Significance of an abnormally low or high hemoglobin concentration during pregnancy: special consideration of iron nutrition

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ABSTRACT An association between moderate anemia and poor perinatal outcomes has been found through epidemiologic studies, although available evidence cannot establish this relation as causal. Anemia may not be a direct cause of poor pregnancy outcomes, except in the case of maternal mortality resulting directly from severe anemia due to hypoxia and heart failure. Preventing or treating anemia, whether moderate or severe, is desirable. Because iron deficiency is a common cause of maternal anemia, iron supplementation is a common practice to reduce the incidence of maternal anemia. Nevertheless, the effectiveness of large-scale supplementation programs needs to be improved operationally and, where multiple micronutrient deficiencies are common, supplementation beyond iron and folate can be considered. High hemoglobin concentrations are often mistaken as adequate iron status; however, high hemoglobin is independent of iron status and is often associated with poor health outcomes. Very high hemoglobin concentrations cause high blood viscosity, which results in both compromised oxygen delivery to tissues and cerebrovascular complications. Epidemiologic studies have also found an association between high maternal hemoglobin concentrations and an increased risk of poor pregnancy outcomes. Evidence does not suggest that this association is causal; it could be better attributed to hypertensive disorders of pregnancy and to preeclampsia. The pathophysiologic mechanism of these conditions during pregnancy can produce higher hemoglobin concentrations because of reduced normal plasma expansion and cause fetal stress because of reduced placental-fetal perfusion. Accordingly, higher than normal hemoglobin concentrations should be regarded as an indicator of possible pregnancy complications, not necessarily as a sign of adequate iron nutrition, because iron supplementation does not increase hemoglobin higher than the optimal concentration needed for oxygen delivery. Am J Clin Nutr 2000;72(suppl):272S–9S.

KEY WORDS Hemoglobin, anemia, polycythemia, iron deficiency, birth outcomes, preeclampsia, iron supplementation, pregnancy

INTRODUCTION

Iron and folate supplementation during pregnancy is commonly practiced to prevent maternal anemia, which is often caused by iron deficiency. Part of the rationale for this practice is the high iron requirement during pregnancy, almost 3 times that required for nonpregnant women of childbearing years, which is difficult to meet from dietary sources (1). Another reason for supplementation is that anemia caused by iron deficiency alone or in combination with other factors, eg, folate deficiency, vitamin A deficiency, and malaria, has been implicated as having several negative effects on maternal and fetal health. Therefore, anemia prevention through iron supplementation may help to improve reproductive outcomes.

In this supplement, Rush (2) questions the benefit of routine iron supplementation in relation to the evidence of the harm or burden of anemia on reproductive outcomes. Specifically, he notes that a high hemoglobin value during pregnancy has been associated with adverse birth outcomes. He questions whether efforts to prevent anemia through iron supplementation can put some women at risk by placing their hemoglobin in a higher range that is associated with poor pregnancy outcomes.

The purpose of this review is to look at normal and abnormal hemoglobin values in terms of their causes and consequences. This review will also reassess the evidence for iron supplementation and the strength of the evidence that implicates either a low or a high hemoglobin concentration in morbidity and mortality during pregnancy and the perinatal period. In doing this, the evidence will be categorized with respect to deficiency, risk, benefit, and feasibility to increase the effectiveness of public health programs.

Evidence of deficiency is provided by a dietary nutrient intake that is inadequate to meet the requirement estimated to be necessary to avoid a deficient state. Often, the deficient state is a clearly defined disease or nutritional disorder with specific signs and symptoms, eg, beriberi for severe thiamin deficiency. A clearly defined pathophysiologic mechanism is required for classification of a nutritional disease or disorder, and an estimated nutrient requirement has been widely used for clinical and public health purposes.

Evidence of risk is based on finding associations between nutritional factors and adverse health outcomes, often by

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observational studies. For example, greater saturated fat intake increases the risk of coronary heart disease. This is regarded as indirect evidence because epidemiologic findings of an association cannot distinguish whether the relation is causal. Because health and nutritional problems may coexist in a population as a result of a common risk factor, evidence of risk alone may not be sufficient to justify program action without greater proof that the association is indeed causal.

Evidence of benefit is obtained when a specific risk factor is thought to contribute to adverse health outcomes, and intervention trials show that removing the risk factor results in improved outcomes. This is regarded as direct evidence to establish a causal relation between the risk factor and poor outcome. The process to prove such evidence often involves controlled trials with proper randomization. The measured beneficial effect under controlled research conditions is known as efficacy, which is the maximum achievable effect under ideal conditions. Often, this is a necessary condition but may not be sufficient for the consideration of large-scale program action.

