Association of cesarean delivery with anemia in infants and children in 2 large longitudinal Chinese birth cohorts1–4

Hong-tian Li, Leonardo Trasande, Li-ping Zhu, Rong-wei Ye, Yu-bo Zhou, and Jian-meng Liu

ABSTRACT
Background: Cesarean delivery may reduce placental-fetal transfusion and thus increase the risk of early childhood anemia compared with vaginal delivery, yet this notion has not been carefully studied in longitudinal cohorts.

Objective: The aim was to assess the association of cesarean delivery with anemia in infants and children in 2 longitudinal Chinese birth cohorts from different socioeconomic settings.

Design: Cohort 1 was recruited from 5 counties in northeastern China and cohort 2 from 21 counties or cities in southeastern China. Cohort 1 involved 17,423 infants born during 2006–2009 to mothers with early pregnancy baseline hemoglobin concentrations ranging from 100 to 177 g/L, whereas cohort 2 involved 122,777 children born during 1993–1996 to mothers with baseline hemoglobin concentrations ranging from 60 to 190 g/L. The main outcomes were anemia at 6 and 12 mo in cohort 1 and at 58 mo in cohort 2. Multiple logistic regressions were used to estimate adjusted ORs of anemia for cesarean compared with vaginal delivery. Stratified analyses were performed by pre- and postlabor cesarean delivery and according to maternal baseline hemoglobin concentration (≤109, 110–119, 120–129, and ≥130 g/L).

Results: Cesarean delivery was not associated with anemia at 6 mo in cohort 1 (adjusted OR: 1.05; 95% CI: 0.93, 1.19); however, cesarean delivery was associated with increased anemia at 12 mo in cohort 1 (adjusted OR: 1.19; 95% CI: 1.04, 1.37) and at 58 mo in cohort 2 (adjusted OR: 1.11; 95% CI: 1.08, 1.15). The positive associations for anemia at 12 and 58 mo were consistent across maternal hemoglobin subgroups and persisted for cesarean delivery subtypes.


Keywords anemia, cesarean delivery, children, cohort, infant

INTRODUCTION

On average, a term fetus has a blood volume of 115 mL/kg, of which approximately one-third is contained in the placenta (1). The blood transfused from the placenta to the fetus is primarily determined by the placental-fetal hydrostatic pressure gradient and the duration between delivery and umbilical cord clamping (2–6). During cesarean delivery, maternal blood pressure is lower, uterine contraction intensity is weaker, time to cord clamping is shorter, infants are often placed at a relatively higher position compared to the level of placenta (such as on mother’s abdomen or on the thigh), and onset of neonatal respiration is often delayed, raising concern that cesarean delivery may reduce placental transfusion (1). Studies in the 1960s and 1970s suggested this possibility (6–9), with a reduction in placental transfusion for cesarean-delivered neonates; yet, in that era, rates of cesarean delivery were quite low and follow-up studies were limited. Placing a newborn on the mother’s abdomen and immediately clamping the umbilical cord therefore remained common practice during cesarean delivery.

During the past 2 decades, the rate of cesarean delivery has increased dramatically in many countries. In China, the rate of cesarean delivery increased from 3.4% in 1988 to 39.3% in 2008 (10); in the United States, the rate is >30% (11), and in the United Kingdom it approaches 25% (12). In some hospital settings, cesarean delivery is now the dominant delivery method (13, 14). In light of the growing number of cesarean deliveries, concern about the potential negative health consequences has increasingly been documented (15, 16). Iron deficiency and anemia were recently shown to be more common in cesarean-delivered children in cross-sectional studies (17, 18); yet, these studies suffered from recall bias and had modest statistical power.

Anemia is a global public health concern (19) because anemia in infancy is associated with reduced cognition (20). Recent surveys documented a prevalence of anemia of 13% among 5–11

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3Supplemental Tables 1–4 and Supplemental Figures 1 and 2 are available from the “Supplemental data” link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.
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mo olds in the United Kingdom (21), an iron deficiency prevalence of 12% among 12–24 mo olds in the United States (22), and prevalences of anemia of 20% in China (23) and 36% in Brazil (24) for children <5 y.

