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Iron Supplementation in Pregnancy-The Most Needed But the Most Neglected Element of Antenatal Care

Dr Ayesha Zafar[1], Dr Humaira Bilqis[2], Dr Rizwana Chaudhri[3] Afifa Saghi[4], Asma Saghir Khan[5], Ayesha Mushtaq[6*]

[1]Post graduate resident Gynaecology and obstetrics, Holy Family Hospital

[2]FCPS, Assistant Professor, Gynaecology and obstetrics, Holy Family Hospital

[3]FCPS, FRCOG, ex HOD Gynaecology and obstetrics Holy family hospital

[4]PhD Scholar Department of Pharmacy Quaid I Azam University Islamabad

[5](Lecturer Food and Nutrition, MUST Mirpur)

[6]Researcher MS, Clinical Consultant Dietitian

***Corresponding Author:** Ayesha Mushtaq, Researcher MS, Clinical Consultant Dietitian.

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Abstract

WHO recommends giving all pregnant women a standard dose of 60 mg Iron and 400 µg Folic Acid supplementation for 6 months on a daily basis to prevent maternal anemia and neonatal neural tube defects. Adherence to iron supplements during pregnancy is poor and has not improved significantly in the last decades among low and middle income countries.

Objectives: To determine the frequency of pregnant women non-adherent to iron supplements in gestational age 16-34 weeks attending antenatal OPD in Holy Family Hospital and to determine the factors responsible for non-adherence with respect to patients.

Study design: Descriptive, cross sectional study.

Settings: OPD of Obstetrics & Gynecology, Holy Family Hospital, Rawalpindi.

Study duration: 4th August 2018 to 3rd February 2019

Materials & Methods: A total of 351 obstetric patients, 18 to 40 years of age were included. Patients with known hemoglobinopathies and psychiatric disorders were excluded. Interview of patients' was carried out by the investigator using structured questionnaire attached as annex including information regarding socio-demographic details, parity, gestational age, antenatal visits, status of adherence or non-adherence to iron supplements during last month and reasons for non-adherence.

Results: Age range in this study was from 18 to 40 years with mean age of 30.50 ± 4.21 years. Majority of the patients 196 (55.80%) were between 31 to 40 years of age. In this study, frequency of pregnant women non-adherent to iron supplements was found in 147 (41.88%) women. Frequency of factors responsible for non-adherence with respect to patients were as follows;

Poor knowledge in 59 (40.14%) women.

Poor counseling in 35 (23.81%) women.

Gastrointestinal Disturbances in 53 (36.05%) women.

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Conclusion: This study concluded that frequency of pregnant women non-adherent to iron supplements was found in 41.88% women with poor knowledge and gastrointestinal disturbances as the common factors for non-adherence.

Key words: *Non-adherent; Iron supplements; Poor knowledge.*

Introduction

Anemia is defined as haemoglobin less than 11gm/dl and a haematocrit of less than 0.33. [1] There are three main types of anemia, that due to blood loss, that due to decreased red blood cell production, and that due to increased red blood cell breakdown. Causes of blood loss include trauma and gastrointestinal bleeding among others. Causes of decreased production include iron deficiency, a lack of vitamin B12, thalassemia and a number of neoplasms of the bone marrow among others. [2] Causes of increased breakdown include a number of genetic conditions such as sickle cell anemia, infections like malaria and some autoimmune diseases among others. It can also be classified based on the size of red blood cells and amount of hemoglobin in each cell. If the cells are small it is microcytic anemia, if they are large it is macrocytic anemia and if they are normal sized it is normocytic anemia. [2,3]

Anemia is the most common medical disorder in pregnancy and is responsible indirectly for 40-60% of the maternal deaths in the developing countries. [4] It affects about 18% of pregnant women in developed and 35-75% of pregnant women in developing countries. [1,5]Anemia is of great concern particularly during pregnancy because of its reported association with a number of adverse outcomes on health. Broadly speaking, the adverse outcomes of anaemia and haemoglobin concentration have a 'U-shaped' association; they occur when maternal haemoglobin values are either at the low or the high end of the range. At the lower end of the range, haemoglobin concentration has been associated with an increased maternal and perinatal mortality, preterm delivery and low birth weight. [6-9]

