

EFFECTS OF IRON SUPPLEMENTATION STARTING FROM EARLY GESTATION IN NON- ANEMIC PREGNANCY AND NEONATAL BIRTH OUTCOMES

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Abstract

Iron supplementation, as early as possible, is commonly recommended for all pregnant women in developing countries to reduce maternal anemia. However, this excessive iron can induce a high hemoglobin level and negatively influence neonatal outcomes. The objective of the present study is to assess the impact of iron supplementation starting from early pregnancy and neonatal birth outcomes. All data in the present retrospective cohort study were obtained from the antenatal records and labor registry of non-anemic pregnant Thai women who attended their first antenatal care and delivery at Vajira Hospital, Bangkok, Thailand between June 2006 and December 2007. The proportions of low birthweight (LBW), small for gestational age (SGA), and preterm delivery were compared between the early supplement group which started oral iron before 16 weeks of gestation and the control group which started later. Among 880 non-anemic pregnancies, there were 477 women in the early supplement group and 403 women in the control group. The incidence of LBW in the early supplement group was significantly lower than in the control group (5.5% vs. 9.4%, risk ratio: 0.58; 95% confidence interval: 0.37-0.94). There were no significant differences in the occurrence of SGA and preterm delivery between groups. Iron supplementation starting from early gestation in non- anemic pregnancy has a significant benefit in reducing the incidence of LBW.

Keywords: Iron supplementation, non-anemic pregnancy, low birthweight, multiple imputation

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Introduction

Despite achievements in maternal and child health-related programs over the past decade (Brannon and Taylor, 2017), anemia remains a common nutritional problem in pregnant women worldwide, particularly in low- and middle-income countries (Black *et al.*, 2013). Maternal anemia is strongly associated with many adverse pregnancy outcomes for both mother and fetus (Black *et al.*, 2013). Traditionally, prophylactic iron supplementation in all pregnant women, as early as possible, has been recommended and practiced by many physicians to prevent iron deficiency anemia and its sequels (Black *et al.*, 2013; World Health Organization, 2016; Brannon and Taylor, 2017).

Although several studies have proved the benefits of iron supplementation in pregnant women with iron deficiency anemia, especially in terms of perinatal outcomes such as decreased risks of low birthweight (LBW) infants and perinatal mortality (Scholl, 2005), the impact of universal iron supplementation in non-anemic pregnant women was still debated (Pena-Rosas *et al.*, 2015). Several prophylactic iron supplementation studies demonstrated the lower risk of maternal anemia at or near term and a higher neonatal birthweight (Iqbal and Ekmekcioglu, 2017). On the other hand, some studies reported a significant inverse correlation of iron supplementation and the incidence of LBW (Dewey and Oaks, 2017). Moreover, routine iron supplementation for pregnant women with adequate iron storage may build up an excessive iron status and induce some deleterious effects on pregnancy. These include preeclampsia and gestational diabetes, which are the results of rising levels of iron-generated free radicals and oxidative stress (Ziaei *et al.*, 2007; Bo *et al.*, 2009). Therefore, concerns about safety for women with an adequate iron intake have limited the use of this intervention.

However, the majority of existing studies have compared between women who received daily prenatal supplementation and those who received no treatment or a placebo from the first trimester of pregnancy to the early third-trimester of pregnancy or throughout the pregnancy period (Siega-Riz *et al.*, 2006; Ziaei

et al., 2007; Chan *et al.*, 2009, Imdad and Bhutta, 2012; Etheredge *et al.*, 2015). Given these extremely contrasting groups, it is not surprising that supplementation has a positive effect on infant birthweight and maternal hemoglobin value. Insufficient data are available about the early and late starting of supplementation. In the present study, we needed to investigate the impact of prophylaxis iron supplement starting from early gestation in non-anemic pregnant women on the occurrence of LBW. During the study, we added the occurrence of small for gestational age (SGA) infants and preterm birth (PTB) as secondary outcomes.

