Published in final edited form as:
J Pediatr. 2016 August ; 175: 106–110.e2. doi:10.1016/j.jpeds.2016.05.011.

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

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Abstract

Objective—To examine 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 or older, 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 two post-partum periods. The risk of infant anemia at 5-7 months 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 [AOR: 1.72, 95% CI: 1.36-2.18]); whereas the risk of anemia during 5-7 months 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).

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The authors declare no conflicts of interest.

Trial registration Clinicaltrials.gov: NCT00133744

Conclusion—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.

Keywords

hemoglobin; anemia; gestation; infant; pregnancy

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 Hb concentration during infancy, maternal Hb levels during gestation is considered one of the most important. Low maternal Hb concentration during gestation may hamper development of fetal iron stores prior to birth and therefore may increase the risk of anemia during infancy[12]. However, only a few studies have directly examined this relationship. 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 hemoglobin 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-blinded randomized controlled trial conducted from 2006 to 2009 in northern China[15].

Methods

As described elsewhere in more detail[15], the primary trial was a double-blinded, randomized controlled study of pregnant women assigned to three 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 five counties in Hebei Province in northern China who were nulliparous, at least 20 years of age, recorded dates of menstruation for at least 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 one of the three treatment groups stratified by county and random block sizes (3, 6 and 9). Women whose Hb level was <100 g/L were excluded from the study and referred for treatment due 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 concentration 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-Hemoglobin 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 WHO, 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.

Eighteen thousand, seven hundred seventy-five women completed the original trial. 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 17748 singleton livebirths. For the present analysis, we further excluded 555 subjects due to incomplete data, as a result, the final sample size included 17,193 mother-infant pairs (Figure 1).

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. Adjusted odds ratios (AORs) for each Hb level relative to the referent and their 95% confidence intervals (CIs) were calculated from the logistic model. All tests were two-sided, and a P value less than 0.05 was considered statistically significant. Data were analyzed with SPSS software (v. 11.5; SPSS, Chicago, IL, USA).

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 more than 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, while 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 5-7 months or 11-13 months. In contrast, maternal Hb levels during

24-28 weeks of gestation were significantly correlated with infant Hb concentrations at both 5-7 months 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 the 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 ≤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 for the highest maternal Hb category included null (Figure 2 and Table V; Table V available at www.jpeds.com).

Discussion

This secondary analysis of data from a randomized controlled trial found that maternal Hb concentrations measured at 24-28 weeks of gestation were positively correlated with infant Hb concentrations at 5-7 as well as 11-13 months of age. Low maternal Hb level was a risk, and high maternal Hb level was a protective factor for infant anemia.

The five rural counties in which this study was conducted are located between 50 to 300 kilometer to the east or south-west of Beijing, with an average altitude lower than 50 meters. The socioeconomic development level is medium or medium-high compared with other northern rural counties. The population is homogeneous, with a vast majority being Han Chinese, not very mobile, and well-nourished relative to other rural populations in the north. The prevalence of hemoglobinopathy is estimated to range from 0.11% (the prevalence in a neighboring province) to 0.21% (the prevalence in Beijing)[16]; the rate of helminths is 1.6%[17], the rate of malaria is 0.006 per 10,000[18], and HIV infection rate is 0.012% in the province[19]. There is no routine iron or multimicronutrient supplement prescription to pregnant women in this population.

Our findings are consistent with those previously discussed in Jordan[3]. In that study, maternal hemoglobin concentrations were measured only in the third trimester (37 weeks of gestation). A study from Indonesia found that maternal anemia was associated with infant anemia, but maternal Hb concentrations were measured at varying times postpartum, with the notion that maternal postpartum Hb reflects Hb during pregnancy[20]. Inconsistent to our findings, a study in Benin did not find an association between infant hemoglobin and maternal anemia when infants were 18 months old[14].

Many factors may contribute to infant anemia. These factors could be genetic, such as hemoglobinopathies[21]; or environmental factors, including high altitude[22]. Other risk factors, including lower birthweight[20], rapid weight gain[23], and male sex[2] can also increase the likelihood of infant anemia. However, undernutrition, including iron deficiency as well as deficiencies of other vitamins and minerals, is considered to be the most important factor[24]. Among these nutritional deficiencies, iron deficiency is considered the most important single factor in the development of infant anemia[25]. In the studied population, hemoglobinopathies, malaria, helminths, and HIV infection are rare; moreover, no iron supplement during pregnancy is routinely prescribed. Consequently, it is believed that most anemia in this population is caused by iron deficiency. Poor maternal iron status contributes to lower iron stores in the newborn infant[26]. It has also been speculated that maternal iron deficiency in pregnancy reduces iron stores throughout the first year of life[27]. Our findings support this notion. Thus, as WHO has suggested, pregnant women should begin iron supplementation early during pregnancy to order to improve infant outcomes[28].