Changes in obstetric practice during cesarean delivery may improve placental transfusion. Indeed, one trial showed that umbilical cord milking can effectively increase hematocrit for cesarean-delivered infants (25). We therefore examined associations of cesarean delivery with anemia in 2 large-scale and well-characterized Chinese birth cohorts. The prespecified hypothesis was that cesarean delivery is associated with increased risks of anemia in infants and children.

SUBJECTS AND METHODS

Study subjects

The first cohort (cohort 1) was drawn from a randomized controlled trial that was implemented in 5 rural counties in the Hebei province of northeastern China and has been described previously (26). Briefly, 18,775 primiparous women were enrolled before 20 wk of gestation from 2006 to 2009 and were randomly assigned to receive daily folic acid, folic acid plus iron, or folic acid, iron, and 13 additional vitamins/minerals. All of these women had hemoglobin concentrations \( \geq 100 \) g/L. The 18,775 women had 17,748 live singleton births with available data from a perinatal health surveillance system; delivery mode information was available for 17,673 (99.6%) infants. Of these, 17,423 (98.6%) and 17,233 (97.5%) had hemoglobin measured at 5–7 mo (mean: 6.3 mo) and at 11–13 mo (mean: 12.3 mo), respectively (Figure 1).

The other cohort (cohort 2) was drawn from a prospective study in 21 cities or counties in Zhejiang and Jiangsu provinces of southeastern China and has been described previously (27, 28). Briefly, 210,849 singleton infants born during 1993–1996 were identified from a population-based perinatal health care surveillance system and followed between March and July 2000 for measurement of height, weight, and hemoglobin at 40–79 mo (mean: 58.0 mo) to evaluate the effects of periconceptional use of 400 \( \mu \)g folic acid on child growth and development (27, 28). In addition to folic acid consumption, maternal prenatal health care, delivery, and birth records (including data on maternal hemoglobin, delivery mode, birth weight, and sex) were recorded. For the present study, of the 210,849 children, 9845 were excluded due to missing information on delivery mode, and we also excluded children who died before the follow-up survey (\( n = 2785 \)), moved out of the study site (\( n = 12,837 \)), or either declined to have a hemoglobin measurement or had a potentially spurious hemoglobin value (\( >200 \) or \( <60 \) g/L; \( n = 5702 \)). To ensure data completeness, we further excluded 738 children with unknown sex/birth weight and 56,165 children born to mothers without hemoglobin records in early pregnancy (before 20 wk of gestation). After these exclusions, 122,777 children from cohort 2 were included in the final analysis (Figure 1).

The Peking University Health Science Center Institutional Review Board approved the original studies. The analyses of already collected data were deemed exempt by the institutional review board.

Exposure and covariates

Data obtained from perinatal health care surveillance systems for the 2 cohorts were consistent in all aspects regarding surveillance procedures and main questionnaire structures (26, 28). Surveillance in county project areas was implemented through 3-tier (county, township, and village) health care networks, whereas surveillance in city project areas was implemented through maternal and child health hospitals. Prenatal health care and delivery records were first completed by trained county/township
or city/district doctors in a brochure, then entered into computers by trained staff from the maternal and child health hospitals, and transferred to the Peking University project center. Cohort 1 used a network-based real-time data transfer system, whereas cohort 2 used a telephone modem–based data transfer system. Project staff in Peking University were responsible for training the local project staff, monitoring data quality, and drafting annual surveillance reports. In both cohorts, >99% of pregnant women delivered an infant in a health facility.

Surveillance with regard to mode of delivery comprised 2 questions. The first categorized delivery method as spontaneous vaginal, assisted breech, breech extraction, vacuum extraction, forceps, cesarean delivery before the onset of labor, cesarean delivery after the onset of labor, or other unspecified/unknown delivery method. For cesarean deliveries, providers chose among the following: fetal distress, cephalopelvic disproportionate, breech presentation, transverse lie, maternal complications, maternal request, previous cesarean delivery, and other unspecified/unknown indications. In the present study, we recategorized births into a vaginal delivery group, which included spontaneous, assisted breech, breech extraction, vacuum extraction, and forceps delivery. We defined cesarean to include pre- and postlabor cesarean delivery. We defined prelabor cesarean delivery on maternal request (CDMR) as a prelabor cesarean delivery indicated by maternal request; prelabor non-CDMR was defined as a prelabor cesarean delivery with other indications.