After the indication for program action is clear on the basis of evidence of deficiency and benefit of the intervention, evidence of feasibility is needed for initiating large-scale programs based on resource and technical capacity. One requirement for a large-scale program is evidence of effectiveness, ie, sufficient benefit under the field conditions. Often, the feasibility of a public health program is based on its cost-effectiveness compared with other programs.

**RELATION BETWEEN MATERNAL ANEMIA AND IRON DEFICIENCY**

**Anemia as an undesirable health outcome**

In maternal anemia and iron deficiency, the anemia itself is often regarded as an adverse outcome. Evidence is strong that in most undeveloped and in many developed countries, iron deficiency is the main cause of anemia in women and that iron supplementation under trial conditions prevents or corrects the anemia (3). In other words, there is evidence of a benefit or efficacy associated with iron supplementation. Consequently, large-scale iron supplementation programs during pregnancy are a common practice, although evidence of supplementation effectiveness has not been impressive (3, 4). The key argument supporting anemia as an outcome measure is related to the fact that red blood cells contain hemoglobin, which is an essential component of the respiratory system for oxygen transport. Any substantial reduction in red blood cells and hemoglobin reflects a reduced capacity of oxygen transport to tissue. Such a reduction in oxygen transport can be regarded as an adverse health outcome; thus, iron deficiency has a definite effect on health because of anemia (evidence of deficiency).

**Anemia as a predictor of reproductive outcomes**

In looking at pregnancy-related or reproductive outcomes, there has been a change from regarding anemia as an undesirable health outcome to regarding it as a predictor or cause of other adverse outcomes, ie, maternal and fetal mortality, preterm birth, and low birth weight. Two interesting issues have emerged from this change in perspective. One issue is that the association between mild-to-moderate anemia and other adverse reproductive outcomes is weak (evidence of risk only). Some studies found an association between anemia and adverse pregnancy outcomes, whereas other studies did not show a significant association (2). Additionally, the positive association observed in several epidemiologic studies does not establish a causal relation without the support of a plausible biological mechanism (5).

Direct evidence showing that a reduction in anemia will lead to fewer adverse birth outcomes (evidence of benefit) is lacking. This leads to the question, Why provide iron supplementation if there is no evidence of beneficial reproductive outcomes? (2).

A second issue, which emerged from some of the same epidemiologic studies that found an association between anemia and a greater risk of poor birth outcomes, is that high hemoglobin values are significantly associated with poor birth outcomes (evidence of risk) (6–9). These observations raised the issue of whether we should be concerned about high hemoglobin concentrations during pregnancy. If higher than normal hemoglobin concentrations lead to poor birth outcomes, then a related question is, Should we be concerned about iron supplementation during pregnancy, given that iron supplementation can increase the hemoglobin concentration of some women? These issues are discussed below.

In examining the evidence related to high and low hemoglobin concentrations, it is important to evaluate the meaning of hemoglobin concentration. Is hemoglobin concentration a predictor or risk factor for poor pregnancy outcomes as used in epidemiologic studies (a potential cause), or is it a physiologic variable that can be regarded as an outcome in itself (a consequence)?

**HEMOGLOBIN CONCENTRATION—NORMATIVE DEFINITION COMPARED WITH PHYSIOLOGIC CONSEQUENCE**

**Defining the normal range of hemoglobin values**

The hemoglobin cutoff value commonly used to define anemia is based on the normality definition often applied to other clinical laboratory tests and in anthropometry (10). For anemia, age- and sex-specific hemoglobin distributions are based on healthy reference samples (samples from persons with disease or nutritional deficiencies identified by other laboratory criteria are excluded) (11, 12). By convention, the central 95% of the reference hemoglobin distribution was considered the normal range. The 2.5th percentile hemoglobin value (–2 SDs from the mean) was the cutoff point for low hemoglobin or anemia. Conversely, the 97.5th percentile (+2 SDs from the mean) of the same distribution was the cutoff for high hemoglobin.

