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ARTICLE

Anemia and pregnancy: A link to maternal chronic diseases

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ABSTRACT

Anemia is a global public health problem. It has serious short- and long-term consequences during pregnancy and beyond. The anemic condition is often worsened by the presence of other chronic diseases such as malaria, tuberculosis, HIV, and diabetes. Untreated anemia also leads to increased morbidity and mortality from these chronic conditions as well. It is surprising that despite these chronic conditions (such as malaria, tuberculosis, and HIV) often being preventable, they still pose a real threat to public health. This article aims to review the current understanding of the pathophysiology, risks, prevention, and treatment of anemia in the light of these chronic conditions.

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1. Introduction

The worldwide pandemic of anemia in pregnancy is not unlike those of tuberculosis or HIV infection in that the specter of the problem looms so large on the care-givers' horizon that often it is hard to see. At the same time, the effect of the condition is so insidious that the individual patient may not feel it until the disease has progressed to a most serious state. Anemia can occur at any age and affect either gender, although it is more prevalent in pregnant women and young children [1]. It not only leads to poor outcomes in pregnancy and reduced work productivity among adults, but also contributes to 20% of deaths among pregnant women. In children, it results in increased risk of morbidity as well as impaired physical and cognitive development [2].

The data regarding the prevalence of anemia are shocking, especially in low-resource regions. The World Health Organization (WHO) estimates that two billion people—over 30% of the world's population—are anemic, although prevalence rates are variable because of differences in socioeconomic conditions, lifestyles, food habits, and rates of communicable and noncommunicable diseases [2]. Nearly half of all pregnant women suffer from anemia: 52% in low-resource countries and 23% in high-resource regions [3]. In the former, every second pregnant woman and about 40% of preschool children are anemic [2].

Iron deficiency is the most prevalent cause of anemia [4], but only rarely does iron deficiency exist by itself. Individuals who are deficient in iron are also deficient in other important micronutrients, although this important correlation is often overlooked by the medical profession and almost always unthought-of by the public at large.

In low-resource nations, iron deficiency is exacerbated by chronic infection with hookworm, schistosomiasis, tuberculosis, HIV, and malaria [2]. Of these, HIV, tuberculosis, and malaria (especially *Plasmodium falciparum* infection) represent leading contributory factors for anemia [5]. In contrast, in high-resource countries, the important contributory factors for anemia are chronic noncommunicable diseases such as inflammatory bowel disease (Crohn's/ulcerative colitis), malignancies (lymphoma, lung or breast carcinoma, aplastic anemia), and malnutrition (anorexia and obesity).

In either case, chronic conditions worsen anemia, while anemia negatively affects the progress of such longstanding conditions. The vicious cycle that exists between the chronic condition and anemia is the subject of this article.

2. Etiology and pathophysiology of anemia related to nutritional deficiency

2.1. Nutritional iron deficiency and the role of other micronutrients

Iron deficiency anemia (IDA) is the most common cause of nutritional anemia. It is the only nutrient deficiency that is significantly prevalent in low-resource countries [2]. In some instances, poor absorption of iron is aggravated by dietary contents. For example, diets rich in phytates and phenolic compounds prevent absorption of iron, thereby contributing to the anemic condition [6–9]. This phenomenon may at least partially explain the prevalence of anemia in parts of the world with dietary predilections to foods containing large quantities of these compounds.

Nutritional iron deficiency rarely occurs by itself; rather, it occurs in the presence of other nutritional deficiencies, although this fact is frequently overlooked. For example, deficiency of micronutrients such as folic acid, vitamins A, B12, riboflavin, and copper increase the risk of anemia because these micronutrients play important roles in hemopoiesis [9]. Unfortunately, most such deficiencies escape detection because they are not thought about. Even if they are, practical tests are either unavailable in most parts of the world or are prohibitively expensive [3].

