



The Impact of Anemia on the Immune System during Pregnancy: A Review

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Abstract

Anemia is a prevalent condition during pregnancy, often leading to significant health consequences for both the mother and fetus. One of the major concerns associated with anemia in pregnant women is its impact on the immune system. Iron deficiency, the most common cause of anemia, can impair immune cell function, reduce the body's ability to respond to infections, and alter inflammatory responses. This review explores the effects of maternal anemia on immune function during pregnancy, highlighting the disruptions to innate and adaptive immunity and the mechanisms involved, such as altered cytokine production and immune cell dysregulation. The immune system undergoes considerable changes during pregnancy to balance maternal and fetal protection, and anemia can disrupt this delicate equilibrium. Anemia's impact on immune cells, particularly neutrophils, macrophages, and T lymphocytes, compromises the body's defense against infections. Moreover, anemia-associated inflammation can promote a pro-inflammatory state, contributing to pregnancy complications like preeclampsia, gestational diabetes, and preterm labor. These immune dysregulations may also affect fetal development, increasing the risk of neonatal infections or immune-related disorders.

Keywords: Anemia, Immune System, Pregnancy, Inflammation, Immunity

Introduction

Pregnancy represents a unique and dynamic physiological state in which the immune system adapts to protect both the mother and the developing fetus. These immune adaptations are crucial for maintaining a healthy pregnancy while ensuring the immune tolerance required to prevent maternal rejection of the fetus, which is genetically distinct. However, during pregnancy, maternal health is influenced by various factors, and one of the most common conditions that can affect both the immune system and overall pregnancy outcomes is anemia. Anemia is a condition characterized by insufficient red blood cells or hemoglobin, which compromises the oxygen-carrying capacity of the blood and can lead to several maternal and fetal complications¹. Anemia is particularly common during pregnancy due to the increased demand for iron, folate, and other essential nutrients needed for fetal development and maternal adaptation. The most prevalent type of anemia during pregnancy is iron-deficiency anemia, which occurs when there is an inadequate supply of iron to meet the increased demands of pregnancy. However, anemia can also be caused by deficiencies in folate, vitamin B12, or chronic diseases. As iron plays a critical role in cellular function, including the proper functioning of immune cells, anemia during pregnancy can significantly alter immune responses. The physiological changes in the immune

system during pregnancy, combined with the impact of anemia, may impair the body's ability to effectively fight infections and manage inflammation, potentially increasing the risk of complications³⁻⁴. The immune system undergoes significant changes during pregnancy to protect both the mother and fetus from infections, while maintaining tolerance to the fetus. These changes include a shift in the balance between the innate and adaptive immune responses. The maternal immune system becomes less aggressive against fetal antigens, and certain immune cells, such as regulatory T cells, become more prominent to prevent fetal rejection. However, these immune alterations also make the mother more susceptible to infections. Iron, a crucial element for immune cell function, plays a key role in modulating these immune adaptations. Therefore, iron deficiency due to anemia can disrupt immune regulation, compromising both the mother's and fetus's ability to mount effective immune responses⁵.

Iron deficiency, the primary cause of anemia in pregnancy, can affect a range of immune cells, including neutrophils, macrophages, and lymphocytes. Neutrophils, the first line of defense against bacterial infections, require adequate iron for proper function. Similarly, macrophages, which play a central role in phagocytosis and antigen presentation, may exhibit altered activity in the absence of sufficient iron, impairing the body's ability to respond to pathogens.

