

Maternal hemoglobin concentration and birth weight¹⁻³

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ABSTRACT Pregnancy requires additional maternal absorption of iron. Maternal iron status cannot be assessed simply from hemoglobin concentration because pregnancy produces increases in plasma volume and the hemoglobin concentration decreases accordingly. This decrease is greatest in women with large babies or multiple gestations. However, mean corpuscular volume does not change substantially during pregnancy and a hemoglobin concentration <95 g/L in association with a mean corpuscular volume <84 fL probably indicates iron deficiency. Severe anemia (hemoglobin <80 g/L) is associated with the birth of small babies (from both preterm labor and growth restriction), but so is failure of the plasma volume to expand. Hemoglobin concentrations >120 g/L at the end of the second trimester are associated with a ≤3-fold increased risk of preeclampsia and intrauterine growth restriction. The minimum incidence of low birth weight (<2.5 kg) and of preterm labor (<37 completed weeks) occurs in association with a hemoglobin concentration of 95–105 g/L. This is widely regarded as indicating anemia in the pregnant woman but, if associated with a mean corpuscular volume >84 fL, should be considered optimal. *Am J Clin Nutr* 2000;71(suppl):1285S–7S.

KEY WORDS Maternal hemoglobin, birth weight, iron deficiency, plasma volume, preterm labor, intrauterine growth restriction, mean corpuscular volume, women

Women are more likely than men to have low iron stores because of blood loss at the time of menstruation. During pregnancy, the fetal demand for iron increases maternal daily iron requirements from ≈1 to 2.5 mg/d in early pregnancy and 6.5 mg/d in the third trimester. The average daily diet in the developed world contains ≈10–14 mg nonheme iron (1) but not all of this can be absorbed. Evidence from stable-isotope studies suggests that the percentage of nonheme iron absorbed from food during normal pregnancy increases from 7% at 12 wk of gestation to 36% at 24 wk and 66% at 36 wk. These dramatic changes enable the healthy pregnant woman to cope with the extra demands of pregnancy without becoming anemic (1), but only if there is adequate iron in her diet. If the woman's diet is deficient in iron, as is the case in many developing countries, fetal requirements can be met only by additional contributions of iron from maternal stores. This demand by the developing fetus may cause the mother to develop iron deficiency anemia if she had inadequate iron stores at the beginning of pregnancy.

Whether a pregnant woman is anemic cannot be assessed simply by measuring the blood hemoglobin concentration because a

major factor influencing hemoglobin concentration in pregnancy is expansion of plasma volume. How this occurs is not fully established but part of the sequence might be as follows. Heat production by the fetoplacental unit causes a rise in body temperature. Heat loss is increased by peripheral vasodilatation, which causes a drop in blood pressure. This in turn stimulates the release of aldosterone from the adrenal gland, causing the retention of salts and water (2). The drop in osmolality that occurs reduces blood viscosity and enhances blood flow in the low-pressure system of the intervillous space. Enhanced blood flow improves fetal growth. In women who are not given supplemental iron, the hemoglobin concentration of the maternal blood falls from an average of ≈133 g/L in nonpregnant women to an average of ≈110 g/L at 36 wk of gestation (3). The fall is steepest up to 20 wk of gestation; the hemoglobin concentration remains fairly constant up to 30 wk and then rises slightly thereafter (4, 5). These changes in hemoglobin concentration are due mainly to changes in plasma volume; the red cell mass and total hemoglobin actually increase during pregnancy.

Failure of the plasma volume to expand adequately can lead to restricted fetal growth, resulting in the infant being small for gestational age at birth (such infants are more vulnerable to the stress of labor). An alternative response is for the infant to initiate labor prematurely. We studied a large database (data on 153 602 pregnancies, collected in the North West Thames region of London between 1988 and 1991, inclusive) that recorded the lowest hemoglobin concentration measured in each pregnant woman during her pregnancy (usually at 28 wk) to discover the values associated with the largest infants at birth. The highest mean birth weight occurred in association with a hemoglobin concentration of 85–95 g/L (6). The minimum incidence of low birth weight (<2.5 kg) and of preterm labor (<37 completed weeks) occurred in association with a hemoglobin concentration of 95–105 g/L. Such values are commonly considered to represent anemia [eg, by the World Health Organization Expert Committee on Nutrition in 1965 (7)].

