Modifying effects of maternal Hb concentration on infant birth weight in women receiving prenatal iron-containing supplements: a randomised controlled trial

Lilin Wang1, Zuguo Mei2, Hongtian Li1, Yali Zhang1, Jianmeng Liu1* and Mary K. Serdula2

1Institute of Reproductive and Child Health/Ministry of Health Key Laboratory of Reproductive Health, Peking University Health Science Center, Beijing 100191, People’s Republic of China
2Division of Nutrition, Physical Activity and Obesity, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention (CDC), Atlanta, GA 30329-4027, USA

(Submitted 29 June 2015 – Final revision received 28 October 2015 – Accepted 3 November 2015 – First published online 21 December 2015)

Abstract

Concerns have been raised about the benefits of Fe-containing supplements on infant birth weight among women with normal/high Hb levels at baseline. Thus far, no clinical trials have examined whether the effects of prenatal Fe-containing supplements on birth weight vary by maternal Hb levels. We compared the effects of Fe–folic acid (IFA) or multiple micronutrients (MMN) with folic acid (FA) supplements on birth weight among pregnant women with mild/no anaemia and high Hb levels. A double-blind randomised controlled trial was conducted in 2006–2009. In total, 18,775 pregnant women with mild/no anaemia (<100 g/l) were enrolled from five counties in north China. During the period from before 20 weeks of gestation to delivery, the women randomly received a daily supplement containing the following: (1) FA (400 μg); (2) IFA (FA, 400 μg; Fe, 30 mg); or (3) MMN (FA, Fe and thirteen additional vitamins and minerals). Birth weight was measured within the 1st hour of birth. Maternal Hb concentration was determined at enrolment. Among women with normal (≥132 g/l) or high (153–145 g/l) baseline Hb levels, IFA or MMN supplementation had no effect on birth weight. Among women with very high (>145 g/l) baseline Hb levels, IFA and MMN supplements increased birth weight by 91·44 (95% CI 3·37, 179·51) g and 107·63 (95% CI 21·08, 193·28) g (P < 0·05), respectively, compared with the FA group. No differences were found between the IFA and the MMN group, regardless of maternal Hb concentration. In conclusion, the effects of Fe-containing supplements on birth weight depended on baseline Hb concentrations. The Fe-containing supplements improved birth weight in women with very high Hb levels before 20 weeks of gestation.

Key words: Iron-containing supplements: Birth weight: High maternal Hb

More than twenty million low birth weight (LBW) infants (15% of all births) are born worldwide annually1. In China, the prevalence of LBW fell from 6% in 2000 to 2.7% in 2008; however, LBW still accounts for about one million newborn babies every year because of the large population(2). LBW is associated with mortality and morbidity in infancy and childhood, and also has long-term effects on health in adult life. It is currently recommended by the World Health Organization(3) that all pregnant women, regardless of baseline Hb status, take prenatal supplementation with Fe-containing supplements such as Fe–folic acid (IFA) to ameliorate maternal anaemia, Fe deficiency and LBW. In addition to Fe and folic acid (FA), supplements can be formulated to include other vitamins and minerals according to the United Nations International Multiple Micronutrient Preparation (UNIMMAP) to ameliorate maternal anaemia and overcome other possible maternal micronutrient deficiencies(4). This guidance has mainly been based on studies in patients with low Hb levels at baseline. However, most clinical trials performed in women with mild/no anaemia in the USA(5), UK(6), Australia(7), Norway(8), Finland(9,10) and Iran(11–13) have shown no benefit of Fe supplementation on birth weight(5–13), although two studies found that birth weight was increased with Fe-containing supplements(14,15). Thus, there are inconsistencies in the literature regarding the benefit of Fe-containing supplements in a well-nourished population with mild/no anaemia.

High maternal Hb concentrations may increase the risk of adverse pregnancy outcomes including preterm birth(16), stillbirth(17), perinatal death(16) and LBW(18) and gestational hypertension(19). Steer et al.(18) found that a U-shaped distribution of LBW incidence and preterm delivery by maternal Hb group with the highest incidence of LBW and preterm delivery occurred among white women with very low (<85 g/l) and very high (>145 g/l) Hb levels. Peña-Rosas et al.(120) reported that women who received higher amounts of Fe (≥60 mg/d) were more likely than controls to have high Hb levels (>130 g/l) at

Abbreviations: FA, folic acid; IFA, Fe–folic acid; LBW, low birth weight; MMN, multiple micronutrients; RCT, randomised controlled trial.

