Chapter 6

Anemia During Pregnancy

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Additional information is available at the end of the chapter

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Abstract

Anemia during pregnancy is a considerable health problem, with around two-fifths of pregnant women worldwide being anemic. Many gynecological and infectious diseases are predisposing factors for anemia during pregnancy. Anemia during pregnancy—especially the severe form—can lead to various maternal and perinatal adverse effects such as preterm labor, low birth weight, and intrauterine fetal death. It is one of the leading causes of maternal mortality. Therefore, preventive measures are needed if anemia and its adverse effects are to be prevented. Iron and folic acid supplements are the cornerstone for the prevention of anemia during pregnancy and one of the earliest preventive measures adopted in antenatal care. Other measures to prevent anemia during pregnancy include the fortification of principle foods with iron, increasing health and nutritional awareness, combating parasitic infections, and improvement in sanitation. There is a controversy concerning the benefit of other elements such as zinc, copper, and magnesium, so the use of these elements is not widely adopted for the prevention of anemia.

Keywords: anemia, pregnancy, prevention, treatment, adverse effects

1. Introduction

Anemia in pregnancy is a major public health problem, where it has been estimated that 41.8% of pregnant women worldwide are anemic [1]. The majority (at least half) of this burden is due to iron deficiency [2]. However, there is a significant variation in prevalence of anemia, both within and between countries. Because of physiological changes during pregnancy, pregnant women are at higher risk of anemia and in particular iron deficiency anemia, which is the most common type of anemia during pregnancy. Hematological changes during

pregnancy, especially expansion of blood volume, often confuse the diagnosis of anemia and its treatment. Because of increased iron and folic acid demands during pregnancy, pregnant women are more susceptible to develop anemia. Moreover, pregnant women are more susceptible to the other types of anemia that affect other women of childbearing age such as hereditary anemia, sickle cell disease and aplastic anemia. Anemia during pregnancy, particularly the severe form, is associated with increased maternal morbidity and mortality and contributes to 20% of the maternal mortality in Africa [2–5]. Anemia in pregnancy is associated with negative consequences for both the woman and neonate. Therefore, great effort is needed to develop/reassess and implement programs to control and prevent anemia during pregnancy.

2. Physiological changes during pregnancy related to anemia

During pregnancy, there is a considerable increase in plasma volume, which increases by 40–45% above the level of nonpregnant women. The blood volume expands by 15% compared with non-pregnancy levels. The disproportionate amount of blood creates the physiological and dilution anemia during pregnancy [5, 6]. However, these changes are of great importance and may protect pregnant woman against supine hypotension, guard against the adverse effects of the expectant blood loss during labor, and meet the demand for increased blood flow to the uterus and fetus [5, 7–9]. Despite this hemodilution, there is usually minimal change in mean corpuscular volume (MCV) or mean corpuscular hemoglobin (Hb) concentration (MCHC). The increase in iron demand during pregnancy is met by increased iron absorption. The maternal plasma erythropoietin level increases during pregnancy and reaches its peak in the third trimester [5, 7–9]. This accelerates erythropoiesis, but hemoglobin concentration and hematocrit decrease.

3. Iron metabolism

In adult men, there is usually little iron loss from the body. Because females lose iron during menses, their iron needs are greater. Usually only around 4% of the ingested iron is absorbed in the upper part of the small intestine, mainly in the ferrous state, while the majority is ingested in the ferric state. Many metal-binding proteins bind not only to iron but the other metals such as zinc and copper. After crossing the intestinal cells, most of the absorbed iron is bound to apoferritin forming ferritin. Usually around 35% of the transferritin is saturated with iron. The details of the process, involving intestine, plasma, liver, and bone marrow are shown in the **Figure 1**.

