Effect of Iron Deficiency Anemia in Pregnancy on Child Mental Development in Rural China

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**WHAT’S KNOWN ON THIS SUBJECT:** In humans, the brain growth spurt begins in the last trimester of pregnancy and extends through the first 2 years of life. Studies show poor cognitive and motor development among children who have iron deficiency anemia in infancy.

**WHAT THIS STUDY ADDS:** Prenatal iron deficiency anemia in the third trimester affects child mental development. Prenatal micronutrient supplementation with sufficient iron protects child mental development even when the woman’s iron deficiency anemia is not properly corrected during pregnancy.

**abstract**

**OBJECTIVE:** To determine the impact of iron deficiency anemia (IDA) in pregnancy on young child development.

**METHODS:** A 2-year follow-up of 850 children born to women who participated in a double-blind cluster randomized controlled trial of prenatal micronutrient supplementation in western rural China. These women were randomly assigned to receive either daily folic acid, iron/folic acid (60 mg iron), or multiple micronutrients (with 30 mg iron) during pregnancy. Children were categorized into the prenatal-IDA and prenatal–non-IDA groups based on the mother’s hemoglobin in the third trimester. Each group contained 3 subgroups based on mother’s treatment: folic acid, iron/folic acid, and multiple micronutrients. Bayley scales of infant development were administered to the children to assess their development at 3, 6, 12, 18, and 24 months of age.

**RESULTS:** Compared with the prenatal–non-IDA group, the prenatal-IDA group showed a significantly lower mental development index at 12, 18, and 24 months of age. The adjusted mean difference was 5.8 (95% confidence interval [CI], 1.1–10.5), 5.1 (95% CI, 1.2–9.0), and 5.3 (95% CI, 0.9–9.7), respectively. Further analysis showed that the mental development indexes in the prenatal-IDA group and prenatal–non-IDA group were similar with supplementation of iron/folic acid but were significantly lower in the prenatal-IDA group with supplementation of folic acid or multiple micronutrients.

**CONCLUSIONS:** Prenatal IDA in the third trimester is associated with mental development of the child. However, prenatal supplementation with sufficient iron protects child development even when the woman’s IDA was not properly corrected in pregnancy. *Pediatrics* 2013;131:e755–e763

**KEY WORDS**

follow-up, iron deficiency anemia in pregnancy, child development

**ABBREVIATIONS**

BSID—Bayley scale of infant development
CI—confidence interval
GLM—general linear model
Hb—hemoglobin
ID—iron deficiency
IDA—iron deficiency anemia
MD—mental development crude score
MDI—mental development index
MMN—multiple micronutrient supplementation
PD—psychomotor development crude score
PDI—psychomotor development index

Drs Chang and Zeng contributed equally to this work.

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Young children and women of reproductive age, especially during pregnancy, have increased iron requirements, placing them at increased risk of deficiency and related adverse consequences. Iron is essential for neurotransmission, energy metabolism, and myelination in the developing brain. In humans, the brain growth spurt begins in the last trimester of pregnancy and extends through the first 2 years of life. Numerous studies showed lower cognitive and motor test scores in infants with iron deficiency anemia (IDA) that persist low even though they received iron treatment as infants. There is direct evidence of biochemical abnormalities in brains of iron-deficient infants, which demonstrated a slowed nerve conduction velocity in iron-deficient infants at 6 months of age.

Brain iron deficiency (ID) in the fetus or neonate could be more detrimental than postnatal ID because of the rapidity of brain growth during pregnancy. Animal studies demonstrated that proper iron nutrition during perinatal development is critical not only for obtaining adequate levels of brain iron, but also for normal behavioral and motor development in the offspring. During pregnancy, the iron requirements of pregnant women are increased threefold to cover needs of expansion of maternal red cell mass and growth of the fetal placenta. Maternal anemia develops unless these needs are met. Epidemiologic studies suggest that maternal ID contributes to reduced fetal iron stores, and infants born to anemic mothers have low iron stores and are more likely to develop anemia. However, knowledge on the impact of prenatal ID and IDA on mental and motor development of children is limited. Study results on prenatal supplementation (with iron) and child development are inconclusive. A study in Nepal found that prenatal supplementation with iron and folic acid was positively associated with general intellectual ability, some aspects of executive function, and motor function in offspring at 7 to 9 years of age. A study in Indonesia did not find an impact of prenatal supplementation of iron on functional development of infants. Li et al reported a follow-up of a randomized trial on prenatal supplementation in rural China and demonstrated a benefit of multiple micronutrient supplementation (MMN) on the mental development of children at 12 months of age; but this positive impact of MMN was not shown at 18- and 24-month follow-up assessments (Li q, Yan H, Zeng L, Cheng Y, Dang S, Duan S and Tsuji I, unpublished data, 2013). Apparently, the anemia prevalence of women in these studies was still high at the end of pregnancy even after iron supplementation, which may have compromised the impact of iron supplementation on child development.