* Corresponding author: J. Liu, fax +86 10 82801141, email liujm@pku.edu.cn
Iron-containing supplements and birth weight

645

term. One small trial found that daily Fe supplementation (50 mg) in women with high Hb levels (>132 g/l) significantly increased the incidence of adverse pregnancy outcomes, including small-for-gestational-age babies and hypertension\(^{12}\). Therefore, concerns have been raised about the risks of routine Fe supplementation among women without anaemia, especially among those with high Hb levels. To the best of our knowledge, no large clinical trial has thus far determined whether the association of Fe-containing supplements with birth weight varies by baseline Hb levels, and specifically whether the effect of supplementation differs between women with normal and high Hb levels.

Recently, we conducted a large randomised controlled trial (RCT) of FA, IFA and multiple micronutrient (MMN) supplementation among pregnant women with low/no anaemia in northern China. We reported that, compared with FA alone, prenatal IFA or MMN supplementation prevented anaemia in late pregnancy, but did not affect infant birth weight or gestational duration\(^{21}\). However, this finding did not eliminate the increasing concerns about potential adverse pregnancy outcomes due to routine Fe supplementation among women with high maternal Hb levels. In addition, data from the clinical studies did not address whether baseline Hb concentrations modify the association of Fe supplementation during pregnancy and birth weight.

Thus, the objectives of the present study were to determine whether the association between Fe supplementation and birth weight differs among women with normal/low Hb concentrations and those with high (>132 g/l) and very high (>145 g/l) baseline Hb concentrations.

Methods

Study setting and design

The present study was a double-blind RCT (Clinicaltrials.gov ID: NCT00133744) conducted according to the guidelines laid down in the Declaration of Helsinki. Detailed information on this trial has been published elsewhere\(^{21}\). In brief, the RCT was conducted in five rural counties in Hebei Province, China, from May 2006 to April 2009. Doctors from village clinics and township hospitals provided prenatal care services, and doctors from county hospitals provided delivery services. During the period from early pregnancy (<20 weeks) to delivery, eligible pregnant women were enrolled and individually randomised in a 1:1 ratio to receive a daily supplement containing the following: (1) FA (400 μg) (FA group); (2) FA (400 μg) + Fe (ferrous fumarate, 30 mg) (IFA group); or (3) FA, Fe and thirteen additional vitamins and minerals (MMN group, the UNICEF/WHO/UNU UNIMMAP supplement included FA (400 μg), Fe (ferrous fumarate, 30 mg), vitamin A (800 μg), vitamin E (10 μg), vitamin D (5 μg), vitamin C (70 mg), thiamine (1-4 mg), riboflavin (1-4 mg), vitamin B\(_6\) (1-9 mg), vitamin B\(_12\) (2-6 μg), niacin (18 mg), Zn (15 mg), Cu (2 mg), I (150 μg) and Se (65 μg)).

The inclusion criteria were as follows: (1) had a Hb concentration ≥100 g/l; (2) had recorded dates of menstruation for 2 or more months before becoming pregnant; (3) were nulliparous; (4) were at least 20 years old; (5) were ≤20 weeks of gestation; (6) were legally competent; (7) had not consumed micronutrient supplements other than FA in the previous 6 months; (8) resided in and received prenatal care in one of five counties; and (9) consented to participate. Periconceptional FA is taken as a single nutrient supplement in China. The study protocol was approved by the Institutional Review Boards of the Centers for Disease Control and Prevention (Atlanta, Georgia, USA) and Peking University (Beijing, China), and was renewed annually. All the women enrolled in this trial provided informed verbal consent.

Sample size

The estimated mean of birth weight was 3290 ± 391 g in the FA group based on our previous report. Compared with the FA group, a 2 % increase in the IFA group and a 4 % increase in the MMN group were hypothesised. With a power of 80 % and α = 0.05, a sample size of 172/group would be needed to detect a 2 % increase in the IFA group and a 4 % increase in the MMN group. As this study was a post hoc analysis, no dropouts were considered.