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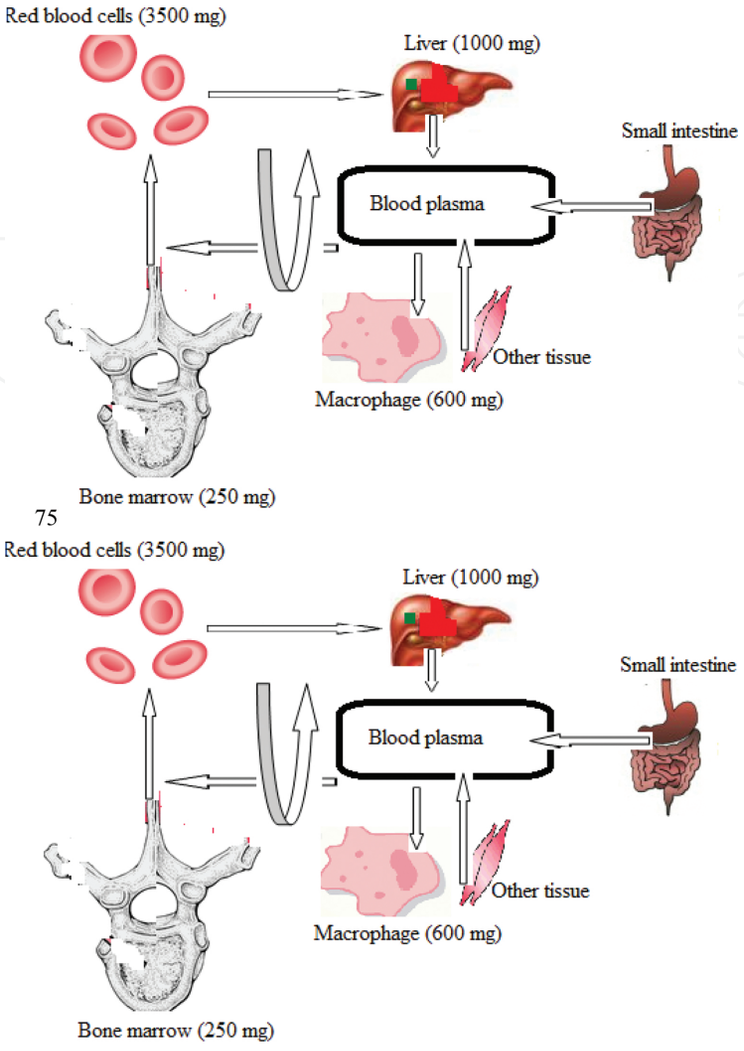

Figure 1. Iron metabolism

4. Iron requirements during pregnancy

The daily requirement of iron is around 1.5 mg in nonpregnant women. This requirement increases dramatically during pregnancy to reach 6–7 mg/day (total 1000 mg) with advanced gestational age. Pregnancy causes a twofold to threefold increase in the requirement for iron and a 10- to 20-fold increase in folate requirement. The increase in demand for iron is mainly due to fetal requirement, placenta, blood volume, tissue accretion, and the intra-partum potential for blood loss [5, 10]. This sixfold increase in need is quite difficult to meet with diet alone, especially in situations of poverty. In many underdeveloped countries, pregnant woman may have depleted iron stores and/or iron-deficiency anemia and, therefore, are at increased risk of becoming anemic during pregnancy and developing the adverse consequences of iron deficiency and anemia. For this reason iron supplementation during pregnancy is very important to keep the maternal hemoglobin within the normal range. It was previously

thought that even in the absence of sufficient iron supplementation, fetal hemoglobin production was not impaired because the fetus obtains iron even if the mother suffers from severe anemia. This is now an obsolete theory, and maternal anemia may lead to fetal anemia and many other perinatal adverse effects.

5. Folate during pregnancy

The normal level of folic acid is not sufficient to prevent megaloblastic changes in bone marrow in about 25% of pregnant women. Moreover, folic acid deficiency is more likely to occur in twin pregnancy, and in women taking anti-convulsion and sulfa-containing drugs. All pregnant women in developing countries should receive daily supplementation of 60 mg iron and 40 mg folic acid. Folate level is affected by sickle cell disease, malaria, and hemolytic anemia. The issue of folate deficiency has received global attention due to its association with neural tube defects.

6. Definition of anemia in pregnancy

The World Health Organization (WHO) defines anemia during pregnancy as a hemoglobin concentration <11 g/dl. However, this cutoff value for hemoglobin concentration is affected by many factors such as ethnicity, altitude, and smoking [10]. Anemia in pregnancy is further classified as mild/moderate (Hb 7–10.9 g/dl) and severe (Hb < 7 g/dl) [2]. The Centers for Disease Control and Prevention (1990) defined anemia as hemoglobin <11 g/dl in the first and second trimesters and <10.5 g/dl in the third trimester. This is based on the reduction in hemoglobin level during pregnancy caused by the disproportion in volume expansion between the plasma and erythrocytes. This disproportion is considerably greater during the second trimester. Postpartum anemia is defined by the WHO as hemoglobin <10 g/dl [10].