Because iron deficiency is often a major cause of anemia in many parts of the world, anemia screening is commonly used as a substitute for screening for iron deficiency. However, the probability of iron deficiency in individuals who are anemic (positive predictive value) depends largely on the actual prevalence of iron deficiency in a specific population. Additionally, because many possible causes of anemia exist, such statistics-based anemia criteria provide only a guideline for establishing the probability of specific health and nutritional causes of anemia for a given population. In essence, the hemoglobin-based definition does not provide sufficient information on the meaning of, or reason for, either anemia or high hemoglobin concentrations. Usually, the further a hemoglobin value is from the central tendency of the distribution, the greater the likelihood of finding pathologic reasons to explain the abnormal value. Because of substantial normal
variations in hemoglobin distribution across age, between sexes and races, and at different stages of pregnancy, the cutoff for low or high hemoglobin concentrations should be specific to sex and life cycle (11, 12). The use of inappropriate evaluative hemoglobin criteria during pregnancy can result in misinterpretation of the relation between anemia and resulting health outcomes. An example of such misinterpretation is the disregard of normal hemoglobin concentration variations related to plasma volume changes during pregnancy, which can result in a striking association between preterm births and anemia (13, 14).

**Physiologic significance of anemia**

Mild anemia is routinely defined as a hemoglobin value within 10 g/L of the anemia cutoff value. The World Health Organization recommends that severe anemia be defined as a hemoglobin concentration <70 g/L (15). Hemoglobin concentrations below that of the mild anemia concentration and >70 g/L can be regarded as indicating moderate anemia. Some investigators have defined very severe anemia as a hemoglobin concentration <50 g/L. Hemoglobin concentrations <50 g/L significantly increase the risk of maternal and fetal mortality because of the effects of hypoxia and anemia on the cardiovascular system, which is known as high-output heart failure (16). Medical evidence shows that very severe anemia is a direct cause of maternal and child mortality. In South Asia and Africa, where severe maternal anemia is common, classifying very severe anemia as a major cause of maternal mortality along with eclampsia, obstructed birth, hemorrhage, and sepsis is appropriate. Ross and Thomas (17) estimated that ≥20% of maternal mortality can be attributed to severe anemia. In the less severe range, however, the evidence that anemia is a direct cause of poor reproductive outcomes is not clear. Epidemiologic studies that showed an association between maternal anemia and increased risk of poor birth outcomes did not establish a causal relation (evidence of risk only) (6–9). It is possible that a common factor can cause both anemia and poor birth outcomes.

Although oxygen carrying capacity is proportional to the circulating hemoglobin concentration, an individual with chronic anemia develops a compensatory mechanism to improve oxygen unloading to tissue from hemoglobin during the resting state. This compensatory mechanism can maintain adequate tissue oxygen delivery down to a hemoglobin concentration of 70–80 g/L (18, 19). In an exercise state, however, any loss of hemoglobin or red blood cell mass can be detected as loss in work capacity, even within a hemoglobin range of 120–130 g/L (20). From a physiologic point of view, the evidence is clear that moderate anemia is undesirable, whatever the cause. If the cause of significant anemia is iron deficiency (evidence of deficiency), prevention and correction of iron deficiency anemia are indicated. From the perspective of reproductive health outcomes, however, the evidence is not clear that anemia or iron deficiency are direct risk factors (2). Perhaps a concern more important than the health consequence of anemia is the cause of the anemia. Some major causes of anemia have many other damaging effects or health consequences beyond anemia. For example, malaria is well known to cause severe anemia in many tropical areas, particularly among primigravidae, and it also contributes to the low birth weight of infants.

In summary, sufficient evidence shows that moderate to very severe anemia can produce undesirable health consequences. From the perspective of reproductive health outcomes, only very severe anemia has clearly been shown to result in maternal mortality. The justification for controlling maternal anemia can be based on the undesirable effects of anemia other than poor birth outcomes and harmful health consequences beyond that of anemia alone.

**Physiologic significance of a high hemoglobin concentration**

As with defining anemia, the normative definition of high hemoglobin can be based on +2 SDs from the reference mean. For nonpregnant women, this is equivalent to a hemoglobin concentration of 155–160 g/L. Analogous with mild anemia being within 10 g/L of the cutoff, a mild-high hemoglobin concentration would be 160–170 g/L. For women, a hemoglobin concentration >170 g/L can perhaps be regarded as a moderately elevated value. During pregnancy, the upper level for defining high hemoglobin would be lower than that in nonpregnant women because of the physiologic changes in the hemoglobin concentration during pregnancy (12). Again, the meaning of the elevated hemoglobin concentration and the probability of association with adverse events depends on the specific individual or population under study.