Materials and Methods

The present retrospective study was conducted after approval from the Bangkok Metropolitan Administration Ethics Committee for researches involving human subjects. We reviewed medical records of pregnant women who came to the antenatal clinic at Vajira Hospital between June 2006 and December 2007.

Inclusion criteria were that all were singleton pregnant women who came to the antenatal clinic at Vajira Hospital for their first antenatal care. Exclusion criteria were women who had anemia or hemoglobin levels lower than 11 g/dl in the first antenatal blood test, who were considered as possibly having a thalassemia trait, who were known to have a medically complicating pregnancy (such as overt diabetes mellitus, chronic hypertension, thyroid disease), and who had delivery at another hospital. The study population was divided into 2 groups, the first one was the study group which started taking oral iron supplementation as early as prior to completing 16 weeks gestational age (ferrous fumarate 200 mg/day) and the other was the control group which started later. The proportions of LBW, SGA, and PTB were compared between the 2 groups. The gestational age was calculated by using the mother's last menstrual period and confirmed with ultrasound measurement of the fetal biometry.

Data collection included maternal demographic characteristics and maternal weight gain during gestation. Information on iron supplementation was obtained by collecting data from the obstetric clinical record and hospital computer-based record. The numbers of tablets from the first fill date to the last fill date were reviewed and compared with the number of days between each visit to check drug adherence in percentage. For the present study, the authors defined good drug adherence as receiving iron tablets sufficient for use during pregnancy of at least 75% of the period starting from the first prescription date to the delivery date. Details of delivery, hemoglobin levels, and neonatal outcomes were recorded as a part of the standard care at our delivery room. LBW and very LBW were defined as infant birth weight less than 2500 grams and 1500 grams, respectively. PTB was defined as delivery before 37 weeks of gestation. SGA was defined as infant birth weight less than the 10th percentile compared with the gestational age. Anemia at delivery was defined as a hemoglobin value lower than 11 g/dl.

The sample size was calculated based on previous studies in which the incidence of LBW, SGA, and preterm birth in iron

supplementation starting at the early trimester of gestation and at the last trimester of gestation were 1.7% vs. 6.3%, 6.8% vs. 17.7%, and 7.5% vs. 13.9%, respectively (Cogswell *et al.*, 2003; Siega-Riz *et al.*, 2006). A sample size of 326 was required in each group to detect the differences of LBW, SGA, and preterm birth with a power of 80% using a 0.05 level of significance. Statistical analysis was performed by using the Stata statistical software (version 14) (StataCorp LLC, College Station, TX, USA). Demographic data and birth outcomes were calculated as mean with standard deviation (SD) for continuous variables and as a number with the percentage for categorical variables. Binary regression analysis was used to estimate the relative risk of having a neonate with LBW, SGA, and preterm delivery in the study group compared to the control group. After adjustments for any possible factors that may be confounders, a p-value of <0.05 was considered to be statistically significant.

Result

Eight hundred and eighty singleton non-anemic pregnant women were included in the present

Table 1. Demographic and clinical characteristics of 880 pregnant women between the 2 groups

Characteristics	Early iron supplement group (N = 477)	Control group (N = 403)	p-value
	n (%) or mean±SD	n (%) or mean±SD	
Maternal age (years)	28.9±5.6	26.6±6.5	<0.001*
Teenage pregnancy	21 (4.4)	70 (17.4)	<0.001*
Elderly pregnancy	82 (17.2)	57 (14.1)	0.229
Nulliparity	183 (38.4)	155 (38.5)	1.000
Maternal weight before pregnancy (kg)	55.8±12.2	55.2±11.3	0.544
Maternal BMI before pregnancy	22.6±4.5	22.3±4.3	0.494
Maternal height (cm)	1.6±0.06	1.6±0.06	0.799
Previous preterm birth	7 (1.5)	9 (2.2)	0.453
Previous infant low birthweight	0	0	NA
Gestational age of starting iron supplement (weeks)	12.1±2.9	20.8±4.6	<0.001*
Good drug adherence	407 (85.6)	318 (78.9)	0.010*
Hemoglobin level at first booking (g/dl)	12.6±0.8	12.0±0.9	<0.001*
Hemoconcentration [#] at first booking	157 (32.9)	59 (14.7)	<0.001*
Gestational weight gain (kg)	14.9±5.5	13.0±5.5	<0.001*