Maternal mortality is the prime health indicator in any society. Anaemia accounts for the majority of maternal death. According to World Health Organization, around 2 billion people, amounting to over 30% of the world's population are anaemic. [10] Most commonly affected population are children and women. It is estimated that 56 million pregnant women (41.8% of the total) are affected with anaemia globally. [11] Iron deficiency is the most common cause of anaemia. During 2nd and 3rd trimester of pregnancyiron requirement is significantly increased which diet alone cannot fulfil. The marked physiological changes during pregnancy increase the iron demand due to normal iron losses, iron used by the fetus and related tissues. The iron dose recommended by WHO for routine prophylaxis is 30 to 60mg of elemental iron per day for women with normal iron stores and 120 to 240 mg/day for those with empty iron stores. [12] Therefore iron supplements are needed to meet this increase demand.Anaemia is defined by Hb < l1.5g/dl in the first trimester < 11g/dl in the second and third trimesters and <10.5g/dl in the postpartum period. [13]

In order to combat iron deficiency anaemia in pregnant ladies various iron supplements programmes have been devised and implemented worldwide considering its ease, safety and feasibility. A study conducted showed preventive iron supplementation reduced maternal anaemia at term by 70%. [14] However, it is well recognized that "Drugs don't work on patients who don't take them". Studies conducted have shown that non-adherence is the main factor for these programmes to be less effective. The WHO defines adherence, a term which is often used interchangeably with compliance, as the extent to which a person's behaviour taking medication, following a diet and executing lifestyle changes, corresponds with agreed recommendations from a health care provider. [15] A study conducted in South Ethiopia showed compliance of 39.2%. [16] Another study in South-eastern Nigeria showed compliance of 65.9%. [17] A study in South India showed compliance of 64.7% and non-adherence in 35.3%. [18] A study in 2 provinces in Cambodia showed adherence of 47%. [19]

Various factors have been highlighted in these studies rendering non-compliance including a) Poor knowledge of the patients of anaemia and iron supplements .b) Poor counselling .c) GIT disturbances. d) Late booking and less frequent antenatal visits. In this paper we aim to analyse frequency of non-adherence and factors associated with it in our antenatal clinic in order to prevent iron deficiency anaemia in pregnant women. In addition to the general consequences of anaemia, there are specific risks during pregnancy for the mother and the fetus such as intrauterine growth retardation, prematurity, feto-placental miss ratio, and higher risk for peripartum blood transfusion. [20] The only way to prevent maternal death arising from anaemia is by early detection, effective management, creating awareness and health education.

The purpose of this study is to evaluate the non-adherence and determinants of non-adherence to iron supplements in order to prevent iron deficiency anaemia by assuring correct dosage and proper intake and overcoming reservations and grievances of patients attending outpatient department in Holy Family hospital.

Review of Literature

Anemia

Anemia is a decrease in amount of red blood cells (RBCs) or the amount of hemoglobin in the blood.18 When anemia comes on slowly the symptoms are often vague and may include: feeling tired, weakness, shortness of breath or a poor ability to exercise. Anemia that comes on quickly often has greater symptoms which may include: confusion, feeling like one is going to pass out, and increased desire to drink fluids. There needs to be significant anemia before a person becomes noticeably pale. There may be additional symptoms depending on the specific underlying cause. [2]

There are three main types of anemia, that due to blood loss, that due to decreased red blood cell production, and that due to increased red blood cell breakdown. Causes of blood loss include trauma and gastrointestinal bleeding among others. Causes of decreased production include iron deficiency, a lack of vitamin B12, thalassemia and a number of neoplasms of the bone marrow among others. Causes of increased breakdown include a number of genetic conditions such as sickle cell anemia, infections like malaria and some autoimmune diseases among others. It can also be classified based on the size of red blood cells and amount of hemoglobin in each cell. If the cells are small it is microcytic anemia, if they are large it is macrocytic anemia and if they are normal sized it is normocytic anemia. Diagnosis in men is based on a hemoglobin of less than 130 to 140 g/L (13 to 14 g/dL) while in women it must be less 120 to 130 g/L (12 to 13 g/dL). [2,3] Further testing is then required to determine the cause. [2]