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2.2. Subclinical iron deficiency

Figure 1 shows that iron stores are depleted over time; clinical features of anemia appear when stores are exhausted. As such, severe IDA represents the proverbial tip of the iceberg, related to but removed from cases of subclinical iron deficiency [10]. Identifying individuals within the larger community of those with subclinical disease and taking appropriate measures to prevent progression to IDA is the challenge confronting physicians, although several biochemical indicators (estimation of serum ferritin, transferrin saturation, transferrin receptor, and erythrocyte protoporphyrin) are helpful when available [8]. Nutritional deficiencies are not gender specific, and the husband and children of the anemic mother are likely to be in a similar nutritional state [11].

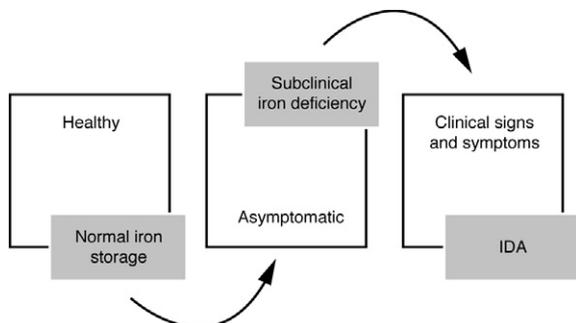


Fig. 1. Gradual depletion of body iron store and development of iron deficiency anemia (IDA).

3. Chronic infections and disorders as causes of anemia

3.1. Role of hepcidin

The exact mechanism by which anemia is caused in chronic inflammatory conditions is unknown. A common factor may be the contribution of hepcidin, a polypeptide hormone. Chronic inflammatory conditions lead to release of cytokines from the reticuloendothelial system as a part of cell-mediated immunity. In response to these cytokines, mainly interleukin 6 (IL-6) [12,13], the liver produces increased amounts of hepcidin, which in turn prevents release of iron from its stores. The process is mediated by blocking iron channels (such as ferroportin). Inflammatory cytokines also appear to influence other important aspects of iron metabolism, such as decreasing ferroportin expression, and possibly directly suppressing erythropoiesis by decreasing the ability of the bone marrow to respond to erythropoietin [14].

The chronic conditions causing anemia are summarized in Table 1.

Table 1

Chronic conditions/diseases associated with anemia

Infections	Malaria, HIV, tuberculosis, osteomyelitis, bacterial endocarditis, pulmonary abscess
Parasitic infestations	Hookworm, ascaris, schistosomiasis
Chronic noninfectious diseases	Diabetes, rheumatoid arthritis, Systemic Lupus Erythematosus, Crohn's disease, ulcerative colitis, chronic liver disease, cirrhosis, hemoglobinopathies
Malignancy	Carcinoma, sarcoma, lymphoma, myeloma

3.2. Malaria

Malaria is discussed separately by Christensen and colleagues in this Supplement [15].

3.3. HIV

Anemia is the most frequent hematologic abnormality associated with HIV infection [16]. It occurs in approximately 30% of patients

with asymptomatic infection and in as many as 75% to 80% of those with AIDS [17]. In pregnancy, HIV infection is associated with lower levels of serum folate and serum ferritin [18].

HIV infection can cause anemia (Fig. 2) through the changes in

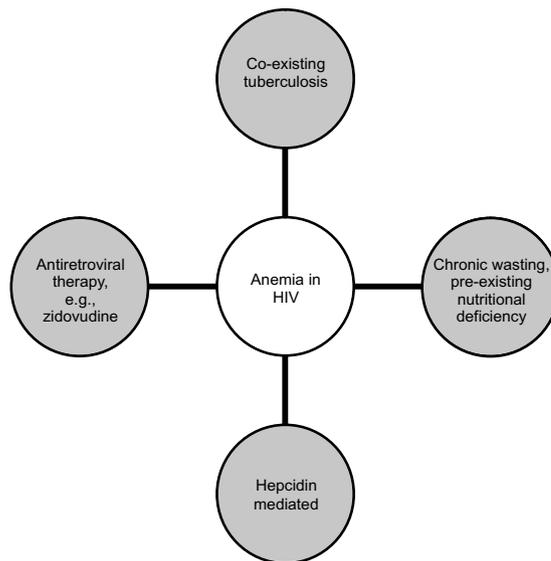


Fig. 2. Causes of anemia in HIV.

cytokine production, altered erythropoietin (EPO) response to bone marrow, use of antiretroviral drugs (especially zidovudine) [16], and interaction with other coexisting chronic infections such as tuberculosis [19,20].