Data collection and outcome measures

The primary outcome of our analysis was infant birth weight. All the women delivered in a health facility, and infants were measured within the 1st hour of birth using an electronic scale (BD 585; Tanita) with precision to the nearest 10 g. The scales were routinely checked and calibrated. Maternal Hb concentration was measured with finger-punctured blood using the HemoCue Hb 201 system (HemoCue AB) at enrolment. The average of two measurements was used. Maternal weight and height were measured at enrolment using an electronic scale (BW 150; UWE) with precision to the nearest 50 g and a collapsible height board to the nearest 0.1 cm, respectively. Gestational age was calculated based on the last menstrual period. Menstrual cycle was closely monitored by trained county or township physicians for 2 or more months before enrollment among volunteers who planned to get pregnant.

Statistical analysis

We conducted stratified analyses by maternal Hb levels according to the cut-off points for high (132 g/l) and very high maternal Hb levels (145 g/l). High (133–145 g/l) and very high (>145 g/l) Hb concentrations were defined according to the studies of Murphy et al.\(^{10}\), Ziaezi et al.\(^{12}\) and Steer et al.\(^{18}\).

We used general linear models to assess the association between birth weight and Fe supplements after adjusting for week of enrolment and gestational age at delivery, as those two variables could have been confounding factors. Preterm infants were not excluded because preterm birth is one of the major reasons for LBW, and the study focused on all LBW infants.

We examined the interaction between Fe supplements and maternal Hb concentration (<132, 133–145 and >145 g/l) by adding a product term to the regression model. A figure was drawn to show birth weight means with 95 % CI by maternal baseline Hb concentrations (2 g/l interval) in each study group (data points were not shown after 160 g/l because of small
sample size). Pearson’s correlation analysis between birth weight and Hb concentration was carried out among women with high and very high baseline Hb concentrations in each study group. P values <0.05 were considered to be statistically significant. All statistical analyses were performed using Empower (R) (www.empowerstats.com, X&Y Solutions Inc.) and R (http://www.R-project.org).

Results

A total of 18,775 women underwent randomisation. After exclusion of women who intentionally terminated their pregnancy or who died, moved or dropped out of the study (n = 878), 17,897 (95.3 %) women remained with known pregnancy outcomes21). Of these, 67 (0.4 %) women had multiple births, 82 (0.5 %) had stillbirths, 37 (0.2 %) had offspring with malformations and 157 (0.9 %) had no information on birth weight (there were some exclusions among these exclusions), leaving a total of 17,705 (98.9 %) women in the study (online Supplementary Table S1). No differences were found between participants and those who dropped out of the study (online Supplementary Table S1).

The baseline characteristics among the Fe supplement groups are shown in online Supplementary Table S2. Mean maternal weight and Hb concentration was carried out among women with high and very high baseline Hb concentrations in each study group. P values <0.05 were considered to be statistically significant. All statistical analyses were performed using Empower (R) (www.empowerstats.com, X&Y Solutions Inc.) and R (http://www.R-project.org).