Moreover, anemia's effects on T cells—key players in adaptive immunity—can lead to impaired activation and response, which further heightens the risk of infection during pregnancy. In addition, the reduction in iron can affect the production of key immune mediators like cytokines, leading to an imbalance in the inflammatory response. This dysregulation may contribute to pregnancy complications such as preeclampsia, gestational diabetes, and preterm labor ⁶⁻⁷. In addition to the direct effects on maternal immune function, anemia-related changes in the immune system can also impact fetal development and health. The inflammatory responses triggered by maternal anemia can potentially disrupt placental function, leading to fetal growth restriction or low birth weight. Furthermore, maternal anemia and the associated immune dysregulation may alter fetal immune development, potentially making the newborn more susceptible to infections and immune disorders later in life. Thus, the relationship between maternal anemia, immune function, and pregnancy outcomes is complex and bidirectional, with maternal health influencing fetal development and vice versa ⁸⁻⁹. The clinical management of anemia during pregnancy is essential for maintaining maternal health and reducing the risk of complications. Iron supplementation is the primary treatment for iron-deficiency anemia, while folate and vitamin B12 supplementation are necessary in cases of nutritional deficiencies. In more severe cases of anemia, intravenous iron or blood transfusions may be required to restore adequate hemoglobin levels and improve oxygen delivery to tissues. Beyond simply addressing the anemia, it is crucial to manage its effects on immune function. Nutritional interventions, anti-inflammatory treatments, and appropriate prenatal care can help mitigate the adverse effects of anemia on both maternal and fetal immune health, ultimately improving pregnancy outcomes ¹⁰⁻¹¹.

Prevalence and Types of Anemia during Pregnancy

Anemia is a widespread and significant public health issue, particularly during pregnancy, where the physiological demands on a woman's body increase substantially. Globally, anemia affects approximately 38% of pregnant women, with rates varying depending on geographic region, socioeconomic status, and access to healthcare. The prevalence of anemia during pregnancy is especially high in low- and middle-income countries, where nutritional deficiencies, limited access to healthcare, and increased parasitic infections contribute to higher rates of anemia. In some regions, such as sub-Saharan Africa and South Asia, the prevalence can exceed 50%, representing a critical concern for maternal health and pregnancy outcomes ¹²⁻¹³. The most common form of anemia during pregnancy is iron-deficiency anemia (IDA), which accounts for around 90% of cases. Iron deficiency occurs due to the increased demands for iron during pregnancies, which are not always met by the mother's dietary intake or stored iron reserves. As pregnancy progresses, the blood volume expands by 30–50%, and iron requirements increase significantly, especially in the second and third trimesters. Without adequate iron,

hemoglobin production is reduced, leading to anemia. Iron-deficiency anemia is associated with several maternal complications, including fatigue, impaired immune function, and a higher risk of infections. It also increases the likelihood of preterm birth, low birth weight, and delayed fetal development due to insufficient oxygen supply ¹⁴.

In addition to iron-deficiency anemia, other types of anemia can occur during pregnancy, though they are less common. Folate-deficiency anemia is another significant cause of anemia during pregnancy, as folate is essential for DNA synthesis and cell division. Folate is crucial in supporting fetal growth and development, and a deficiency can lead to megaloblastic anemia, characterized by the presence of large, immature red blood cells. Folate deficiency also increases the risk of neural tube defects in the fetus. Similarly, vitamin B12 deficiency anemia can occur when maternal B12 levels are insufficient, typically due to poor dietary intake or malabsorption conditions. Vitamin B12 plays an essential role in red blood cell production and neurological function, and its deficiency can result in megaloblastic anemia and neurological complications for both the mother and child ¹⁵⁻¹⁶. Anemia can also arise from chronic disease, such as chronic kidney disease or inflammatory conditions like autoimmune disorders. This type of anemia, known as anemia of chronic disease (ACD), is less prevalent during pregnancy but can complicate existing medical conditions. ACD is typically characterized by low iron availability due to chronic inflammation or infection. In such cases, the body produces elevated levels of inflammatory cytokines, which reduce iron mobilization and impair the production of red blood cells. Lastly, hemolytic anemia can occur due to inherited blood disorders such as sickle cell disease or thalassemia, conditions that affect the red blood cells' structure and function, leading to premature destruction of these cells and, consequently, anemia ¹⁷. Each type of anemia during pregnancy has distinct pathophysiological mechanisms and treatment approaches. Iron-deficiency anemia is most commonly addressed with iron supplementation, while folate and vitamin B12 deficiencies are treated with appropriate vitamin supplementation. For anemia of chronic disease or hemolytic anemia, the management often focuses on treating the underlying condition, and in some cases, blood transfusions may be necessary. Identifying the type of anemia is crucial for determining the most effective treatment and preventing complications related to maternal and fetal health ¹⁸.