Certain groups of individuals, such as pregnant people, benefit from the use of iron pills for prevention. [21] Dietary supplementation, without determining the specific cause, is not recommended The use of blood transfusions is typically based on a persons signs and symptoms. [2] In those without symptoms they are not recommended unless hemoglobin levels are less than 60 to 80 g/L (6 to 8 g/dL). [2] These recommendations may also apply to some people with acute bleeding. [2]Erythropoiesis-stimulating medications are not recommended in those with mild or moderate anemia. [21]

Anemia is the most common disorder of the blood with it affecting about a quarter of people globally. [2] Iron-deficiency anemia affects nearly 1 billion. [21] It is more in females than males [21] among children, during pregnancy and in the elderly. [2] Anemia both increases both costs of medical care and lost productivity through a decreased ability to work. [3]

Epidemiology

The prevalence of anemia in population studies of healthy, non-pregnant people depends on the Hb concentration chosen for the lower limit of normal values. The World Health Organization (WHO) chose 12.5 g/dL for both adult males and females. In the United States, limits of 13.5 g/dL for men and 12.5 g/dL for women are probably more realistic. Using these values, approximately 4% of men and 8% of women have values lower than those cited. A significantly greater prevalence is observed in patient populations. Less information is available regarding studies using RBC or Hct.

The prevalence of anemia in Canada and northern Europe is believed to be similar to that in the United States. In underprivileged countries, limited studies of purportedly healthy subjects show the prevalence of anemia to be 2-5 times greater than that in the United States. Although geographic diseases, such as sickle cell anemia, thalassemia, malaria, hookworm, and chronic infections, are responsible for a portion of the increase, nutritional factors with iron deficiency and, to a lesser extent, folic acid deficiency play major roles in the increased prevalence of anemia. Populations with little meat in the diet have a high incidence of iron deficiency anemia, because heme iron is better absorbed from food than inorganic iron.

Sickle cell disease is common in regions of Africa, India, Saudi Arabia, and the Mediterranean basin. The thalassemias are the most common genetic blood diseases and are found in Southeast Asia and in areas where sickle cell disease is common.

Race-related demographics

Certain races and ethnic groups have an increased prevalence of genetic factors associated with certain anemias. Diseases such as the hemoglobinopathies, thalassemia, and G-6-PD deficiency have different morbidity and mortality in different populations due to differences in the genetic abnormality producing the disorder. For example, G-6-PD deficiency and thalassemia have less morbidity in African Americans than in Sicilians because of differences in the genetic fault. Conversely, sickle cell anemia has greater morbidity and mortality in African Americans than in Saudi Arabians.

Race is a factor in nutritional anemias and anemia associated with untreated chronic illnesses to the extent that socioeconomic advantages are distributed along racial lines in a given area; [22] socioeconomic advantages that positively affect diet and the availability of health care lead to a decreased prevalence of these types of anemia. [23-25] For instance, iron deficiency anemia is much more

prevalent in the populations of developing nations, who tend to have little meat in their diets, than it is in populations of the United States and northern Europe.

Similarly, anemia of chronic disorders is commonplace in populations with a high incidence of chronic infectious disease (e.g. malaria, tuberculosis, acquired immunodeficiency syndrome [AIDS]), and this is at least in part worsened by the socioeconomic status of these populations and their limited access to adequate health care.

Sex-related demographics

Overall, anemia is twice as prevalent in females as in males. This difference is significantly greater during the childbearing years due to pregnancies and menses.

Approximately 65% of body iron is incorporated into circulating Hb. One gram of Hb contains 3.46 mg of iron (1 mL of blood with an Hb concentration of 15 g/dL = 0.5 mg of iron). Each healthy pregnancy depletes the mother of approximately 500 mg of iron. While a man must absorb about 1 mg of iron to maintain equilibrium, a premenopausal woman must absorb an average of 2 mg daily. Further, because women eat less food than men, they must be more than twice as efficient as men in the absorption of iron to avoid iron deficiency.

Women have a markedly lower incidence of X-linked anemias, such as G-6-PD deficiency and sex-linked sideroblastic anemias, than men do. In addition, in the younger age groups, males have a higher incidence of acute anemia from traumatic causes.