Although much of the clinical and public health focus has been on anemia or the low end of the hemoglobin distribution, there are also problems at the high end. The most notable consequence is increased blood viscosity. The relation between hemoglobin and blood viscosity is linear when the hematocrit is <0.50 (equivalent to a hemoglobin value of 160 g/L). Above this hemoglobin concentration, the relation becomes exponential—a small increase in hemoglobin or hematocrit results in a large increase in viscosity (18). Once hemoglobin concentrations reach ≥180 g/L, the blood viscosity reaches a level that impairs microcirculation and an inadequate amount of oxygen is transported to tissues, similar to the situation with severe anemia. This is often manifested as peripheral cyanosis and impaired mental function resulting from compromised cerebral blood circulation (21). Additionally, because of the poor blood flow, the risk of thromboembolism increases substantially (21). A study of individuals with chronic mountain sickness (or polycythemia), which is due to a combination of high altitude residency and poor pulmonary function, showed that long-term survival with a hemoglobin >200 g/L is not possible (21).

**CAUSES OF ABNORMAL HEMOGLOBIN CONCENTRATION RELEVANT TO PREGNANCY**

**Low hemoglobin concentration (anemia)**

Anemia is the consequence of either less-than-optimal production of red blood cells or hemoglobin, or increased destruction or shortened life span of red blood cells. The production of red blood cells and their principal component—hemoglobin—is a complex process, one that can be adversely affected by many congenital and acquired conditions (22). In most developed countries, iron deficiency is the main cause of significant anemia during pregnancy (23), as shown by the efficacy of iron supplementation in preventing maternal anemia (evidence of benefit). In developing countries, especially where severe maternal anemia is more common, other nutritional factors and infections, including malaria, can often coexist with iron deficiency, contributing to anemia (23). In addition to poor intakes of bioavailable iron, which is a common problem in developing countries
and is related to low intakes of heme iron from animal sources, hookworm infection is prevalent in many tropical areas (24). Hookworm causes upper gastrointestinal blood loss, which contributes directly to iron deficiency anemia (25).

The coexistence of multiple causes of anemia within the same individual or population makes it difficult to define anemia by using conventional biochemical markers, especially when infections are involved (26). Moreover, if multiple deficiencies contribute to the severity of anemia, supplementation with iron alone may not achieve adequate hemoglobin response. A good example is a supplementation study done by Suharno et al (27) in Indonesia, in which combined iron and vitamin A supplementation had a greater effect in correcting maternal anemia than did iron or vitamin A alone. When multiple factors contribute to the severity of anemia, iron deficiency is always a major factor (evidence of deficiency) (23). In such settings, improving iron nutrition is a necessary—but not a sufficient—measure for the reduction of anemia.

Elevated hemoglobin concentration

An elevated hemoglobin concentration is usually the result of 2 mechanisms: increased red blood cell production as a compensatory mechanism when blood oxygen carrying capacity is compromised to meet the demand of tissue (with a net increase in red cell mass), or contracted plasma volume resulting in an appearance of greater red cell volume (without a net increase in red cell mass) (28). One of the 2 most common nonpathologic reasons for elevated hemoglobin or red cell mass is residence at a higher altitude, where ambient oxygen concentration is lower. (29). The other is cigarette smoking, which causes part of the hemoglobin to become nonfunctional as a result of binding with carbon monoxide (30). Respiratory and cyanotic cardiac conditions, which compromise proper oxygenation of blood, are the principal pathologic reasons for elevated hemoglobin concentration (28). The only condition of elevated hemoglobin that is due to the production of defective red blood cells, but not subject to the control of tissue oxygen drive, is polycythemia vera (31). These conditions of increased red blood cell production share the one basic feature of increased red cell mass with normal or increased total blood volume.

When the red cell mass does not increase, the contraction of the plasma volume results in the appearance of an elevated hemoglobin concentration, or hemoconcentration (32). The most common example is acute dehydration, which can raise the hemoglobin concentration by 10−15%. Throughout normal pregnancy, blood volume expands by an average of 50% compared with the nonpregnant state (33). This rapid expansion of blood volume starts in the first trimester. Plasma volume increases more than does red blood cell mass, which produces a declining hemoglobin concentration during the first half of pregnancy. This is known as the physiologic anemia of pregnancy.

In women who have hypertensive disorders of pregnancy, particularly those with preeclampsia, blood volume does not increase, which results in a relatively higher hemoglobin concentration. In the study by Pritchard et al (34), the average hematocrit for women with preeclampsia was 0.405, compared with a mean of 0.374 for women with a normal pregnancy. This difference in hematocrit is equivalent to a 20–25% difference in hemoglobin and shows the extent of the severe failure of plasma expansion due to preeclampsia. Several other studies showed that higher hemoglobin concentrations during pregnancy result from hypovolemia or hemoconcentration, which is usually the result of preeclampsia or pregnancy-induced hypertension (35, 36).

