



Maternal Hemoglobin Concentration during Gestation and Risk of Anemia in Infancy: Secondary Analysis of a Randomized Controlled Trial

Yiting Zhang, MD^{1,2}, Lei Jin, MD, PhD¹, Jian-meng Liu, MD, PhD^{1,2}, Rongwei Ye, MD, PhD^{1,2}, and Aiguo Ren, MD, PhD^{1,2}

Objective This study examined the relationship between maternal hemoglobin (Hb) concentration and the risk of anemia in infancy.

Study design This analysis included 17 193 women who entered the trial when they were ≥ 20 years of age, no more than 20 weeks of gestation, had mild or no anemia, and delivered singleton live births. Maternal Hb concentrations were measured in the first trimester and during 24-28 weeks of gestation; infant Hb concentrations were measured at 5-7 months and 11-13 months of life. The associations between maternal Hb concentrations and infant Hb concentrations were examined.

Results Maternal Hb concentrations measured during 24-28 weeks of gestation, but not in the first trimester, were correlated with infant Hb concentrations measured at either of the 2 post-partum periods. The risk of infant anemia at 5-7 months of age increased when maternal Hb concentration was ≤ 109 g/L during 24-28 weeks of gestation (aOR, 1.95; 95% CI, 1.59-2.40) and 11-13 months of age (aOR, 1.72; 95% CI, 1.36-2.18), whereas the risk of anemia during 5-7 months of age as well as 11-13 months in infancy decreased when maternal Hb level at 24-28 weeks of gestation was 120-129 g/L (aOR for 5-7 months, 0.74 [95% CI, 0.64-0.85]; aOR for 11-13 months, 0.72 [95% CI, 0.61-0.85]), or ≥ 130 g/L (aOR for 5-7 months, 0.75 [95% CI, 0.63-0.90]; aOR for 11-13 months, 0.89 [95% CI, 0.73-1.08]).

Conclusions Low maternal Hb concentration during 24-28 weeks of gestation was associated with an increased risk of anemia in infancy, whereas high maternal Hb concentration was associated with a reduced risk of anemia. (*J Pediatr* 2016;175:106-10).

Trial registration ClinicalTrials.gov: NCT00133744.

According to recent studies, 30%-50% infants aged 6 months in the developing countries suffer from anemia.¹⁻³ Infant anemia can lead to lack of oxygen in organs and tissues, thus increasing the risk of infectious diseases,⁴ mortality, and other morbidities,^{5,6} including impaired cognitive^{7,8} and physical development,⁹ which may be irreversible, even after correction of anemia.^{10,11}

Among the many factors that affect hemoglobin (Hb) concentration during infancy, maternal Hb levels during gestation is considered one of the most important. Low maternal Hb concentration during gestation may hamper the development of fetal iron stores before birth and therefore may increase the risk of anemia during infancy.¹² However, few studies have examined this relationship directly. In a study conducted in Jordan, anemic pregnant mothers tended to have infants at increased risk of developing anemia, but the sample size was very small, with 232 mother-infant pairs.¹³ In contrast, a prospective study of 617 mother-infant pairs in Benin concluded that there was no association between maternal anemia and infant Hb level at 18 months of age.¹⁴

In the present study, we investigated the association between maternal Hb concentration measured during the first trimester and again at 24-28 weeks of gestation and the risk of developing anemia during infancy in a population without routine iron supplementation by secondary analysis of data from a double-blind, randomized, controlled trial conducted from 2006-2009 in northern China.¹⁵

Methods

As described elsewhere in more detail,¹⁵ the primary trial was a double-blind, randomized, controlled study of pregnant women assigned to 1 of 3 treatment groups: folic acid only, folic acid plus iron, or multiple micronutrients containing folic acid, iron, and 13 additional vitamins and minerals, with perinatal mortality being the primary outcome of interest (ClinicalTrials.gov: NCT00133744). The subjects were women in 5 counties in Hebei Province in northern China who were nulliparous, ≥ 20 years of age, recorded dates of menstruation for ≥ 2 months before pregnancy, had not yet reached 20 weeks' gestation, and were pregnant between May 2006 and April 2009. Eligible women were randomly assigned to 1 of 3 treatment groups stratified by county and random block sizes (3, 6, and 9). Women

From the ¹Institute of Reproductive and Child Health/ Ministry of Health Key Laboratory of Reproductive Health; and ²Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China

Supported by a cooperative agreement between Peking University Health Science Center and the Centers for Disease Control and Prevention (5U01DD000293). The authors declare no conflicts of interest.

