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Inadequate Iron Stores in Early Term Neonates

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Abstract

Objective—To characterize neonatal iron stores depending on gestational age (GA) at term.

Study Design—Participants were 751 mother-newborn pairs from the placebo arm of a randomized clinical trial of prenatal iron-folate supplementation in China. We compared mean cord serum ferritin (SF) by weeks GA and, following the general linear model, assessed whether maternal iron deficiency (ID) influenced relations between GA and cord SF.

Results—Controlling for covariates, cord SF increased between 37 and 41 weeks (ps<0.05-0.01). Cord SF was lower in infants of ID vs. non-ID mothers (geometric mean 96.3 [95%CI:91.3 – 101.6] μg/L vs. 115.9 [95%CI:105.0 – 127.8] μg/L, effect size = 0.33SD, p=0.0012). There was no significant increase with GA among infants of ID mothers. For non-ID mothers, cord-blood SF increased sharply with GA until 38 5/7 weeks, after which it plateaued.

Conclusions—The findings emphasize that neonates at 37-38 weeks, although considered term, are not fully mature.

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Xing Li assisted in organizing the pregnancy study, including cord blood iron collection, participated in conceiving the research question, revised the manuscript, and approved the final version.

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Ming Li helped conceptualize the pregnancy trial, organized and supervised the pregnancy and infant components, critically reviewed the manuscript, and approved the final version.

Betsy Lozoff conceptualized the pregnancy trial, organized and supervised the pregnancy and infant components, critically reviewed and revised the manuscript, and approved the final version.

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Keywords

Iron deficiency; early term; full term; late term; gestational age; cord blood serum ferritin

Introduction

It has long been appreciated that infants born preterm do not receive as much iron during gestation as term infants. Since human fetuses accumulate a substantial portion of their iron endowment during the third trimester of pregnancy, infants born prematurely do not have a chance to receive the full expected endowment of iron.[1] However, within the relatively narrow range of “term” birth (37 0/7 weeks to 41 6/7 weeks), there is mounting evidence of important functional immaturity in infants born at 37-38 weeks, resulting in a greater risk of morbidity and mortality.[2,3] In this context, we sought to understand fetal iron accretion by assessing a biomarker of fetal iron stores across the weeks of gestation of term birth.

Previous studies reporting neonatal iron status by gestational age (GA) generally aggregated data by preterm, term, and, less frequently, post-term. For instance, the most comprehensive review to date, by Lorentz et al. in 2013,[4] summarized typical values on a range of cord-blood iron status measures by GA group (23-29 weeks, 30-36 weeks, and 37-42 weeks). The sample sizes in many of the studies were small and the specific assays varied, but some differences between 30-36 weeks and 37-42 weeks seemed pronounced, especially for serum ferritin (SF). However, comparisons were limited, since reporting the central tendency for SF in the different studies varied from mean to geometric mean, median, or percentile. Furthermore, there was no breakdown by week gestation in the term range, with the exception of a graphic presentation in Siddappa et al.[5] which suggested a linear increase in cord SF from 37 to 42 weeks.

To understand the effect of GA on fetal iron stores within the range of term birth, we examined cord-blood SF in over 750 healthy Chinese infants born between 37 0/7 and 41 6/7 weeks' gestation to mothers who did not receive supplemental iron in pregnancy. The goal was to provide insight into neonatal iron accretion at term under the commonly observed condition of inadequate iron during pregnancy. Despite WHO recommendations,[6] many pregnant women worldwide receive limited supplemental iron, and iron deficiency (ID) in pregnancy remains widespread.[7]

Methods

Participants

Participants were mother-newborn pairs from the placebo arm of a randomized clinical trial (RCT) of prenatal iron-folate supplementation in northeastern China. The clinical trial was registered at ClinicalTrials.gov, NCT02221752. As previously reported,[8] pregnancy iron supplementation did not affect neonatal iron status in this trial.

The RCT design and findings are detailed elsewhere.[8] In brief, pregnant women were enrolled from June 2009 through December 2011. Those with uncomplicated singleton pregnancies and first prenatal visit at the enrollment site ≤ 20 weeks' gestation were eligible.

