



ANEMIA IN PREGNANCY- AN OVERVIEW

Palani.S^{1*}, Nisha Mary Joseph², Yonatan Tegene¹, Anish Zacharia³

1. College of Medicine and Health Sciences, Jijiga University, Ethiopia
2. School of Pharmacy, College of Health Sciences, Addis Ababa University, Ethiopia
3. School of studies in Biochemistry, Jiwaji University, Gwalior, India

Abstract:

Anemia is one of the most commonly encountered medical disorders during pregnancy. In developing countries it is a cause of serious concern as, besides many other adverse effects on the mother and the fetus it contributes significantly high maternal mortality. Anaemia, the most common nutritional disorder in the world affecting 2 billion people worldwide with pregnant women particularly at risk. WHO data indicates that iron deficiency anemia is a significant problem throughout the world ranging from 1% in the industrialized countries to an average of 56% in developing countries. The major risk groups for iron deficiency include women of childbearing age, pregnant women, and lactating postpartum women. It is a major public health problem particularly among pregnant women in developing countries with adverse effects on the mother and the newborn. Present literature findings, shows that iron deficiency anemia is more likely to have adverse effects on fetal health outcomes. It has increased the substantial risk of maternal and child mortality. According to the recommendations of the leading obstetrics and gynecology societies, all pregnant women should be offered screening for anemia.

Key words: *Anemia, Hemoglobin, pregnancy, Iron*

Introduction: Anemia is a condition in which the number of red blood cells and their oxygen-

carrying capacity is insufficient to meet the body's physiological needs. RBCs play a role to deliver oxygen from the lungs to the tissues and carbon dioxide from the tissues to the lungs which is facilitated by hemoglobin, a tetramer protein composed of haem and globin. The reduction in the number of RBCs transporting oxygen and carbon dioxide results in impairment of gas exchange and this is due to anemia which may be either due to defective red cell production, increased red cell

For Correspondence:

Dr.S.Palani, Professor, College of Medicine and Health Sciences, Jijiga University, Ethiopia
palanibu@gmail.com

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destruction or blood loss. Iron is necessary for synthesis of hemoglobin. Iron deficiency is thought to be the most common cause of anemia globally, but other nutritional deficiencies (including folate, vitamin B₁₂ and vitamin A), acute and chronic inflammation, parasitic infections, and inherited or acquired disorders that affect Hb synthesis, red blood cell production or red blood cell survival also result in anemias. Iron deficiency anemia results in impaired cognitive and motor development in children and decreased work capacity in adults. The effects are most severe in infancy and early childhood. In pregnancy, iron deficiency anemia can lead to perinatal loss, prematurity and low birth weight babies. Iron deficiency anemia also adversely affects the body's immune response. The most common types of anemia are- iron deficiency anemia, Thalassaemia, Aplastic anemia, Haemolytic anemia, Sickle cell anemia, Pernicious anemia, Fanconi anemia. Iron deficiency is the most prevalent cause of anemia which is usually due to chronic blood loss caused by excessive menstruation increased demand for iron, such as fetal growth in pregnancy [1]. Anemia can occur at any age and affect either gender, although it is more prevalent in pregnant women and young children [2]. The major risk groups for iron deficiency include women of childbearing age, pregnant women, and lactating postpartum women [3]. Maternal consequences of anaemia are also well known and include cardiovascular symptoms, reduced physical and mental performance, reduced immune function, tiredness, reduced peripartal blood reserves and finally increased risk for blood transfusion in the postpartum period. For clinical management, proper diagnosis and therapy are mandatory to reduce maternal and fetal risks and to enable optimal obstetrical outcome of both. The World Health Organization (WHO) estimates that two billion people over 30% of the world's populations are anemic, although prevalence rates are variable because of differences in socioeconomic conditions, lifestyles, food habits, and rates of communicable and noncommunicable diseases [4]. The lowest normal hemoglobin in the healthy non-pregnant woman is defined as