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<http://dx.doi.org/10.1016/j.jpeds.2016.05.011>

Hb hemoglobin

whose Hb level was <100 g/L were excluded from the study and referred for treatment owing to ethical reasons. At the time of enrollment in the trial, information on social, demographic, and anthropometric characteristics of the women was documented. During the trial, maternal Hb concentrations were measured in the first trimester and at 24-28 weeks of gestation, and the infant Hb concentrations at 5-7 months as well as 11-13 months of age, with the HemoCue B-Hb system (HemoCue AB, Angelholm, Sweden) according to the manufacturer's instructions.

All data were collected uniformly according to predefined criteria and entered into an electronic reproductive health surveillance system by trained local health care workers. The project was approved by the institutional review board of Peking University, Beijing, China, and renewed annually. Verbal informed consent was obtained from all subjects.

According to the recommendation proposed by the World Health Organization, both maternal and infant anemia were defined as Hb < 110 g/L. Gestational age was calculated from the first day of the mother's last menstrual period. Infant age was calculated from the date of birth.

The original trial included 18 775 women to completion. During the follow-up period, 61 women were lost to follow-up, 2 died, 815 had abortions, and there were 67 multiple pregnancies and 82 stillbirths, leaving 17 748 singleton live births. For the present analysis, we further excluded 555 subjects owing to incomplete data; as a result, the final sample size included 17 193 mother-infant pairs (Figure 1; available at www.jpeds.com).

Statistical Analyses

Pearson correlation was used to examine the linear relationship between maternal Hb concentration and infant Hb concentration. Unconditional logistics regression was used to examine maternal Hb level (independent variable) as a risk or protective factor for infant anemia (dependent variable), with adjustment for potential confounding factors including education and preterm birth. Hb concentrations were categorized into 4 levels in 10-g/L intervals, with 110-119 g/L being used as the referent. aORs for each Hb level relative to the referent and their 95% CIs were calculated from the logistic model. All tests were 2-sided, and $P < .05$ was considered significant. Data were analyzed with SPSS software (v. 11.5; SPSS, Chicago, Illinois).

Results

Subjects were enrolled between May 2006 and April 2009. Maternal social, demographic, and anthropometric characteristics are presented in Table I. The participants were predominantly young women (mean age, about 23 years) with a relatively low level of education (almost 80% had completed a secondary education). Almost all participants (99%) were Han Chinese, and >90% of the women were farmers. The rate of preterm birth was 5.4%.

Mean age for the first infant Hb measurement was 6.3 ± 0.4 months, and 12.3 ± 0.4 months for the second measurement. Mean infant Hb concentration was 121.7 g/L at 5-7 months and 122.1 g/L at 11-13 months of age. With increasing age in this population, the prevalence of anemia decreased: 6.7% infants were anemic at 5-7 months and 5.3% were anemic at 11-13 months of age.

There was no correlation between maternal Hb concentration in the first trimester and infant Hb concentration at ages 5-7 months or 11-13 months. In contrast, maternal Hb levels during 24-28 weeks of gestation were correlated significantly with infant Hb concentrations at both 5-7 and 11-13 months of age (Table II).

To further examine the association between maternal Hb concentrations during 24-28 weeks of gestation and the risk of infant anemia, we classified maternal Hb concentration into 4 categories, with a Hb concentration of 110-119 g/L as reference category and adjustment for potential confounding factors (Table III; available at www.jpeds.com). As presented in Figure 2 and Table IV (Table IV available at www.jpeds.com), a maternal Hb concentration of ≤ 109 g/L during 24-28 weeks of gestation was associated with an increased risk of infant anemia at 5-7 months (aOR, 1.95; 95% CI, 1.59-2.40) as well as 11-13 months of age (aOR, 1.73; 95% CI, 1.36-2.18), whereas maternal Hb levels of 120-129 g/L and ≥ 130 g/L showed a protective effect on the development of infant anemia at 5-7 months of age (aOR, 0.74 [95% CI, 0.64-0.85] for 120-129 g/L; aOR, 0.75 [95% CI, 0.63-0.90] for ≥ 130 g/L). A similar relationship was observed for infants at 11-13 months of age (aOR, 0.72 [95% CI, 0.61-0.85] for 120-129 g/L; aOR, 0.89 [95% CI, 0.73-1.08] for ≥ 130 g/L), although the confidence intervals

Table I. Characteristics of the study subjects in northern rural China, 2006-2009

Characteristics	Mean or n	SD or %
Maternal age (y)	23.6	2.8
Mean body mass index	22.1	2.9
Mean gestational weeks at enrollment	12.1	4.6
Ethnic group		
Han	16 988	98.8
Other	205	1.2
Education		
High school or above	3113	18.1
Secondary	13 806	80.3
Primary or less	274	1.6
Occupation		
Farmer	15 644	91.0
Other	1549	9.0
Group		
Folic acid	5737	33.4
Iron/folic acid	5750	33.4
Multiple micronutrients containing iron and folic acid	5706	33.2
Preterm birth	933	5.4
Child sex		
Male	9022	52.5
Female	8171	47.5

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