Moderate to Severe, but Not Mild, Maternal Anemia, Is Associated with Increased Risk of Small-for-Gestational-Age Outcomes1–3

Naoko Kozuki,4 Anne C. Lee,4,5 and Joanne Katz,4* on behalf of the Child Health Epidemiology Reference Group

Abstract

Anemia is highly prevalent globally, estimated at 40–50% in women of reproductive age. Prior studies have produced inconclusive evidence as to the association between maternal anemia and intrauterine growth restriction (IUGR). We conducted a systematic review of the literature containing associations between maternal anemia and small for gestational age (SGA) outcomes (as a proxy for IUGR). A meta-analysis was performed to pool associations, categorized by the hemoglobin cutoffs presented by the authors. We identified 12 studies reporting associations between maternal anemia and SGA. For the meta-analysis, there were 7 associations with a hemoglobin cutoff <110 g/L, 7 with a cutoff <100 g/L, and 5 with a cutoff <90 or <80 g/L. Although the <110- and <100-g/L categories showed no significant relationship with SGA, the <90- or <80-g/L category was associated with a 53% increase in risk of the newborn being SGA (pooled OR = 1.53 [95% CI: 1.24–1.87]; P < 0.001). Moderate to severe, but not mild, maternal anemia appears to have an association with SGA outcomes, but the findings must be viewed with caution due to the great heterogeneity of the studies. Further examination should be conducted using datasets with better standardized definitions and measurements of exposure and outcome.

Introduction

Anemia is characterized as a “low level of hemoglobin in the blood, as evidenced by a reduced quality or quantity of red blood cells,” which impairs oxygen delivery to the tissues (1). The WHO uses the following hemoglobin cutoffs to define anemia in pregnant women: 100 to <110 g/L for mild anemia, 70 to <100 g/L for moderate, and <70 g/L for severe (1). Decreased erythrocyte production, increased loss of erythrocytes, or a combination leads to anemia; determinants of these causes include nutrition (i.e., iron deficiency, folic acid deficiency), infectious disease (i.e., malaria, helminthes), and genetic disorders (i.e., thealassasemias) (2). In developing countries, pregnant women are at high risk of experiencing anemia and associated complications due to the combined effect of the physiological demands of pregnancy and the high prevalence of aforementioned etiologies. The United Nations Standing Committee on Nutrition estimated anemia prevalence to be 40–50% in developing countries in pregnant and nonpregnant women of reproductive age (3).

During pregnancy, hemodilution also affects maternal hemoglobin measures. Plasma volume expands to facilitate uteroplacental circulation, and proper expansion has been associated with better pregnancy outcomes (4). With the plasma volume increase, the hemoglobin concentration falls until around the late second to early third trimester, then increases slightly around wk 30, when production of RBC mass catches up (5,6). The estimated hemoglobin reduction from prepregnancy to mid-pregnancy is ~15 g/L (7). For this reason, early pregnancy measures of hemoglobin may most accurately reflect the mother’s prepregnancy hemoglobin levels.

The literature remains inconclusive on the association of maternal anemia and neonatal mortality and morbidities. A meta-analysis estimated a decreased risk of perinatal mortality by 28% [RR = 0.72 (95% CI: 0.62–0.89)] with each 10-g/L increase in hemoglobin (8). However, a large prospective cohort study involving 163,313 live births found no relationship (9). Multiple studies reported a U-shaped relationship between maternal hemoglobin and preterm birth and low birthweight, respectively (10). A separate meta-analysis found maternal anemia determined in the first and second trimesters significantly associated with preterm birth [OR = 1.32 (95% CI: 1.01–1.74)] but not with low birthweight (11). Xiong et al.’s (11) meta-analysis found no association between hemoglobin <100–110 g/L and IUGR8; however, it only included 3 studies.