Note: * p-value<0.05 indicates statistical significance; [#]Hemoglobin level 13 g/dl or higher

study, with 477 women in the early supplement group and 403 women in the control group. A total of 64 pregnancies (7.3%) delivered infants with LBW, and a half of them were term infants with LBW (32/880; 3.6%). There were 78 infants with PTB (8.7%) and 29 with SGA (3.3%).

The demographic and clinical characteristics of the 880 pregnant women are shown in Table 1. There were no significant differences in gravidity, maternal height, pre-pregnancy body weight, pre-pregnancy BMI, previous preterm birth, and previous infant birth with LBW. However, the number of women with a high hemoglobin level at the first antenatal booking

was greater in the study group. Furthermore, the mean maternal age and weight gain during pregnancy were statistically significantly higher in the study group, but this difference had no clinical significance.

There was no neonatal death or neonatal birth asphyxia in our cohort. As shown in Table 2, there was no significant difference in the gestational age, incidence of PTB, and SGA infants between the 2 groups. However, the incidence of LBW was significantly lower in the study group; this difference was found only in the subgroup of term infants. The hemoglobin level was significantly higher at

Table 2. Delivery outcomes of 880 pregnant women between the 2 groups

Delivery outcomes	Study group (N = 477)	Control group (N = 403)	<i>p</i> -value
	n (%) or mean±SD	n (%) or mean±SD	
Infant birthweight <2500 g.	26 [#] (5.5)	38 (9.4)	0.027*
Term infant birthweight <2500 g.	10 (2.3)	22 (6.0)	0.010*
Small for gestational age	14 (2.9)	15 (3.7)	0.572
Preterm birth ⁺	41 (8.6)	37 (9.18)	0.812
Very preterm birth [§]	7 (1.5)	5 (1.2)	1.000
Maternal anemia at labor [¶]	27 (5.7)	23 (5.7)	1.000
Maternal hemoglobin (g/dl)	12.6±1.0	12.4±1.0	0.002*

Note: * *p*-value<0.05 indicates statistical significance; [#] 1 infant with birthweight < 2000 g; ⁺Preterm birth, delivery at gestational age < 37 weeks; [§] Very preterm birth, delivery at gestational age<34 week; [¶] Maternal anemia at labor, Hemoglobin level < 11 g/dl

Table 3. Demographic and clinical characteristic between groups with and without missing data

Characteristics	No missing data group (N = 503)	Missing data group (N = 377)	<i>p</i> -value
	n (%) or mean±SD	n (%) or mean±SD	
Maternal age (years)	27.9±6.2	27.9±6.0	0.960
Nulliparity	196 (39.0)	142 (37.7)	0.726
Maternal height (cm.)	1.6±0.06	1.6±0.06	0.529
Previous preterm birth	7 (1.4)	9 (2.4)	0.314
Previous infant low birthweight	0	0	NA
Gestational age of starting iron supplement	16.4±5.7	15.8±5.8	0.135
Hemoglobin level at first booking (g/dl)	12.3±0.8	12.3±0.9	0.643
Infant birthweight <2500 gm.	34 (6.8)	30 (8.0)	0.514
Term infant birthweight <2500 gm.	19 (4.1)	13 (3.8)	1.000
Small for gestational age	17 (2.9)	12 (3.7)	1.000
Preterm birth	41 (8.2)	37 (9.8)	0.403

Note: Preterm birth, delivery at gestational age<37 weeks; Small for gestational age, infant birth weight less than 10th percentile compared with gestational age.

delivery for the study group, but this difference had no clinical significance and there was no difference in the incidence of maternal anemia at delivery.

