Relation of Hemoglobin Measured at Different Times in Pregnancy to Preterm Birth and Low Birth Weight in Shanghai, China

Li-Ming Zhou,1 Wen-Wei Yang,2 Jia-Zeng Hua,2 Chun-Qin Deng,1 Xuguang Tao,1 and Rebecca J. Stoltzfus3

This paper addresses two questions: 1) What is the relation of hemoglobin in the second gestational month to preterm birth and low birth weight? 2) How does the relation differ when hemoglobin in the fifth or eighth month or the lowest pregnancy hemoglobin are examined in place of first trimester values? These relations were examined prospectively in 829 women from Shanghai, China in 1991–1992. The population was nearly homogeneous by race, parity, antenatal care, and smoking. Rates of birth outcomes were compared between hemoglobin categories based on 10 g/liter groupings, with 110–119 g/liter as the reference group. Rates of low birth weight and preterm birth (but not small-for-gestational age) were related to early pregnancy hemoglobin concentration in a U-shaped manner. The relative risks (95% confidence intervals) for preterm birth in women by g/liter of hemoglobin were 2.52 (0.95–6.64) for >130 g/liter, 1.11 (0.41–2.99) for 120–129 g/liter, 1.64 (0.77–3.47) for 100–109 g/liter, 2.63 (1.17–5.90) for 90–99 g/liter, and 3.73 (1.36–10.23) for 60–89 g/liter. Use of hemoglobin values in the fifth or eighth month attenuated the association with preterm birth. When lowest pregnancy hemoglobin values were used, the association of anemia with both outcomes was obscured, and risk of preterm birth at high hemoglobin values increased dramatically. Am J Epidemiol 1998;148:998–1006.

The significance of low hemoglobin values during pregnancy for the health of the fetus has been a source of continuing controversy. Because around half of the world’s women experience anemia during pregnancy (1), the impact of pregnancy anemia on fetal development is a question of great public health importance. Because of its high prevalence, if pregnancy anemia puts the fetus at even a modest risk of low birth weight, then a significant proportion of the low birth weight in the world could be prevented through anemia prevention. Preventing low birth weight will save child lives, because low birth weight is one of the strongest predictors of infant mortality (2).

This question would be answered best by a randomized trial of iron supplementation. However, few trials have been conducted because it is unusual to find settings where the standard of antenatal care does not include iron supplementation to women who are known to have anemia. Those trials that have been conducted have been too small to generate definitive conclusions, and most have been conducted in populations where iron-deficiency anemia is rare (3, 4).

Several prospective studies have reported an association between pregnancy anemia and low birth weight (5–10), but a causal relation has not been established (4, 11–14). These studies have suffered from several problems. First, in most populations, women who are anemic also have other characteristics that cause low birth weight. In the United States, for example, anemic women are more likely to be African American and poor (6). It is very difficult to control adequately for these differences between anemic and non-anemic women, because our measurement variables do not capture all that it means to be black and poor in the United States.

Second, plasma volume expansion and lowered hemoglobin concentration are a physiologic response to pregnancy (15). Thus, women with mild “pregnancy anemia” may be a combination of those with iron deficiency (possibly associated with poor pregnancy outcome), and healthy women with a large plasma volume expansion (associated with good pregnancy outcome (16, 17)).

Third, investigators of this question have measured hemoglobin at different times in pregnancy. In mid-
pregnancy, hemoglobin concentrations drop as plasma volume expansion outpaces expansion of the red cell mass, while in late pregnancy, plasma volume ceases to expand and hemoglobin concentrations rise if iron stores are adequate. These physiologic processes drive the hemoglobin concentration in different directions at different stages of pregnancy, and are also related to birth outcome. Thus, the shape of the relation of hemoglobin concentration to birth outcome will probably depend on when the hemoglobin is measured, although this has not been fully described. A spurious relation between anemia and preterm birth is created when hematocrit values at delivery are used, because of the physiologic rise in hematocrit in the late third trimester (14). Biologic interpretation of associations is especially problematic when investigators relate birth outcome to the lowest measured pregnancy hemoglobin value (9, 10), which might occur at different times in pregnancy in different women and thus reflect different processes.