Table 1. Baseline maternal characteristics by study intervention and Hb concentrations* (Number of participants and percentages)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>FA (n 4801)</th>
<th>IFA (n 4859)</th>
<th>MMN (n 4801)</th>
<th>FA (n 931)</th>
<th>IFA (n 872)</th>
<th>MMN (n 904)</th>
<th>FA (n 160)</th>
<th>IFA (n 178)</th>
<th>MMN (n 199)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Mean</td>
<td>23.6</td>
<td>23.7</td>
<td>23.6</td>
<td>23.6</td>
<td>23.6</td>
<td>23.6</td>
<td>23.6</td>
<td>23.6</td>
<td>23.6</td>
</tr>
<tr>
<td>SD</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Han ethnicity</td>
<td>4736</td>
<td>98.6</td>
<td>4804</td>
<td>98.9</td>
<td>4747</td>
<td>98.9</td>
<td>923</td>
<td>99.1</td>
<td>865</td>
</tr>
<tr>
<td>Farmer</td>
<td>4348</td>
<td>90.6</td>
<td>4442</td>
<td>91.4</td>
<td>4380</td>
<td>91.2</td>
<td>856</td>
<td>91.9</td>
<td>779</td>
</tr>
<tr>
<td>Primary education or less</td>
<td>67</td>
<td>1.4</td>
<td>81</td>
<td>1.7</td>
<td>64</td>
<td>1.3</td>
<td>18</td>
<td>1.9</td>
<td>16</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Mean</td>
<td>22.2</td>
<td>22.2</td>
<td>22.2</td>
<td>22.2</td>
<td>22.2</td>
<td>22.2</td>
<td>22.2</td>
<td>22.2</td>
<td>22.2</td>
</tr>
<tr>
<td>SD</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Gestational week at enrolment</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Mean</td>
<td>12.4</td>
<td>12.5</td>
<td>12.4</td>
<td>12.4</td>
<td>12.4</td>
<td>12.4</td>
<td>12.4</td>
<td>12.4</td>
<td>12.4</td>
</tr>
<tr>
<td>SD</td>
<td>2.9</td>
<td>2.9</td>
<td>2.9</td>
<td>2.9</td>
<td>2.9</td>
<td>2.9</td>
<td>2.9</td>
<td>2.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Gestational week at delivery</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Mean</td>
<td>39.6</td>
<td>39.6</td>
<td>39.6</td>
<td>39.6</td>
<td>39.6</td>
<td>39.6</td>
<td>39.6</td>
<td>39.6</td>
<td>39.6</td>
</tr>
<tr>
<td>SD</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Hb (g/l)</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Mean</td>
<td>121.0</td>
<td>121.8</td>
<td>121.1</td>
<td>121.0</td>
<td>121.8</td>
<td>121.1</td>
<td>121.0</td>
<td>121.8</td>
<td>121.1</td>
</tr>
<tr>
<td>SD</td>
<td>7.3</td>
<td>7.4</td>
<td>7.1</td>
<td>7.3</td>
<td>7.4</td>
<td>7.1</td>
<td>7.3</td>
<td>7.4</td>
<td>7.1</td>
</tr>
<tr>
<td>FA consumption in peri-conceptional period</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>296</td>
<td>6.2</td>
<td>287</td>
<td>5.9</td>
<td>260</td>
<td>5.4</td>
<td>41</td>
<td>4.4</td>
<td>45</td>
</tr>
</tbody>
</table>

Discussion

Although concerns have been raised about the benefits and risks associated with Fe supplementation among women with high Hb levels, in the present study, prenatal supplements containing Fe were not associated with lower birth weight in this pool of women. Among women with baseline Hb concentrations of 100–132 or 133–145 g/l, the consumption of Fe-containing
Iron-containing supplements and birth weight

---

**Fig. 1.** Birth weight by maternal baseline Hb concentration in the study groups. Data are not shown for women with Hb concentrations >160 g/l (n 6, 10, and 10 in folic acid (FA), iron-FA (IFA), and multiple micronutrients (MMN) groups, respectively).
women with Hb concentrations >145 g/l before 20 weeks of gestation and had no effect on birth weight in women with Hb concentrations of 100–145 g/l. We highlighted the differential response to prophylactic supplementation by various baseline Hb concentrations. Our findings provide additional evidence for prophylactic supplementation with Fe-containing supplements to improve birth weight in well-nourished pregnant women, particularly in women with very high Hb concentrations. However, confirmation of these findings in other populations and additional studies on the use of Fe-containing supplements at conception and its effect on other pregnancy outcomes are needed.

Acknowledgements

This study was supported by a cooperative agreement between Peking University Health Science Center and the Centers for Disease Control and Prevention. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. The sponsor had a role in the study design, data collection, data analysis and interpretation and writing of the report.

We thank all of the study participants and health care workers from Yuanshi, Mancheng, Xianghe, Fengrun, and Laoting counties in China.

The authors’ contributions are as follows: Z. M., M. K. S., J. L. and L. W. conceived and designed the study; L. W. posed the hypothesis, analysed the data and drafted the manuscript; H. L. and Y. Z. contributed to acquisition of data; Z. M. and M. K. S. contributed to reviewing the manuscript; J. L. had the primary responsibility for the final content. All the authors had full access to the data in the study, and take responsibility for the integrity of the data and accuracy of the data analysis.

The authors declare that there are no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit http://dx.doi.org/doi:10.1017/S0007114515004870

References