1 Supported by a grant from the Bill and Melinda Gates Foundation (810-2054), Seattle, WA.
2 Author disclosures: N. Kozuki, A.C. Lee, and J. Katz, no conflicts of interest.
3 Search terms and search tree of the systematic review, summary table of the studies included in the meta-analysis, table of detailed descriptions of each included study, and the scoring breakdown of the Newcastle-Ottawa scale are all available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at jn.nutrition.org.
4 To whom correspondence should be addressed. E-mail: jkatz@jhsphs.edu.
5 Department of International Health, Johns Hopkins School of Public Health, Baltimore, MD; and 6 Department of Newborn Medicine, Brigham and Women’s Hospital, Boston, MA.

6 Abbreviations used: IUGR, intrauterine growth restriction; LMP, last menstrual period; SGA, small for gestational age.
There are some plausible biological mechanisms linking maternal anemia to IUGR. Low hemoglobin levels restrict oxygen circulation in the body, creating an environment of oxidative stress or chronic hypoxia, which could then cause fetal growth restriction. Another possible mechanism with iron deficiency anemia is that iron deficiency causes an increased production of norepinephrine, which then stimulates production of corticotropin-releasing hormone and in turn possibly restricts fetal growth (12). IUGR has been linked to major morbidities such as hypoglycemia, hypocalcemia, low Apgar scores, birth asphyxia (13), hyperbilirubinemia (14), reduced immunocompetence (15), lowered mental capacity (16), poor growth, and even morbidities well into adulthood (17). In developing countries, a majority of low birthweight outcomes can be attributed to IUGR (16), and low birthweight is associated with ~60–80% of neonatal deaths in those regions (18).

The objective of this systematic review and meta-analysis is to evaluate the association between maternal anemia, at any point in gestation and at different levels of severity, and IUGR by using SGA as a proxy. We focus on maternal anemia caused by common etiologies, such as nutritional deficiencies. Investigating this possible link may shed new light on our understanding of causes of neonatal mortality and morbidity and appropriate interventions, particularly in developing country settings.

**Methods**

**Search strategy.** We searched for associations between maternal anemia or low hemoglobin assessed during pregnancy and SGA, as a proxy for IUGR. The PubMed, Embase, Cochrane, and WHO regional databases were searched in February 2011 with no language, date, or study subject restrictions. Search terms included combinations of the following categories: hemoglobin/anemia, IUGR/SGA, and maternal pregnancy (Supplemental Text 1). In addition, we ran another search with the same hemoglobin/anemia and IUGR/SGA terms but with the addition of a comprehensive list of developing countries and variations on the phrase “developing country.” We also scanned the references for other relevant studies.

**Inclusion/exclusion criteria.** We used the population, intervention/exposure, comparator, outcome, time/duration, study design, or PICOTS, format to define the inclusion/exclusion criteria. The population of interest was mothers with hemoglobin or hematocrit measurement prior to pregnancy (i.e., for every trimester), measurements from earliest gestation and at different levels of severity, and IUGR by using SGA as a proxy. We included only cohort and case-control studies. In cases of women or neonates with severe morbidities (i.e., diabetes, transplant recipient) or hematological diseases (i.e., sickle cell), we considered only studies reporting a comparison group. SGA may represent infants who are constitutionally small or pathologically growth restricted; however, it is a useful and practical proxy for IUGR. Thus, we considered SGA as our primary outcome measure, defined as birthweight below the 10th percentile of a reference distribution by gestational age. We excluded other measures of IUGR such as low birthweight or term-low birthweight. We included only cohort and case-control studies. In cases where information on anemia definition, SGA definition, timing of hemoglobin assessment, and other pertinent information were not available, we contacted the authors for clarification.

The Newcastle-Ottawa Scale was used to assess the quality of studies included in the meta-analysis (19). The primary author and an independent reviewer scored each of the final collection of studies and revisited the studies for which the reviewers had discrepant scores.