The rate of infant anemia in our population is lower than that in many other developing countries. One of the reasons is that the population is relatively well-nourished compared with rural populations in other developing countries. The other reason is the exclusion at the time of enrollment in the original trial of those mothers with an Hb level lower than 100 g/L. The third reason is the variation in the definition of infant anemia used in different investigations.

Studies have shown that the infant anemia rate is highest around the time of the infant's growth spurt, especially between 6 and 24 months of age[29, 30]. With the infant's rapid growth, the blood volume is expanded, whereas the iron stores from mother have usually been depleted; as a result, diets become the vital source of iron. If exogenous iron is inadequate, infant anemia occurs. However, the amount of available iron in infant foods is usually low and often it cannot meet the needs of infants, which will further increase the likelihood of infant anemia. Our results support prior recommendations of exclusive breastfeeding for the first 6 months of age, with complementary foods starting at age of 6 months and breastfeeding continuing until 2 years of age[2]. Also, as suggested by WHO, food fortified with iron and other micronutrients may help reduce the risk of anemia, especially for infants in their first year of life[31].

Our study has several strengths. All data were collected prospectively; this helps reduce the recall bias that is common in cross-sectional or case-control studies. Second, Hb measurements for mothers and infant were standardized, thus minimizing the potential problems associated with routine measurement of Hb levels in clinical settings. In addition, women had their menstrual period recorded 2 months before enrollment, which can ensure a more accurate ascertainment of gestational age. Third, this population has a very low incidence of other major factors for anemia, such as HIV infection, parasite infection, hemoglobinopathy, and malnutrition, thus minimizing the possibility that these factors confounded the observed associations. Finally, our sample size is big enough for detailed analysis.

Our findings should be interpreted cautiously because at the time of enrollment of the original trial, women with an Hb level below 100 g/L were excluded; this may have weakened the finding of a relationship between low Hb concentration and infant anemia[32, 33]. Another limitation is that we did not have information on infant feeding practices. However, there is no evidence to show that mothers with low Hb concentrations during pregnancy tend to have feeding practices that differ from mothers with normal Hb and that might predispose infants to anemia. This means that the observed associations are less likely to be confounded by feeding practices. Finally, genetic factors, such as inheriting a hemoglobinopathy trait from the mother might have affected the results. However, since hemoglobinopathies are rare in this population, these inheritable diseases should not have had a meaningful impact on the associations we observed in this study.

In conclusion, maternal Hb concentration at 24-28 weeks of gestation was correlated with infant Hb concentrations at 5-7 months as well as 11-13 months of age. Low maternal Hb levels during pregnancy were associated with an increased risk of infant anemia and high maternal Hb level were associated with a reduced risk of infant anemia. Further studies are warranted to reveal the mechanism underlying these associations.

Acknowledgments

We are grateful to all study participants and the local health care workers from Yuanshi, Mancheng, Xianghe, Fengrun, and Laoting counties in China. We thank Dr Sen Chen for his assistance in preparation of the dataset.

Supported by a cooperative agreement between Peking University Health Science Center and the Centers for Disease Control and Prevention.

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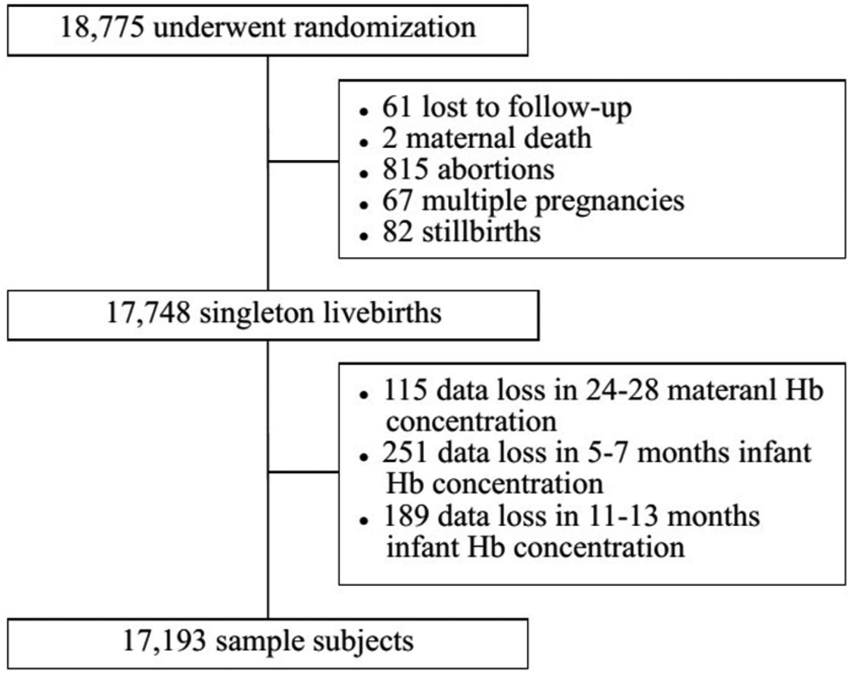