The current study is a follow-up of the same randomized trial used in Li et al. We followed children until 24 months of age and explored the relation between iron status in pregnancy and child development. We predict that IDA in pregnancy is associated with the development of the child and that iron supplementation in pregnancy is beneficial to child development.

METHODS

This study focused on the follow-up assessments of mental and psychomotor development of children at 3, 6, 12, 18, and 24 months of age. These children were born to women involved in a double-blind cluster randomized controlled trial of prenatal micronutrient supplementation. The aim of the original project was to evaluate the impact of prenatal supplementation on birth weight, duration of pregnancy, and perinatal mortality in rural western China from 2002 to 2006. The details of the trial are described elsewhere. Briefly, the trial was conducted in 2 poor rural counties. Villages were randomly assigned to 3 treatments: MMN, iron/folic acid, or folic acid supplementation before recruitment of subjects. The MMNs were formulated to approximately contain the World Health Organization/United Nations Children’s Fund recommended dietary allowances for each of 15 minerals or vitamins as follows: 30 mg iron, 400 μg folate, 15 mg zinc, 2.0 mg copper, 65.0 μg selenium, 150.0 μg iodine, 800 μg vitamin A, 1.4 mg vitamin B12, 1.4 mg vitamin B6, 1.9 mg vitamin B12, 26 μg vitamin B12, 5 μg vitamin D, 70 μg vitamin C, 10 mg vitamin E, and 18 mg niacin. The iron/folic acid supplementation contained 60 mg iron and 400 μg folic acid. The folic acid supplementation contained 400 μg folic acid.

Figure 1 summarizes the recruitment, randomization, and participation of subjects in the trial. All women resident in the project sites who became pregnant during the study period, fulfilled trial selection, and filled out the consent form for this trial were recruited by village doctors. Newly identified pregnant women received an initial prenatal care check-up for baseline information. Altogether, 5828 eligible women were recruited in the trial. Among them, 16.7% did not attend the hemoglobin (Hb) check because of lack of follow-up, withdrawing from the trial, or fetal losses before the third trimester, and another 28.3% missed the prenatal care check in the third trimester. Approximately 55% (3233) of the women attended the Hb check in the third trimester.

During 2004 to 2006, a follow-up study was conducted to assess the development of these children. A total of 1286 women with a singleton full term live birth attended the study. The current study focused on women whose Hb had been tested at the third trimester and who attended the follow-up study: 850 women and their children met this
inclusion criterion. Among them, 95 (11%) young children missed their first development assessment, 61 (7%) missed the second assessment, and 84 (10%), 96 (11%), and 96 (11%) missed their third to fifth assessment, respectively. In total, 600 (71%) children were assessed on all 5 occasions (Fig 1). The women and their children were categorized into prenatal-IDA and prenatal–non-IDA groups based on Hb in the third trimester. Each group contained 3 subgroups based on mother’s treatment: MMN, iron/folic acid, and folic acid subgroup.

**Data Collection**

Previously published papers regarding this trial described data collection during pregnancy and delivery and data collection of the follow-up study. Bayley scales of infant development (BSID) were used as a measure of each child’s development. The mental scale, psychomotor scale, and infant behavior record are the 3 parts of the BSID. The BSID was translated into Chinese and locally standardized to become culturally appropriate.