The population was almost entirely Han Chinese. Exclusion criteria were age < 18 years, not living in the area, not anticipating delivery at a participating hospital, not mentally competent, chronic health problems, hemoglobin (Hb) < 100 g/L, or consuming supplemental iron. For this analysis, additional exclusion criteria were birth before 37 weeks' gestation or 42 weeks or later or evidence of inflammation as indicated by high cord serum ferritin. Since ferritin is an acute-phase reactant, cord SF > 370 μg/L was considered suggestive of inflammation.[5] The ethics committees of the Peking University First Hospital and University of Michigan approved the study and the assessments of maternal and neonatal iron status. Participants provided signed informed consent.

Procedures

GA was based on last menstrual period. Iron status was assessed at enrollment and at or near term for mothers (venous blood) and at birth for neonates (cord blood). Cord blood samples were obtained by sterile needle puncture immediately after cord clamping. Routine hospital practice was to clamp the cord within 1 min of delivery. Iron status measures for the present study included Hb by automated cell counter and serum ferritin (SF) by chemiluminescent immunoassay (Beckman Coulter Access 2 Immunoassay System, Beckman Coulter Inc., Brea, CA, USA). We defined maternal anemia as Hb < 110 g/L and maternal ID as SF < 15 μg/L per WHO criteria.[7,9]

Data analysis

All analyses were conducted using SAS Version 9.4 (SAS Institute Inc.). Analyses were run using a log normal distribution for cord-blood SF to account for positive skewness. Results are reported and interpreted using geometric means. Based on GA at birth (in days), we compared geometric mean cord SF by GA week, using a general linear model with birth weight, cesarean section, and sex as potential covariates. Using piecewise linear regression models,[10] we tested for and estimated a possible inflection point (or threshold) at which the effect of GA on cord-blood SF changed. This analysis used Proc MCMC in SAS, which simultaneously estimates a threshold and the corresponding slopes above and below threshold using a Bayesian approach implemented through Markov chains Monte Carlo simulations. We performed this analysis separately for infants of ID and non-ID mothers. Tests of statistical significance used an alpha < 0.05.

Results

Of the 788 maternal-infant dyads randomized to the placebo arm, 11 infants were excluded because they were born before 37 weeks GA and 16 were excluded after being born at 42 weeks GA or more. Ten infants were excluded due to presumed inflammation (cord SF > 370 μg/L). After exclusions, 751 mother-infant pairs provided data for this analysis (see Table 1 for sample characteristics). Mothers were enrolled and the 1st venous blood sample obtained early in the 2nd trimester (15.8 weeks, on average). The 2nd maternal blood sample was obtained at 39.4 weeks, on average, generally upon admission to the maternity unit for delivery. Between enrollment and 2nd blood sample, the prevalence of maternal anemia almost tripled (from 8.8% to 25.1%), and ID showed a ~4-fold increase (from 19.0% to 77.0%). Infant birth weight averaged 3368 g at a mean GA of 39 5/7 weeks. Most infants

were first-born (78%), and delivery by cesarean section was common (66%). The geometric mean of cord SF for the sample was 100.4 μg/L.

The number of infants born at each week of term gestation was as follows: 37 weeks (37 0/7 to 37 6/7 weeks),*n* = 36; 38 weeks (38 0/7 to 38 6/7) weeks, *n* = 122; 39 weeks (39 0/7 to 39 6/7 weeks),*n* = 304; 40 weeks (40 0/7 to 40 6/7 weeks),*n* = 215; and 41 weeks (41 0/7 to 41 6/7 weeks),*n* = 74. The infant characteristics that were statistically significant in analyzing relations between GA and cord SF were birth weight and cesarean section. Controlling for birth weight and cesarean section, the cord blood SF geometric mean increased from 76μg/L at 37 weeks GA to a plateau of 101 - 107 μg/L at 39 - 41 weeks (Figure 1). The mean SF was significantly lower in infants born at 37 weeks compared to those born at 39-41 weeks. Mean SF was also lower for 38 vs. 39 weeks' gestation. There was no significance difference in SF variance by gestational age.