We report the results of a prospective observational study of pregnancy hemoglobin concentration and low birth weight in Shanghai, China. This population offered a unique opportunity to examine this issue, because the population is relatively homogeneous, anemia is common, and other known risk factors for low birth weight are uncommon. In addition, women report for prenatal care very early in pregnancy, so that hemoglobin concentration could be measured before the plasma volume had expanded significantly. Two major questions are addressed: 1) What is the relation of hemoglobin in the second gestational month to preterm birth and low birth weight? 2) How does the relation differ when hemoglobin in the fifth or eighth month or the lowest pregnancy hemoglobin are examined in place of second month values?

MATERIALS AND METHODS

The study population comprised pregnant women in the urban area of Shanghai, China. Five out of 23 urban districts were randomly selected, and, from each of those districts, two communities were randomly selected as the study communities. By law, every woman who intends to become pregnant must apply for an approval of birth from the local Family Planning Office before becoming pregnant. Women were also required to report to this office as soon as they knew they were pregnant. By reporting their pregnancies, they received free antenatal care and other benefits. Because Chinese women are usually permitted to bear only one child, a great deal of care and attention is given to this pregnancy. From June 1991 to June 1992, all women who reported a pregnancy were eligible for the study, and 900 women were identified and enrolled. Informed consent was obtained from each woman at time of entry into the study.

The study sample comprises 829 women who completed the pregnancy follow-up and had singleton live deliveries. Of the 71 women who were enrolled but who are excluded from this sample, four delivered twins, 15 had induced abortions, eight had spontaneous abortions, 29 moved and could not be followed, and 15 were lost to follow-up. Complete hemoglobin data were obtained from the remaining 829 women.

When women reported to the community health care facility for antenatal care, an enrollment profile was established. The mean (standard deviation (SD)) gestational age at enrollment was 7.1 (0.9) weeks (range: 6.1–8.4 weeks). Gestational age was based on the last menstrual period. Hemoglobin concentrations were measured at enrollment and again in the fifth and eighth months of pregnancy. Treatment for anemia, consisting of vitamin C (500 mg/d), iron sulfate (250 mg/d), and folic acid (5 mg/d), was offered free to women with hemoglobin values <110 g/liter, and vitamin and mineral preparations were also available in shops. Women were asked at each trimester follow-up whether they were taking iron supplements. A positive response to this question included women who expressed willingness to take iron tablets offered to them at that visit.

The height and weight of the women were measured at the enrollment visit, but were not measured thereafter. The infants’ weights and lengths were measured at birth. Low birth weight was defined as <2,500 g. Preterm birth was defined as <37 completed weeks of gestation. Small-for-gestational age was defined as birth weight below the sex-specific 10th percentile of weights for gestational age published by Alexander et al. (18) from the 1991 US Live Birth File of the National Center for Health Statistics. Although this reference was not based on Chinese infants, US references are appropriate for defining small-for-gestational age in Chinese populations (19).

To examine the relation between early pregnancy anemia and low birth weight, the cohort of women was divided into six groups based on their first-trimester hemoglobin level. Women with first-trimester hemoglobin concentrations 110–119 g/liter were considered the reference group. The rates of low birth weight, preterm birth, and small-for-gestational age were examined by hemoglobin group, and relative risks (with 95 percent confidence intervals) were calculated for each group relative to the reference group. Other maternal characteristics that might influence birth weight were also examined by hemoglobin group. Multiple logistic regression (20) was used to calculate odds ratios for the three birth outcomes, adjusting for other
Results

Early pregnancy hemoglobin and birth outcomes

At enrollment, the mean (SD) hemoglobin concentration of the sample was 110 (12) g/liter, and the prevalence of anemia (hemoglobin <110 g/liter) was 48.7 percent. As pregnancy progressed, the mean hemoglobin concentration fell about 5 g/liter (table 1), and the prevalence of anemia rose to 66.2 percent in the third trimester. The longitudinal trends in hemoglobin concentration stratified by initial hemoglobin group reflect the overall decline in hemoglobin values, combined with a strong tendency for high and low values to regress toward the mean (table 1).