Unfortunately, there was a lot of missing data (as high as 43%) for 3 important parameters in our study, i.e. pre-pregnancy body weight, pre-pregnancy BMI, and total weight gain during pregnancy. Other demographic and clinical characteristics between the groups that are present either with or without these 3 missing parameters of data were similarly comparable, as shown in Table 3. Under the assumption that the missing data was said to be missing at random and a monotone missing pattern was detected, we dealt with the missing data in this study using the multiple imputation (MI) method to generate 50 data sets. The imputation model included all predictors relevant to the missing data mechanism and reserved all data characteristics likely to be explored at the analysis stage. We performed a MI diagnostic to check that this imputation model fitted the observed data well, and that the imputed values themselves are reasonable.

Iron supplementation prior to completing 16 weeks of gestational age decreased the risk of LBW, as shown in Table 4. After adjusting for possible confounders in complete case (CC) analysis, the risk of LBW was insignificantly

lower in the early supplementation group compared to the late supplementation group (RR: 0.75; 95% CI 0.37-1.47). In addition, after analysis by using multivariable logistic regression with MI, the impact of early oral iron supplementation on the occurrence of LBW was consistent with the result from univariable analysis (RR: 0.62; 95% CI 0.34-1.09). Moreover, iron supplementation starting from early pregnancy was significantly associated with a lower risk of LBW in the subgroup of term infant births (RR: 0.41; 95% CI 0.18 -0.92).

Discussion

The overall prevalences of LBW, SGA, and preterm births in the present study were 7.3%, 3.3%, and 8.7%, respectively, which were consistent with those in recent reports in Southeast Asian and in non-anemic Thai pregnant women, respectively (Black, 2015; Traisrisilp *et al.*, 2017).

In the present retrospective cohort study, we directly assessed the possible effect of prophylactic iron supplementation starting during early gestation on the occurrence of LBW, SGA, and preterm delivery in non-anemic pregnant Thai women. We observed a significantly lower incidence of LBW and term infants with

Table 4. Associations between early iron supplementation and neonatal birth outcomes from binary regression analysis

Characteristics	CC analysis			MI Analysis
	(n = 880) Crude RR (95% CI); <i>p</i> -value	(n = 880) Adjusted* RR (95% CI); <i>p</i> -value	(n = 503) Adjusted# RR (95% CI); <i>p</i> -value	(n = 880) Adjusted# RR (95% CI); <i>p</i> -value
Infant birthweight < 2500 g.	0.58 (0.37-0.94); 0.025	0.56 (0.41-0.77); <0.001	0.75 (0.37-1.47); 0.405	0.62 (0.34-1.09); 0.097
Term infants with birthweight < 2500 g.	0.38 (0.18-0.80); 0.010	0.39 (0.27-0.57); <0.001	0.66 (0.25-1.68); 0.382	0.41 (0.18-0.92); 0.032
Small for gestational age	0.79 (0.39-1.61); 0.516	0.81 (0.56-1.15); 0.233	1.52 (0.58-3.97); 0.393	0.92 (0.42-2.22); 0.946
Preterm birth	0.94 (0.61-1.43); 0.761	0.88 (0.65-1.20); 0.417	1.02 (0.55-1.88); 0.952	0.94 (0.57-1.57); 0.859

Note: * Adjusted for nulliparity, maternal age, hemoconcentration (hemoglobin level ≥ 13 g/dl) at first antenatal care booking, diabetes mellitus, and drug adherence $\geq 75\%$; # Adjusted for nulliparity, maternal age, hemoconcentration (hemoglobin level ≥ 13 g/dl) at first antenatal care booking, diabetes mellitus, drug adherence $\geq 75\%$, BMI pre-pregnancy and gestational weight gain; CC=completed case; MI=multiple imputation; RR= risk ratio; CI= confident interval