The BSID was administered at the village clinic or the child’s own home in a standardized manner. Both examiners and participating women were blinded with respect to the supplementation group. The child’s development and its feeding practices were proposed to be assessed at 3, 6, 12, 18, and 24 months of age; however, because of logistical problems, this schedule could not always be followed. If the child was sick, was unavailable, or could not cooperate, assessment was arranged for a later date within 1 month. The mental development crude score (MD) and psychomotor development crude score (PD) signify the items that a child passes on the mental scale and psychomotor scale of the BSID, respectively. The mental development index (MDI) and psychomotor development index (PDI) are nonlinear transformations of the MD and PD, which were transformed by using standard procedures that are based on data for Chinese children. We did not report the infant behavior record in this paper.

Iron status was determined on the basis of Hb at the third trimester by HemoCue portable spectrophotometers (Angelholm, Sweden). They were calibrated daily, and all measurements were made within the temperature operating range of this.

**FIGURE 1**

Participant flowchart.
device (15–30°C) by research team members. The cutoff for anemia in pregnancy women was Hb < 110 g/L.27

Data Analysis
All data were checked manually for completeness and were double-entered into a data management system. We conducted range, extremum and logical checks for accuracy. We compared baseline characteristics between women who were and who were not involved in the current study and between the prenatal-IDA and prenatal–non-IDA groups by using analysis of variance or \(\chi^2\) tests.

The missing values of MD and PD in each assessment were estimated by linear regression between age of children with MD and PD. A general linear model (GLM) repeated measurements was used to compare the overall MDI and PDI of the 5 assessments and the MDI and PDI per assessment. The mean differences for the MDI and PDI between the 2 groups were adjusted for treatment and for interaction term between treatment and Hb in the third trimester.21 We considered baseline characteristics that differed between the 2 groups as potential confounders in the GLM repeated measurement–adjusted model: low birth weight, mother’s age at enrollment, gestation weeks when Hb was checked, parity of pregnant women, gestation weeks at birth, and child’s age at assessment.

All analyses were conducted with Stata version 9.2 (Stata/SE 9.2; StataCorp, College Station, TX). All reported \(P\) values were 2-tailed, and values <0.05 were considered statistically significant.

RESULTS
Baseline characteristics of the women who were and who were not involved in this study are comparable (data not shown). Table 1 shows the baseline characteristics of the pregnant women and their children in the current study. The socioeconomic characteristics, women’s education, women’s BMI at enrollment, mean gestation weeks at enrollment, and BMI at enrollment were comparable between the 2 groups. Pregnant women in the prenatal-IDA group were significantly older \((P = .024)\), reported greater parity \((P = .025)\) at enrollment, and had a smaller number of gestation weeks when Hb was checked \((P = .006)\). Child birth weight, gestation weeks at birth, gender distribution, breastfeeding rate, formula introduction, prevalence of stunting and underweight of children and age at each assessment were comparable between the 2 groups except child age at the 18-month assessment \((P = .001)\), breastfeeding rate at 3 months \((P = .013)\), and formula introduction at 24 months \((P = .025)\).

Impact of Prenatal Iron Status on Mental Development of Young Children
Table 2 summarizes study findings related to the MDI of children during the first 24 months of life. Overall analysis showed significantly lower MDI \((P = .036)\) in the prenatal-IDA group by using the GLM repeated measurement–adjusted model. Assessed at individual time points, the prenatal-IDA group showed significantly lower MDI at 12, 18, and 24 months of age. The adjusted mean MDI difference was 5.8 (95% confidence interval [CI], 1.1–10.5), 5.1 (95% CI, 1.2–9.0), and 5.3 (95% CI, 0.9–9.7), respectively.

Impact of Prenatal Iron Status on Psychomotor Development of Young Children
Table 3 describes PDI of children at the 5 assessments points. No significant differences in PDI were found between the 2 groups by using the GLM repeated measurement–adjusted model.

Modifying Effect of Maternal Supplementations in Pregnancy on the Response of Prenatal Iron Status on Child Development
We initially hypothesized that iron supplementation in pregnancy would be beneficial to child development. Accordingly, a subgroup analysis was conducted to explore the modifying effect of maternal supplementations on the response of prenatal iron status on child development.