7. Etiology of anemia

There are several different factors responsible for anemia. The most common is iron deficiency anemia (IDA), which is generally assumed to represent 50% of cases [11]. Among the various risk factors for IDA nutritional or low iron intake together with acute blood loss are the leading causes. During pregnancy, symptoms such as nausea and vomiting together with other contributing factors may cause maternal anemia; the other factors include history of heavy menstruation, high parity, short birth spacing, lack of antenatal nutritional education, and multiple pregnancy. Malabsorption interferes with iron absorption and parasitic infestation such as hookworm may also lead to low hemoglobin levels. Iron absorption is enhanced by ascorbic acid and inhibited by phytic acid and tannins present in tea, coffee, and chocolate.

The second common leading cause of anemia in pregnancy is folic acid deficiency. Other micronutrient deficiency such as vitamin A, B12, and riboflavin, zinc, and copper may also

contribute to anemia. Malaria, hookworm infestation, infection, and deficiency of a number of micronutrients are leading causes of anemia during pregnancy. The relative contribution of each of these factors to anemia during pregnancy varies greatly by geographical location. Iron deficiency in anemic subjects in poor communities may be complicated by one or more additional micronutrient deficiencies. The etiologic pattern of anemia during pregnancy is often complex such that, for example, infection and nutritional deficiencies coexist.

Obstetric/gynecologic
Previous history of menorrhagia/metrorrhagia
History of miscarriage
Fibroid
Multiple pregnancies
Teenagers
Infections
Infections, for example, urinary tract infection
Parasitic infections, for example
Malaria, schistosomiasis, and hookworms
HIV
Helicobacter pylori
Bleeding from other site
Peptic ulcer
Hemorrhoids
General
Pica, for example, eating mud
Nutrition habits, for example, vegetarian

Table 1. Causes of and predisposing factors for anemia during pregnancy.

Other etiologies for anemia in pregnancy include malaria, chronic infection including HIV/AIDS, hemolytic anemia, thalassemia, and sickle cell disease.

Pregnancy is suggested as a possible cause for aplastic anemia due to the suppression of hematopoiesis by placental lactogens [12]. This is supported by the clinical observation that pregnancy-associated aplastic anemia is frequently self-limiting, ending with delivery. Pregnancy is one cause of bone marrow suppression, and aplastic anemia is likely to be immune-mediated since pregnancy is a state of hypo-immunity, likely involving suppression by cytotoxic T lymphocytes. In patients with aplastic anemia, CD4 and HLA-DR+ are detectable in both blood and bone marrow. The cells produce inhibitory cytokines such as tumor necrosis factor and gamma interferon, which affect the mitotic cells and induce nitric

oxide synthase and nitric oxide production by bone marrow cells, related to immune-mediated cytotoxicity and elimination of hematopoietic cells.

Table 1. shows causes and predisposing factors for anemia in pregnancy.

8. Diagnosis

While mild anemia is usually asymptomatic and may be detected during routine prenatal check up for hemoglobin, moderate and severe anemia may present with different symptoms, including fatigue, dizziness, tiredness, lethargy, fainting, palpitation, symptoms of congestive heart failure, and leg swelling. In severe cases, there may be difficulty in swallowing and/or blindness if there is a vitamin A deficiency. It is worth mentioning that some of these symptoms can overlap and hence be attributed to symptoms detected in normal pregnancy (**Table 2**).

Fatigue
Dizziness
Tiredness
Lethargy
Fainting
Palpitation
Symptoms of congestive heart failure
Legs swelling

Table 2. Symptoms of anemia during pregnancy.

Pallor and physical findings of iron deficiency may also be present, such as angular stomatitis, smooth tongue, and koilonychias, in the **Figure 2**.