ASSOCIATION BETWEEN ELEVATED HEMOGLOBIN CONCENTRATION AND ADVERSE BIRTH OUTCOMES

Several epidemiologic studies showed that both low and high hemoglobin concentrations are associated with increased adverse birth outcomes, including fetal death, intrauterine growth retardation, preterm delivery, and low birth weight (6−9). The hemoglobin concentration at which observed risk starts to increase is ≈120–130 g/L. This is much lower than the high hemoglobin concentration known to cause circulation complications and reduced oxygen transport to tissue (hemoglobin > 170 g/L) (6, 7) and is well within the normal hemoglobin range for pregnant women. The most plausible explanation for the observed association between a high hemoglobin concentration and perinatal morbidity and mortality is that both conditions are often the result of hypertensive disorders of pregnancy or preeclampsia. Clinical and epidemiologic evidence shows that this association is a causal relation (35–38).

The principal mechanism for perinatal morbidity and mortality due to preeclampsia is poor placental and fetal perfusion. The mechanism for the observed higher hemoglobin concentration is the failure of normal plasma expansion, hypovolemia, or hemococoncentration. Hypertension, hypovolemia, and poor placenta perfusion are all part of the physiologic disturbances of preeclampsia (39). Because these known mechanisms can explain the observed association, attributing the increased perinatal complications to the increased hemoglobin concentration in women with pregnancy-induced hypertensive disorders would be difficult.

Another condition known to elevate maternal hemoglobin concentration and cause low birth weight is smoking during pregnancy, and the mechanisms for this are well established (28, 40). There is no evidence that the observed low birth weight of infants from mothers who smoke is due to elevated hemoglobin. In fact, infants born to women who chewed tobacco also had low birth weights (41).

Existing evidence does not support the hypothesis that high hemoglobin concentrations during pregnancy, within a range not classified as high, result in poor pregnancy outcomes. The observed associations between high hemoglobin concentrations and poor outcomes can be better explained by the underlying reasons for both elevated hemoglobin and adverse birth outcomes.

RISK OF HIGH HEMOGLOBIN CONCENTRATION DUE TO IRON SUPPLEMENTATION DURING PREGNANCY

Besides the lack of evidence supporting the causal association between high hemoglobin concentrations and adverse birth outcomes, there is a lack of evidence indicating that iron supplementation can result in abnormally high hemoglobin concentrations. This is related to each person having a set optimal hemoglobin concentration and the only driving force that can increase this above the set point is the need to maintain the blood’s oxygen carrying capacity (42). A greater supply of the components for hemoglobin or red blood cells, including iron, will not result in a higher hemoglobin concentration without a tissue hypoxia drive. One piece of evidence comes from individuals with iron overload conditions who do not have higher hemoglobin concentrations than those of healthy individuals. In addition, several
Iron supplementation studies of children and women showed that the resulting mean hemoglobin concentration, or the hemoglobin distribution, never exceeded that of the reference populations who were iron replete (43, 44).

It is to be expected that pregnant women as a group, in most populations, including those in developed countries, have some degree of iron deficiency; iron supplementation can cause a significant rise in hemoglobin concentrations in those who are iron deficient. Such increases in hemoglobin concentrations represent the correction of iron deficiency. In fact, hemoglobin response to iron supplementation is by far the most reliable method for diagnosing iron deficiency anemia in an individual or a population (44). The extensive experience from iron supplementation trials and programs does not support the possibility that abnormally high hemoglobin values can be the result of correcting iron deficiency.

**RISK OF IRON SUPPLEMENTATION DURING PREGNANCY**

Although an abnormally high hemoglobin concentration is not a risk or consequence of iron supplementation during pregnancy, these are definite risks—but without adverse consequences for pregnancy outcome—during pregnancy. One such risk is accidental iron poisoning of young children through ingestion of iron tablets intended for maternal supplementation (45). Acute iron poisoning is one of the most common fatal accidental childhood poisonings in some countries.

Another risk in many populations is that a small subset of women have conditions known as iron-loading diseases and can be harmed by the extra iron over the long term (1, 46). The most common types of iron-loading disease in developing areas are the severe form of hereditary anemia, eg, thalassemia major, and the iron overloading is often the result of repeated transfusion (47). In such known clinical cases, iron supplementation can be avoided, but only if a sophisticated laboratory is available to diagnose the type of anemia. In reality, there is the risk that all severe anemia in developing countries will be assumed to be due to iron deficiency regardless of whether it actually is, subjecting patients to unneeded iron treatment.