**Data analysis.** We conducted a meta-analysis of studies meeting the inclusion/exclusion criteria and with comparable exposure and outcome measures. We categorized the OR by the hemoglobin cutoffs used by each study: <110 g/L (for mild anemia or worse), <100 g/L (for moderate anemia or worse), and <70 g/L (for severe anemia) based on the WHO cutoffs (1). Examining a birth registry from Northwest Thames, Steer (6) found 95–115 g/L as the hemoglobin range associated with optimal neonatal outcomes. Thus, we also explored outcomes immediately below this range by examining the cutoff of hemoglobin <90 or <80 g/L (moderate to severe anemia or worse). We calculated pooled estimates if there were three or more OR in a category. If a study published associations for multiple hemoglobin cutoffs, we included no more than one association per study in each of these hemoglobin categories. When associations were available at multiple time periods in pregnancy (i.e., for every trimester), measurements from earliest gestation were used to best reflect prepregnancy conditions.

Studies with Newcastle-Ottawa Scale scores ≤6 (of 9) were removed in a sensitivity analysis to determine if poor-quality studies affected the resulting OR. Other sensitivity analyses were conducted, removing studies with unique characteristics (i.e., reported unadjusted associations only) to examine the impact of study heterogeneity. A random effects model was used due to the heterogeneity of the studies presented. An α of 0.05 was considered significant. We used STATA (Stata Corp.) for analysis.

**Results**

We screened 1669 studies without duplicates (Supplemental Fig. 1). Thirteen studies from the following countries met the criteria: Malawi (3 studies), Peru (1), USA (2), UK (1), Finland (1), Sri Lanka (1), Korea (1), and China (3). Because two of the Malawi studies used the same dataset, one (20) was excluded. A total final of 12 studies (Supplemental Table 1) and a sample size of 341,823 mother-child dyads were included in the analysis. The sample size of the studies ranged from 178 to 173,031. The studies were all cohort designs, except for one case-control study (21). The hemoglobin cutoffs for the published associations differed widely, ranging from 70 to 110 g/L, with one study providing different cutoffs by trimester. One study presented its associations in relation to Z-scores of hemoglobin by gestational age in the study population (22). Five studies had a hemoglobin or hematocrit measurement taken before or around the end of the first trimester (~12 wk), one had the mean time of hemoglobin assessment in the second trimester (16.7 wk), one made assessments 2 wk before delivery, 5 had assessments at the first antenatal care visit with average time of visit undeclared, and two did not indicate time of assessment. Two studies had an assessment at each trimester (22,23).

Six studies specified the etiology of anemia in their context. Those studies all declared iron deficiency as the predominant cause. One study from Malawi had a malaria prevalence of 20.2% at booking and 21.5% at delivery, and malaria at delivery had increased odds of IUGR [OR = 1.4 (95% CI: 1.0–1.9)]. The same population had an HIV prevalence of 25.7%, but HIV status had no significant association with IUGR (20). Three articles derived their data from a national database. The reference distribution used for identifying SGA infants varied widely; only two studies shared the same reference distribution (see Supplemental Table 2 for more details on each study.)

We conducted three meta-analyses, including a total of 12 studies. There were seven studies examining a cutoff of <110 g/L (all anemia): four <110 g/L, one with 90 to <110 g/L, one with different cutoffs per trimester (<110 g/L for first, <105 g/L for second, <110 g/L for 3rd), and one with −2 Z-scores of hemoglobin in the study population. For the article presenting Z-score associations (22), the authors reported <110 g/L at gestational wk 6 and <104 g/L at gestational wk 12 as the −2 Z-score cutoffs. There were seven studies examining a cutoff of <100 g/L (moderate anemia or worse): four <100 g/L, one with 90 to <100 g/L, one with 80 to <100 g/L, and one with −3 Z-
scores of hemoglobin in the study population (<100 g/L at gestational wk 6 and <95 g/L at gestational wk 12). Finally, there were five reported associations for cutoff <90 or <80 g/L (moderate to severe anemia or worse): two <80 g/L, one <0.25 hematocrit or <83 g/L, and two <90 g/L. Only one study presented an association for a hemoglobin cutoff of 70 g/L (24), reporting an OR = 1.0 (95% CI: 0.4–2.3). However, the extremely small sample size of those with hemoglobin <70 g/L (11 of 5290) made this finding imprecise.

