Maternal Serum Ferritin Concentration Is Positively Associated with Newborn Iron Stores in Women with Low Ferritin Status in Late Pregnancy[1–3]

Jie Shao,[4,5] Jingan Lou,[5] Raghavendra Rao,[6] Michael K. Georgieff,[6] Niko Kaciroti,[7] Barbara T. Felt,[7,8] Zheng-Yan Zhao,[4,5]* and Betsy Lozoff[7,8]

[4]Department of Child Health Care, Children's Hospital, Zhejiang University School of Medicine, Hangzhou, China; [5]Key Laboratory of Reproductive Genetics, Ministry of Education, Zhejiang University, Hangzhou, China; [6]Division of Neonatology, Department of Pediatrics, Center for Neurobehavioral Development, University of Minnesota, Minneapolis, MN; [7]Center for Human Growth and Development, and [8]Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI

Abstract

Iron deficiency (ID) is common in pregnant women and infants, particularly in developing countries. The relation between maternal and neonatal iron status remains unclear. This study considered the issue in a large sample of mother-newborn pairs in rural southeastern China. Hemoglobin (Hb) and serum ferritin (SF) were measured in 3702 pregnant women at ≥37 wk gestation and in cord blood of their infants born at term (37–42 wk gestation). Maternal anemia (Hb <110 g/L) was present in 27.5% and associated with maternal SF <20 μg/L in 86.9%. Only 5.6% of neonates were anemic (Hb <130 g/L) and 9.5% had cord-blood SF <75 μg/L. There were low-order correlations between maternal and newborn iron measures (r = 0.07–0.10 for both Hb and SF; $P \leq$ 0.0001 due to the large number). We excluded 430 neonates with suggestion of inflammation [cord SF >370 μg/L, n = 208 and/or C-reactive protein (CRP) >5 mg/L, n = 233]. Piecewise linear regression analyses identified a threshold for maternal SF at which cord-blood SF was affected. For maternal SF below the threshold of 13.6 μg/L (β = 2.4; P = 0.001), cord SF was 0.17 SD lower than in neonates whose mothers had SF above the threshold (167 ± 75 vs. 179 ± 80 μg/L). The study confirmed that ID anemia remains common during pregnancy in rural southeastern China. Despite widespread maternal ID, however, iron nutrition seemed to meet fetal needs except when mothers were very iron deficient. The impact of somewhat lower cord SF on iron status later in infancy warrants further study.   J. Nutr. 142: 2004–2009, 2012.

Introduction

Iron is an essential micronutrient that plays an important role in critical cellular functions in all organ systems. It is vital for early brain growth and function because it supports neuronal and glial energy metabolism, neurotransmitter synthesis, and myelination (1–4). Studies in animal models have shown that maternal iron deprivation/deficiency prenatally is associated with behavioral effects in infant monkeys and rodent pups, even in the absence of maternal iron deficiency (ID)[9] anemia (IDA)

(3,5). Low iron stores at birth and IDA in infancy may also adversely influence cognitive, emotional, motor, and neurophysiological development in humans, with short- and long-term consequences that are not corrected by iron therapy (6,7). Understanding the relationship between maternal and fetal iron status may help inform efforts to prevent ID in pregnancy and infancy and improve outcomes for mothers and infants.

A pregnant woman requires ~1000 mg/d of iron to meet the needs of the expanding maternal blood volume and fetal red cell mass (8). Although there is a substantial increase in maternal iron absorption during pregnancy (9,10), ~50% of women worldwide are anemic in pregnancy, mostly due to ID, and transfer of iron to the fetus might be affected. The transfer of iron from the mother to the fetus is regulated by the placenta. The placental iron transfer system involves placental structure, iron transporters [e.g., transferrin receptor (TfR)-1 (11,12), divalent metal transporter-1 (DMT-1), ferroportin], and regulation of placental expression of these proteins (13). The regulatory system is intact beginning at ~24 wk of gestation (14). The fetus accumulates iron at a rate of 1.35 mg/(kg · d) of fetal weight in the third trimester, when the fetal brain is undergoing rapid development (8,15).

It seems logical that the capacity of the placental system to transfer sufficient iron to the fetus would be compromised when the mother is iron deficient (16). However, no consistent pattern of results has emerged in more than 20 studies on maternal-neonatal iron status. Some studies find little or no correlation (17–20), whereas others suggest that the fetus is vulnerable to maternal ID (21–24), particularly if the degree of anemia is marked (22). The reasons for differing results may relate to population differences in the prevalence and severity of maternal ID. Small sample size could be another factor. Studies generally involved fewer than 200 participants; the 2 largest studies had 300 and 432 participants (25,26). The purpose of our study was to assess the relation between maternal and full-term neonate iron status in a large sample that included >3700 mother-neonate pairs. The study was undertaken in China, where a nationwide survey in 2000 found a prevalence of ID and IDA for 3 trimesters in pregnant women of 42.6 and 19.1%, respectively, with the highest prevalence in the third trimester (85.4% ID with or without anemia, 33.8% IDA) (27).

