Pregnancy and anemia

Relation between maternal anemia and iron deficiency

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.

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. 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.

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.
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 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.

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. 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.

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. Additionally, the positive association observed in several epidemiologic studies does not establish a causal relation without the support of a plausible biological mechanism. 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?

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). 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?

Because of substantial normal variations in hemoglobin distribution across age, between sexes and races, and at different stages of pregnancy, the
A cutoff for low or high hemoglobin concentrations should be specific to sex and life cycle.

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.

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.

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.

It is 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). It is possible that a common factor can cause both anemia and poor birth outcomes.

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.
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. 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.

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, 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-g/L 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.

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. 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.

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 hemoconcentration. Hypertension, hypovolemia, and poor placenta perfusion are all part of the physiologic disturbances of preeclampsia. 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. 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.

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.

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.

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. 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. 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. 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. 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. 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.