Age-related demographics

Previously, severe, genetically acquired anemias (e.g. sickle cell disease, thalassemia, Fanconi syndrome) were more commonly found in children because they did not survive to adulthood. However, with improvement in medical care and breakthroughs in transfusion and iron chelation therapy, in addition to fetal hemoglobin modifiers, the life expectancy of persons with these diseases has been significantly prolonged. [26]

Acute anemia has a bimodal frequency distribution, affecting mostly young adults and persons in their late fifties. Causes among young adults include trauma, menstrual and ectopic bleeding, and problems of acute hemolysis. During their childbearing years, women are more likely to become iron deficient.

In people aged 50-65 years, acute anemia is usually the result of acute blood loss in addition to a chronic anemic state. This is the case in uterine and GI bleeding.

Neoplasia increases in prevalence with each decade of life and can produce anemia from bleeding, from the invasion of bone marrow with tumor, or from the development of anemia associated with chronic disorders. The use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and warfarin also increases with age and can produce GI bleeding.

Types of Anemia

Microcytic

Microcytic anemia is primarily a result of hemoglobin synthesis failure/insufficiency, which could be caused by several etiologies:

- Heme synthesis defect
  - Iron deficiency anemia (microcytosis is not always present)
  - Anemia of chronic disease (more commonly presenting as normocytic anemia)
- Globin synthesis defect
  - Alpha-, and beta-thalassemia
  - HbE syndrome
  - HbC syndrome
  - Various other unstable hemoglobin diseases
- Sideroblastic defect
  - Hereditary sideroblastic anemia
  - Acquired sideroblastic anemia, including lead toxicity
  - Reversible sideroblastic anemia

Iron deficiency anemia is the most common type of anemia overall and it has many causes. RBCs often appear hypochromic (paler than usual) and microcytic (smaller than usual) when viewed with a microscope.

- Iron deficiency anemia is due to insufficient dietary intake or absorption of iron to meet the body's needs. Infants, toddlers, and pregnant women have higher than average needs. Increased iron intake is also needed to offset blood losses due to digestive tract issues, frequent blood donations, or heavy menstrual periods. Iron is an essential part of hemoglobin, and low iron levels result in decreased incorporation of hemoglobin into red blood cells. In the United States, 12% of all women

of childbearing age have iron deficiency, compared with only 2% of adult men. The incidence is as high as 20% among African American and Mexican American women. Studies have shown iron deficiency without anemia causes poor school performance and lower IQ in teenage girls, although this may be due to socioeconomic factors. [27,28] Iron deficiency is the most prevalent deficiency state on a worldwide basis. It is sometimes the cause of abnormal fissuring of the angular (corner) sections of the lips (angular stomatitis).

- In the United States, the most common cause of iron deficiency is bleeding or blood loss, usually from the gastrointestinal tract. Fecal occult blood testing, upper endoscopy and lower endoscopy should be performed to identify bleeding lesions. In older men and women, the chances are higher that bleeding from the gastrointestinal tract could be due to colon polyps or colorectal cancer.
- Worldwide, the most common cause of iron deficiency anemia is parasitic infestation (hookworms, amebiasis, schistosomiasis and whipworms).

The Mentzer index (mean cell volume divided by the RBC count) predicts whether microcytic anaemia may be due to iron deficiency or thallasemia, although it requires confirmation.

Macrocytic

- Megaloblastic anemia, the most common cause of macrocytic anemia, is due to a deficiency of either vitamin B_{12}, folic acid, or both. Deficiency in folate and/or vitamin B_{12} can be due either to inadequate intake or insufficient absorption. Folate deficiency normally does not produce neurological symptoms, while B_{12} deficiency does.
- Pernicious anemia is caused by a lack of intrinsic factor, which is required to absorb vitamin B_{12} from food. A lack of intrinsic factor may arise from an autoimmune condition targeting the parietal cells (atrophic gastritis) that produce intrinsic factor or against intrinsic factor itself. These lead to poor absorption of vitamin B_{12}.
- Macrocytic anemia can also be caused by removal of the functional portion of the stomach, such as during gastric bypass surgery, leading to reduced vitamin B_{12}/folate absorption. Therefore, one must always be aware of anemia following this procedure.
- Hypothyroidism
- Alcoholism commonly causes a macrocytosis, although not specifically anemia. Other types of liver disease can also cause macrocytosis.
- Drugs such as Methotrexate, zidovudine, and other substances may inhibit DNA replication such as heavy metals (e.g. Lead)