Figure 1.
Flowchart of participants

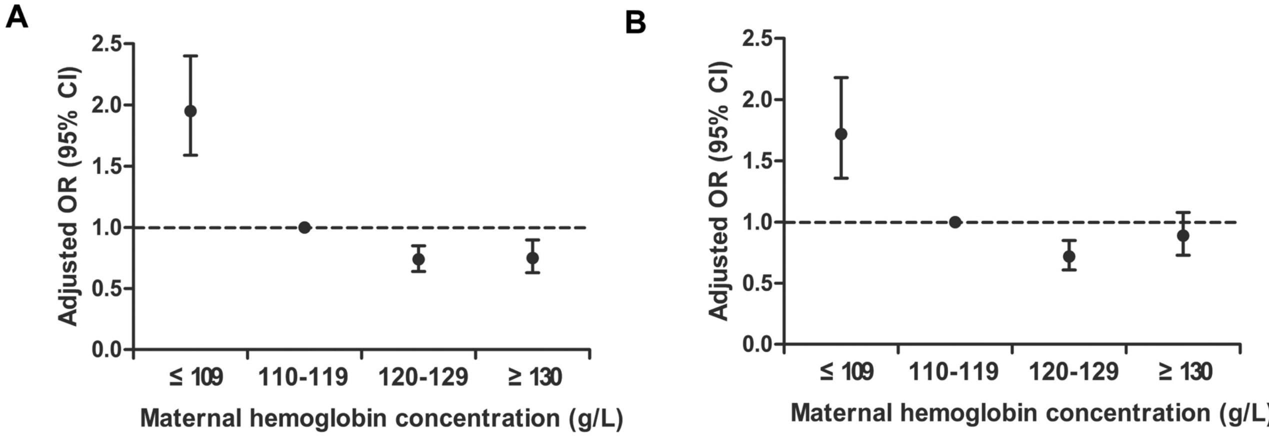

Figure 2.

Risk (odds ratio) of infant anemia during A, 5-7 months and B, during 11-13 months by maternal hemoglobin level of 24-28 weeks of gestation in a Chinese population, 2006-2009. A, AOR (95% CI) for Maternal Hb concentration ≤109 is 1.95 (1.59-2.40); 0.74 (0.64-0.85) for 120-129 g/L; 0.75 (0.63-0.90) for ≥130 g/L. B, AOR (95% CI) for Maternal Hb concentration ≤109 is 1.72 (1.36-2.18); 0.72 (0.61-0.85) for 120-129 g/L; 0.89 (0.73-1.08) for ≥130 g/L.

TABLE 1

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

Characteristics	$\bar{x}$ **or** n	**SD or %**
Maternal age (year)	23.6	2.8
Mean BMI	22.1	2.9
Mean gestational weeks at enrollment	12.1	4.6
Ethnic group		
Han	1,6988	98.8
Other	205	1.2
Education		
High school or above	3113	18.1
Secondary	1,3806	80.3
Primary or less	274	1.6
Occupation		
Farmer	1,5644	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

TABLE 2

Correlation between maternal Hb concentration and infant Hb concentration during 5-7 and 11-13 months in infancy in a rural population in northern China, 2006-2009

Infant Hb concentration	**Maternal Hb concentration in the first trimester**		**Maternal Hb concentration of 24-28 weeks of gestation**	
	Pearson correlation coefficient	***P***	**Pearson correlation coefficient**	***P***
Infant Hb concentration of 5-7 months	0.02	0.056	0.14	0.001
Infant Hb concentration of 11-13 months	0.02	0.058	0.11	0.001