LBW in the study group compared with the control group. After adjusting for many reasonable confounders, the benefit of iron supplementation starting as early as <16 weeks gestational age on the LBW outcome was detected only in the term infant subgroup. Thus, iron supplementation starting from early gestation in non-anemic pregnant women was associated with a reduced risk of LBW only in term neonates. These findings were similar to the results of previous reports on maternal iron supplementation and infant birth weight (Cogswell *et al.*, 2003; Palma *et al.*, 2008; Moin and Lassi, 2015). On the other hand, some studies reported no different impact of prophylactic iron supplementation on birth weight and LBW outcomes (Siega-Riz *et al.*, 2006; Etheredge *et al.*, 2015). Recently, there has been inconclusive evidence from meta-analysis showing that prophylactic iron supplementation, especially in non-anemic pregnancy, improves infant birth outcomes (Imdad and Bhutta, 2012; Cantor *et al.*, 2015; Pena-Rosas *et al.*, 2015).

Our trial also investigated the association between iron supplementation during early pregnancy and other birth outcomes, including PTB and SGA. We found no association between supplementation during early gestation and either SGA or PTB. The recent comprehensive meta-analysis showed no significant associations of routine iron supplementation during pregnancy with PTB and SGA, which is also consistent with our data (Imdad and Bhutta, 2012; Cantor *et al.*, 2015; Pena-Rosas *et al.*, 2015; Brannon and Taylor, 2017).

This study demonstrated no preventive effect of early iron supplementation on maternal anemia which is inconsistent with the findings of previous reports (Imdad and Bhutta, 2012; Moin and Lassi, 2015). However, these inconsistent findings may be due to the effect of different supplemented periods during gestation. Theoretically, an anemia during pregnancy is a contributing factor of adverse neonatal outcomes; however, our study still found an association of iron supplementation with LBW, even though it did not have an impact on maternal anemia, which is consistent with some epidemiologic studies that have shown that there was an association of LBW

and maternal anemia that has been detected during first- or second-trimester of pregnancy, but not in a later period of pregnancy (Haider *et al.*, 2013). Thus, the protective effect of iron supplementation on LBW might be due to some biological mechanism other than a decrease of evidence of maternal anemia (Allen, 2001).

Missing data is a common problem in epidemiological and clinical research, and in consequence there are several methods to handle these incomplete data sets (Baraldi and Enders, 2010). The complete-case approach or listwise deletion, which is restricted to an individual without missing data in any of the variables required for analysis, leads to a loss in power of hypothesis testing in etiologic research. In addition, if the missingness mechanism depends on the outcome, given the covariates a complete-case analysis can be biased. MI, which allows individuals with incomplete data to be included in the analysis, is a principled statistical method for dealing with this problem (Baraldi and Enders, 2010). In our study, there was a large percentage of the missing of some confounding variables; the outcome of interest may deviate in a complete-case analysis approach. Eventually, we used the MI approach that was a reasonable method for handling missing data.

The limitation of the present study was a retrospective study design that usually found the missing data problem and could not well control for the confounding variables. Nevertheless, the statistical adjustment method in this study is a reasonable appropriated approach to deal with these problems. Regarded as the strength of this study was a statistical analysis method using multivariable logistic regression analysis to adjust for several reasonable confounders which could cause an outcome deviation, and use of the MI method to deal with the missing data of important confounding factors.

In summary, our data confirmed that prophylactic iron supplementation of non-anemic pregnant women was effective for reducing the risk of low birth weight. Although the majority of previous prophylactic iron supplementation studies had compared between women who received daily prenatal supplementation and those who received no treatment or a placebo

for the entire gestational period (Cantor *et al.*, 2015; Pena-Rosas *et al.*, 2015), our study still found a negative impact of a late start of supplementation on the neonatal outcome. This indicated that the practice of routine iron supplementation is reasonable for prevention of term infants with LBW, and that an early starting prescription was more beneficial than a late one.

Conclusions

Prophylactic iron supplementation started during early gestation has a significant benefit in reducing the incidence of neonatal LBW.

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