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A REVIEW ON ANEMIA DURING PREGNANCY WITH ITS COMPLICATIONS AND THERAPEUTIC INTERVENTIONS

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ABSTRACT
Anemia is one of the most frequent complications that is prevalent among pregnant women. Anemia is clinically manifested by decreased count of red blood cells and decreased level of serum hemoglobin. Anemia ultimately leads to poor oxygen carrying capacity of blood. According to World Health Organization's criteria, pregnant women whose haemoglobin levels less than 11.0 g/dl during first and third trimesters and less than 10.5 g/dl during the second trimester are said to be anaemic. Increase in plasma volume during pregnancy plays a significant role as the etiology for anaemia during pregnancy. Iron deficiency and folic acid deficiency anaemia are the common types of gestational anaemia. Moreover iron and folic acid requirements are peaked during pregnancy. In order to prevent or mitigate the complications of anaemia in pregnancy, iron and folic acid supplements are necessitated. Further folic acid is supportive in preventing neural tube defects in infants. The main objective of this review is to emphasise the causes and pathogenesis of different types of gestational anaemia with their respective therapeutic options to treat and mitigate. It also sheds light towards the maternal and foetal complications of anaemia in pregnancy.

KEYWORDS: Anemia, Pregnancy, Iron deficiency, Folic acid deficiency, Neural tube defects.

INTRODUCTION
Anemia is commonly classified as microcytic, normocytic, or macrocytic anemias. Iron deficiency anemia adds to 75% of all anemias in pregnancy. Oral iron supplementation is recommended for the treatment of iron deficiency anemia in pregnancy. Parenteral iron and erythropoietin can also be used in severe or refractory cases.[1]

The plasma volume starts to increase at about 6 weeks of pregnancy in a healthy woman.[2] This increase which is disproportionately greater than the corresponding changes on the red blood cell volume, accounts for fall in serum Hb concentration during pregnancy. As a result, there is a significant reduction in arteriovenous oxygen extraction at the heart and hike of the oxygen carrying capacity of the pregnant woman occurs, despite the downfall in the Hb level.

The increase in plasma volume is about 1,250 ml at term, a total increase of about 48% above the non pregnant state. This results in the initial rapid increment, followed by a slower increment after the 30th week of pregnancy. Several studies exemplify the positive correlation between the weight of the newborn and the increase in the plasma volume.[3,4,5,6,7]

It is noteworthy that the increase in plasma volume is an indication for normal growth of the fetus and one of the hallmarks of a successful pregnancy. As far as the red cell mass is concerned, it also increases although, in contrast to the plasma volume, it does so more slowly. The total increase is about 18% or 250 ml at term. After stimulation with iron supplements, however, the red cell mass may reach 400 ml—a total increase of about 30% compared with the non-pregnant state. Similar to the plasma volume, the increased red cell mass is linked to fetal growth, although probably to a lesser degree.[8]

Causes of anemia in pregnancy
Because of the normal physiologic changes occurring during pregnancy the hematocrit and certain other parameters, such as hemoglobin, reticulocytes, plasma ferritin, and unsaturated iron-binding capacity are vastly affected. Diagnosing true anemia, as well as determining the etiology of anemia during pregnancy is challenging. The most common types of anemias are iron-deficiency anemia and folate deficiency megaloblastic anemia. These anemias are more common in women who have insufficient diets and who are not receiving prenatal iron and folate supplements.[8]

Other infrequent etiologies of acquired anemia in pregnancy are aplastic anemia and hemolytic anemia. In addition, anemias such as thalassemia and sickle cell disease can have an influence on the health condition of the mother and fetus. The most common causes of true or absolute anemia are nutritional deficiencies. Frequently, these deficiencies are multiple, and the clinical presentation may be complicated by attendant infections, generally poor nutrition,or hereditary disorders such as hemoglobinopathies.[9,10] However, the fundamental sources of nutritional anemia embodies insufficient intake, inadequate absorption, increased losses, expanded requirements, and insufficient utilization of hemopoietic nutrients. Approximately 75% of all anemias diagnosed during pregnancy are due to iron deficiency. Significant shortage of haem leads to characteristic hypochromic, microcytic red blood cells on the peripheral blood smear. Other causes of hypochromic anemias, even rare, must be considered, including hemoglobinopathies, inflammatoryprocesses, chemical toxicity, malignancy, and pyridoxine-responsive anemia.