Usage of iron supplements was low, around 9 percent in the first two trimesters, and did not vary greatly by maternal hemoglobin level or stage of pregnancy (table 1). However, 40.6 percent of women with initial hemoglobin values <90 g/liter reported that they were currently taking or would begin to take iron supplements at the enrollment visit, compared with only 8.2 percent of women in the higher hemoglobin groups combined (p < 0.001).

Most women were aged 20–30 years (table 2); none was below 20 years of age. Body mass index, a measure of fatness (calculated as weight (kg)/height (m)^2) averaged 20 at enrollment—a value on the thin side of the normal range. Only 4.5 percent of women had given birth previously. On average, women in the study made more than eight visits to the antenatal clinic, approximately one visit per month of pregnancy. Maternal age was significantly and directly associated with hemoglobin level. None of the other variables in table 2 varied significantly with women’s hemoglobin level at enrollment, nor did maternal height, weight, or blood pressure (data not shown). Eight women reported smoking at the enrollment visit, but then stopped during the pregnancy. No woman reported consuming alcohol at any pregnancy visit.

The average (SD) birth weight of study infants was 3,267 (457) g, and the overall rates of preterm birth, low birth weight, and small-for-gestational age were 6.9 percent, 4.6 percent, and 11.5 percent, respectively. Mean birth weight declined with descending hemoglobin stratum (table 2), but this trend was not statistically significant (p = 0.36). However, the simple linear regression of birth weight on hemoglobin concentration was highly statistically significant (p < 0.0001), with each 10 g/liter increment in hemoglobin associated with a 67 g increment in birth weight.

### Table 1. Mean hemoglobin concentration and percent iron supplement usage during pregnancy, by hemoglobin group, Shanghai, China, 1991–1992

<table>
<thead>
<tr>
<th>Hemoglobin group* (g/liter)</th>
<th>No.</th>
<th>Hemoglobin concentration (g/liter), by week</th>
<th>Iron supplement usage (%), by week</th>
</tr>
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<tbody>
<tr>
<td>130</td>
<td>57</td>
<td>135 (6)</td>
<td>109 (12)</td>
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<tr>
<td>120–129</td>
<td>129</td>
<td>122 (3)</td>
<td>111 (11)</td>
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<tr>
<td>110–119</td>
<td>239</td>
<td>114 (3)</td>
<td>108 (11)</td>
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<tr>
<td>100–109</td>
<td>263</td>
<td>104 (3)</td>
<td>103 (9)</td>
</tr>
<tr>
<td>90–99</td>
<td>109</td>
<td>95 (3)</td>
<td>97 (9)</td>
</tr>
<tr>
<td>&lt;90</td>
<td>32</td>
<td>82 (6)</td>
<td>97 (13)</td>
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</table>

* Hemoglobin groups are based on initial (4–8 weeks) hemoglobin concentrations.
† Pregnancy weeks.
‡ SD, standard deviation.
§ Chi-square test for trend of iron supplement usage by hemoglobin group, p = 0.05.

The rates of preterm birth and low birth weight were related to women’s enrollment hemoglobin level in a U-shaped fashion, with the lowest risk found for women in the 110–119 g/liter hemoglobin group (table 3). When the relative risk of preterm birth was calculated separately for enrollment hemoglobin strata, the 95 percent confidence limits did not include unity for hemoglobin groups below 100 g/liter. The relative risk of low birth weight was significantly different from unity for women in hemoglobin groups 100–109 g/liter and 90–99 g/liter. In the <90 g/liter hemoglobin group, the relative risk for low birth weight was large (relative risk (RR) = 2.99), but the confidence interval was wide because of the small sample size. The risks of preterm birth and low birth weight in the highest hemoglobin group (≥130 g/liter) were 2.5 times higher than in the reference group, but the confidence limits included unity. For all anemic women combined, the risk of preterm birth was doubled and the risk of low birth weight was tripled compared with the reference group. In contrast, the rate of small-for-gestational age did not vary significantly across hemoglobin groups.