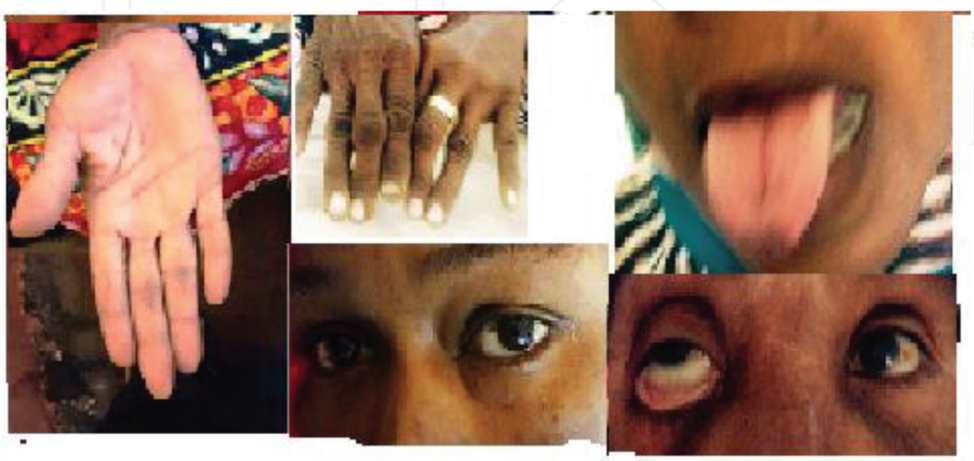

Figure 2. Signs of IDA (iron deficiency anemia)

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8.1. Signs of IDA

An abdominal examination to rule out enlarged spleen and/or liver is mandatory in approaching anemic pregnant woman. A complete blood picture (include peripheral blood film) is the first step in tailoring the next investigations aimed at determining etiology as shown in the **Figure 3**.

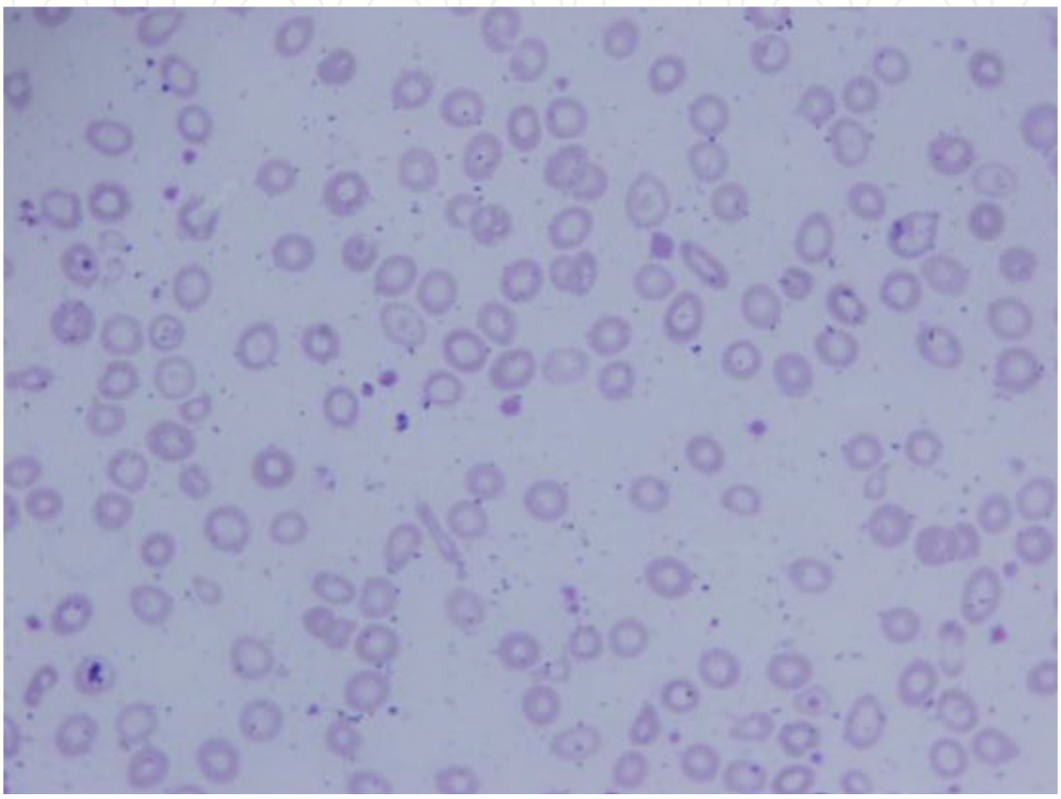

Figure 3. Peripheral blood picture in IDA

These may include stool examination for hookworms, hemoglobin electrophoresis, and tests for infectious organisms such as malaria, tuberculosis, and HIV. Bone marrow aspirate or biopsy may be needed to diagnose the underlying cause of anemia.