Table 4 summarizes MDI and PDI by prenatal iron status and treatment groups. Children in the prenatal-IDA group whose mother received folic acid or MMN had a lower MDI compared with their peers in the prenatal–non-IDA group \((P = .046\) in folic acid; \(P = .034\) in MMN), with significant lower MDIs at 3-, 18-, and 24-month assessments for folic acid subgroups and at 12-, 18-, and 24-month assessments for MMN subgroups. Children in the prenatal-IDA group whose mother received iron/folic acid (with 60 mg iron) supplementation had a comparable MDI in all 5 assessments \((P = .641)\).

We did not find significant differences in PDI between the prenatal-IDA and the prenatal–non-IDA groups, regardless of treatment.

DISCUSSION
Our findings show that IDA in pregnancy is associated with the mental development of young children. Further analysis on subgroups showed that the differences in the MDI between the 2 groups (prenatal-IDA and prenatal–non-IDA) were only present in the folic acid and MMN subgroups but not in the iron/folic acid subgroup that received 60 mg iron daily.

This study used a longitudinal observation approach based on data from a previous randomized trial and explored the impact of prenatal IDA on child development. There is no sample
selection bias between this study and the randomized trial. To our knowledge, this is the first longitudinal observation on prenatal iron status and child development. We had consistent results for all 5 assessments in children 3 to 24 months of age. Our study was in a socioeconomically disadvantaged area, with no child iron supplementation after birth. This allowed us to observe the impact of prenatal iron status and iron supplementation on child development.

The study was limited with respect to measurement of iron status. IDA was estimated by Hb in this study. Hb generally overestimates the prevalence of IDA, because it also accounts for anemia caused by other nutritional deficiencies, infections, hemoglobinopathies, or ethnic differences in normal hemoglobin distribution. From results of the baseline survey that showed a prevalence of anemia among children <2 years of age, reproductive-aged women, and adult men of 33.2%, 37.6%, and 8.8%, respectively (Zeng L, Dang S, Yan H, unpublished data, 2003), we can infer that ID was the main cause of anemia in our study area. Furthermore, for women with adequate iron, Hb starts to decline during the early part of the first trimester, reaches its nadir near the end of the second trimester because of a physiologic response, including plasma volume expansion, and then gradually rises during the third trimester. Studies among Chinese pregnant women showed Hb did not improve from the second to third trimester, providing evidence that pregnant women’s iron stores were not sufficient to continue the expansion of red cell mass in the third trimester. Hence, the high prevalence of anemia in the third trimester is mainly caused by ID in China.

We cannot eliminate the possibility that the altered behavior of the prenatal-IDA group in this study was caused by some relevant but unmeasured factor(s), such as maternal depression or other environmental disadvantages, which could account for a lack of stimulation (leading to altered behavior and development).