In addition to information on micronutrient supplementation for cohort 1 and folic acid consumption status for cohort 2, other continuous covariates obtained from surveillance systems included maternal age, BMI at first prenatal visit, hemoglobin in early pregnancy, week of gestation at hemoglobin measurement, gestational age at delivery (calculated on the basis of last menstrual period), and birth weight; other categorical covariates included maternal education, occupation, and child’s sex.

Outcome measures

In cohort 1, infants’ hemoglobin was measured by using capillary blood via the HemoCue system (HemoCue AB). Before study initiation, township and county doctors were trained in standard measurement procedures, with county doctors training newly arriving township doctors as needed. To ensure compliance with standard procedures, a step-by-step instruction leaflet was pasted on the wall of the township doctors’ rooms. To minimize testing bias, the doctors’ rooms were equipped with heating devices in the winter to maintain temperature at ≥18°C. In cohort 2, children’s hemoglobin was measured with a standard cyanmethemoglobin method by using capillary blood via devices available at each hospital; 2 commonly used devices were the 721 visible spectrophotometer and hemoglobinimeter. All project hospitals were provided with standard hemoglobin solutions (50, 100, 150, and 200 g/L) and with a step-by-step procedure for calibrating the hemoglobinimeter and for preparing the standard curve for the 721 visible spectrophotometer. Following WHO recommendations (29), we defined anemia as hemoglobin concentrations <110 g/L for children aged <60 mo and concentrations <115 g/L for children aged ≥60 mo.

Statistical analysis

In each cohort, we first estimated crude ORs of anemia for children born by cesarean delivery compared with vaginal delivery using univariate logistic regression. We then estimated adjusted ORs using multiple logistic regression with the following covariates: maternal age (<25, 25–29, and ≥30 y), education (primary school or less, middle school, and high school or above), occupation (farmer or other), BMI (kg/m²) at first prenatal visit (<18.5, 18.5–24.9, and ≥25.0), hemoglobin in early pregnancy (≥109, 110–119, 120–129, and ≥130 g/L), and week of gestation at hemoglobin measurement (≥8, 9–12, 13–16, and 17–20 wk) and child’s birth weight (<2500, 2500–3999, and ≥4000 g), sex (male or female), gestational age (<37 or ≥37 wk), and age at follow-up visit (as a continuous variable). An additional covariate in cohort 1 was prenatal consumption of micronutrient supplementation (folic acid, iron–folic acid, and multiple micronutrients); additional confounders for cohort 2 were periconceptional folic acid consumption status (yes or no) and parity (primigravida or multigravida). There were no missing data on all covariates for cohort 1. Percentages of missing data on maternal age and BMI for cohort 2 were 0.1% and 0.6%, respectively. We performed a sensitivity analysis where we used multiple imputation methods with 5 imputations for missing values on the 2 covariates. We found that the analysis that used multiple imputation methods and the complete case analysis were almost identical, possibly because of the quite low percentage of missing data. For simplicity, we only show results of the complete case analyses.

Because mothers’ hemoglobin status is likely to affect that of their children (30), we performed stratified analyses to examine the cesarean-anemia association according to early pregnancy hemoglobin concentration; significant differences in stratified models were further assessed by adding an interaction term between maternal hemoglobin and delivery type into logistic regression models in full-sample models. We used stratified models of the delivery mode–anemia relation to assess the effects of cesarean subtypes by classifying delivery mode into 4 categories (vaginal delivery, prelabor CDMR, prelabor non-CDMR, and postlabor cesarean delivery). We reprinted the above-mentioned models using linear regression to examine associations of delivery mode with continuous hemoglobin.

IBM SPSS 20.0 was used for all analyses. A 2-sided P value <0.05 was considered significant, and no adjustment for multiple comparisons was made.