However the greater percentage of the remaining cases of anemia in pregnancy other than the iron-deficiency type consists of the megaloblastic anemia of pregnancy dueto folic acid deficiency and, to a lesser extent, to vitamin B12 deficiency.

Maternal effects of anemia

Obviously, severe anemia has adverse effects on the mother and the fetus. There is also evidence that less severe anemia is associated with poor pregnancy outcome. Major maternal complications directly related to anemia are not common in women with a hemoglobin level greater than 6 g/dL. However, Hb levels even lower may lead to notable morbidity in pregnant women, such as infections, increased hospital stays, and other general health problems.[10]

A lot of subjective and objective evidences may accompany this clinical state, to a variable degree. The most frequent ones are headache, fatigue, lethargy, paresthesia, and the clinical signs of tachycardia, tachypnea, pallor, glossitis, and cheilitis. In more severe cases, especially in pregnant women with hemoglobin levels less than 6 g/dl, significant life-threatening problems secondary to high-output congestive heart failure and decreased oxygenation of tissues, including heart muscle may be encountered. Such conditions are less common as a result of nutritional deficiency anemias, at least in developed nations or when the pregnant woman being supplied with iron supplements.

However, severe iron deficiency anemia or methemorragic anemia may be presented by complications of pregnancy, such as placenta previa or abruptio placenta, operative delivery and post partum bleeding.[11] These conditions left untreated by iron supplementation or blood transfusion leads to severe complications.

Effects on the fetus

When serum ferritin is used as an indicator of iron status, it was found that infants born to mothers who did not take iron supplements during pregnancy had reduced iron stores at birth.[12,13] Most authors agree that only severe anemia may have direct adverse effects on the fetus and neonate and that a mild to moderate maternal iron deficiency does not appear to cause a significant effect on fetal hemoglobin concentration.[14] There are several reports that correlate the anemia during pregnancy with premature delivery and low-birth weight infants, presenting a direct relationship between low birth weight and low maternal Hb level.[15,16,17]

In addition, they demonstrated an association between low maternal Hb levels and poor pregnancy outcomes such as prematurity, low birth weight, fetal death, and other medical abnormalities with increasing complication rates when there were lower maternal Hb concentrations.[18] Moreover, it is important to stress that low maternal Hb levels are often associated with other pathologic conditions, so it is difficult to be sure whether maternal anemia itself is responsible for increased mortality and morbidity rates. In other words, low Hb levels are often a secondary phenomenon caused by previous infections or chronic illnesses that in turn leads to severe complications during pregnancy that need not basically depend on the hematologic profile of the pregnant woman.

Recommended dosage of folic acid and iron supplements

Pregnant women should be prescribed with 1 adult tablet per day for 100 days. Each tablet contains 100 mg of elemental iron and 500 mcg of folic acid. These tablets should be provided to women after the first trimester of pregnancy.[19]

Iron-deficiency anemia in pregnancy

Iron metabolism

Iron is a crucial element in the metabolic processes involved in tissue oxygenation. A normal individual contains 3-5 grams of iron. A balanced diet could supply up to 15 mg of iron per day. The acidic environment helps iron absorption. Iron absorption takes place in the first and second parts of the small intestine. Iron absorption is therefore augmented by the concomitant administration of acidic compounds, such as ascorbic acid. Iron absorption is also upgraded in response to heightened needs. After absorption, protein-bound iron is transported into the bone marrow for incorporation in the production of red blood cells. Excess iron is stored as ferritin, a labile, and easily available provider of iron.[20]

Iron requirements during pregnancy

The high prevalence of iron deficiency undermines the need for iron supplementation in pregnancy. Iron supplementation is especially important because the demand for iron by the mother and the foetus increases during pregnancy. This heightened demand can be met with iron supplementation. During pregnancy the total maternal need for extra iron averages close to 800 mg (elemental iron), of which about 300 mg is for the foetus and the placenta and the rest is for maternal haemoglobin mass expansion. The placental and foetal requirement is mandatory and dietary intake will be diverted to this end even if the mother is iron-deficient. Approximately 200 mg more is eliminated via the gut, urine, and skin. This total amount of 1000 mg quite depletes the iron stores of most women, even in Western countries. Practically all of this iron is used during the latter half of pregnancy. Therefore, the iron requirement enhanced from a 0.8 mg/day in the first trimester to 6 to 7 mg/day in the second half of pregnancy.[21]

Overall, a pregnant woman needs about 2 to 4.8 mg of iron per day. The woman is obliged to consume 20 to 48 mg of dietary iron to absorb this quantity of iron daily. An average vegetarian diet will not provide more than 10 to 15 mg of iron per day. Thus, the amount of iron absorbed from diet, in combination with that mobile iron stores, is usually insufficient to meet the demands imposed by pregnancy. This is evident even though the absorption of iron from the gastrointestinal (GI) tract is slightly increased during pregnancy and menstrual iron loss ceases. Therefore, iron supplements during pregnancy are recommended globally even for non-anemic women.