Another limitation of this work was the low power to detect changes in the MDI.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Iron Status in Third Trimester</th>
<th>Prenal-ID (N = 384)</th>
<th>Prenal–Non-IDA (N = 466)</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>Pregnant women</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age at enrollment, years [mean (SD)]</td>
<td>24.5 (4.5)</td>
<td>24.1 (4.5)</td>
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<td>BMI at enrollment [mean (SD)]</td>
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<td>20.8 (2.3)</td>
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<td>Gestation at enrollment, wk [mean (SD)]</td>
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<td>13.5 (5.5)</td>
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<td>Gestation Hb checked, wk [mean (SD)]</td>
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<td>&lt;3 y</td>
<td>20 (5.2)</td>
<td>18 (4.1)</td>
<td>0.213</td>
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<td>Primary</td>
<td>103 (26.8)</td>
<td>102 (21.9)</td>
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<td>Secondary</td>
<td>204 (53.1)</td>
<td>280 (60.2)</td>
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<td>High school+</td>
<td>57 (14.8)</td>
<td>64 (13.8)</td>
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<td>Household wealth</td>
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<td>Poor</td>
<td>91 (23.7)</td>
<td>112 (24.0)</td>
<td>0.751</td>
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<tr>
<td>Middle</td>
<td>155 (40.4)</td>
<td>178 (38.2)</td>
<td></td>
<td></td>
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<tr>
<td>Wealthy</td>
<td>138 (35.9)</td>
<td>176 (37.8)</td>
<td></td>
<td></td>
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<tr>
<td>Parity at enrollment&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>0</td>
<td>237 (61.7)</td>
<td>321 (68.9)</td>
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<td>1</td>
<td>122 (31.8)</td>
<td>123 (26.4)</td>
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<tr>
<td>&gt;2</td>
<td>25 (6.5)</td>
<td>22 (4.7)</td>
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<td>Child</td>
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<td>Birth weight [mean (SD)]</td>
<td>3228 (388)</td>
<td>3162 (402)</td>
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<td>Gestation at birth [mean (SD)]</td>
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<td>Gender</td>
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<tr>
<td>Boy</td>
<td>244 (64)</td>
<td>273 (59)</td>
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<tr>
<td>Girl</td>
<td>140 (36)</td>
<td>153 (41)</td>
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<td>Age of the 5 assessments, mo[mean (SD)]</td>
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<td>3</td>
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<td>3.2 (0.2)</td>
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<td>6.2 (0.3)</td>
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<td>12</td>
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<td>3</td>
<td>324 (87)</td>
<td>421 (92)</td>
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<td>292 (80)</td>
<td>362 (81)</td>
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<td>Formula introduction, mo</td>
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<td>46 (12)</td>
<td>47 (10)</td>
<td>0.344</td>
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</tr>
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<td>6</td>
<td>58 (15)</td>
<td>65 (14)</td>
<td>0.748</td>
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<td>12</td>
<td>77 (20)</td>
<td>93 (20)</td>
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<td>18</td>
<td>108 (28)</td>
<td>117 (25)</td>
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<td>24</td>
<td>100 (26)</td>
<td>89 (19)</td>
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<td>Underweight, mo</td>
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<td>14 (3)</td>
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<td>54 (14)</td>
<td>65 (14)</td>
<td>0.872</td>
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<td>24</td>
<td>54 (14)</td>
<td>61 (13)</td>
<td>0.897</td>
<td></td>
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</table>

Values are number (percentage) unless otherwise noted.

<sup>a</sup> P < 0.05.

TABLE 1 Comparison of Baseline Characteristics of the Women and Children in the Prenatal IDA Group and Non-IDA Group by Iron Status in the Third Trimester, Shaanxi Province, China, 2004 to 2006.
TABLE 2 Comparison of Mean, SD, and 95% CIs of Adjusted Difference of the MDI of Children Born to Mothers Enrolled in the Prenatal Supplementation Trial by Prenatal Iron Status in the Third Trimester, Shaanxi Province, China, 2004 to 2006

| Age, mo | Group          | Number | Mean (SD)           | Adjusted Difference (95% CI) a | p  
|---------|----------------|--------|---------------------|-------------------------------|------
| 3       | Prenatal-IDA   | 384    | 133.0 (17.0)        | −1.7 (−5.9 to 2.5)             | 0.429 |
|         | Prenatal–non-IDA | 466    | 135.2 (16.7)        | 0.2 (−0.1 to 0.5)              |      |
| 6       | Prenatal-IDA   | 384    | 110.0 (23.7)        | −3.4 (−6.6 to 0.0)             | 0.262 |
|         | Prenatal–non-IDA | 466    | 113.5 (24.3)        | 0.5 (−0.4 to 1.4)              |      |
| 12      | Prenatal-IDA   | 384    | 98.3 (16.2)         | 2.5 (−0.8 to 5.8)              | 0.16  |
|         | Prenatal–non-IDA | 466    | 100.5 (15.9)        | 0.7 (−0.1 to 1.5)              |      |
| 18      | Prenatal-IDA   | 384    | 106.0 (21.9)        | 3.2 (−0.4 to 6.9)              | 0.019 |
|         | Prenatal–non-IDA | 466    | 107.8 (21.0)        | 1.8 (−1.0 to 3.6)              |      |
| 24      | Prenatal-IDA   | 384    | 103.9 (12.8)        | 3.4 (0.6 to 6.2)               | 0.019 |
|         | Prenatal–non-IDA | 466    | 105.3 (12.4)        | 1.5 (−0.8 to 3.8)              |      |

a Adjusted by treatment, interaction between treatment and gestation Hb, low birth weight, mother age at enrollment, gestation week when Hb was checked, parity, gestation week at delivery, and age of children at assessment.

and PDI because the findings presented are based on post hoc analysis. We had a 64% power to detect a 5-score change in MDI and 73% power to detect a 4-score change in PDI, with a = 0.05. Our results require replication using larger sample sizes.

