes between group with two 50mg tablet per week and group with daily

50mg iron tablet[28]. Hemminki et al. at 2016 shows a pragmatic randomizer controlled clinical trial in pregnant women(>18 years old; non high-rise pregnancy) were randomly allocated to routine iron (receiving 60mg ferrous sulphate plus 400 microgram folic acid daily) and selective iron (receiving 1mg of folic acid per day). The results showed that two policies of giving iron to pregnant women either as routine supplementation to everyone or treating only women with low Hb has similar health outcomes during pregnancy and at birth, however women death during pregnancy were more common in selective group than in the routine group but in subgroup analysis number of deaths in the selective group did not differ by Hb levels and it is unclear whether the deaths number differences was due to intervention, other factors or chance finding. [29]

The prevalence of low birth weight infants in the whole study was 11% of all the 508 patients , this prevalence was 16% for the 254 patients with daily iron intake and 4% for the other 254 patients with a iron intake of twice a week.

Studies reports that the LBW prevalence in Iran is 4.1%-11.8% [30-33]. According to the figures published so far in Iran, the incidence of LBW infants in people with daily iron diet appears high. The several studies that have been done in this area gave different results. Cogwell et al. (1998) argued that iron supplement increased the child's weight at birth[34]. Hemminki and colleagues in 1991, showed similar results for non-anemic pregnant women who take 100mg iron tablets regularly compare with pregnant women who took iron occasionally[35]. In 2001 Rusmussen due to present debate, claimd the necessity of more carefully studies in iron relationship between birth weights. It is necessary to note that some of these old studies had been done on anemic women [36].Consistent with our study confirmation, there are many studies that can generalize our results. .Rodenberg confirmed the study of the relationship between maternal serum Hb level and Ferritin with weight and height neonatal [37]Goldenberg Studies [9]Tamura[38] have shown the inverse relationship between serum ferritin level and birth weight. Allen considered this as mother's body infection result [39].Sieg-Riz and Ziaei studies in 2006 and 2007 [14, 24] showed the effect of iron supplement in non-Anemic women for small size, time of delivery and low birth weight in which the low birth weight is consistent with our studies. The study of Sieg-Riz was a comparison between a group without iron and also a group getting 30 mg of iron also Ziaei study compared groups without iron and a group receiving 50 mg iron per day, which should be noted as a difference in generalizing of our results. Scalon research in 2000, showed SGA associated with hemoglobin concentration above 14.9 mg/dl treatment at 12 weeks was and the risk of SGA 1.27 times and in 14.4 mg /dl this risk increased to 1.79 times[40].Lewis in 2002 and 2001 on animal models showed that high dose iron in RAT caused low birth weight [41,42]. More recent studies confirms the results of our study and the effect of high-dose iron on low birth weight [43,44].

CONCLUSION:

Our results showed that using daily iron supplementation in non-anaemic pregnant women significantly increase preeclampsia and low birth weight. This finding can help us in managing on pregnant women and can be considered in the mother's prenatal care.

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