12g/dl. The World Health Organization (WHO) recommends that hemoglobin ideally should be maintained at or above 11.0 g/dl, and should not be allowed to fall below 10.5 g/dl in the second trimester [5]. As per WHO guidelines, Anaemia is classified as (1) mild anemia (Hb 10 to 10.9 g/dl); (2) moderate anemia (Hb 7 to 9.9 g/dl); (3) severe anemia (Hb less than 7 g/dl); (4) very severe (Hb less than 4 g/dl). Iron absorption during pregnancy is determined by the amount of iron in diet, its bioavailability and the changes in iron absorption that occur during pregnancy. An acid environment in the duodenum helps in the absorption of iron. The frequent ingestion of antacids and chronic use of H₂ blockers and proton pump inhibitors diminishes the iron absorption. Vitamin C, in addition to the iron, may increase acid environment of the stomach and increase absorption. Iron requirements are greater in pregnancy than in non-pregnant state. Although iron requirements are reduced in the first trimester because of absence of menstruation these raise steadily thereafter as high as ≥ 10 mg/day [6]. The amounts that can be absorbed from even an optimal diet, however are less than the iron requirement in later pregnancy and a women must enter pregnancy with iron stores of >300 mg if she is to meet her requirement fully [7]. Iron requirements are increased in pregnancy, especially in the third trimester when they may be several times higher than at other stages of the life cycle, the net iron requirements for pregnancy are 840 mg approximately [8].

Maternal Changes during Pregnancy

During pregnancy, there is an increase in both red cell mass and plasma volume to accommodate the needs of the growing uterus and fetus. The circulating plasma volume increases linearly to reach a plateau in the 8th or 9th month of pregnancy. The increment is about 1000 ml, which corresponds to 45% of the circulating plasma volume in non-pregnancy. The plasma volume decreases rapidly after delivery and is then restored to the non-pregnancy level at about 3 puerperal weeks. However, plasma volume increases more than the red cell mass leading to a fall in the concentration of hemoglobin in the blood,

despite the increase in the total number of red cells. This drop in hemoglobin concentration decreases the blood viscosity and it is thought this enhances the placental perfusion providing a better maternal-fetal gas and nutrient exchange [9]. Physiological hemodilution of pregnancy and at what level of hemoglobin, women and babies would get benefit from iron treatment. Some studies suggest that the physiological decrease in hemoglobin is associated with improved outcomes for the baby. An adult woman has about 2,000 mg iron in the body, 60–70% of which is present in erythrocytes, with the rest stored in the liver, spleen, and bone marrow. When a woman becomes pregnant, the demand for iron increases. Specifically, about 1,000 mg more is required, comprising 300 mg for the fetus and placenta, 500 mg for increased maternal hemoglobin, and 200 mg that compensates for excretion. Therefore, an additional 50% of the amount of iron present in the non-pregnant state should be ingested during pregnancy [10].

Iron Deficiency Anemia during Pregnancy

Iron deficiency anemia (IDA) is the most common cause of nutritional anemia. Poor absorption of iron is aggravated by diet rich in phytates and phenolic compounds which prevent absorption of iron thereby resulting in anemic condition. Iron deficiency anemia is characterized by a defect in hemoglobin synthesis, resulting in red blood cells that are abnormally small (microcytic) and contain a decreased amount of hemoglobin (hypochromic) [11]. The capacity of the blood to deliver oxygen to body cells and tissues is thus reduced. Iron is essential to all cells. Functions of iron include involvement in energy metabolism, gene regulation, cell growth and differentiation, oxygen binding and transport, muscle oxygen use and storage, enzyme reactions, neurotransmitter synthesis, and protein synthesis [11-13]. Approximately 1190 mg of iron is required to sustain pregnancy from conception through delivery [14]. The iron requirement during pregnancy is increased gradually through gestation from 0.8 mg/day in the first trimester to 7.5 mg/day in the third trimester. The average requirement of iron in the entire gestation period is approximately

4.4mg/day [15-17]. The required iron is used to expand the woman's erythrocyte mass, fulfill the fetus's iron requirements, compensate for iron losses (i.e. blood losses) at delivery. The newborns body iron content depends to a large extent on their birth weight. At a low birth weight of approx 2,500 g, the iron content of the newborn is approx 200 mg and at a "normal" birth weight of approx 3,500 g, the iron content is approx 270 mg [18]. Maternal iron deficiency in pregnancy increases the neonatal mortality and morbidity [19]. If the hemoglobin level is less than 8 grams/dl, then the risk of death during delivery increases 2-3 folds. Further, if the hemoglobin drops below 5grams/dl, then the risk of death increases 8-10 folds [20]. The low maternal hemoglobin concentration is more likely to result in preterm delivery and thus low fetal birth weight [21].