Multivariate logistic regression models were constructed to estimate the relative risk of preterm and low birth weight associated with hemoglobin group adjusted for other maternal characteristics. Variables entered into the model were maternal age, gravidity, parity, height, weight, body mass index, blood pressure, and infant sex. With low birth weight as the outcome variable, no additional variables remained statistically significant in the model. The expected relation between body mass index and both small-for-gestational age and low birth weight (11) was apparent in these data, but was not statistically significant because of the small variance in body mass index (not shown). With preterm birth as the outcome, having had a previous pregnancy was found to be significantly protective. The adjusted relative risks for preterm birth for each hemoglobin group were within 10 percent of the unadjusted relative risks presented in table 3, with no meaningful changes in the confidence intervals.

Based on the relative risks observed in all anemic women and the prevalence of anemia in the second month of pregnancy, anemia in early pregnancy accounted for 25 percent of preterm births and 33 percent of low birth weight in this population. These

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<tr>
<td>Hemoglobin group*</td>
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<tr>
<td>≥130</td>
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<td>120–129</td>
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<td>110–119</td>
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<td>100–109</td>
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<td>90–99</td>
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<tr>
<td>&lt;90</td>
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<td>All women</td>
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* Hemoglobin groups are based on initial (4–8 weeks) hemoglobin concentrations.
† Body mass index (BMI) at first report of pregnancy.
§ SD, standard deviation.

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<th>TABLE 3. Relative risks (RR) of preterm birth, low birth weight, and small-for-gestational age by hemoglobin group, Shanghai, China, 1991–1992</th>
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<tr>
<td>Hemoglobin group*</td>
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<td>≥130</td>
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* Hemoglobin groups are based on initial (4–8 weeks) hemoglobin concentrations.
† CI, confidence interval.
values may be interpreted as the maximal proportions of preterm birth and low birth weight that could be prevented if early pregnancy anemia was eradicated in this population (21).

Relation of other hemoglobin measurements to low birth weight and preterm birth

As pregnancy progressed, the hemoglobin distribution of the study cohort shifted toward lower values (figure 1). The distributions in the fifth and eighth months of pregnancy were very similar to each other, with distinct modes at 100–109 g/liter and less spread than in the second month. The distribution of lowest pregnancy hemoglobin had more values in the lowest category (<90 g/liter, 18.5 percent of values) than in the normal range (≥110 g/liter, 15.0 percent of values).

The relation of preterm birth to second and third trimester hemoglobin concentrations had a U-shape similar to the curve for first trimester values (figure 2). However, the curves were somewhat attenuated, especially with second trimester values. None of the relative risks for any hemoglobin strata defined by second or third trimester values differed significantly from unity (data not shown). When the lowest pregnancy hemoglobin value was used, the risk of preterm birth was not as high at lower hemoglobin values compared with the first trimester curve, although the risk was much higher at high hemoglobin values. Using lowest pregnancy hemoglobin value, the relative risk (95 percent confidence interval (CI)) of preterm birth was 4.90 (1.33–18.07) in women with values ≥120 g/liter compared with women with values 110–119 g/liter.

The relation of low birth weight to second and third trimester hemoglobin values was nearly identical to the curve based on first trimester values (figure 3). The relative risks for hemoglobin strata using later pregnancy values were very similar in magnitude and statistical significance to those based on first trimester values (data not shown). The relation of low birth weight to lowest pregnancy hemoglobin differed from the curves based on specific gestational times. The point of minimal risk was 10 g/liter lower using lowest hemoglobin values compared with first trimester values, and the relative risks were lower at both ends of the curve. Using lowest hemoglobin values, the relative risk of low birth weight with 110–119 g/liter as
Early Pregnancy Anemia and Preterm Birth

FIGURE 2. Rates of preterm birth by hemoglobin strata based on measurements in the second, fifth, or eighth month of pregnancy or the lowest pregnancy hemoglobin: Shanghai, China, 1991-1992.

DISCUSSION

We have observed a strong relation between early pregnancy anemia and risk of low birth weight that derives from preterm birth and cannot be explained by other known risk factors. In previous observational studies, pregnancy anemia was associated with race, smoking, or low prepregnancy body mass index (6–10). These factors are independently associated with low birth weight (11, 12), and therefore might be the true explanation for the observed association between anemia and low birth weight. In the present study, anemia was not associated with these other risk factors. Pregnancy weight gain was not measured in this study, but is not a risk factor for preterm birth (13), so unmeasured differences in pregnancy weight gain cannot explain our findings.