Macrocytic anemia can be further divided into "megaloblastic anemia" or "nonmegaloblastic macrocytic anemia". The cause of megaloblastic anemia is primarily a failure of DNA synthesis with preserved RNA synthesis, which results in restricted cell division of the progenitor cells. The megaloblastic anemias often present with neutrophil hypersegmentation (six to 10 lobes). The nonmegaloblastic macrocytic anemias have different etiologies (i.e. unimpaired DNA globin synthesis,) which occur, for example, in alcoholism.

In addition to the nonspecific symptoms of anemia, specific features of vitamin B_{12} deficiency include peripheral neuropathy and subacute combined degeneration of the cord with resulting balance difficulties from posterior column spinal cord pathology. Other features may include a smooth, red tongue and glossitis.

The treatment for vitamin B_{12}-deficient anemia was first devised by William Murphy, who bled dogs to make them anemic, and then fed them various substances to see what (if anything) would make them healthy again. He discovered that ingesting large amounts of liver seemed to cure the disease. George Minot and George Whipple then set about to isolate the curative substance chemically and ultimately were able to isolate the vitamin B_{12} from the liver. All three shared the 1934 Nobel Prize in Medicine.

Normocytic

Normocytic anemia occurs when the overall hemoglobin levels are decreased, but the red blood cell size (mean corpuscular volume) remains normal. Causes include:

- Acute blood loss
- Anemia of chronic disease
- Aplastic anemia (bone marrow failure)
- Hemolytic anemia

Iron Deficiency Anemia

Iron deficiency is defined as a decreased total iron body content. Iron deficiency anemia occurs when iron deficiency is severe enough to diminish erythropoiesis and cause the development of anemia. Iron deficiency is the most prevalent single deficiency state on a worldwide basis. It is important economically because it diminishes the

capability of individuals who are affected to perform physical labor, and it diminishes both growth and learning in children.

Post-hemorrhagic anemia is discussed in this article because it is an important cause of iron deficiency. The acute and potentially catastrophic problems of hypoxia and shock that can occur from significant hemorrhage or severe iron deficiency are discussed elsewhere; however, daily blood losses can be small and may be overlooked.

Occasionally, patients with severe iron deficiency anemia from slow but persistent gastrointestinal (GI) bleeding have repeatedly negative testing of stool for hemoglobin. Therefore, it is important for the clinician to be aware of characteristics of the anemia at all intervals after the onset of bleeding.

Epidemiology [29]

In North America and Europe, iron deficiency is most common in women of childbearing age and as a manifestation of hemorrhage. Iron deficiency caused solely by diet is uncommon in adults in countries where meat is an important part of the diet. Depending upon the criteria used for the diagnosis of iron deficiency, approximately 4-8% of premenopausal women are iron deficient. In men and postmenopausal women, iron deficiency is uncommon in the absence of bleeding.

In countries where little meat is in the diet, iron deficiency anemia is 6-8 times more prevalent than in North America and Europe. This occurs despite consumption of a diet that contains an equivalent amount of total dietary iron; the reason is that heme iron is absorbed better from the diet than nonheme iron. In certain geographic areas, intestinal parasites, particularly hookworm, worsen the iron deficiency because of blood loss from the GI tract. Anemia is more profound among children and premenopausal women in these environs.

Age

Healthy newborn infants have a total body iron of 250 mg (80 ppm), which is obtained from maternal sources. This decreases to approximately 60 ppm in the first 6 months of life, while the baby consumes an iron-deficient milk diet. Infants consuming cow milk have a greater incidence of iron deficiency because bovine milk has a higher concentration of calcium, which competes with iron for absorption. Subsequently, growing children must obtain approximately 0.5 mg more iron daily than is lost in order to maintain a normal body concentration of 60 ppm.

During adult life, equilibrium between body loss and gain is maintained. Children are more likely to develop iron deficiency anemia. In certain geographic areas, hookworm adds to the problem. Children are more likely to walk in soil without shoes and develop heavy infestations.