Iron Absorption, Metabolism and Storage

Body iron stores are predominantly located in the reticuloendothelial cells in the bone marrow, liver and spleen, as well as in the hepatocytes. Intracellular iron is stored inside the spherical ferritin molecules, thereby protecting the cell from the toxicity of free iron. At small body reserves, the iron is present in ferritin. At larger iron reserves, ferritin is condensed into haemosiderin [22]. Iron is absorbed mainly in the proximal part of the small intestine (duodenum and jejunum) by complex process involving specific receptors and iron associated proteins [23]. Absorption depends on gastric acid (ascorbic acid enhances the absorption of iron), which maintains iron in its soluble ferrous (Fe^{2+}) form rather than the insoluble ferric (Fe^{3+}) form. Trivalent Fe^{3+} is virtually not taken up from the neutral milieu of the small bowel, where the divalent Fe^{2+} is markedly better absorbed. Intracellular iron within macrophages is liberated from senescent erythrocytes during erythrophagocytosis. Iron from both intestinal epithelial cells and macrophage is transported, via ferroportin channels, to the circulation, where it is bound to serum transferrin, which carries the bound iron to target cells. Transferrin receptors on the surfaces of erythroid progenitors, lymphocytes, and other proliferating cells bind and internalize the transferrin-iron complex, releasing iron

intracellularly through the transferrin cycle. Ferritin (protein apoferritin + Fe^{3+}), an intracellular protein that binds and sequesters iron, is leaked into the circulation in small levels; serum ferritin levels are an accurate indicator of total body iron stores [24]. Ferritin is the main storage form of iron. A negative regulator of gastrointestinal mucosal absorption of iron (hepcidin) synthesized by the liver may contribute to the anemia of chronic disease. Transferrin, ferritin, and hepcidin are produced by the liver.

Nutrients That Interfere with Body's Ability to Absorb Iron

Calcium supplements or an antacid that contains calcium should not be taken while taking iron-rich foods or taking iron supplement. Calcium hinders with body's ability to absorb iron. For that reason it should not be supplement with milk. Tea and coffee, which contain substances that interfere with the absorption of iron from supplements and plant sources.

Nutrients That Helps Body to Absorb Iron

Foods rich in vitamin C with iron supplement or iron-rich plant foods can help body to absorb significantly more iron. Good vitamin C choices include a glass of orange or tomato juice, a handful of strawberries, sliced bell peppers, or half a grapefruit.

Pharmacokinetics

Gastro-intestinal (GI) absorption is the primary mechanism controlling total body iron. This remains remarkably constant (1–1.4 mg/day) in healthy individuals despite variations in diet, erythropoiesis and iron stores. Iron absorption occurs in the small intestine and is influenced by several factors:

I. The physico-chemical form of the iron

(a) Inorganic ferrous iron is better absorbed than ferric iron.

(b) Absorption of iron from the diet depends on the source of the iron. Most dietary iron exists as non-haem iron (e.g. iron salts) and is relatively poorly absorbed (approximately 5–10%), mainly because it is combined with phosphates and phytates (in cereals). Haem iron is well absorbed (20–40%).

II. Factors increasing absorption

(a) Acid: e.g. gastric acid and ascorbic acid facilitate iron absorption.

(b) Ethanol increases ferric but not ferrous iron absorption.

III. Factors Reducing Iron Absorption

(a) Partial gastrectomy reduces gastric acid and iron deficiency is more common than vitamin B_{12} deficiency following partial gastrectomy.

(b) Malabsorption states, e.g. celiac disease.

(c) Drug–iron binding interactions in the GI tract; tetracyclines chelate iron, causing malabsorption of both agents; oral bisphosphonates and magnesium trisilicate reduce iron absorption [25].

Management of Iron Deficiency Anemia

Oral iron therapy is the most widely prescribed treatment for iron deficiency anemia, many patients do not respond adequately to oral iron therapy due to difficulties associated with ingestion of the tablets and their side effects. Oral iron is applied normally as ferrous sulphate tablets (200 mg). Healthy, pregnant females additionally take 100 mg iron/day. Side effects of oral iron therapy were reported with 10% of dyspepsia, 5% constipation, and 3% diarrhea [26]. These side effects increase in severity with the amount of iron given [27]. Other side effects of oral iron therapy include gastrointestinal disturbances characterized by colicky pain, nausea, vomiting and occur in about 50% of patients taking iron preparations. Iron absorption requires an acidic medium; therefore its absorption may be decreased by intake of antacids or proton pump inhibitors and histamine receptor antagonists. Interference of iron absorption may occur with the intake of certain medications, which thereby minimizes the benefit received from oral iron treatment [28]. Other oral salts also available as Ferrous fumarate (200 mg), ferrous gluconate (300 mg), Ferrous glycine sulphate (225 mg), Ferrous succinate (100 mg), Ferrous sulphate (300 mg), Ferrous sulphate dried (200 mg).