The shown impact on child development in the prenatal-IDA group could have occurred during the period of fetal brain development or during the young children’s development. Developing rats subjected to prenatal IDA have demonstrated neurometabolic, structural, electrophysiological, and behavioral alterations.34–36 The postnatal consumption of iron-deficient diets among marginal iron offspring will not fully reverse all of the observed biochemical disturbances.37 In humans, when maternal iron status is poor, the number of placental transferrin receptors increases so that more iron is taken up by the placenta. Evidence is accumulating that the capacity of this system may be inadequate to maintain iron transfer to the fetus when the mother is iron deficient.38 Maternal Hb is significantly correlated with cord blood erythrocyte count, Hb, and hematocrit values, and these were significantly lower when maternal Hb was <110 g/L at 32 to 35 weeks of gestation.39 Newborn infants with low cord blood Hb and iron have altered temperament during the first week of life.40 In our study, prenatal IDA appears to have impacted fetus brain iron, having adverse effects on neurodevelopment.

Publications have suggested that prenatal IDA is related to reduced fetal iron stores. Infants of mothers with mild or moderate IDA during pregnancy are at risk for ID,4,16 and infants with IDA show poorer cognitive, motor, social-emotional, and neurophysiologic functioning than those without.3,23,41–45 In our population, children were not provided iron supplementation after birth. Children in the 2 groups have no differences in terms of feeding practices, growth, and other related background characteristics. Probably, more children in the prenatal-IDA group suffered IDA because of low fetal iron stores, which can explain delayed mental development of children in this group. We did not test children’s Hb in our follow-up assessments because of ethical considerations.

Our finding that the impacted child development was not present in the iron/folic acid group (with 60 mg iron), even when the mothers’ IDA was not corrected, demonstrated the benefit of sufficient iron supplementation during pregnancy. Most fetal iron uptake occurs after week 30, and fetal and placental iron needs are presumably met by increased efficiency of maternal iron absorption.39 Iron supplementation in pregnancy improves maternal iron status39 and can reduce the extent of iron depletion in the third trimester.44 However, for women who enter pregnancy with low iron stores, iron supplementation fails to prevent ID.39 In our randomized trial, the prenatal anemia prevalence in the third trimester was still high, being 43.1%, 45.1%, and 61% among the MMN, iron/folic acid, and folic acid groups, respectively.20 This showed that a high percentage of pregnant women had exhausted their iron stores. Prenatal iron supplementation studies in other poverty-stricken areas also showed a high prevalence of prenatal anemia at the end of pregnancy.11,45 The compliance and timing of supplementation may explain part of the high anemia prevalence, but in our study, the rates of adherence were 93%, 92%, and 93% among the folic, iron/folic acid, and MMN groups, respectively, and
the mean number of supplementations consumed was 165, 166, and 165, respectively. In this respect, it seems many women were iron deficient when entering pregnancy, and supplemental iron was not sufficient to cover the needs during pregnancy. Study results of others indicate that IDA in pregnancy compromised fetal iron reserves and that iron needs of the fetus take priority over maternal requirements, supporting our result on the benefit of prenatal iron supplementation. A previous study followed the same randomized trial and showed a benefit of prenatal MMN on mental development at 12 months of age. The inconsistent conclusion with the present study is probably because the prenatal iron status was not considered in previous analyses.

CONCLUSIONS

In summary, prenatal IDA impacts child mental development. Sufficient iron supplementation during pregnancy is beneficial to the mental development of children in areas with poor iron intake. Our results support the practice of routine iron supplementation during pregnancy in poor rural areas of China.

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REFERENCES


3. McCann JC, Ames BN. An overview of evidence for a causal relation between iron deficiency during development and deficits in cognitive or behavioral


41. Walker SP, Wachs TD, Gardner JM, et al; International Child Development Steering


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