During adult life, equilibrium between body loss and gain is maintained. Children are more likely to develop iron deficiency anemia. In certain geographic areas, hookworm adds to the problem. Children are more likely to walk in soil without shoes and develop heavy infestations.

Gastrointestinal neoplasms become increasingly more prevalent with each decade of life. They frequently present with GI bleeding that may remain occult for long intervals before it is detected. Usually, bleeding from neoplasms in other organs is not occult, prompting the patient to seek medical attention before developing severe iron depletion. Investigate the etiology of the iron deficiency anemia to evaluate for a neoplasm.

Sex

An adult male absorbs and loses about 1 mg of iron from a diet containing 10-20 mg daily. During childbearing years, an adult female loses an average of 2 mg of iron daily and must absorb a similar quantity of iron in order to maintain equilibrium. Because the average woman eats less than the average man does, she must be more than twice as efficient in absorbing dietary iron in order to maintain equilibrium and avoid developing iron deficiency anemia.

Healthy males lose body iron in sloughed epithelium, in secretions from the skin and gut lining, and from small daily losses of blood from the GI tract (0.7 mL daily). Cumulatively, this amounts to 1 mg of iron. Males with severe siderosis from blood transfusions can lose a maximum of 4 mg daily via these routes without additional blood loss.

A woman loses about 500 mg of iron with each pregnancy. Menstrual losses are highly variable, ranging from 10 to 250 mL (4-100 mg of iron) per period. These iron losses in women double their need to absorb iron in comparison to males. A special effort should be made to identify and treat iron deficiency during pregnancy and early childhood because of the effects of severe iron deficiency upon learning capability, growth, and development.

Race

Race probably has no significant effect upon the occurrence of iron deficiency anemia; however, because diet and socioeconomic factors play a role in the prevalence of iron deficiency, it more frequently is observed in people of various racial backgrounds living in poorer areas of the world.

Pathophysiology

Iron is vital for all living organisms because it is essential for multiple metabolic processes, including oxygen transport, DNA synthesis, and electron transport. Iron equilibrium in the body is regulated carefully to ensure that sufficient iron is absorbed in order to compensate for body losses of iron (Figure I). Whereas body loss of iron quantitatively is as important as absorption in terms of maintaining iron equilibrium, it is a more passive process than absorption. [30]

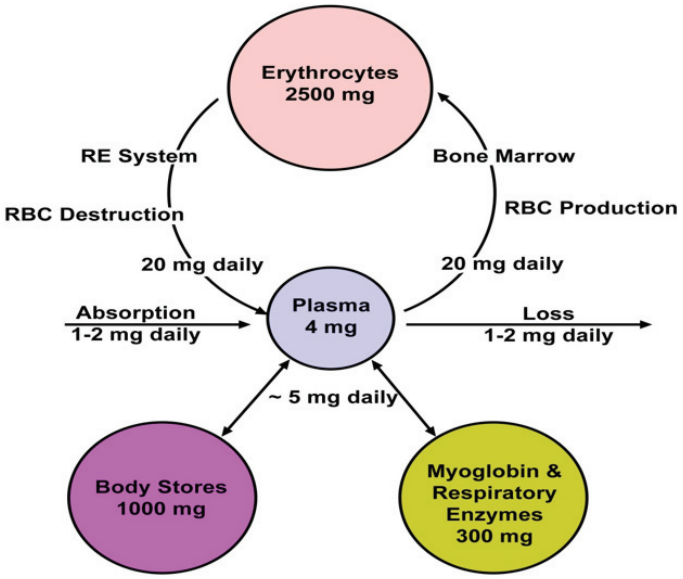


Figure I: *Iron metabolism.*

Either diminished absorbable dietary iron or excessive loss of body iron can cause iron deficiency. Diminished absorption usually is due to an insufficient intake of dietary iron in an absorbable form. Hemorrhage is the most common cause of excessive loss of body iron, but it can occur with hemoglobinuria from intravascular hemolysis. Malabsorption of iron is relatively uncommon in the absence of small bowel disease (sprue, celiac disease, regional enteritis) or previous GI surgery.

Iron uptake in the proximal small bowel occurs by 3 separate pathways (Figure II). These are the heme pathway and 2 distinct pathways for ferric and ferrous iron.