Impact of Anemia on Immune Cell Function

Anemia during pregnancy has a profound impact on the immune system, primarily by altering the function and activity of key immune cells. Iron, a vital nutrient, plays an essential role in the proper functioning of various immune cells, including neutrophils, macrophages, and T lymphocytes. A deficiency in iron, as seen in iron-deficiency anemia (IDA), can disrupt the normal immune response, leading to an increased susceptibility to infections and impaired inflammatory responses. These immune alterations can exacerbate pregnancy

complications and negatively affect both maternal and fetal health ¹⁹. Neutrophils, which are the first responders to bacterial infections, rely heavily on iron for optimal function. Iron is required for the production of reactive oxygen species (ROS) by neutrophils, which are essential for killing invading pathogens. In iron-deficient states, neutrophil function is compromised, leading to a diminished ability to control bacterial infections. Furthermore, neutrophils in iron-deficient individuals exhibit decreased motility and phagocytic capacity, impairing the body's ability to clear infections effectively. This dysfunction may contribute to the higher incidence of infections observed in anemic pregnant women, putting both the mother and fetus at risk of adverse outcomes such as preterm birth and low birth weight ²⁰. Macrophages, which play a central role in immune defense by engulfing and digesting pathogens, also require iron for their proper functioning. Iron deficiency impairs macrophage phagocytosis and antigen presentation, which are vital for initiating adaptive immune responses. Additionally, iron deficiency can alter the cytokine profile produced by macrophages, leading to an imbalance in the inflammatory response. Under normal conditions, macrophages help regulate inflammation and repair tissues, but in anemia, the altered cytokine secretion may shift the immune response toward a pro-inflammatory state. This chronic low-grade inflammation can contribute to complications such as preeclampsia, gestational diabetes, and premature labor, all of which have been associated with maternal anemia ²¹.

T lymphocytes, which are integral to adaptive immunity, are also affected by anemia. Iron plays a critical role in the proliferation and activation of T cells, which are responsible for targeting and eliminating infected or abnormal cells. In iron-deficient states, the activation and differentiation of T cells are impaired, leading to reduced immune surveillance and a diminished capacity to mount an effective immune response. This can contribute to a weakened defense against infections, as well as a reduced ability to control inflammatory processes during pregnancy. Moreover, iron deficiency has been shown to alter the balance between pro-inflammatory Th1 and anti-inflammatory Th2 immune responses, potentially exacerbating inflammatory complications and affecting pregnancy outcomes ²². Iron deficiency also influences regulatory T cells (Tregs), which are crucial for maintaining immune tolerance during pregnancy. Tregs help prevent maternal immune rejection of the fetus by suppressing immune responses that could harm the developing baby. In anemic conditions, the dysregulation of Tregs may impair the immune tolerance required for a successful pregnancy, increasing the risk of fetal rejection or pregnancy-related complications. Furthermore, altered Treg function due to iron deficiency may contribute to an imbalance in immune responses, promoting autoimmune-like phenomena or exacerbating existing inflammatory conditions ²³.

Anemia, Inflammation, and Pregnancy Outcomes

Anemia during pregnancy, particularly iron deficiency, is closely linked to both systemic inflammation and adverse pregnancy outcomes. Iron plays a pivotal role in regulating the immune system and inflammation, which are key factors in maintaining a healthy pregnancy. When anemia occurs, the body's immune response can become dysregulated, often leading to a heightened inflammatory state. This chronic low-grade inflammation, in turn, can significantly impact pregnancy outcomes, contributing to complications such as preeclampsia, gestational diabetes, preterm labor, and fetal growth restriction. Understanding the relationship between anemia, inflammation, and pregnancy outcomes is crucial for improving maternal and fetal health and preventing long-term complications ²⁴. Iron deficiency anemia (IDA) is often associated with an inflammatory response characterized by increased levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and C-reactive protein (CRP). These molecules are typically elevated in response to stress or infection but also serve as markers of chronic inflammation. In pregnancy, the presence of anemia exacerbates this inflammatory response, leading to an imbalance in immune function. Chronic inflammation resulting from anemia can lead to endothelial dysfunction, impaired placental blood flow, and changes in the maternal immune system that are detrimental to both maternal and fetal health. For instance, the pro-inflammatory state associated with anemia can lead to the development of preeclampsia, a condition characterized by high blood pressure and damage to organs such as the kidneys and liver. The inflammatory cytokines that are elevated in anemia also contribute to placental insufficiency, which affects fetal development and may result in preterm birth or low birth weight ²⁵.