Participants and Methods

Participants. The study was conducted in rural areas of Zhejiang province. Zhejiang, located in southeastern China, is a rapidly industrializing, prosperous region with excellent maternal and child health care services. The population is mainly middle-class ethnic Han. Pregnant women aged 20–35 y were recruited from Maternal and Child Health Care system hospitals in Fuyang, Huzhou, and Yongkang counties between December 2005 and April 2007. Iron supplementation during pregnancy was not routine at the time. Potential participants were contacted during regular 37- to 38-wk prenatal visits or upon admission for delivery. Enrollment criteria included singleton birth, parity ≤1, and no maternal chronic diseases. Specifically, there were no participants with maternal conditions known to alter fetal/neonatal iron status, such as diabetes mellitus, hypertension, intrauterine growth restriction, or maternal smoking (28). The study protocol was approved by the ethics committees of Children's Hospital Zhejiang University and the University of Michigan. Signed, informed consent was obtained at enrollment.

Blood sampling and hematologic assessment. Maternal blood samples (5 mL) were collected by venipuncture. Cord blood samples (5 mL) were obtained by sterile needle puncture immediately after cord clamping. Cord clamping generally occurred within 60 s of delivery, with the infant ~20 cm below the perineum for vaginal births and on the mother's lap for caesarean sections. Each sample was divided into 2 aliquots: one aliquot of whole blood was sent immediately for measurement of hemoglobin (Hb) (Sysmex SE-9000 Auto Hematology Analyzer), the remainder was left to clot at room temperature. After centrifugation, the serum was separated and stored at −20°C at the local hospital until it was shipped on dry ice to the Children's Hospital Zhejiang University in Hangzhou, where serum ferritin (SF) was determined by chemiluminescent immunoassay (IMMULITE, Diagnostic Products) and C-reactive protein (CRP) was measured by rate nephelometry using a QuikRead 101 instrument (Orion Diagnostica).

Maternal anemia in the third trimester was defined as Hb <110 g/L (29). In the newborn, low Hb was defined as cord blood Hb ≤130 g/L. This cutoff is ~2 SD below the mean for term births (153–156 ± 12–13g/L using modern machines) (30,31). Low iron stores in cord blood was defined as SF <75 μg/L (to convert to the SI unit pmol/L, multiply by 2.247) (7,32). Cord SF <35 μg/L was defined as severe ID, because this level indicates brain ID (33). Cord SF >370 μg/L and/or CRP >5 mg/L was considered suggestive of perinatal inflammation or infection (28,34).

Statistical analysis. All analyses were conducted using SAS version 9.2 (SAS Institute). Analyses of relations between maternal and newborn iron status excluded pairs where there was a suggestion of inflammation

(high cord-blood SF and/or CRP), because inflammation can affect iron measures and thus interfere with their interpretation regarding iron status. Tests of significance used an $\alpha < 0.05$. We determined Pearson correlations between maternal and cord-blood iron measures and considered whether there was a threshold for maternal Hb or SF at which cord-blood iron status was worse. The latter analyses used piecewise linear regression models with an inflection point to estimate potential differential linear relationships between maternal iron status and cord-blood iron measures for values of maternal Hb or SF above and below some threshold. That is, we tested for and estimated a possible inflection point, namely x0, at which the effect of maternal Hb or SF on cord-blood Hb or SF changed. We then fitted different slopes for values of maternal Hb or SF above or below threshold (x0) (35). Such models were fitted using Proc NLIN in SAS, which simultaneously estimates x0 and the corresponding slopes above and below x0. The piecewise regression models were run using log cord-blood SF to improve normality and convergence of the analysis, but results are reported and interpreted using the original scale. We also explored the joint effect of low maternal Hb or low maternal SF using a modified sensitivity analysis approach.

Results

Sample. Of a total of 3891 pregnant women who fulfilled the enrollment criteria, 97.0% agreed to blood sampling. Blood samples were obtained for 3702 pairs of mothers and their full-term (37–42 wk gestational age) singleton neonates (cord blood). However, Hb and SF results were not always available for the same mothers and infants, and clotting resulted in smaller sample size for Hb (*n* = 3603 and 3243 for mothers and infants, respectively) than SF (*n* = 3684 and 3699, respectively) (**Table 1**).