3.4. Tuberculosis

Anemia is a common complication of pulmonary tuberculosis with a prevalence that ranges from 16% to 76% [21]. No studies have shown that pregnant women are specifically prone to develop tuberculosis, and the risk factors are similar to those of nonpregnant women [22]. Although the exact cause of anemia in tuberculosis is not known, it is thought to be due to cytokine mediated response of chronic infection (described above) [21], blood loss (as in hemoptysis in pulmonary tuberculosis), and bone marrow involvement [23] with tubercular granulomata in disseminated tuberculosis (Fig. 3). Nutritional deficiency is

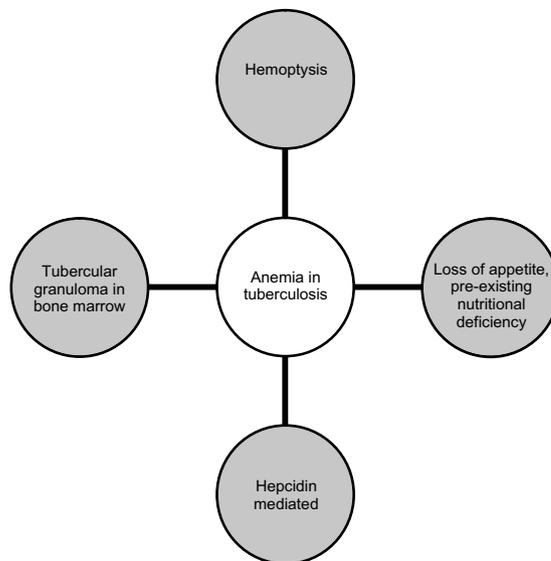


Fig. 3. Causes of anemia in tuberculosis.

common, as is loss of appetite, fever, or malabsorption (as in intestinal tuberculosis) [21].

3.5. Co-infection of HIV and tuberculosis

Tuberculosis infection is commonly present in patients with HIV owing to immune suppression. Patients with HIV are 37 times more likely to develop tuberculosis compared with the HIV-negative population; patients living with HIV represent over 10% of annual tuberculosis cases [24]. HIV and tuberculosis may coexist and aggravate anemia, thereby increasing pregnancy complications and maternal and infantile morbidity and mortality [25].

3.6. Diabetes

Anemia occurs in diabetes (Fig. 4) when the kidney is affected in the disease process. It can appear in the early stage of renal disease as a key indicator of early impairment of kidney function. Approximately one-third of people with diabetes develop kidney damage, and a significant proportion of this group progresses to end-stage renal disease [26]. Diabetes is somewhat unique because of its importance in both low- and high-resource regions of the world [27], where it has clearly been linked to the explosive epidemic of obesity witnessed in the past two decades.

The pathophysiologic mechanism of anemia in diabetes is thought to be mediated through a combination of dietary iron

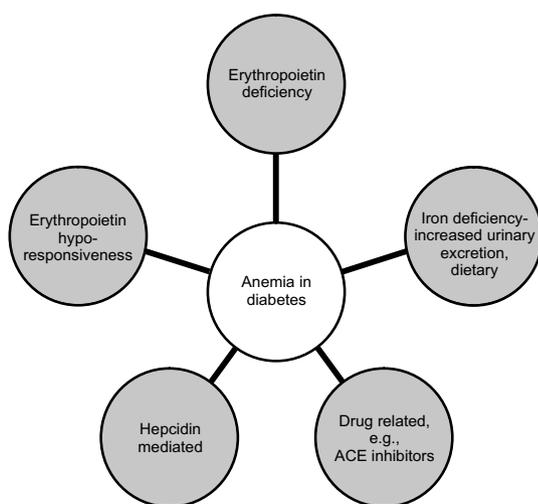


Fig. 4. Causes of anemia in diabetes.

deficiency, functional iron deficiency due to IL-6 and hepcidin activities, erythropoietin deficiency/hypo-responsiveness, and the action of ACE inhibitor and angiotensin receptor antagonists [28].