The effects of anemia-induced inflammation extend beyond maternal health and have serious implications for fetal well-being. Chronic inflammation due to anemia can affect placental function, leading to reduced oxygen and nutrient delivery to the fetus. This can result in fetal growth restriction, as the fetus may not receive sufficient resources for optimal development. Additionally, the increased inflammatory markers can affect the fetal immune system, potentially making the newborn more susceptible to infections and immune disorders later in life. Furthermore, maternal anemia, by impairing the immune system's ability to respond effectively to infections, increases the risk of maternal and fetal morbidity. Women with anemia during pregnancy are more vulnerable to infections such as urinary tract infections, respiratory infections, and other bacterial and viral conditions, which further exacerbate the inflammatory response and increase the risk of pregnancy complications ²⁶. Inflammation and anemia are also linked to a higher risk of preterm labor, a condition that occurs when labor starts before 37 weeks of gestation. The inflammatory cytokines elevated in anemia, such as IL-6 and tumor necrosis factor-alpha (TNF- α), have been implicated in triggering the onset of labor. These cytokines play a critical role in

regulating the immune system and inflammatory responses during pregnancy and their overproduction can contribute to the early initiation of labor. Moreover, the chronic inflammatory state associated with anemia may lead to uterine contractions and cervical changes, which can result in preterm delivery. This increases the likelihood of preterm birth, which is a major contributor to neonatal morbidity and mortality. Newborns born prematurely may face challenges such as respiratory distress, low birth weight, and developmental delays ²⁷. The management of anemia during pregnancy is essential not only for improving maternal health but also for mitigating its impact on inflammation and pregnancy outcomes. Iron supplementation is the primary treatment for iron-deficiency anemia and can significantly reduce the inflammatory markers associated with the condition. By restoring iron levels and improving red blood cell production, iron supplementation helps reduce systemic inflammation and improve immune function. In cases of more severe anemia, intravenous iron or blood transfusions may be necessary to restore hemoglobin levels and oxygen delivery to the tissues, reducing the associated inflammatory response. Additionally, addressing other factors such as folate and vitamin B12 deficiencies, as well as managing chronic conditions like infections or autoimmune disorders, can help reduce inflammation and improve overall pregnancy outcomes ²⁸.

Management and Therapeutic Approaches

Effective management and treatment of anemia during pregnancy are critical to improving maternal and fetal outcomes, particularly in preventing the associated risks of inflammation and pregnancy complications. The primary goal of therapy is to restore normal hemoglobin levels, correct nutritional deficiencies, and reduce inflammation. Treatment strategies vary depending on the type and severity of anemia, and they may include dietary interventions, iron supplementation, addressing underlying conditions, and in more severe cases, blood transfusions. A multifaceted approach is essential to mitigate the adverse effects of anemia and its impact on the immune system, as well as to enhance the overall health of both the mother and the developing fetus ²⁹. Iron supplementation is the cornerstone of treatment for iron-deficiency anemia (IDA) during pregnancy. Oral iron supplements are commonly prescribed, with ferrous sulfate being the most widely used form due to its cost-effectiveness and efficacy. However, some women experience gastrointestinal side effects, such as constipation and nausea, which can reduce compliance with therapy. In such cases, alternative formulations like ferrous gluconate or liquid iron supplements may be recommended. The recommended dose for pregnant women with iron-deficiency anemia is typically around 30–60 mg of elemental iron per day, depending on the severity of anemia. For women with poor tolerance to oral iron or severe anemia, intravenous (IV) iron infusion is an option. IV iron offers rapid correction of iron deficiency and is particularly beneficial for women with gastrointestinal malabsorption issues or those who require immediate correction of their hemoglobin levels ³⁰⁻³¹.