In developed countries, especially among populations of mainly European extraction, hereditary hemochromatosis is a major concern. This genetic disorder enables affected individuals to absorb excessive amounts of iron. Once the lifelong accumulation of excess iron reaches a critical level—often by middle age—tissue and organ damage can result (48). For individuals with this condition, any extra iron will contribute to their iron burden, including iron supplementation during pregnancy. For practical purposes, the risk of harming women with iron-loading disease is not a major problem in most developing countries; rather, dietary iron intakes are often poor and severe iron deficiency anemia is generally a great concern.

Another concern with iron supplementation in areas with endemic malaria is related to the possible interaction between better iron status and greater severity of malaria. A preponderance of studies have shown the greater rate of clinical malaria attack mortality, including iron supplementation (49). A more recent study, however, did not show that the risk of malaria justifies the withholding of iron (50). It is unlikely that withholding iron from individuals with significant iron deficiency will ever be an effective means of controlling malaria. The more appropriate approach for the areas with high endemic malaria is to provide malaria treatment or prophylaxis when iron supplementation is indicated.

**CONCERN ABOUT THE LACK OF EFFECTIVENESS OF CURRENT IRON SUPPLEMENTATION PROGRAMS DURING PREGNANCY**

There is sufficient indication for iron supplementation in populations where iron deficiency and resulting anemia are common. Supplementation is justified on the basis that moderate and severe anemia is undesirable (evidence of deficiency and risk). An appropriate trial has not yet been conducted to test the benefit of iron supplementation in reducing adverse reproductive outcomes. Such an evaluation has not been conducted because iron supplementation during pregnancy is a standard practice in most countries and, ethically, iron cannot be withheld from women assigned to a control group. The efficacy of iron supplementation in correcting iron deficiency anemia has been shown under research conditions (evidence of benefit).

A major factor that has limited the benefit of iron supplementation programs is the lack of clear evidence of an effective reduction in maternal anemia in field settings (3, 4). There are 2 aspects to this problem: one is related to the nature of the supplementation and the other is related to the operation of the program. In many developing countries, the principal reason that iron deficiency is common and can be severe is that diet quality is poor and the intake of bioavailable iron is low (51), not necessarily that dietary iron intake is poor. The best source of bioavailable iron is heme iron, which is found in animal muscle (1, 51). Additionally, the absorption of nonheme iron can be affected by inhibitors or enhancers. In poor areas, the usual diet often consists mainly of unprocessed grain products that are relatively high in phytate, which is a known inhibitor of iron absorption.

Under conditions of poor diet quality, micronutrients other than iron are affected, including vitamin A, zinc, calcium, riboflavin, and vitamin B-12, and some of these micronutrient deficiencies also contribute to the severity of anemia (27, 51, 52). Therefore, supplementation with iron (and folate) alone may not be effective in correcting nutritional anemia and may address only part of the problem concerning nutritional deficiencies. Consequently, where multiple nutrient deficiencies are common, a more appropriate micronutrient supplement formulation beyond iron and folate should be considered. The commonly used iron and folate formulation is clearly suited for developed countries where the overall bioavailability of dietary iron is quite high and women at risk of iron deficiency anemia are often those with greater menstrual blood loss (53).

From an operational viewpoint, implementing iron supplementation programs is not an easy task because of the cost and multiple steps involved, including adequate communication with health workers and expectant mothers (3, 4, 23). Evaluations of large-scale programs have found that the reduction of anemia is often limited because of a breakdown in the chain of events required to ensure proper functioning of programs (3, 4). Perhaps the best argument against iron supplementation programs is the lack of effectiveness of these programs in controlling maternal anemia in some areas, not the lack of a medical indication for prevention of iron deficiency and anemia. Better efforts to ensure program functioning appear to be a prudent alternative to abandoning programs.

To ensure the intended benefit of preventing significant iron deficiency anemia, efforts must be devoted toward improving the operation of supplementation programs and toward improving iron nutriture before pregnancy (54). Combining other micronutrients with iron supplements is likely to increase the cost-effectiveness of programs because the same amount of effort will be exerted to pro-
vide not only iron, but other micronutrients as well. This may also increase the effectiveness of anemia control because other nutrient deficiencies can contribute to the burden of anemia.

SUMMARY

The effect of very low or very high hemoglobin concentrations on the cardiovascular system and resulting compromised delivery of oxygen to tissues can directly cause severe morbidity or mortality. Iron deficiency can be a major contributory factor to very severe anemia, but no evidence exists to show that a very high hemoglobin concentration is due to too much iron or to iron supplementation. The clinical significance of low or high hemoglobin concentrations that are less extreme has more to do with underlying conditions that cause abnormally high or low hemoglobin concentrations.