The usual diet of a population strongly affects iron bioavailability; thus recommended intakes for iron depend on diet characteristics (Table 1).[22] In developing countries, where average meals may be poor in iron, iron supplementation may be considered in pre-pregnant woman and adolescent girls as well. Women might then enter pregnancy with adequate iron reserves.[23]

Causes of iron deficiency

Iron deficiency is caused due to depleted iron stores and occurs when iron absorption is unable keep pace over an extended period with the metabolic needs for iron to continue growth and to restore iron loss, which is primarily related to blood loss.[24]

The primary causes of iron deficiency include low intake of bio-available iron, increased iron requirements as a result of rapid growth, pregnancy, menstruation, and excess blood loss caused by pathologic infections by hook worms and whipworms causing gastrointestinal blood loss and impaired iron absorption.[25,26,27,28]

When iron stores are depleted and insufficient iron is available for erythropoiesis, hemoglobin synthesis in erythrocyte precursors become impaired and hematologic signs of iron deficiency anemia appear.[29]

Table 1: Recommended daily iron by estimated dietary iron bioavailability.

	Children (1-3 years)	Children (4-6 years)	Women (19-50 years)	Women pregnancy (second trimester)	Women during breastfeeding (0-3months lactation)	Men (19-50 years)
15%	3.9	4.2	19.6	>50.0	10.0	9.1
10%	5.8	6.3	29.4	>50.0	15.0	13.7
5%	11.6	12.6	58.8	>50.0	30.0	27.4

Numbers are mg per day

Recommended daily intake for iron depends on the bioavailability of the diet: diet rich in vitamin C and animal protein = 15%; diet rich in cereals, low in animals protein, but rich in vitamin C = 10%; diet poor in vitamin C and animal protein = 5%.

Iron deficiency (ID) is the most common nutritional deficiency and is a major cause of morbidity and mortality that is responsible for the majority of cases of anemia up to 20% of perinatal and ~10% of maternal mortalities in developing countries.[30]

The majority of all anemias diagnosed during pregnancy are characterized as iron deficiency anemias. It is estimated that about 80% of pregnant women at term who do not use iron supplementation have hemoglobin concentrations less than 11 g/dL.[31] The increased fetal need for iron as well as a number of other factors contribute to the iron-deficiency profile of the pregnant woman and the need for supplementation. The factors include impaired iron absorption during pregnancy, multiple gestations or subsequent gestations less than two years apart, adolescent pregnancy, and any associated chronic blood loss, as well as decreased reserve of total body iron before the pregnancy.

The most common clinical manifestations of iron-deficiency anemia are lethargy and fatigue, in fact they are also seen in normal pregnancy. Other symptoms are headache, paresthesia, burning sensation of the tongue, and pica, which is the ingestion of substances with no dietary value and appears in severe cases of anemia after the twentieth week of gestation. Glossitis, pallor and cheilitis are clinical manifestations of iron deficiency, whereas koilonychia and “spooning” nails are infrequent findings. In cases of severe anemia, retinal bleeding, conjunctivitis, tachypnea or tachycardia, and splenomegaly may be found. Nevertheless, these signs are rarely seen in developed countries because of the rarity Hb levels of 5 or 6 g/dL.

Folic acid deficiency anemia

Folic acid supplementation and pregnancy

Folate (vitamin B_9) is a vital nutrient that is necessary for DNA replication and as a substrate for a range of enzymatic reactions involved in amino acid synthesis and vitamin metabolism. Demands for folate increases during pregnancy because it is also required for growth and development of the foetus. Folate deficiency has been linked with abnormalities in both mothers (anemia, peripheral neuropathy) and foetuses (congenital abnormalities). Dietary folic acid supplements around the time of conception has long been recommended to mitigate the risk of neural tube defects (NTDs) in newborns.[32]