Overall, cord SF was lower in infants of mothers with ID at or near term vs. infants of non-ID mothers (96.3 [95%CI: 91.3 – 101.6] μg/L vs. 115.9 [95%CI: 105 – 127.8] μg/L, Cohen's effect size = 0.33 SD, p=0.0012). The relation between GA and cord-blood SF varied depending on maternal iron status. Among infants of ID mothers, there was a non-significant linear relation between GA and cord SF, indicating limited increase in cord SF from 37 0/7 to 41 6/7 weeks. In contrast, the relation among infants of non-ID mothers was non-linear. There was a marked increase in cord SF between 37 and ~39 weeks and little or no change thereafter. The inflection point for the change in the relation was 38 5/7 weeks GA (Figure 2). The difference in cord SF at 37 weeks GA between infants of ID and non-ID mothers was not statistically significant. In analyses stratified by maternal iron status, none of the infant characteristics were statistically significant and were not included in the final models.

Discussion

This study demonstrated a substantial increase in neonatal iron stores within the 5-week range considered term gestation. Cord SF increased from 37-38 weeks to 39-41 weeks in this sample of healthy Chinese neonates whose mothers did not receive prenatal iron supplementation. The increase was most pronounced in neonates born to mothers who did not have ID at or near term. For such infants, cord SF increased from 37 weeks GA up to about 39 weeks GA and plateaued thereafter.

Lower cord SF at 37-38 weeks GA is consistent with other evidence of physiologic and developmental differences between infants born earlier vs. later in the term range. A multi-organization workgroup (Defining “Term” Pregnancy Workgroup), convened in late 2012, reviewed neonatal/infant mortality and morbidity within the term range and summarized evidence of reduced mortality and morbidity, especially respiratory, at 39 0/7 to 40 6/7 weeks, compared to 37 0/7 to 38 6/7 weeks or 41 0/7 to 42 6/7 weeks.[2,3] In 2013, the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine[2,3] endorsed the workgroup's recommendation that term be divided into 3 stages: early term (37 0/7 to 38 6/7 weeks of gestation), full term (39 0/7 to 40 6/7 weeks), and late term (41 0/7 to 41 6/7 weeks). Our data indicate that iron accumulation, as reflected by cord SF, is another physiologic system where infants born at 37-38 weeks differ from infants born

later. However, we did not find a difference in cord SF between full and late term neonates. Thus, our findings primarily support the utility of the early term distinction and the relative immaturity of infants born at 37-38 weeks. It appears that, in the context of no prenatal iron supplementation, there is functional immaturity of the fetal iron system in early term infants.

The mean cord SF in our sample (100 μg/L) is low, compared to 17 studies included in a comprehensive 2013 review by Lorenz et al.[4] *N*s were generally small in the studies summarized, and cord SF varied widely in the smaller studies. In the 4 largest studies (> 300 term births[5,11-13]), the central tendency ranged from a 50th percentile of 170 μg/L in our previous study of 3,699 mother-infant pairs in a prosperous area of southeastern China[13] to an arithmetic mean of 196 μg/L in a study of 363 Norwegian neonates.[12] The lower cord SF in our sample may reflect generally poorer maternal iron status in this population than in other studies. Not only were the infants born to mothers in the placebo arm of a RCT of iron supplementation, but ID was common in mothers and neonates overall. As previously reported, over 2/3 of mothers met criteria for ID, as did about half of the newborns, regardless of iron supplementation.[8] In contrast, all but 3 studies in the Lorenz review were conducted in Northern Europe or the US, where prenatal iron supplementation is routine and ID is less common than in our sample. We hypothesized that the combination of relatively small maternal size and relatively high infant birth weight contributed to widespread ID in our sample.[8] This disproportion would likely challenge maternal capacity to maintain her own iron status and that of the fetus in the absence of adequate iron supplementation.

The overall 0.33 SD difference in cord SF between infants of ID and non-ID mothers was of larger magnitude than in some other studies,[13] further indicating the compromised iron status of mothers and neonates in this population. Differing relations between GA and cord SF depending on maternal iron status highlights potentially important aspects of iron transfer from mother to fetus. Among infants of mothers without ID in late pregnancy, cord SF increased rapidly from early term to full term (i.e., 39 weeks). Thus, iron seemed to be sufficient for continued iron transfer from mother to fetus in the first two weeks of the term gestation period. In contrast, among ID mothers, there was little increase in cord SF over 37-42 weeks' gestation, suggesting insufficient maternal iron for the expected transfer to the fetus in early term and limits on buffering the fetus from maternal ID.