The definition and identification of iron deficiency have been problematic, especially in situations in which chronic inflammation is present. The gold standard for identifying iron deficiency anemia has been the examination of suitably stained bone marrow aspirates for storage iron as hemosiderin. Biochemical measurement of iron status is influenced by inflammation and clearly defined and validated cutoffs for diagnosing iron deficiency in pregnancy in the presence of coexisting infection have been lacking. A lowered MCV is the most sensitive indicator of iron deficiency, where serum iron is low and the total binding capacity raised. Macrocytosis with megaloblastic changes in bone marrow in an indicator of folate deficiency anemia (**Table 3**).

Factor	Lower cutoff
Hemoglobin	11 g/dl
Hematocrit	30%
Mean corpuscular volume	80 fl
Mean cell hemoglobin	28 pg
Mean cell hemoglobin concentration	32 g/dl
Serum ferritin	12 μg/l
Total iron binding capacity	15%

Table 3. The lower cut off points of the hematological indices during pregnancy.

9. Consequences of anemia in pregnancy

Anemia during pregnancy is associated with increased maternal morbidity and mortality. Anemia in pregnancy is associated with negative consequences for both the woman and neonate. Fetal anemia, low birth weight, preterm birth, and stillbirth have been associated with anemia [13]. Anemia was observed as a predictor for poor perinatal outcomes such as fetal anemia and low birth weight deliveries [13, 14]. A meta-analysis showed that anemia during early pregnancy, but not late pregnancy, is associated with slightly increased risk of preterm delivery and low birth weight [15]. Interestingly, recent reports revealed that the prevalence of preeclampsia and eclampsia was significantly higher in women with severe anemia [16]. In some African countries, anemia was reported to be associated with stillbirth [17, 18]. In addition, there is also association between anemia and postpartum hemorrhage and pulmonary edema.

Maternal
Anemic heart failure
Maternal death
Septicemia
Preterm labor
Low tolerance to systemic diseases, for example, heart disease
Postpartum hemorrhage
Lack of tolerance of minimal bleeding
Impaired ability to push during the second stage of labor
Impaired lactation
Breast milk of low nutritional value
Deep venous thrombosis

Puerperal psychosis
Cognitive abnormalities
Perinatal
Intrauterine growth restriction
Intrauterine fetal death
Low birth weight
Fetal anemia
Low APGAR score
Increased perinatal motility
Increased infant death

Table 4. Complications/adverse effects of anemia during pregnancy.

10. Treatment and prevention

10.1. Dietary advice

As physiological iron requirements are several times higher in pregnancy than they are in the nonpregnant women, the recommended daily intake of iron for the second half of pregnancy is 30 mg with iron absorption increasing threefold. The amount of iron absorbed depends upon the following factors: (1) amount of iron in the diet, (2) its bioavailability, and (3) physiological requirements. Dietary heme iron is found mainly in red meats, fish, and poultry. Heme iron absorption is twofold to threefold greater than non-heme iron. Moreover, meat contains organic compounds (including peptides), which promote the absorption of iron from other less bioavailable non-heme iron sources. While heme iron is more readily absorbed than non-heme iron, the latter still forms approximately 95% of dietary iron intake. Ascorbic acid significantly increases iron absorption from non-heme sources, with the magnitude of this effect concordant with the increase in quantity of vitamin C in the meal. The bioavailability of non-heme iron is enhanced by germination and fermentation of cereals and legumes which results in a decrease in the phytate content, a food constituent that hinders iron absorption. Tannins in tea and coffee hinder iron absorption on consumption with or shortly after a meal.

Nutritional education is the main objective of antenatal care to assist in the prevention of anemia. In addition, family planning and control of birth spacing is another preventive measure that should be considered by health-care providers. The WHO jointly with the International Nutritional Anemia Consultative Group and the United Nations Children's Fund recommend routine supplements of 60 mg iron per day and 400 μg folate per day to all pregnant women for at least 6 months. This guideline also recommends continuation until 3 months postpartum in areas of high prevalence of anemia (>40%). The standard oral preparation, Fefol, comprising 100 mg iron and 350 μg folate, is suitable for both prevention and treatment. Parenteral iron does not provide rapid correction of hemoglobin levels compared

with oral form but is an option for those with poor compliance and who cannot tolerate the oral formulation. It is also suitable in cases of malabsorption. The maximum rise in hemoglobin achievable with either oral or parenteral formulations is 0.8 g/dl/week. Blood transfusion is indicated in cases of severe anemia (Hb% < 7 g/dl) and anemia in late pregnancy when delivery is due.