Folic acid in preventing neural tube defects

Dietary supplementation with folic acid at the time of conception has long been involved in reducing the risk of neural tube defects in the offspring.[33,34,35,36] Although such an intervention is effective, it targets only women planning a pregnancy or recently pregnant.[37] Additional measures to increase the intake of folic acid in the general population include multivitamin supplementation and fortification of grain-based products such as flour, cereal, and pasta.[38] Within months, these legislative amendments become mandatory and were associated with a significant increase in the concentrations of erythrocyte folate among women of childbearing age and a decrease in the incidence of infants born with NTDs.[39,40,41]

Table 2: Canadian recommendations for folic acid and multivitamin supplementation in pregnancy.[42]

Option	Population	Folic acid dose	Duration of supplementation
A	Patients with no personal health risks, planned pregnancy	Good diet of folate-rich foods; daily supplementation with folic acid 0.4-1.0 mg	At least 2 to 3 months before Conception and throughout pregnancy and the postpartum period (4-6 weeks) and as long as breastfeeding
B	Patients with health risk, family history of neural tube defect, high risk of ethnic group	Folate –rich foods, daily supplementation-on with 5mg folic acid Daily supplementation--on with folic acid 0.4-1.0mg	(1) Beginning at least 3 months before conception and continuing until 10 to 12 weeks postconception (2) From 12 weeks postconception and continuing throughout pregnancy and the postpartum period (4-6 weeks or as long as breastfeeding continues)
C	Patients with history of poor compliance with medications, additional lifestyle issues, variables diet, no consistent birth control, and possible teratogenic substance use	Folate-rich foods, daily supplementation with 5mg folic acid	Counsel about folic acid supplementation to prevent birth defects and additional health benefits

Adapted with permission from Cunningham Fetal

Folic acid and the prevention of anemia

Expanded blood volume resulting from an increase in both plasma and erythrocytes is a normal physiologic phenomenon of pregnancy. Although more plasma than RBCs is not unusually added to the maternal circulation, the increase in RBC volume is considerable, averaging about 450 mL.[43] Due to increase in plasma volume, hemoglobin concentration and hematocrit normally decrease slightly during pregnancy. However, although hemoglobin concentrations at term average 12.5 g/dL, approximately 5% of women are anemic, with hemoglobin concentrations below 11.0 g/dL.[44]

Table 3: Haemoglobin concentrations in 85 healthy women with proven iron tore's.

Haemoglobin (g/dL)	Nonpregnant	Midpregnancy	Late pregnancy
Mean	13.7	11.5	12.3
Less than 12.0	1%	72%	36%
Less than 11.0	None	29%	6%
Less than 10.0	None	4%	1%
Lowest	11.7	9.7	9.8

Adapted with permission from Cunningham F et al

Risks of high-dose folate supplementation

Although folic acid supplementation to supra physiologic levels has demonstrated many of the benefits to pregnant women and foetuses noted above, the potential risk of high-dose folate supplementation must also be scrutinised. First, folate supplementation will mask vitamin B_{12} deficiency (pernicious anemia) and caution must be taken with susceptible individuals to avoid missing this diagnosis. Also, concerns have been raised about the potentially untoward effects of un metabolized synthetic folic acid with regard to cancer, depression, and cognitive impairment.[45] With all these concerns, early data suggest supplementation with L-methylfolate rather than folic acid may mitigate these risks.[46]

Folic acid deficiency

Folic acid deficiency causes a megaloblastic type of anemia that is second in prevalence as a cause for nutritional deficiency anemia of pregnancy after iron deficiency anemia. Folates and especially their derivative formyl FH4 are essential for appropriate DNA synthesis and amino acid production. Insufficient amount of folic acid leads to the manifestations noted in megaloblastic anemia.[47]

Folic acid should be provided in the diet. Common sources are green vegetables, fruits (lemons, melons), and meats (liver, kidney). The absorption takes place in the proximal jejunum. The etiology of folic acid deficiency is multi factorial and decreased intake is associated with poor nutrition and impaired absorption as well as increased folic acid requirements seen in pregnancy due to increased needs for fetal growth and maternal RBC production. In addition to that, higher amount of circulating estrogen and progesterone during pregnancy seem to have an inhibitory effect on folate absorption. The signs of folic acid deficiency are those of general anemia together with rough skin and glossitis.

The erythrocyte precursors are morphologically bigger ("macrocytic"), and an abnormal nuclear–cytoplasmic appearance as well as normochromic and macrocytic findings are diagnostic criteria for megaloblastic anemia. MCH and MCHC are usually within normal range, whereas the large MCV aids in differentiation of this anemia from physiologic changes of pregnancy or iron-deficiency anemia. Neutropenia and thrombocytopenia are the results of abnormal maturation in granulocytes and thrombocytes. A low serum level (<3 g/L) may occur early in folic acid deficiency.