TABLE 3

Maternal and infant characteristics and the risk (odds ratio) of infant anemia in a rural population in northern China, 2006-2009

Characteristics	Infant anemia during 5-7 months		Infant anemia during 11-13 months	
	P	**OR (95% CI)**	***P***	**OR (95% CI)**
Maternal age (year)	0.118	0.98 (0.96-1.00)	0.220	0.99 (0.96-1.01)
BMI	0.050	1.02 (1.00-1.04)	0.990	1.00 (0.98-1.02)
Gestational weeks at enrollment	0.885	1.00 (0.99-1.01)	0.995	1.00 (0.99-1.02)
Ethnic group	0.608		0.944	
Han		1.17 (0.65-2.10)		0.98 (0.53-1.80)
Other		1.00		1.00
Education	0.001		<0.001	
High school or above		0.48 (0.32-0.71)		0.35 (0.23-0.53)
Secondary		0.55 (0.38-0.81)		0.44 (0.30-0.65)
Primary or less		1.00		1.00
Occupation	0.100		0.770	
Farmer		0.85 (0.70-1.03)		1.04 (0.82-1.31)
Other		1.00		1.00
Group	0.904		0.152	
Folic acid		1.03 (0.89-1.19)		0.92 (0.78-1.08)
Iron/folic acid		1.00 (0.86-1.16)		0.85 (0.72-1.00)
Multiple micronutrients		1.00		1.00
Child Sex	0.614		0.255	
Male		1.03 (0.92-1.16)		1.08 (0.95-1.24)
Female		1.00		1.00
Preterm birth	0.044		0.231	
No		0.78 (0.62-0.99)		0.85 (0.64-1.11)
Yes		1.00		1.00

TABLE 4

Risk (odds ratio) of infant anemia during 5-7 months by maternal hemoglobin level measured during 24-28 weeks of gestation in a rural population in northern Chinese, 2006-2009

Variable	Infant anemia, n (%)	*Crude P*	Crude OR (95% CI)	*Adjusted P*	Adjusted OR[a] (95% CI)
Maternal Hb concentration (g/L)		<0.001		<0.001	
≤109	151 (14.0)	<0.001	1.96 (1.60-2.40)	<0.001	1.95 (1.59-2.40)
110-119	343 (7.6)		1.00		1.00
120-129	467 (5.7)	<0.001	0.73 (0.63-0.84)	<0.001	0.74 (0.64-0.85)
≥130	199 (5.8)	0.002	0.75 (0.62-0.89)	0.002	0.75 (0.63-0.90)
Education		0.001		0.005	
High school or above	185 (5.9)	<0.001	0.48 (0.32-0.71)	0.001	0.52 (0.35-0.77)
Secondary	943 (6.8)	0.002	0.55 (0.38-0.81)	0.007	0.60 (0.41-0.87)
Primary or less	32 (11.7)		1.00		1.00
Preterm birth		0.044		0.080	
No	1082 (6.7)		0.78 (0.62-0.99)		0.81 (0.63-1.03)
Yes	78 (8.4)		1.00		1.00

[a] Adjusted for education and preterm birth.

TABLE 5

Risk (odds ratio) of infant anemia during 11-13 months by maternal hemoglobin level measured during 24-28 weeks of gestation in a rural population in northern China, 2006-2009

variate	Infant anemia, n (%)	*Crude P*	Crude OR (95% CI)	*Adjusted P*	Adjusted OR[a] (95% CI)
Maternal Hb concentration (g/L)		<0.001		<0.001	
≤109	106 (9.8)	<0.001	1.72 (1.36-2.18)	<0.001	1.72 (1.36-2.18)
110-119	266 (5.9)		1.00		1.00
120-129	353 (4.3)	<0.001	0.71 (0.61-0.84)	<0.001	0.72 (0.61-0.85)
≥130	179 (5.2)	0.185	0.88 (0.72-1.07)	0.249	0.89 (0.73-1.08)
Education		<0.001		<0.001	
High school or above	133 (4.3)	<0.001	0.35 (0.23-0.53)	<0.001	0.37 (0.25-0.56)
Secondary	740 (5.4)	<0.001	0.44 (0.30-0.65)	<0.001	0.47 (0.32-0.69)
Primary or less	31 (11.3)		1.00		1.00
Preterm birth		0.231		0.348	
No	847 (5.2)		0.85 (0.64-1.11)		0.88 (0.66-1.16)
Yes	57 (6.1)		1.00		1.00

[a] Adjusted for education and preterm birth.