In addition to iron supplementation, folic acid and vitamin B12 supplementation may be indicated in cases of anemia resulting from folate or vitamin B12 deficiency. Folate deficiency is particularly prevalent in pregnant women and is associated with megaloblastic anemia, which can lead to maternal fatigue and an increased risk of neural tube defects in the fetus. The recommended daily dose of folic acid during pregnancy is 400-800 mcg, with higher doses sometimes used for women with known deficiencies or at higher risk of deficiencies. Vitamin B12 deficiency, though less common, also requires supplementation to restore normal hematologic function. Pregnant women are advised to consume at least 2.6 mcg of vitamin B12 daily, though higher doses may be required if a deficiency is detected ³²⁻³³. For women with anemia of chronic disease (ACD) or anemia associated with conditions such as chronic kidney disease, treatment focuses on managing the underlying disease. In ACD, iron supplementation may not be as effective due to impaired iron utilization, and in these cases, therapies targeting inflammation may be necessary. The use of erythropoiesis-stimulating agents (ESAs), such as erythropoietin, may be considered in severe cases of ACD to stimulate red blood cell production. Additionally, careful management of chronic diseases, such as treating infections or optimizing the management of autoimmune disorders, is crucial in reducing the inflammatory response and improving red blood cell production ³⁴.

In more severe cases of anemia, particularly in cases where hemoglobin levels are critically low, blood transfusions may be necessary. Blood transfusions are typically reserved for pregnant women who are symptomatic or at risk of cardiovascular instability due to anemia. They can rapidly restore hemoglobin levels, improve oxygen delivery to tissues, and alleviate symptoms of severe anemia such as dizziness, fatigue, and shortness of breath. However, blood transfusions come with potential risks, including the transmission of infections, alloimmunization, and transfusion reactions, so they are generally considered when other treatments have been insufficient or when anemia poses a significant threat to maternal health ³⁵. Monitoring and preventive measures play a key role in managing anemia during pregnancy. Regular screening for anemia should be part of routine prenatal care, with hemoglobin levels measured early in pregnancy and at least once during the second and third trimesters. Early detection allows for timely intervention, preventing the development of more severe anemia. Pregnant women at higher risk of anemia, such as those with inadequate dietary intake, multiple pregnancies, or a history of anemia, should be closely monitored and provided with additional counseling on nutrition and supplementation. Iron-rich foods, such as lean meats, legumes, spinach, and fortified cereals, should be emphasized as part of a balanced diet, alongside proper vitamin C intake, which enhances iron absorption. In addition, women should be educated about the signs and symptoms of anemia, such as fatigue, pallor, and shortness of breath, to ensure early recognition and intervention ³⁶.

Conclusion

Anemia during pregnancy is a common and significant health concern that can lead to a range of adverse maternal and fetal outcomes, including impaired immune function, preterm birth, fetal growth restriction, and increased susceptibility to infections. The impact of anemia on the immune system is particularly concerning, as it can trigger an inflammatory response that exacerbates pregnancy complications and disrupts normal fetal development. The close relationship between anemia and inflammation highlights the importance of early detection, proper management, and preventive strategies to mitigate its effects. Effective management of anemia during pregnancy primarily involves addressing the underlying causes, such as iron, folate, or vitamin B12 deficiencies, and treating conditions that contribute to anemia, including chronic diseases. Iron supplementation remains the cornerstone of treatment for iron-deficiency anemia, with intravenous iron or blood transfusions reserved for more severe cases. Monitoring for anemia, along with nutritional counseling and education on proper supplementation, is essential to ensure maternal and fetal well-being. Additionally, addressing other modifiable risk factors, such as poor diet or untreated infections, can further reduce the risk of anemia-related complications.

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