The importance of adequate plasma volume expansion in allowing adequate fetal growth is attested to by several studies that showed an increased incidence of low birth weight in association

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with either a high maternal hemoglobin concentration (8–15) or high hematocrit (16–18). The mechanism by which this effect is mediated is unknown but may be related to blood viscosity. Maternal blood is supplied to the intervillous space of the placenta by spiral arteries, which are adapted to provide an almost continuous low pressure flow. High pressure flow would probably cause an excessively high incidence of placental abruption (a condition in which the placenta separates prematurely from the uterine wall, often with fatal consequences for the fetus) and shock (due to hemorrhage and clotting disturbances in the mother). At low flow velocities, blood is very viscous and this promotes stasis and thrombosis, which in any case are more likely as clotting factors are increased in pregnancy. A drop in viscosity would thus promote efficient blood flow within the placenta and vice versa.


Another mechanism through which hemoglobin concentration might affect growth is the development of preeclampsia (a syndrome of hypertension, proteinuria, and multiorgan dysfunction), which complicates $\approx 2\%$ of all pregnancies. Failure of the plasma volume to expand (and of the hemoglobin concentration to drop) is associated with a ≤ 3 -fold increase in the incidence of preeclampsia in pregnancy (19). Thus, the poor placental flow associated with not only high hemoglobin concentrations but also maternal vascular dysfunction might be implicated in fetal growth restriction.

In developed countries, it is likely that disorders of plasma volume expansion and associated high hemoglobin concentrations are more important than is anemia in the genesis of low birth weight and preterm labor. Nonetheless, substantial iron deficiency anemia (usually considered to be < 80 g/L) is also associated with an increased incidence of low birth weight (20–27). The mechanism by which anemia could produce this effect is unknown; it may be that nutrient deficiencies other than iron are the important factors. This hypothesis is strengthened by a review of 20 randomized, controlled trials that showed that "routine supplementation (with iron and folic acid) has no detectable effect on any substantive measures of either maternal or fetal outcome, [in particular] . . . on preterm delivery, low birthweight, stillbirths or neonatal morbidity" (28). One study that looked at outcome in a subsequent pregnancy also found no benefit of supplementation (29).

Are there ways of assessing iron deficiency in pregnancy other than measuring hemoglobin concentration and mean corpuscular volume? Ferritin is not a useful measure because concentrations decrease dramatically in pregnancy irrespective of whether iron supplementation is given (30). Bone marrow aspiration seems to be an excessive response to moderately low hemoglobin concentrations. A pragmatic trial of oral iron therapy is probably the best approach unless the anemia is severe (< 60 g/L).

Should oral iron be given routinely to pregnant women? Over the past 10 y, Barker et al (31–33) proposed that intrauterine malnutrition leads to adverse sequelae in adult life, notably causing hypertension. These researchers proposed that not only low birth weight but also high placental weight (presumably a compensatory phenomenon) is a sign of intrauterine nutrition (32). Subsequently, they showed that lower hemoglobin concentrations in pregnancy are associated with larger placentas (34) and suggested that this indicated that $\approx 50\%$ of well-nourished women in the Oxford region of the United Kingdom were significantly iron deficient during pregnancy. They further suggested that this discordance between placental and fetal growth could result in long-term consequences for the infant, such as an increase in the incidence of hypertension in later life. Barker et al made these conclusions despite having also shown that the

lowest hemoglobin concentrations were associated with the highest birth weights, which might otherwise be thought to be advantageous. A subsequent study failed to show any evidence of a relation between placental ratio and hemoglobin concentration or mean cell volume at the first antenatal visit, and placental ratio was not associated with change in mean cell volume during pregnancy or with third-trimester serum ferritin concentration (35). Barker's group has since reported that a high maternal carbohydrate intake in early pregnancy is associated with a lower placental weight and a lower birth weight (36), so the interrelationships are complex; as they commented in their 1991 article (34), "specific advice to pregnant women must await further studies." This is particularly true given that recent studies failed to show any relation between birth weight and blood pressure in young adulthood (37–42). In 1998, data were reported suggesting that low birth weight is a feature of an inherited predisposition to hypertension, perhaps because it is associated with higher maternal blood pressure during pregnancy (43). Parental blood pressure may be an important confounding factor in the relation between low birth weight and subsequent hypertension.

In summary, plasma volume expansion in normal pregnancy causes a drop in maternal hemoglobin to concentrations commonly regarded as indicating anemia; in fact, concentrations of 95–115 g/L with a normal mean corpuscular volume (84–99 fL) should be regarded as optimal for fetal growth and well-being and are associated with the lowest risk of preterm labor. Routine hematinic administration to women with values in these ranges is probably unnecessary. 

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