The strengths of this study include SF data for a large group of healthy term neonates, with the largest *n* to date except for our previous study in southeastern China.[13] The sample size was adequate to provide a breakdown by week GA in the term range, which has not been available in previous studies with the exception of graphed data points by GA in Sidappa et al.[5] Furthermore, there were sufficient numbers of neonates born to ID and non-ID mothers to consider how maternal iron status influenced cord SF over the final weeks of gestation. Despite these strengths, there are important limitations to consider. The number of infants born at 37 weeks' or 41 weeks GA was relatively small, and replication with larger *n* at these GAs is needed. Our results might not generalize to populations where neonates are not as healthy or well-nourished as our sample. Infants born small- or large-for-gestational age, who may have low iron stores,[14] were uncommon in our sample, since perinatal complications was an exclusion criterion. Maternal characteristics might also limit generalizability. Our sample excluded teen pregnancies, which are also at risk for

compromised iron status. Most women were having their first baby, and primiparous women tend to have better iron status than multiparous women. Furthermore, the relations we observed between maternal iron status, GA, and cord SF might not apply in settings where there is less maternal or fetal-neonatal ID. Differences in maternal-fetal iron dynamics depending on population specifics is an important area for further investigation. There may also be ethnic/racial differences that limit generalizability from our Han Chinese sample to other groups.

Our results support the value of assessing maternal iron status by more than Hb alone, not only because of the U-shaped curve for risk associated with maternal Hb.[15,16] In fact, the majority of ID mothers in this sample were not anemic. Yet the iron status of their neonates was compromised, especially if born at early term, pointing to the vulnerability of fetal-neonatal iron stores to maternal ID. While early term infants did not generally have overt ID at birth, their lower iron stores likely increase the risk of developing ID earlier in infancy compared to infants born with adequate iron stores. Correspondingly, the infant brain may be less mature when ID develops and thus more vulnerable. Our findings are also especially pertinent to the clinical issue of the timing of non-medically indicated induction or cesarean section. Our results demonstrate that low neonatal iron stores, indicating incomplete maternal-fetal iron transfer, is a risk to the early term neonate. Non-medically indicated delivery before full term should be avoided to help insure that the newborn has sufficient iron for optimal growth and development.

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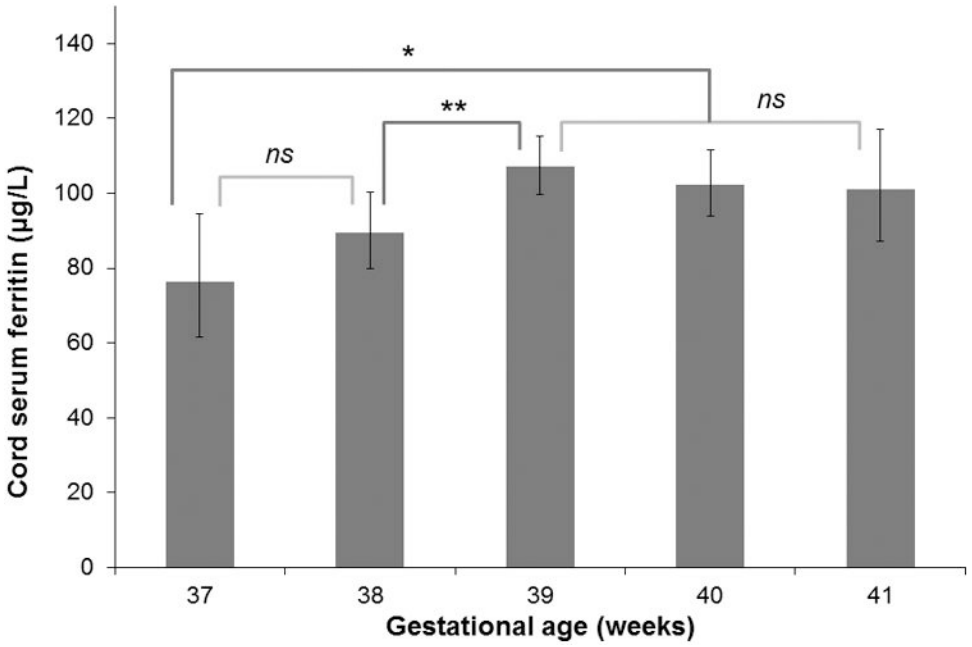

Figure 1.