The daily requirement in a non pregnant state is at least 0.4 mg. In pregnancy or increased growth states, such as during infancy and adolescence, however, the requirements are increased to 0.8–1.0 mg.[48,49] It is possible that multiple gestations or short intervals between pregnancies increase folate requirements further. It has been reported that folate deficiency affects about 60 to 95% of untreated women at term. Half of the pregnant women with this type of anemia present before delivery with the remaining cases being detected only afterwards.

Most of the folic acid deficiencies during pregnancy occur in the third trimester. The fetus seems to have the ability to succor stable hemoglobin and folate levels even in cases of severe maternal folate deficiency anemia. It is evident that the fetus has the ability to remove folic acid from maternal circulation even its mother has deficit state. Thus, the infants in such situations are not anemic and remain unaffected. However, it has been found that megaloblastic anemia in pregnancy may be accompanied by smaller blood volume40 and may be related to fetal growth retardation in some cases.[50]

Other deficiency anemias in pregnancy

Hemic nutrients, trace elements, vitamins, and proteins are vital for the growth and maintenance of various physiological functions, especially for the hematologic system functions of the mother, fetus, and newborn. They are crucial in facilitating the metabolism of amino acids, carbohydrotes, and fat and are therefore involved in anemias. The increased nutritional requirements during pregnancy leads to inadequate dietary intake. Nutritional anemia is uncommon in developed countries, except for iron-deficiency or folic acid deficiency anemia.

However, anemia caused by deficiencies in a number of iron, folic acid, vitamins, and proteins may be an important problem in poor, underdeveloped countries. Except iron deficiency anemia, deficiencies in some other minerals may add to some rare variants of anemias. Severe phosphorus deficiency can cause hemolytic anemia because of adenosine triphosphate depletion in the red cells with subsequent osmotic fracture.

Moreover, severe copper deficiency has been characterized to iron supplementation.[51] Zinc deficiency has been noted in patients with sickle cell anemia and thalassemia. However, there is no evidence that this deficiency causes worsening of anemia.[52] Of the water-soluble vitamins, folic acid deficiency accounts for a large pregnancy which is megaloblastic in type. Except for folic acid, vitamin B12 deficiency is clinically important because of its role in the metabolism of folate through the production of active FH4. When serum B12 levels are depressed during pregnancy, it may lead to a type of megaloblastic anemia which exists in common with folic acid– related anemia in 98% of megaloblastic anemias at pregnancy.[53]

Though rare, vitamin B6 (pyridoxine) deficiency is noted during pregnancy by a decrease to about 75% of normal levels. A correlation between this deficiency and hypochromic microcytic anemia has been reported. Another hypochromic-type anemia has been noted in 80% of pregnant women with ascorbic acid (vitamin C) deficiency (scurvy). The interaction of ascorbic acid and iron metabolism has been found as the etiologic reason for this anemia. Among the fat-soluble vitamins (A, D, E, K), vitamin A deficiency has been reported by some investigators to produce an anemia similar to iron-deficiency anemia.

A mixed scenario of anemias has been linked with protein deficiency in pregnancy. The increasing needs of the mother and the demands from the fetus increase protein requirements from about 45 g in the non pregnant state. Protein deficiency is common in a great part of the world, and anemia associated with kwashiorkor is a characteristic normochromic and hormocytic anemia that is associated with decreased erythropoiesis and reduced iron intake.[54] A variety of anemias are associated with chronic ingestion of alcohol. Alcohol intake depletes folate reserves through a direct mechanism on folate metabolism, and poor dietary intake leading to nutritional deficiency is common in pregnant women. Therefore alcohol-induced anemia may manifest with microcytic red cells or normochromic and macrocytic cells, with an elevated number of ring sideroblasts**.**

CONCLUSION

Anemia in pregnancy is not like other anemic conditions because it affects both mother and fetus adversely. Hence women in child bearing age and those who are pregnant should be cautious enough to fulfill their dietary requirements in order to prevent the occurrence of anemia. Iron deficiency anemia is the most common form of anemia during pregnancy. Pregnant women must consume 20-48mg of dietary iron daily to prevent iron deficiency. Folic acid supplements are highly recommended during pregnancy as it avoids the incidence of folic acid deficiency in mother and also evades the risk of neural tube defects in infants.

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