Sufficient evidence exists to indicate that from a general health viewpoint, an iron-deficient state of nutriture can result in moderate and severe anemia, which is undesirable. Such evidence justifies efforts to prevent and treat significant iron deficiency, including iron supplementation during pregnancy when iron requirements are particularly difficult to meet.

The only evidence of risk associated with anemia is based on epidemiologic studies that showed an association between increased risk of poor birth outcomes and anemia or iron deficiency anemia. Nevertheless, it has not been established that there is any benefit to iron supplementation during pregnancy to prevent iron deficiency anemia and thus reduce adverse pregnancy outcomes. This lack of evidence does not negate the evidence for controlling maternal anemia.

The association between adverse birth outcomes and high hemoglobin concentrations observed in epidemiologic studies does not establish that high hemoglobin concentrations are the direct cause of such adverse outcomes (evidence of risk only). The observed association is better explained by underlying causes of high hemoglobin concentrations, such as hypertensive disorders of pregnancy, which are well known to contribute to poor birth outcomes, including infant low birth weight and fetal death.

There is no evidence to support the proposition that iron supplementation during pregnancy can cause abnormally high hemoglobin concentrations, beyond the optimal level for an individual or population. The upward drive for hemoglobin is the need for oxygen delivery to tissues and not the supply of iron or other key components for hemoglobin production.

Iron supplementation during pregnancy has been shown to be efficacious in preventing iron deficiency anemia. Nevertheless, in many developing countries, limiting nutritional factors besides iron have to be considered if a meaningful reduction in anemia is to be achieved. Furthermore, operational aspects of iron supplementation programs must be improved to ensure effectiveness.

REFERENCES

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DISCUSSION

Dr Johnston: One risk that you did not mention was that of unmasking malaria, especially in pregnant women. Primiparas have very little immunity to malaria. Because iron supplementation can increase risk of malaria by \( \approx 10\% \), primiparas are a high-risk group for iron supplementation.

Dr Yip: The issue of whether iron supplements worsen the severity of malaria is still open. Some studies suggest that it is a problem whereas others do not, but I do not think having significant nutrition deficit should be considered as an option for controlling the severity of malaria. In areas where malaria is endemic or can be severe, any nutrition supplementation program probably should also be combined with an effective program of either chemoprophylaxis or treatment for malaria.

Dr Rush: I agree with Dr Yip's comment. I do not think that making a blanket statement that iron unmasks malaria is possible. We have to evaluate the endemicity of malaria, which will help determine the immune status of the population.

Mr Alnwick: I thought that there was a consensus, at least for young children, that antimalarial treatment with iron was good and that there was no complication with oral iron. I think the situation of parenteral iron is different.

Dr Yip: I do not think anybody is discussing parenteral iron as an option right now.

Dr Loudon: What was interesting to me, when I started working on the historical investigation of maternal mortality, was that certain obstetricians who were working in the 1930s said that maternal mortality was caused by anemia. They said that women used to come into the hospital and they bled to death. Nevertheless, this did not ring true. First, if iron deficiency anemia was more common in the 1930s and 1920s than it is now, we should have seen a fall in deaths from hemorrhage and we did not. Second, if iron deficiency anemia was an important factor causing maternal mortality, it should have been much more common in the deprived poor in industrial slums, where it was known that iron deficiency anemia was more common than in the professional classes. However, it was not; it was the same. In fact, sometimes it was higher in the upper classes. Third, during the Great Depression of the 1930s, when it was established that there was much anemia, it seemed to me that we should have seen a rise in deaths from hemorrhage but we did not.

Although a very crude and indirect way of looking at it, if you plot the deaths from hemorrhage, the graph remains level throughout the second half of the 19th century up until ergometrine was introduced. Once ergometrine was available, death from hemorrhage started to fall. When blood transfusion became widely available to the public, which was during World War II, hemorrhage-related deaths also fell. There was a further significant fall when the chief medical officer of health at the Ministry of Health in the beginning of the postwar period introduced a rule to the flying squads sent out for cases of hemorrhages. This rule was that
no woman should be moved to a hospital without having had a drip put up. Three elementary and clinical factors—ergometrine, blood transfusion, and the rule for flying squads—suggest that iron deficiency anemia does not seem to come into the historical picture for hemorrhage-related maternal mortality on a crude basis.

I would not for a moment think that it had been anything but a good idea to introduce, in the late 1930s, the routine administration of iron for women. However, I do not think that anemia was a major factor in maternal mortality in Britain in the period before and immediately after World War II. It makes me wonder whether iron deficiency anemia is likely to be a major factor in developing countries.