Neither the hemoglobin <110-g/L cutoff category \( n = 7 \), pooled OR = 1.01 (95% CI: 0.88–1.16); \( P = 0.88 \); I-squared 38.0% nor the <100-g/L cutoff category \( n = 7 \), pooled OR = 1.15 (95% CI: 0.93–1.44); \( P = 0.23 \); I-squared 84.9% had significant associations with SGA. However, hemoglobin with a cutoff <90 or <80 g/L was significantly associated with SGA. Excluding one study that did not state which confounding variables were controlled for (23), and by excluding studies examining mild or moderate anemia that omits more severe anemia from the exposure category (i.e., 90 to <110 g/L as the exposed group, excluding <90 g/L (24,26,27). One study (21), which was also the only case-control study, presented 95% CI that appeared asymmetric in log form. The accuracy of association was confirmed with the authors (personal communication, Bernard Brabin, Liverpool School of Tropical Medicine), and a sensitivity analysis excluding this study did not alter the associations.

Due to the small number of studies in each meta-analysis \( n < 10 \), the power was too low to properly assess for publication bias (28), particularly with studies as heterogeneous as the ones presented above.

**Discussion**

The systematic review identified 12 articles with published associations between maternal anemia and SGA. The meta-analysis revealed a close to 50% increase in odds of SGA for mothers with moderate to severe anemia when pooling associations for hemoglobin cutoffs <90 or <80 g/L. However, these pooled associations need to be examined with great caution, because methods and definitions differed across studies and publication bias may be present. To more accurately determine the association between low maternal hemoglobin and SGA, future studies must take into account the following points given major heterogeneity across the studies in this meta-analysis.

**Exposure and outcome measurement.** Hemoglobin levels are not directly comparable across trimesters, because hemodilution and the associated drop in hemoglobin begin by the second trimester. Measurements made during or after the second trimester most likely overestimate the prevalence of anemia, thereby attenuating the association between low hemoglobin and SGA. Hemoglobin must be measured in the first trimester to accurately assess the associations. Also, anemia prevalence can differ widely depending on the method of measurement. Sari et al. (29) found that using the cutoff of hemoglobin <120 g/L,
anemia prevalence ranged from 14.0% when using the direct cyanmethemoglobin measurement on venous blood (gold standard) to 38.0% using the indirect cyanmethemoglobin method on capillary blood. Overestimation of anemic individuals due to measurement error would attenuate the association. Only two studies identified the tool used to test hemoglobin.

The birthweight distribution by gestational age can differ significantly depending on how gestational age is determined. Although ultrasound, clinical, and obstetric estimates give comparable gestational ages, LMP estimates appear to shift the birthweight for gestational age distribution to the right (30). Dietz et al. (31) found that 17.2% of the California birth certificate records were more than 2 wk off in gestational age, comparing LMP to ultrasound estimates, and that LMP tended to overestimate the proportion of both preterm and post-term babies. Both of these findings hint that LMP misclassifies heavier neonates as SGA, thereby possibly diluting the association. Two studies in the meta-analysis relied solely on LMP and four did not state their assessment methodology. If LMP is to be used, investigators should conduct routine pregnancy surveillance to assess time of conception as accurately as possible.

Data analysis. A majority of studies categorized mothers’ hemoglobin status in dichotomous terms (anemic vs. non-anemic). Including high hemoglobin in the reference group may attenuate the effect size. It has been suggested that insufficient hemodilution leads to poor neonatal outcomes, possibly due to poor utero-placental circulation associated with hyperviscosity (32). If inadequate plasma volume expansion is associated with poor intrauterine growth (22), high hemoglobin levels could have an association with IUGR, unrelated to the mother’s anemia status. Therefore inclusion of high hemoglobin values in the reference group may push the association between maternal anemia and SGA toward the null.