Referral to secondary care level should be considered if any of the following situations exist:

1. Significant symptoms and/or severe anemia (Hb < 70 g/l), or
2. Advanced gestation (>34 weeks), or
3. If there is no rise in Hb at 2 weeks.
4. In non-anemic women who are at increased risk of iron depletion such as those with:
    a. Previous anemia,
    b. Multiple pregnancy,
    c. Consecutive pregnancies with <1 year's interval between
    d. Vegetarians
    e. Women at high risk of bleeding
    f. Pregnant teenagers
    g. Jehovah's witnesses.

10.2. Postnatal anemia

The WHO definition for postnatal anemia is Hb < 10 g/dl. Complete blood count should be checked within 48-hour post-delivery in all women with an estimated blood loss >500 ml and in women with uncorrected anemia in the prenatal period or symptoms suggestive of postpartum anemia. Elemental iron 100–200 mg daily for at least 3 months should be offered to women with Hb < 100 g/l, who are hemodynamically stable, asymptomatic, or have mild symptoms, and a repeat complete blood count and ferritin level assessment should be undertaken to ensure hemoglobin and iron stores are replete [17].

10.3. Parenteral iron therapy

Indications for parenteral iron therapy [19]:

1. absolute noncompliance with oral iron therapy
2. intolerance to oral iron therapy
3. proven malabsorption.

Parenteral iron therapy bypasses the natural gastrointestinal regulatory mechanisms to supply nonprotein-bound iron to the red blood cells. It is characterized by fast increases in Hb and

better replenishment of iron stores compared with oral therapy, particular iron sucrose. However, issues concerning its safety are waiting to be addressed.

Contraindications for parenteral iron use are as follows:

1. history of anaphylaxis or reactions to parenteral iron therapy
2. first trimester of pregnancy
3. active acute or chronic infection
4. chronic liver disease.

Appropriate setting and staff trained in management of anaphylaxis should be available on contemplating usage of parenteral iron.

10.4. Dealing with delivery of women with iron deficiency anemia

With good practice, this situation should generally be avoided; nonetheless, there are instances when women book late have recently arrived from abroad or have not engaged with antenatal care. In such circumstances, it may be essential to take active measures to minimize blood loss at parturition. Attention should be paid to delivery in hospital, securing an intravenous access and blood group and save, and consideration of active management of the third stage of labor to reduce postpartum blood loss.

10.5. Blood transfusion: indications and risks

There are multiple potential hazards from blood transfusions but most arise from clinical and laboratory errors. Moreover, specific risks for women of child-bearing age include the potential for transfusion-induced sensitization to red blood cell antigens, creating a future risk of fetal hemolytic disease. Massive obstetric hemorrhage is widely appreciated as an important cause of morbidity and mortality and necessitates prompt use of blood and components as part of appropriate management.

Both clinical assessment and hemoglobin concentration are of immense significance postpartum to decide on the optimum method of iron replacement. In the absence of bleeding, the decision to transfuse blood should be made on an informed individual basis.

Blood transfusion should be reserved for women with:

a. continued bleeding or at risk of further bleeding,
b. imminent cardiac compromise
c. significant symptoms requiring urgent correction.

If, after careful consideration, elective blood transfusion is needed, women should be fully counseled about potential risks and given written information, and consent should be obtained.

10.6. Prophylaxis

Efforts aimed at preventing iron deficiency and iron deficiency anemia among pregnant women include iron supplementation, fortification of staple foods with iron, increasing health and nutritional awareness, combating parasitic infections, and improvement in sanitation [20]. A prophylactic dose of 300 μg (0.3 mg) daily during pregnancy was proposed in 1968 by the WHO.

During pregnancy, women need iron supplementation to ensure they have sufficient iron stores to prevent iron deficiency [21]. Hence, in most developing countries, iron supplements are used extensively during pregnancy to prevent and correct iron deficiency and anemia during gestation.

A dose of 60 mg of elemental iron was accepted as standard supplemental dose in 1959, depending on estimates of iron needs during pregnancy [22]. This has since been endorsed by several experts [23, 24]. Gastrointestinal discomfort is a common observation among women consuming large amounts of supplemental iron, especially if taken on an empty stomach. Gastrointestinal side effects are recognized as the critical adverse effect on which the tolerable upper limit of intake for iron is determined. Use of high-dose iron supplements commonly leads to gastrointestinal manifestations, such as constipation nausea, vomiting, and diarrhea, with the frequency and severity being determined by the amount of elemental iron released in the stomach.