Intramuscular route is more acceptable and is associated with less side effects. The dose can be given daily on alternate buttocks by deep intramuscular injection by Z technique. Oral iron should be stopped before, giving iron sorbitol as it is associated with toxic reaction such as headache, nausea and vomiting. Disadvantages of intramuscular route are pain, nausea, vomiting, headache, fever,

lymphadenopathy, allergic reactions and rarely anaphylaxis.

An alternative way to supplement iron is intravenous administration. Bioavailability of intravenous iron is higher than of oral supplementation, and it more effectively repletes iron stores. Intravenous iron is stored in macrophages, enterocytes, and hepatocytes—it is critical to monitor the iron status of the patient to avoid iron toxicity [29]. Intravenous preparations available as iron dextran and iron gluconate. Iron gluconate is considered to have a lower reaction rate and therefore a test dose is not recommended with only 3.3 allergic events per million doses per year with iron gluconate reported. There were no life-threatening reactions recorded as a result of iron gluconate infusion. On the other hand, there were 31 fatalities among 196 allergic/anaphylactic reactions, which were reported for iron dextran [30].

Diagnosis

Knowledge of different haemoglobin cut off levels during pregnancy to differentiate between hydraemia and true anaemia is important in the first step of diagnosis. Lower haemoglobin cut off is 11.0 g/dL in the first and last trimester and 10.5 g/dL in the second trimester. Therefore any level below 10.5 g/dL should be regarded as anaemia and consequently checked.

The next step includes differential diagnosis of anaemia. Iron deficiency the major cause of anaemia during pregnancy, but others such as infection, abnormal haemoglobin, renal disease or parasites (malaria, worms) must be ruled out before therapy starts to guarantee optimal therapeutic effects

Laboratory Parameters

In addition to clinical assessment, laboratory parameters are of major importance for differential diagnosis of anaemia. More than 100 years ago first tests including blood smear, red cell being the actual gold standard of iron status testing. However, in certain conditions such as underlying infections, ferritin is not valuable, since it reacts as an acute phase reactant and shows false normal results, e.g. in the postpartum period. During pregnancy, ferritin shows also weak correlations to other

iron parameters and then severity of anaemia, therefore additional tests are helpful.

Hypochromic Red Cells

Hypochromic red cells are released into the blood in cases of severe anaemia, e.g. iron deficiency, or during functional iron deficiency, e.g. erythropoietic stress with insufficient iron supply. Using modern automated red cell analyzer systems it is possible to measure the quantity of hypochromic red cells (HRBC) and the percentage of HRBC of total red cells. These data are helpful to determine the severity of iron deficiency, for differential diagnosis (e.g. thalassaemia vs. iron deficiency) of anaemia, for assessment of functional iron deficiency (e.g. during rhEPO treatment) and finally the monitoring of therapy and its effects, namely decrease of hypochromics due to efficient iron administration.

Soluble Serum Transferrin Receptors

Serum transferrin receptor (sTfR) assay is another important new laboratory test which is increasingly used in obstetrics. STfR are on the surface of every iron incorporating cell and are released into the blood in cases of increased tissue iron needs such as during severe iron deficiency or during forced erythropoiesis. As HRBC, increased sTfR levels indicate functional iron deficiency but also increased erythropoiesis and body iron needs.

Therapeutic Options

Traditional therapeutic options of iron deficiency anaemia in pregnancy were administration of oral iron or in severe cases administration of blood transfusion. While oral iron shows limited effectiveness in cases of severe anaemia due to various factors such as side effects, lack of compliance and often limits intestinal absorption and bioavailability, blood transfusion must be avoided due to considerable transfusion risks such as infections, risk of incorrect transfusion, transfusion reactions and negative impact on the immune system. There is also an increasing number of patients who deny blood transfusion.

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