Dr Rush: A comment on the ethics committee problem. I sat on the committee that wrote the 1993 Institute of Medicine report. We did not recommend routine iron supplementation in pregnancy in the United States. There is thus some support for not obligating iron supplements during pregnancy. The Hemminki trial was of selective compared with routine iron use [Murray MJ, Murray AB, Murray MB, et al. The adverse effect of iron repletion on the course of certain infections. Br Med J 1978; 2:1113–5; Menendez C, Kahigwa E, Hirt R, et al. Randomized placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. Lancet 1997;350:844–9; Hemminki E, Uski A, Koponen P, et al. Iron supplementation during pregnancy—experiences of a randomized trial relying on health services personnel. Control Clin Trials 1989;10:290–8]; there were no placebos. Clinicians were free to treat in whatever way they chose. That was a very powerful trial and it is almost surely a model for all future trials. A placebo-controlled trial is unlikely. Although the association between high hemoglobin concentration and adverse pregnancy outcome is probably best explained by inadequate plasma volume expansion, this has not been directly demonstrated. A third trimester hemoglobin of 130 or 140 g/L can be induced by oral iron supplements. This level is associated with adverse outcomes for both mother and fetus. These issues need careful and intensive further study.

Finally, and most importantly, we are conflating 2 issues. One concerns whether we intensively address severe anemia. The other is whether we continue with routine supplementation for all women. These issues are separate and, given sufficient resources, we could pursue both programs. Clearly, women with severe anemia are far more liable to many hazards during pregnancy than those with mild or moderate anemia; indeed, it remains unproven that there is any additional risk for those with mild or moderate anemia. Routine, universal, unmonitored supplementation with oral iron is unlikely to be of much benefit to the severely anemic woman. The data from Malawi presented this morning confirm that severe anemia is typically not due to dietary iron deficiency alone [van den Broek EN, Letsky EA. Etiology of anemia in pregnancy in south Malawi. Am J Clin Nutr 2000;72(suppl):247S–56S]. Severe anemia has multiple causes much more often than does moderate or mild anemia.

Dr Yip: Assume that you have a normal hemoglobin distribution for women in the second trimester of pregnancy under normal healthy conditions. Regarding the high-end hemoglobin issue, let us assume the population mean hemoglobin concentration is \( \approx 140 \) g/L. A woman who is in the so-called normal healthy population with a hemoglobin concentration in the higher tail-end is, to me, at no risk. A woman who has a normal hemoglobin concentration when she is perfectly healthy but because of some condition (eg, pulmonary emphysema) has her hemoglobin shift from 120 to 140 g/L is at risk. This is because she has some primary disease condition that puts her in a different position—her increased value of 140 g/L is very different from that of someone who normally has a hemoglobin of 140 g/L. This works at both ends of the distribution.

Dr Rush: I believe that this is a hypothesis and only ask that we test it.

Dr Martorell: I want to go back to the question of terminal mortality risk from hemorrhage, because one often reads about the interaction between anemia and hemorrhage. In terms of moderate anemia, the assumption is that it could be related to mortality in the face of hemorrhage. Could you comment on that possible interaction and, also, whether there is a larger literature outside women and pregnancy just relating anemia to the risk of blood loss from X, Y, and Z in men and women?

Dr Yip: That has always been a common-sense assumption but I am not aware of prospective studies on women with various degrees of anemia and the incidence of postpartum hemorrhage or survival after that. Some studies hinted at a relation but none has clearly established an association. Common sense, for example, will keep surgeons from operating on patients with a hemoglobin concentration <80 or 90 g/L because they know the postoperative or intraoperative mortality will be higher.

Mr Alnwick: There was a multicenter trial in the United States with 2000 adult male and female patients, all of whom elected not to have a blood transfusion after surgery for all causes. There was a remarkable linear association between hemoglobin concentration and risk of surgical mortality and morbidity 30 d after surgery.

Dr Fleming: The study Mr Alnwick refers to showed an increase of mortality when the hemoglobin was <80 g/L and the blood loss was >500 mL without transfusion.

Dr van den Broek: Most women in developing countries die of postpartum hemorrhage and there is some evidence in the literature that the uterus contracts less well if the woman is anemic [Goepel E, Ulmer HU, Neth RD. Premature labor contractions and the value of serum ferritin during pregnancy. Gynecol Obstet Invest 1988;26:265–73; Ulmer HU, Goepel E. Anemia, ferritin and preterm labor. J Perinat Med 1988;16:459–65]. This needs further research and would be a more direct link because not everyone goes to surgery.