TABLE 1 Sample characteristics and maternal and neonatal iron status in the study population[1]

	n	Values
Maternal age, *y*	3653	26.4 ± 3.6
Gestational age, *wk*	1867	39.3 ± 0.9
Newborn gender, *% male (n)*	2669	49.1 (1310)
Maternal iron status, *%*		
Hb		
≥110 g/L	2611	72.5
95 to <110 g/L	897	24.9
<95 g/L	95	2.6
SF[2]		
≥50 μg/L	210	5.7
20–49 μg/L	692	18.8
10–19 μg/L	1510	41.0
<10 μg/L	1272	34.5
Neonatal iron status (cord blood),%		
Hb, *g/L*		
≥130	3060	94.4
<130	183	5.6
SF,[2] *μg/L*		
>370	208	5.6
75–370	3142	85.0
35 to <75	299	8.1
<35	50	1.4
CRP, *mg/L*		
>5	233	7.4
≤5	2927	92.6

[1] Values are means ± SD for continuous variables and percent for categorical variables. Hb, hemoglobin; SF, serum ferritin.
[2] SI conversion factor: to convert SF to pmol/L, multiply by 2.247.

Maternal iron status. A total of 3603 samples were available for maternal Hb and 3684 for SF (Table 1). In the last month of pregnancy, mean Hb was 116 ± 12 g/L. Over one-quarter of the women (27.5%) were anemic (Hb <110 g/L). Anemia was relatively mild; only 2.6% of the women had Hb <95 g/L. Most anemia appeared to be due to ID, because 86.9% of the women with Hb <110 g/L had SF <20 μg/L. In fact, SF was relatively low across the sample. The mean SF was 18.6 ± 20.3 μg/L. Values ≥ 50 μg/L were observed in only 5.7%.

Cord-blood iron status. Cord-blood SF was obtained for 3699 neonates; Hb was missing for 456 samples, primarily due to clotting (Table 1). Cord-blood CRP concentrations were available for 3160 neonates. The mean Hb was 154 ± 16 g/L; Hb was <130 g/L for 183 neonates (5.6%). The mean cord-blood SF was 189 ± 105 (median = 170) μg/L. Table 2 shows the 5th, 25th, 50th, 75th, and 95th percentiles of SF concentrations in the sample and in a summary of prior studies. Low SF (<75 μg/L) was observed in 9.5%; only 50 (1.4%) had severe ID (<35 μg/L) indicative of brain ID. Very high SF levels or elevated CRP concentrations, suggesting perinatal inflammation, were relatively uncommon in this sample of uncomplicated term births; 5.6% of SF values were >370 μg/L and 7.4% of CRP concentrations were >5 mg/L; only 11 samples had both high SF and high CRP, for a total of 430 samples with suggestion of inflammation. There were no background differences between these neonates and their mothers and the rest of the sample.

Relations between maternal and neonate iron status. After excluding samples with suggestion of inflammation, there were 3275 mother-newborn pairs; Hb was available for both mother and neonate for 2775 pairs and SF for 3247 pairs. Pearson correlations showed low-order relations between maternal and cord-blood Hb and maternal and cord-blood SF(r values = 0.10 and 0.07, respectively), which were significant due to the large n ($P \leq 0.0001$). We considered whether relations might be stronger among anemic (Hb <110 g/L) than nonanemic women. They were not. Table 3 shows the overall correlations among iron variables and separately for anemic and nonanemic women.

A threshold (or inflection point, x0) was identified for maternal SF regarding the effect of maternal iron status on neonates (Fig. 1). Maternal SF was related to cord-blood SF below the threshold of maternal SF = 13.6 μg/L (β = 2.4; P = 0.001) but not above. For every 1 μg/L lower in maternal SF below this threshold, cord-blood SF was 2.4 μg/L lower. Almost 60% (1933/3247) of the neonates in our study had mothers with SF below the threshold. Their mean cord-blood SF (167 ± 75 μg/L, n = 1933) was 0.17 SD lower than that of neonates whose mothers had SF above the threshold (179 ± 80 μg/L, n = 1314) ($P < 0.0001$).

There were no detectable thresholds in the relations between maternal SF and cord-blood Hb or between maternal Hb and either cord-blood iron measure. There was no additional effect of maternal Hb above and beyond the effect of maternal SF identified from the inflection point analysis (data not shown).