10.7. Folic acid supplementation

Following publication of a number of studies supporting the periconceptional use of folic acid in the prevention of neural tube defects, the supplemental dose was increased to 400 μg (0.4 mg) of folic acid daily in 1998. This dose was considered to provide more folic acid than needed to produce an optimal hemoglobin response in pregnant women. If supplementation is delayed till after the first trimester of pregnancy, it will not contribute to preventing birth defects [25]. Interestingly, a recent Cochrane review showed that supplement with folic acid, alone or in combination with vitamins and minerals, prevents neural tube defects, but it does not have a clear effect on other birth defects [26].

Likewise, it has been found that folic acid alone, or in combination with vitamin and mineral supplements during pregnancy, improved iron status in women without affecting perinatal anemia, perinatal mortality or other infant outcomes [27, 28].

11. Hemoglobinopathies

Hemoglobinopathies such as thalassemias and sickle cell diseases should be considered during pregnancy because of their impact on maternal and perinatal outcomes. They are genetic disorders of hemoglobin structure and synthesis and may transmit to the offspring. The main clinical manifestation of these disorders during pregnancy is anemia. Usually the iron store is quite normal necessitating folate supplementation without iron to avoid iron overload. Pre-

conceptual counseling is a very important issue in patients with hemoglobinopathies. It allows establishment of the hemoglobin status of the parents and prediction of the likelihood of an affected offspring [29].

11.1. Sickle cell disease

Sickle cell disease is caused by the substitution of glutamic acid by valine at position 6 of the globin chain. It includes sickle cell anemia, sickle hemoglobin C disease, sickle beta thalassemias, and sickle cell anemia with alpha thalassemia. Sickling and crystallization of the hemoglobin are induced by de-oxygenated states such hypoxia, acidosis, and dehydration. Almost always the patients are already diagnosed prior to pregnancy, but the diagnosis is made by hemoglobin electrophoresis. Sickle cell disease substantially increases maternal and perinatal mortality. It leads to miscarriage, intrauterine growth restriction, preterm labor, preeclampsia, abruptio placentae, and thrombosis [29]. There is also an increased incidence of infection, and the sickle cell crisis should be managed as aggressively as in nonpregnant women. The management of sickle cell disease in pregnancy should be in collaboration with hematologist. Folic acid supplementation with avoidance of iron is very important together with penicillin prophylaxis. The patient should be removed from factors that may have triggered the crisis. These may include dehydration in early pregnancy (hyperemesis gravidarum) and during labor. Regular antenatal monitoring, serial growth scans, and intrapartum avoidance of dehydration, hypoxia, acidosis, and infection are very important, as are consideration of analgesia and anesthesia. The routine use of prophylactic blood transfusion is controversial in this situation.

11.2. Thalassemias

The genetically determined hemoglobinopathies termed thalassemias are characterized by impaired production of one or more of the normal globin peptide chains. Thalassemias occur according to which globin chain is deficient.

Alpha thalassemia minor (three normal alpha gene) is usually asymptomatic, but the patient may become anemic. Alpha thalassemia major is incompatible with life, and the fetus is severely hydropic. Beta thalassemia minor may also be a symptomatic but may present with iron deficiency anemia with lowered MCV, MCH, and MCHC. The patient will need oral folate and iron supplementation. Beta thalassemia major in adults presents with iron overload.

12. Acquired hemolytic anemia

This is an uncommon type of anemia and is either primary or secondary. It is usually due to antibody production. Secondary hemolytic anemia may be due to chronic infection, drugs, or connective tissue disease. Typically both direct and indirect Coombs tests are positive and spherocytosis and reticulocytosis are the typical characteristics of a peripheral blood smear. Steroids are usually effective treatment (prednisolone 1 mg/kg/day). The presentation and symptoms depend on the severity of hemolysis. Very rarely, as in gestational thrombocyto-

penia, there is pregnancy-induced hemolytic anemia. However, usually the condition is benign and resolves spontaneously. Some obstetric conditions such as pre-eclampsia and eclampsia may induce micro-angiopathic hemolysis, and this might progressed to hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome [29].

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