4. Risks to pregnant women and children: Short term

The short-term risks to women are summarized in Table 2. The exact pathophysiologic mechanisms for these complications are unknown. However, the propensity to infections is thought to be caused by altered cellular immunity due to iron deficiency [29,30]. Postpartum hemorrhage may be due to uterine atony as a result of impairment of uterine muscle contraction capabilities [31,32]. Cardiac failure/angina may result from increased cardiac output secondary to a hyperdynamic circulation to meet increased demands of hypoxia at the tissue level [33,34]. Children are affected by the increased perinatal morbidity and mortality that result from complications of preterm labor and prematurity [35,36].

Table 2
Short-term risks of anemia

Mother	
Antepartum	Prone to infections, preterm labor, left ventricular failure
Intrapartum	Heart failure, postpartum hemorrhage, shock
Postpartum	Heart failure, puerperal sepsis, uterine sub-involution, increased cesarean delivery morbidity
Fetus/child	
	Increased stillbirth and morbidity and mortality due to intrauterine growth restriction, prematurity, sepsis

5. Risks to pregnant women and children: Long term

The long-term risks of anemia (Table 3) are considerable and are described as follows.

5.1. Maternal

Anemia leads to debilitating physical (tiredness, lethargy, reduced exercise tolerance, dyspnea, dizziness, anginal pain, and palpitation) and mental (impaired cognitive function) symptoms, both of which negatively affect quality of life [3].

In terms of the effect of anemia on HIV, some studies [37,38] strongly suggest that adverse pregnancy events (such as low birth weight, stillbirth, preterm birth, and intrauterine growth restriction) are worsened in the presence of anemia. Moreover, mother-to-child transmission (MTCT) of HIV may be increased [38]. HIV infection in pregnancy also increases anemia-related maternal deaths [39]. Anemic condition, in turn, can result in HIV disease progression [40,41].

Table 3
Long-term risks of anemia

Impaired quality of life	
Effects on chronic infections	Malaria: possible increased morbidity and mortality HIV: accelerated disease progression and mortality, increased mother-to-child transmission Tuberculosis: increased morbidity
Effects on chronic disease	Diabetes: increased mortality, heart failure, worsening nephropathy, neuropathy, foot ulcer
Economic impact	
Effects on children born to anemic women	Cognitive impairment, poor growth and development, possible adult hypertension

There is limited evidence to suggest that presence of anemia accelerates tuberculosis progression or worsens its prognosis (maternal or fetal). Despite this, it is easy to presume that anemia and other nutritional deficiencies increase maternal morbidity because of their effects on the immune system.

Morbidity and mortality in diabetes are aggravated by anemia in the following manner [28]. Renal disease progresses as a result of tissue hypoxia and reduced renal blood supply; the same may be said for peripheral neuropathies, ocular retinopathy, and foot ulcers [42]. In diabetes with renal disease, anemia is considered to be an independent and modifiable risk factor for worsening hypertension, left ventricular hypertrophy, heart failure, and cardiovascular mortality [43,44].

5.2. Neonates and children

Neonates of anemic mothers are born with suboptimal iron stores and are at high risk of developing IDA [45]. Good

evidence suggests that iron deficiency causes poor cognitive, motor, neurophysiological, and socio-emotional development of children [46]. Studies in animals have shown the importance of iron in the function of neurotransmitters and overall function of the brain [47].