Discussion

We found that ID and IDA were still common in late pregnancy in rural southeastern China in the mid 2000s, but maternal anemia was generally mild, and neonatal anemia and low cord-blood SF were uncommon. Correlations between maternal and newborn iron measures were of low order in this population. Infants of iron-depleted mothers, as indicated by maternal SF below an empirically- derived threshold of 13.6 μg/L, had lower cord-blood SF than the rest of the sample. The majority of infants in the study were born to mothers with SF below this threshold. Our findings are consistent with several previous studies (36–39) and support the conclusion that maternal and neonatal iron status are related only if maternal iron status is compromised.

Previous studies indicated that this compromise to fetal iron status occurs at maternal SF <10 μg/L (23) or <12 μg/L (40). The empirical threshold we identified (13.6 μg/L) is only somewhat higher. The similarity across studies is surprising in light of major differences in the prevalence and severity of maternal anemia and ID. It may be no coincidence that the thresholds are close to the cutoff for depleted iron stores in Cook's (41) classic model. It would be interesting to test whether maternal transferrin saturation drops precipitously at around this degree of iron depletion, which would indicate less deliverable iron to the placenta and thus less to the fetus. Such a finding would account for the relationship between mother and fetus that we found only at very low maternal iron status.

The clinical importance of a difference in cord SF of the magnitude we observed (0.17 SD, 12 points) is unclear. However, Hay et al. (42) concluded that the cord SF level is a strong predictor of iron status during the first 2 y of life and other studies found that effects of maternal iron status on infant iron status are more apparent in later infancy than in the newborn period (18,43–45). Even somewhat lower cord SF, indicating lower iron stores at birth, could be important at the population level. It could shift the period when ID becomes widespread to earlier in infancy, when the brain is less mature. This could be a concern in many populations such as ours, where almost 60% of infants were born to mothers with SF below the threshold. Further study is needed to determine if a difference in cord SF of the magnitude we observed predicts more ID and IDA and poorer developmental outcomes later in infancy.

TABLE 2 Cord-blood SF concentration percentiles for full-term infants[1]

		Cord SF concentration by percentile				
	n	5th	25th	50th	75th	95th
		μg/L				
All newborns in the sample	3699	59.8	115	170	239	381
Newborns with SF ≤ 370 μg/L and CRP ≤ 5 mg/L	3269	57.8	112	164	225	315
Published data in term newborns[2]	308	40	84	134	200	309

[1] Values are SF concentrations at the stated percentiles. SF, serum ferritin.

[2] Values are from a review by Siddappa et al. (28) of studies of full-term newborns. These studies included infants with such factors as intra-uterine growth restriction, diabetic mothers, or maternal smoking but excluded those with SF >370 μg/L as suggestive of inflammation.

TABLE 3 Correlations between maternal and cord-blood iron measures for healthy, full-term infants[1,2]

	All mothers		Anemic mothers (Hb <110 g/L)		Nonanemic mothers (Hb ≥110 g/L)	
	Hb	SF	Hb	SF	Hb	SF
			r (n)			
Cord-blood Hb	0.10*** (2775)	0.01 (2825)	0.02 (757)	0.02 (753)	0.10*** (2018)	0.00 (2009)
Cord-blood SF	0.00 (3174)	0.07*** (3247)	0.00 (873)	0.07* (867)	−0.04 (2301)	0.06** (2287)

[1] Values are the Pearson correlation coefficient between maternal and cord blood for the entire sample and separately for anemic and nonanemic mothers, *n* for each correlation is shown next to *r* in parentheses. Mother-newborn pairs with cord-blood SF >370 μg/L and/or CRP >5 mg/L are not included. Hb, hemoglobin; SF, serum ferritin.

[2] Symbols indicate correlations between maternal Hb/SF and cord-blood Hb/SF: ***$P \leq 0.0001$; **$P = 0.0042$; *$P = 0.0536$.

In contrast to SF, we did not find a threshold for maternal Hb. Prior studies found such a threshold at <86 g/L (21,38); higher risk of maternal mortality has been observed for maternal Hb <100 g/L at or close to delivery (46). The relative mildness of anemia in our sample may have prevented us from detecting a threshold for low maternal Hb; Hb <95 g/L was observed in only 2.6%.