RESULTS

Among the 17,423 children in cohort 1, 8480 (48.7%) were born by cesarean delivery, whereas among the 122,777 children in cohort 2, 28,186 (23.0%) were born by cesarean delivery. Maternal and child characteristics are shown by mode of delivery in Table 1. For both cohorts, children born by cesarean delivery were more likely to be males, more likely to have a birth weight ≥4000 g, and less likely to have a gestational age <37 wk. Mean age at follow-up for children in cohort 1 was similar across the 2 delivery groups, whereas cesarean-delivered children were younger than those born vaginally in cohort 2. The administration of folic acid, iron–folic acid, and multiple micronutrients was similar between cesarean and vaginally delivered groups in cohort 1 (P = 0.22), whereas the percentage of periconceptional use of folic acid supplements was higher in the cesarean delivery (67.0%) than in the vaginal delivery (63.6%) group in cohort 2 (P < 0.001). More detailed information on maternal and child characteristics for different subtypes of cesarean delivery is provided in Supplemental Table 1.
Cesarean delivery and anemia

Overall anemia prevalence at 6 and 12 mo in cohort 1 was 6.8% and 5.3%, respectively, and at 58 mo in cohort 2 was 21.4%. In crude analyses, cesarean delivery was not associated with anemia at 6 mo (OR: 1.07; 95% CI: 0.95, 1.21) or at 58 mo (OR: 0.99; 95% CI: 0.95, 1.02) but was associated with increased anemia at 12 mo (OR: 1.19; 95% CI: 1.04, 1.36). After adjustment for confounders, associations of cesarean delivery with anemia at 6 and 12 mo remained almost unchanged [ORs (95% CI): 1.05 (0.93, 1.19) and 1.19 (1.04, 1.37), respectively], whereas association of cesarean delivery with anemia at 58 mo became significant (OR: 1.11; 95% CI: 1.08, 1.15) (Table 2). In the analyses stratified by maternal hemoglobin in early pregnancy, we observed no significant interactions between delivery mode and maternal hemoglobin (all P values for interaction tests >0.05) (Table 3).

Subtypes of cesarean delivery and anemia

Prelabor CDMR and postlabor cesarean delivery were not associated with anemia at 12 mo [ORs (95% CI): 1.05 (0.89, 1.25) and 1.45 (0.84, 2.53), respectively], whereas prelabor non-CDMR was significantly associated with anemia at 12 mo (OR: 1.34; 95% CI: 1.14, 1.58). Three subtypes of cesarean delivery were all associated with anemia at 58 mo (ORs ranged from 1.07 to 1.18) (Figure 2).