In China, known risk factors for low birth weight are relatively uncommon (19). In part, this is because of the very high value placed on the health of the fetus, combined with good access to antenatal care. The mean birth weight of 3.267 g in this sample of women is similar to other published data from Chinese populations (23–27). The rate of low birth weight (4.6 percent) is very close to the rate observed in a previous study of birth weight in Shanghai (4.4 percent (27)), and slightly below the surveillance rates for China reported by the World Health Organization (6.0 percent (24)). The good health characteristics of pregnant Chinese women explain the low incidence of low birth weight consistently observed in Chinese populations (23). The intensive prenatal care system explains the high follow-up rates achieved in this study.

Anemia, however, remains common among Chinese women, who consume a diet low in heme sources of iron and vitamin C (28). In some parts of China,
hookworm infection is prevalent and likely contributes to the prevalence of anemia, but this is not true of urban Shanghai (29). The fact that hemoglobin values did not improve from the fifth to eighth month of pregnancy is evidence that the women’s iron stores were not sufficient to continue the expansion of red cell mass in the third trimester of pregnancy. If iron stores are adequate, hemoglobin concentrations rise from the second to the third trimester of pregnancy (22). Although inflammation from other chronic and infectious disease causes a proportion of anemia in this and other settings (30), given the high prevalence of anemia observed, the most important cause of anemia was undoubtedly dietary iron deficiency.

The observed relation between early pregnancy hemoglobin concentration and birth outcomes cannot be explained by variation in the maternal plasma volume response to pregnancy. At 7 weeks gestation, the average time of the enrollment visit in this study, the hemoglobin concentration has fallen 4 g/liter (95 percent CI 2.3–5.5) from its pre-pregnancy level (15), mostly due to an increase in plasma volume. This change is very small compared with the 30 g/liter range in initial hemoglobin concentration over which we observed a dose-dependent relation with preterm birth. To the extent that women’s initial hemoglobin levels were influenced by the size of their plasma volume response, the association between lower hemoglobin concentration and adverse birth outcomes would be attenuated. This would lead to an underestimation of the true role of iron deficiency anemia as a cause of low birth weight.

Despite the fact that the first trimester hemoglobin concentrations were measured before the plasma volume has expanded much, the risks of preterm birth and low birth weight were higher in women with relatively high hemoglobin levels in early pregnancy. The relative risk of 2.5 that we observed for both preterm birth and low birth weight was higher in women with relatively high hemoglobin levels in early pregnancy. The relative risk of 2.5 that we observed for both preterm birth and low birth weight was higher in women with relatively high hemoglobin levels. The relative risk of 2.5 that we observed for both preterm birth and low birth weight was higher in women with relatively high hemoglobin levels. The relative risk of 2.5 that we observed for both preterm birth and low birth weight was higher in women with relatively high hemoglobin levels.
expansion in women with high hemoglobin concentrations (5, 8–10). Our findings cannot be explained in this way, which raises the potentially important question of what underlies high hemoglobin concentration early in pregnancy.

Higher hemoglobin concentrations (i.e., >120 g/liter) around the 10th week of pregnancy were weakly correlated with lower concentrations of chorionic gonadotropin and placental lactogen concentrations in British women (31). From those findings, Wheeler et al. (31) speculated that when the oxygen content of blood is quite high, early placental development is adversely affected. Fleming (32) has also proposed that the oxygen tension of the blood influences placental growth, based on observations of increased placental:fetal weight ratios in women with anemia caused by β-thalassemia minor. The hypothesis that high hemoglobin concentration in early pregnancy leads to poor placental development and increased risk of preterm birth should be pursued in larger studies.