The current understanding of placental iron transport mechanisms helps explain how the relation between maternal and fetal iron status changes as ID becomes marked. Placental iron transport is largely driven by fetal need (13), which is signaled to the placenta via saturation of fetal transferrin binding transferrin receptor on the fetal-facing (basal) layer of the syncytiotrophoblast (11,12). Increased fetal iron demand or maternal iron insufficiency is related to both an increase of TfR mRNA concentrations and the placental TfR expression, which gets more iron to the apical (maternal facing) surface for increased placental iron uptake (12,47). When maternal iron reserves are depleted, the placenta responds to fetal cues with an increased transfer of maternal iron, steadily draining the mother of iron (48). Ultimately, however, the entire maternal unit becomes iron deficient and upregulation of the placental TfR cannot result in enough iron transfer to restore fetal iron pools to normative levels. The fetus will then start showing decreased SF and ultimately decreased Hb or signs of ID at birth.

The particulars of iron absorption in pregnancy may also explain why more infants are not born markedly anemic or ID in the face of widespread maternal ID in pregnancy. Some research suggests that the placenta and fetus have a special affinity for

iron in the mother's circulation and iron is transported through the placenta irrespective of the concentration gradient (49). Proportionately more fetal iron seems to come from iron absorbed by the maternal gut than from maternal iron stores (50). Most iron transfer to the fetus occurs after 30 wk of gestation, when the efficiency of maternal iron absorption is at its peak (16). O'Brien et al. (48) found a significantly higher amount of iron tracer from maternal oral dosing in neonates born to mothers with depleted iron reserves than those with adequate stores. The iron needs of the fetus thus seem to take priority over maternal requirements with respect to iron absorbed from the gut.

Some aspects of the traditional culture for pregnant women in China, especially in rural areas, may be pertinent in light of the role of intestinal absorption in transferring iron to the fetus. Pregnant women are thought to need special food for "blood production." They are encouraged to eat not only extra meat, fish, and eggs but also liver and blood pudding. Animal blood is used to make a jelly-like pudding, which pregnant women may eat several times per month. We speculate that these traditional dietary practices help meet fetal iron needs, because these food items contain high amounts of bioavailable iron and the amount of transfer to the fetus should increase with more efficient iron absorption in iron-depleted mothers. The result would be to buffer the fetus from maternal ID. However, the fact that over one-half of mothers had SF below the threshold that affected the neonate indicates that these beneficial cultural practices may not be fully able to meet the huge needs for iron in the pregnant woman, placenta, and fetus.

Our specific findings may not generalize to populations where maternal anemia is more or less common and severe. The generalizability of our results may also be limited, because our sample was restricted to normal pregnancies. By design we excluded premature infants and those whose mothers had pregnancy conditions that compromise iron status, such as hypertension, diabetes, etc. (51,52). Our results may also not pertain to contexts where maternal smoking is common. Maternal smoking, another risk factor for fetal or neonatal ID, is rare in Chinese women (53).

Small sample size did not limit our ability to detect significant effects but may well have been a factor in other studies. For instance, some studies reporting no significant maternal cord-blood iron status correlations (19,20,36,37) actually found correlations of the same low order that we observed. They were not significant, likely due to much smaller sample size (*n* = 51–192). However, our study is limited in that we had maternal iron status measures only at the end of pregnancy. There is some evidence in humans and nonhuman primates that maternal iron status before conception or earlier in pregnancy has more impact on infant iron status than at or near term (54,55).
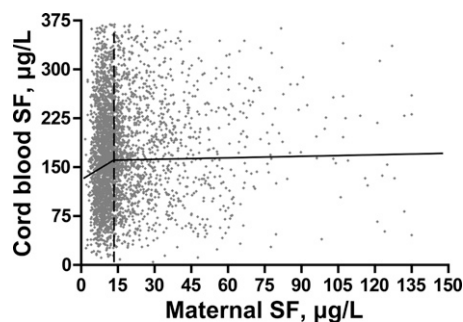

FIGURE 1 The effect of maternal SF on cord-blood SF in healthy term infants. A threshold (or inflection point, x0) was identified using piecewise linear regression analyses. Dashed vertical line at maternal SF concentration of 13.6 μg/L indicates the threshold. Maternal SF related to cord-blood SF for maternal SF below this threshold ($\beta = 2.4$; $P = 0.001$) but not above, n = 3247 pairs. Data for mother-newborn pairs with suggestion of neonatal inflammation and 2 pairs with maternal SF >250 μg/L were excluded, because the model did not converge when these outliers were included. SF, serum ferritin.

In conclusion, this is the largest study to date of maternal-neonate iron status. IDA was common in mothers in rural China, but anemia was generally not severe. Cord-blood SF was lower in neonates whose mothers had a low SF. Thus, it seems that fetal iron needs could not be fully met once maternal iron stores were depleted but could otherwise be fulfilled. The impact of the observed degree of lower cord SF on iron status and developmental outcome in later infancy warrants further study.

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