Cord-blood SF by weeks of term gestation. Values are geometric means and 95% confidence intervals controlling for birth weight and cesarean section. *$p < 0.05$, **$p < 0.01$, *ns* = not significant

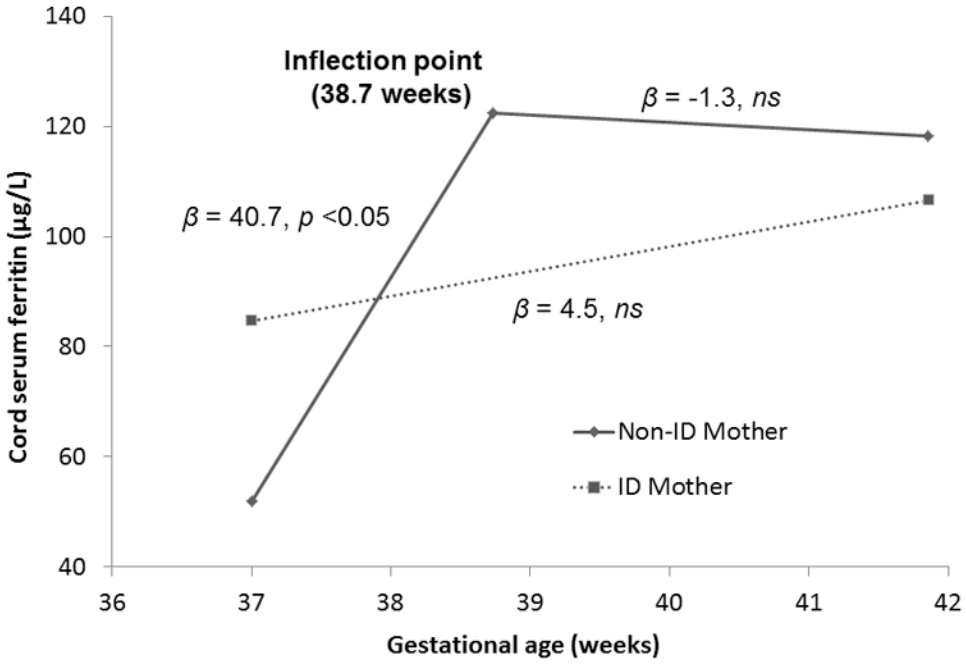

Figure 2.
Associations between GA and cord-blood SF depending on maternal iron status. ID = iron-deficient

Table 1

Sample characteristics

Mothers	**Mean (SD) or % (*n*/total *n*)**
Age, y	24.5 (3.5)
Gestational age at enrollment and 1st iron measures, wk	15.9 (1.9)
Gestational age at 2nd iron measures, wk	39.4 (1.1)
Firstborn (%)	78.1 (574/735)
Pre-pregnancy weight, kg	57.1 (9.4)
Smoking (%)[1]	1.1 (8/739)
Anemia (% HB < 110 g/L)	
At enrollment	9.9 (74/750)
At or near term	25.1 (187/745)
ID (% SF < 15 μg/L)	
At enrollment	19.2 (144/750)
At or near term	70.1 (574/745)
Education ≤ middle school (%)	65.3(484/741)
Infants	
Male (%)	51.5 (386/751)
Birth weight, g	3382 (377)
Gestational age at birth, wk	39.7 (1.0)
Birth by cesarean section (%)	68.0 (503/740)
Iron deficiency (% SF<75 μg/L or ZPP/H > 118 μmol/mol)	45.1 (339/751)

[1]Information on maternal alcohol intake was not collected.