The oxygen carrying capacity of the blood does not seem an adequate explanation for the relation between low hemoglobin and preterm birth. Early placental hyperplasia in anemic women (32) might increase the probability of an abrupted placenta in later pregnancy. However, other factors that influence birth weight through decreased oxygen supply to the fetus (e.g., smoking and high altitude) are more strongly associated with intrauterine growth retardation than with preterm birth (11). The observation by Scholl et al. (6) that only iron deficiency anemia, not other anemias, was related to preterm birth suggests that some iron-specific mechanism may be at play. The basis for this has not been studied (33).

The exclusion of a number of confounding factors in this study reduces the plausibility that anemia is acting as a marker for other maternal sociodemographic characteristics. However, it is possible that anemia is a marker for some other physiologic process that causes preterm birth. Uterine bleeding is associated with preterm birth and might cause anemia, but at week 7 of pregnancy, when hemoglobins were first measured in this study, the embryo has implanted for only 4 weeks. The opportunity seems small for bleeding in those 4 weeks to contribute substantially to the variation in hemoglobin in this sample. The later that hemoglobin is assessed in pregnancy, the greater the opportunity for uterine bleeding in pregnancy to cause anemia. In the study by Scholl et al. (6), anemia and vaginal bleeding were assessed in pregnancy week 17, but no association between these variables was found (RR of anemia associated with bleeding = 1.18, 95 percent CI 0.88–1.57). Unfortunately, uterine bleeding was not ascertained in this study, and therefore we cannot test the reverse hypothesis, i.e., that women who enter pregnancy with low hemoglobin are more prone to experience uterine bleeding. The basis for the relation between pregnancy anemia and preterm birth remains obscure.

Based on their observational study of pregnancy anemia and low birth weight, Steer et al. (10, p. 491) have recently stated that "hemoglobin concentrations <95 g/liter seem to be remarkably harmless." The difference between their conclusion and ours likely stems from their use of lowest pregnancy hemoglobin in their analysis. The lowest pregnancy hemoglobin value is influenced greatly by the adequacy of maternal plasma volume expansion, especially in the British population, where iron deficiency anemia in women is much less common than in Shanghai. As Steer et al. (10) point out, lowest pregnancy hemoglobin values of 100–110 g/liter likely reflect good maternal response to pregnancy more than poor iron status. Similarly, when lowest pregnancy hemoglobin value was examined in this population, the relative risk of low birth weight was close to unity at values ranging from 90–120 g/liter. Our results demonstrate that whether moderately low hemoglobin concentrations are harmless depends on when they occur in pregnancy.

Although several influential studies of this issue have been based on the lowest pregnancy hemoglobin value, the concept is illogical from a number of perspectives. The lowest value only has a reliable meaning if the number and timing of the measurements are standardized. This has not occurred in epidemiologic studies and is unlikely to be the case in clinical practice, because physicians will tend to reevaluate at closer intervals women who are at greater risk of anemia. The concept also lacks biologic validity, as hemoglobin concentrations in the second month of pregnancy mean something quite different from values in the sixth month of pregnancy, when plasma volume expansion is at its peak. As much as possible, continuing research in this area should measure hemoglobin at standard times of gestation to specifically test biologically plausible hypotheses. Unless hemoglobin concentration is deliberately used as a marker of plasma volume expansion, the best test of most hypotheses will involve hemoglobin measurements around conception or very early in pregnancy, when hemoglobin concentration does not reflect the changing plasma and red cell volume dynamics of pregnancy. The fact that the relation of hemoglobin concentration to preterm birth was strongest using early pregnancy measurements provides evidence that the relation does not derive from blood volume dynamics, but instead tends to be obscured by them.

In conclusion, this study provides strong evidence
that maternal anemia in early pregnancy increases the risk of preterm low birth weight. Because around half of the world’s women are anemic, this finding has implications for programs to prevent low birth weight and subsequent infant mortality in many settings. A practical question is whether antenatal iron supplementation, which is often started in the second half of pregnancy, will reduce the rates of preterm low birth weight, or whether anemia plays a unique role in placental development during early pregnancy and therefore must be prevented prior to pregnancy. Other than smoking and urogenital infections, currently established risk factors for preterm birth are largely not preventative (13). This finding represents an opportunity for reducing preterm low birth weight and infant mortality, because iron deficiency, the most common cause of anemia globally (30), is both preventable and treatable.

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