Some studies did not control for confounders potentially associated with IUGR, such as hypertension, smoking (33), weight gain during pregnancy (34), short maternal stature, and low maternal BMI (35). Failure to account for these confounders may have altered associations.

Reporting results. Some studies did not report key components of their studies, such as timing of anemia measurement, SGA reference distribution, or the primary etiology of anemia in their study population. The pathophysiology of anemia and IUGR may differ depending on the etiology. Although iron deficiency is the most prominent cause of anemia globally (36), other etiological factors contribute to its development in many developing countries. Particularly in Africa, infections such as malaria, helminthes, and HIV contribute to anemia. Iron deficiency results in low hemoglobin production that may be caused by blood loss, poor absorption of iron, or insufficient dietary intake. Malaria leads to both increased destruction and dietary intake. Malaria (20,25) and HIV (39) have both been associated with IUGR after controlling for anemia. Indicating the prevalence of these potential causes of anemia would allow us to better interpret the results.

Standardization of definitions. Better standardization of definitions for anemia and SGA should be considered. The highly sensitive cutoff of <110 g/L includes most anemic women. However, for determining maternal and neonatal risk, it may be valuable to adjust the cutoff downwards. Using a cutoff of 90 g/L, which falls under Steer’s (6) 95–115 g/L optimal hemoglobin range for minimizing adverse newborn outcomes, may be more predictive of poor perinatal outcomes. The cutoff of <90 g/L has previously been recommended for surveillance purposes, because the severity of anemia in the population is not properly reflected using the <110-g/L cutoff (40). Stoltzfus (40) noted that progress made by anemia control programs would also be easier to see when examining how the lower tail of the hemoglobin spectrum shifts rather than how prevalence at the <110-g/L level changes. In addition, WHO defines severe anemia as <70 g/L, which may be too low to instigate action in programs, given that less severe anemia may already show negative consequences and that its prevalence hovers at 5–7%, even in areas with high anemia prevalence (40).

SGA prevalence can differ significantly by reference distribution; only 2 of 12 studies in our meta-analysis shared the same reference distribution. Such deviations could affect the associations, with greater SGA prevalence biasing the association toward the null. WHO is currently developing a fetal growth reference population that will standardize the definition of SGA once available.

In conclusion, moderate to severe anemia (<90 or <80 g/L) was significantly associated with SGA, whereas there was no relationship with milder anemia. The associations reported in this meta-analysis must be viewed with great care, however, because the studies identified in this review reveal great heterogeneity in methods and definitions. To arrive at stronger conclusions, it would be beneficial for future investigators to critically evaluate their study methodology and for the public health community to standardize definitions to allow for greater comparability across studies. The advantages of having a better consensus on definitions also apply to evaluating other possible associations between maternal risk factors and birth outcomes.

Both anemia and SGA are highly prevalent in developing countries, and the results of the meta-analysis may serve as additional motivation to target moderate to severe maternal anemia in these regions. The widely recognized anemia cutoff of <110 g/L may be too inclusive; programs may benefit from taking a less sensitive approach and concentrating their resources on pregnant women with lower hemoglobin values that are more predictive of poor health outcomes. Furthermore, although not addressed here, low maternal hemoglobin values may also be linked to other negative outcomes such as stillbirths, prematurity, and mortality. If so, the overall impact of maternal anemia on newborn health would be even greater than what is reported in this paper.

Acknowledgments
The authors thank Melissa Ko for serving as the second reviewer for the articles included in the meta-analysis. N.K., A.C.L., and J.K. designed the research; N.K. conducted the research, analyzed data, and wrote the paper; and N.K. had primary responsibility for final content. All authors read and approved the final manuscript.
Literature Cited