### Table 1

Maternal and child characteristics according to delivery mode

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Vaginal delivery (n = 8943)</th>
<th>Cesarean delivery (n = 8480)</th>
<th>Vaginal delivery (n = 94,591)</th>
<th>Cesarean delivery (n = 28,186)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age at delivery, y</td>
<td>23.5 ± 2.71</td>
<td>23.7 ± 3.02</td>
<td>24.8 ± 3.1</td>
<td>24.8 ± 2.8</td>
</tr>
<tr>
<td>Education, n (%)</td>
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<tr>
<td>Primary school or less</td>
<td>1571 (17.6)</td>
<td>1598 (18.8)</td>
<td>27,367 (28.9)</td>
<td>6601 (23.4)</td>
</tr>
<tr>
<td>Middle school</td>
<td>7245 (81.0)</td>
<td>6730 (79.4)</td>
<td>57,338 (60.6)</td>
<td>16,848 (59.8)</td>
</tr>
<tr>
<td>High school or above</td>
<td>127 (1.4)</td>
<td>152 (1.8)</td>
<td>9886 (10.5)</td>
<td>4737 (16.8)</td>
</tr>
<tr>
<td>Farmer occupation, n (%)</td>
<td>8171 (91.4)</td>
<td>7678 (89.4)</td>
<td>54,825 (58.0)</td>
<td>13,357 (47.4)</td>
</tr>
<tr>
<td>BMI at first prenatal visit, kg/m²</td>
<td>21.9 ± 2.5</td>
<td>22.7 ± 3.12</td>
<td>20.4 ± 2.2</td>
<td>20.7 ± 2.42</td>
</tr>
<tr>
<td>Hemoglobin before 20 wk of gestation (g/L), n (%)</td>
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<td></td>
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<tr>
<td>≤100–109</td>
<td>565 (6.3)</td>
<td>435 (5.1)</td>
<td>36,424 (38.5)</td>
<td>10,074 (35.7)</td>
</tr>
<tr>
<td>110–119</td>
<td>2187 (24.4)</td>
<td>1846 (21.8)</td>
<td>32,091 (33.9)</td>
<td>9713 (34.5)</td>
</tr>
<tr>
<td>120–129</td>
<td>3797 (42.5)</td>
<td>3586 (42.3)</td>
<td>17,751 (18.8)</td>
<td>5649 (20.0)</td>
</tr>
<tr>
<td>≥130</td>
<td>2394 (26.8)</td>
<td>2613 (30.8)</td>
<td>8325 (8.8)</td>
<td>2750 (9.8)</td>
</tr>
<tr>
<td>Child</td>
<td></td>
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</tr>
<tr>
<td>Male sex, n (%)</td>
<td>4631 (51.8)</td>
<td>4524 (53.5)</td>
<td>48,032 (50.8)</td>
<td>15,144 (53.7)</td>
</tr>
<tr>
<td>Birth weight (g), n (%)</td>
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<tr>
<td>&lt;2500</td>
<td>193 (2.2)</td>
<td>143 (1.7)</td>
<td>1893 (2.0)</td>
<td>463 (1.6)</td>
</tr>
<tr>
<td>2500–3999</td>
<td>8571 (95.8)</td>
<td>7761 (91.5)</td>
<td>87,905 (92.9)</td>
<td>24,660 (87.5)</td>
</tr>
<tr>
<td>≥4000</td>
<td>179 (2.0)</td>
<td>576 (6.8)</td>
<td>4793 (5.1)</td>
<td>3063 (10.9)</td>
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<tr>
<td>Gestational age (wk), n (%)</td>
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<tr>
<td>&lt;37</td>
<td>544 (6.1)</td>
<td>413 (4.9)</td>
<td>4485 (4.7)</td>
<td>818 (2.9)</td>
</tr>
<tr>
<td>≥37</td>
<td>8399 (93.9)</td>
<td>8067 (95.1)</td>
<td>90,106 (95.3)</td>
<td>27,368 (97.1)</td>
</tr>
<tr>
<td>Age at follow-up visit, mo</td>
<td>6.3 ± 0.5; 12.3 ± 0.4</td>
<td>6.3 ± 0.4; 12.3 ± 0.4</td>
<td>58.5 ± 7.9</td>
<td>56.6 ± 8.2</td>
</tr>
</tbody>
</table>

1Mean ± SD (all such values).
2Significantly different from vaginal delivery, P < 0.05 (t test for continuous variables and chi-square test for categorical variables).
3First follow-up visit.
4Second follow-up visit.

### Table 2

Crude and adjusted ORs of anemia for cesarean compared with vaginal delivery

<table>
<thead>
<tr>
<th>Mean age at follow-up</th>
<th>Vaginal delivery</th>
<th>Cesarean delivery</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6 mo</td>
<td>586 (6.6)</td>
<td>594 (7.0)</td>
<td>1.07 (0.95, 1.21)</td>
<td>1.05 (0.93, 1.19)</td>
</tr>
<tr>
<td>12 mo</td>
<td>429 (4.9)</td>
<td>483 (5.8)</td>
<td>1.19 (1.04, 1.36)</td>
<td>1.19 (1.04, 1.37)</td>
</tr>
<tr>
<td>Cohort 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>58 mo</td>
<td>20,247 (21.4)</td>
<td>5966 (21.2)</td>
<td>0.99 (0.95, 1.02)</td>
<td>1.11 (1.08, 1.15)</td>
</tr>
</tbody>
</table>

1Common confounders adjusted for in the multiple logistic regressions for both cohorts included maternal age, education, occupation, BMI at first prenatal visit, hemoglobin in early pregnancy, and week of gestation at hemoglobin measurement and child’s birth weight, sex, gestational age, and age at follow-up visit. One additional confounder for cohort 1 was micronutrient supplementation; additional confounders for cohort 2 were parity and periconceptional use of folic acid.
Cesarean delivery and hemoglobin