6. Assessment of anemia: New technology and new possibility

It is well accepted that early detection and effective management of anemia in pregnancy can substantially reduce maternal mortality and improve perinatal outcomes. According to the recommendations of the leading obstetric and gynecology societies, all pregnant women should be offered screening for anemia. However, this is easier said than done, primarily because of the technology involved and its cost. Many of the classic methods to assess iron or serum ferritin levels involved venipuncture and subsequent laboratory analysis; recently, new noninvasive technologies have been introduced and allow massive screening opportunities in low-resource countries [48–50]. Occlusion red/near-infrared spectroscopy technology is a general platform for noninvasive detection of blood analytes. At the core of this technology is the generation of a new biophysical signal, resulting from temporarily occluding the blood flow to the measurement site. The measurement is performed by using an annular, multi-wavelength probe with pneumatically operated cuffs, with which an over-systolic pressure is produced at the finger base. This new biophysical signal creates the sensitivity and specificity required for measuring hemoglobin. It is also capable of measuring oxygen saturation even in cases of weak peripheral pulsation, when standard pulse oximeters fail. These noninvasive readings for hemoglobin and hematocrit are accurate and measure with an acceptable relative absolute difference (RAD) when compared with accepted measurement systems (complete blood count).

7. Prevention and treatment of anemia in the presence of chronic maternal infections: Controversies

Although iron supplementation is the only specific treatment for iron deficiency, uncertainties exist regarding iron supplementation in chronic infections such as malaria, HIV, and tuberculosis, because iron deficiency in such cases is often “functional,” i.e. relative iron deficiency in blood as a result of excess storage of iron as ferritin, as mentioned above.

There are also some concerns on routine iron supplementation in endemic areas [51,52], because functional iron deficiency is thought to be protective against disease progression. Moreover, iron is thought to have a pro-oxidant role, which may enhance disease progression [53]. However, robust evidence is lacking in support of these hypotheses [54].

The current literature reveals the following in terms of the use of micronutrient supplementation in chronic infections.

7.1. HIV

A Cochrane review [55] concluded that there is a lack of evidence to suggest the best intervention to treat anemia in HIV. However, they found some evidence of benefit using human recombinant erythropoietin in treatment of anemia in such cases. Awaiting further evidence, WHO has recommended daily iron and folic acid supplementation (400 µg of folate and 60 mg of iron) in HIV prevalent areas [54]; treatment of anemia requires twice this dose on a daily basis. WHO also recommends routine micronutrient intakes at the RDA level for HIV infected women during pregnancy and lactation. In resource-poor countries, where dietary inadequacy persists, supplementing with multivitamin preparations (B-complex vitamins, Vitamins C and E, and selenium) is preferable.

Highly active antiretroviral therapy (HAART) treatment avoiding zidovudine and treatment of associated tuberculosis (if present) are extremely important both to prevent and treat anemia in such cases.

7.2. Tuberculosis

Recent evidence supports treatment with iron supplements in mothers with tuberculosis [21]. In mild to moderate anemia, iron supplementation accelerates the normal resumption of hematopoiesis and increases iron saturation of transferrin. However, persistent improvement of anemia needs general control of tuberculosis by reducing inflammatory cytokine mediated response, improving appetite, reducing hemoptysis episodes, and intestinal absorption of iron (intestinal tuberculosis) [21,56].

8. Conclusions

Despite a better understanding of the etiology and pathogenesis of anemia, it still remains a public health challenge throughout the world. Anemia is often worsened by chronic communicable and noncommunicable diseases, the most important being malaria, HIV, tuberculosis, and diabetes. When anemia occurs in pregnancy it not only results in poor pregnancy outcome in the short term but, in the long term, it also leads to worsening of these chronic conditions, reduced work capacity, and an impaired cognitive development of the child. A joint social and political approach is necessary to control anemia in pregnancy, as it represents a life-threatening but preventable cause of maternal and childhood morbidity and mortality.

Conflict of interest statement

None of the authors has a financial disclosure or a conflict of interest.

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