Mean (±SD) hemoglobin concentrations at 6 and 12 mo in cohort 1 were 121.7 ± 8.7 g/L and 122.1 ± 8.2 g/L, respectively. Cumulative percentage curves of hemoglobin at 6 and 12 mo for cesarean delivery and vaginal delivery nearly overlapped (Supplemental Figure 1), except in the lower end of the curves (hemoglobin <110 g/L) in which cumulative percentages for cesarean delivery were consistently higher than those for vaginal delivery (see the enlarged lower end of the whole curve in Supplemental Figure 2). The cumulative percentage curves for child hemoglobin are shown separately for children aged 40–59 mo and 60–79 mo because different hemoglobin cutoffs were used; for younger children, cumulative percentages of lower (Supplemental Figure 2) and moderate (Supplemental Figure 1) concentrations of hemoglobin were consistently higher for cesarean-delivered children; similar but weaker differences between the 2 delivery groups were also observed for older children (Supplemental Figures 1 and 2).

Mean (±SD) hemoglobin concentration at 58 mo in cohort 2 was 119.3 ± 10.1 g/L. Hemoglobin at 58 mo was −0.59 g/L lower (95% CI: −0.73, −0.46 g/L) among cesarean-delivered children; the difference remained almost unchanged after adjustments for confounders (Supplemental Table 2). The association was identified in children from the lowest 3 categories of maternal hemoglobin in early pregnancy but not in the highest category (Supplemental Table 3). Prelabor CDMR, prelabor non-CDMR, and postlabor cesarean delivery were all associated with significantly reduced hemoglobin concentrations at 58 mo; associations were stronger in children born to mothers in the lowest hemoglobin category (Supplemental Table 4).

We observed no obvious difference in mean hemoglobin concentration at 6 and 12 mo between the 2 delivery groups, either in full-sample or stratified analyses (Supplemental Tables 2 and 3); similar results were also observed for cesarean delivery subtypes, with few exceptions (Supplemental Table 4).

DISCUSSION

The main finding of this study is that cesarean delivery is associated with increased anemia in children aged 12 and 58 mo but not at 6 mo. The cesarean delivery–anemia association at 12 and 58 mo tended to persist across all subtypes and across maternal hemoglobin subgroups. To the best of our knowledge, this is the largest prospective longitudinal study to specifically examine the relation between cesarean delivery and anemia. Our findings support those from other studies that reported reduced placenta-to-fetus cord blood transfusion and decreased iron storage at birth in cesarean-delivered infants (1, 31). Biological plausibility for the persistence of the adverse effect of cesarean delivery on anemia is provided by existing knowledge that iron stores inherited from the cord blood are repeatedly used for erythropoiesis later in life. These transplacental losses are not recouped readily postnatally without substantial dietary supplementation. We did not observe an association of cesarean delivery with anemia at 6 mo in overall analysis, but we identified an association in the subgroup of infants born to mothers with low hemoglobin. Although the interaction test did not support that the effect of delivery type on anemia depends on maternal hemoglobin concentration, the findings appear to be consistent with the notion that children with normal iron stores before birth have substantial reserves to overcome a reduced placental transfusion during cesarean delivery compared with
those in whom maternal supply of iron is more modest (32). Future studies with adequate power are needed to confirm this.

As with most epidemiologic studies on child anemia, iron deficiency was unable to be distinguished from other causes because of the lack of serum iron indicators such as ferritin and transferrin saturation. Child hemoglobin was measured with different devices in cohort 2, and the measurement differences across devices were not assessed, possibly leading to misclassification of anemia. However, this misclassification, if present, is unlikely to differ between cesarean-born and vaginally delivered children, leading to underestimation of the true association (33). In cohort 2, up to 31% children with information on delivery mode and hemoglobin were excluded from analyses because their mothers had no hemoglobin records in early pregnancy; a post hoc analysis suggested that the adjusted ORs with and without inclusion of those children were similar. In addition, we did not collect data about the cord clamping procedures, which would be helpful in understanding the cesarean delivery–anemia association. Yet, having voiced these concerns, replication of the association in 2 cohorts in dramatically different socioeconomic settings enhances the validity of the findings. Good access to prenatal health care and delivery service as well as the well-implemented health care surveillance system in study settings enabled us to collect reliable information on various variables; in particular, detailed information on indications for performing cesarean delivery made it possible for us to examine the effects of subtypes of cesarean delivery, including prelabor CDMR.

Interestingly, we noted a dramatic difference between crude and adjusted ORs for anemia at 58 mo. To assess this further, we performed post hoc analyses, removing individual confounders from the fully adjusted model to assess confounding effects of covariates. We found that the OR was markedly reduced from 1.11 (95% CI: 1.08, 1.15) to 1.04 (95% CI: 1.01, 1.07) after the removal of month at follow-up visit, suggesting a strong confounding effect. To further assess associations stratified by follow-up month (<60 or ≥60 mo), post hoc stratified analyses revealed similar adjusted ORs [1.10 (95% CI: 1.05, 1.16) and 1.11 (95% CI: 1.06, 1.16), respectively]. The magnitude of the cesarean delivery–anemia association in our study was weaker than that of one Brazilian study in children aged 6–84 mo (prevalence ratio of anemia for cesarean vs. vaginal delivery: 1.61; 95% CI: 1.09, 2.38) (17) but was similar to that of another (prevalence ratio of anemia for cesarean vs. vaginal delivery: 1.11 (95% CI: 1.06, 1.16), respectively). The magnitude of the cesarean delivery–anemia association in our study was weaker than that of one Brazilian study in children aged 6–84 mo (prevalence ratio of anemia for cesarean vs. vaginal delivery: 1.61; 95% CI: 1.09, 2.38) (17) but was similar to that of another Brazilian study in children aged <2 y (prevalence ratio of iron deficiency: 1.18; 95% CI: 1.03, 1.35) (18). It is worth noting that even the modest association may still be of considerable public health importance given the extremely high rates of cesarean delivery in many parts of the world, especially in developing societies such as Brazil (14) and China (10), where anemia remains a major threat to childhood growth and development (23, 24). The presence of an association of prelabor CDMR with anemia suggests that the adverse effects of cesarean delivery are probably related to the delivery itself or associated procedures rather than maternal medical indications. In the analyses of continuous hemoglobin, we observed that cesarean delivery was consistently associated with reduced hemoglobin at 58 mo, although we did not observe obvious reductions in hemoglobin in infants, possibly because the modest effect of cesarean delivery on anemia in a fraction of vulnerable infants (Supplemental Figure 2) did not lead to obvious changes in the mean hemoglobin for all infants (Supplemental Figure 1). An alternative, speculative explanation for the more consistent association at 58 mo could invoke the microbiome, because infants born by cesarean delivery, compared with those born vaginally, had particularly low bacterial richness and reduced diversity (34), which might be linked to lower absorption and net retention of iron (35) and therefore cause anemia by a chronic process.

As with any observational studies, causation cannot be inferred, even when the association is biologically plausible. No effect of delivery type was identified at 6 mo, and the 95% CIs of the ORs for 12 and 58 mo have lower limits of 1.04 and 1.08, indicating that the true effect might be very small. Also, the effect of multiple comparisons, residual confounding, or other factors relating to cesarean delivery may have played a role in these results. However, when considered in the context of the recent recommendations to increase placental-fetal transfusion for vaginally delivered newborns by delayed cord clamping (36–38), our findings suggest the need for studying interventions to increase blood volume of cesarean-delivered newborns; otherwise, the gap in anemia prevalence between cesarean- and vaginally delivered children will grow after widespread adoption of delayed cord clamping during vaginal delivery. Can delayed cord clamping be generalized to cesarean delivery? Delayed cord clamping may unfortunately cause blood to pool in placenta due to the relatively higher position of the infants compared with the level of placenta (8). Cord blood milking has comparable effectiveness to delayed cord clamping (39) and is probably applicable to cesarean delivery as shown by a small-scale randomized study (25), but further studies are needed.

To summarize, cesarean delivery is associated with increased risk of anemia in children. Further observational and intervention studies are indicated, especially in countries with high rates of cesarean delivery, given the serious morbidity associated with childhood anemia.

The authors’ responsibilities were as follows—H-tL and J-mL: designed the research and analyzed the data; H-tL, R-wY, and J-mL: conducted the research; H-tL, LT, L-pZ, R-wY, Y-bZ, and J-mL: wrote the manuscript; and J-mL: had primary responsibility for final content. All of the authors read and approved the final manuscript. None of the authors declared a conflict of interest with regard to this work.

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