In North America and Europe, one third of dietary iron is heme iron, but two thirds of body iron is derived from dietary myoglobin and hemoglobin. Heme iron is not chelated and precipitated by numerous dietary constituent that render nonheme iron nonabsorbable (Figure III), such as phytates, phosphates, tannates, oxalates, and carbonates. Heme is maintained soluble and available for absorption by globin degradation products produced by pancreatic enzymes. Heme iron and nonheme iron are absorbed into the enterocyte noncompetitively. [30,31]

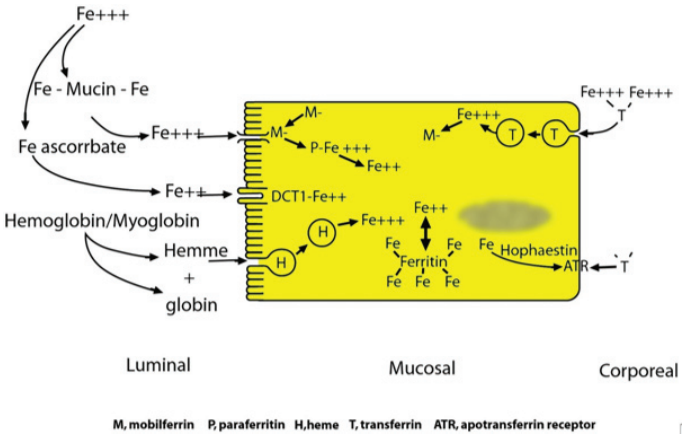


Figure II: *Mechanism of iron Absorption.*

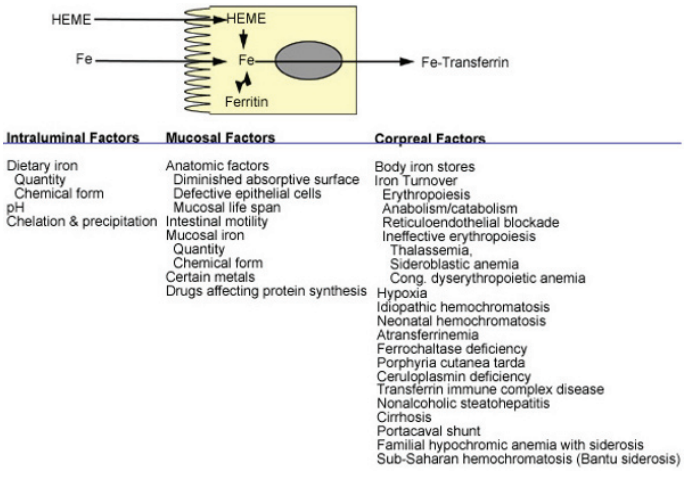


Figure III: *Factors affecting various stages of iron absorption.*

Heme enters the cell as an intact metalloporphyrin, presumably by a vesicular mechanism. It is degraded within the enterocyte by heme oxygenase with release of iron so that it traverses the basolateral cell membrane in competition with nonheme iron to bind transferrin in the plasma.

Ferric iron utilizes a different pathway to enter cells than ferrous iron. This was shown by competitive inhibition studies, the use of blocking antibodies against divalent metal transporter-1 (DMT-1) and beta3-integrin, and transfection experiments using DMT-1 DNA. This research indicated that ferric iron utilizes beta3-integrin and mobilferrin, while ferrous iron uses DMT-1 to enter cells.

Which pathway transports most nonheme iron in humans is not known. Most nonheme dietary iron is ferric iron. Iron absorption in mice and rats may involve more ferrous iron because they excrete moderate quantities of ascorbate in intestinal secretions. Humans, however, are a scorbutic species and are unable to synthesize ascorbate to reduce ferric iron.

Other proteins appear to be related to iron absorption. These are stimulators of iron transport (SFT), which are reported to increase the absorption of both ferric and ferrous iron, and hephaestin, which is postulated to be important in the transfer of iron from enterocytes into the plasma. The relationships and interactions among the newly described proteins are not known at this time and are being explored in a number of laboratories.

The iron concentration within enterocytes varies directly with the body's requirement for iron. Absorptive cells of iron-deficient humans and animals contain little stainable iron, whereas those of subjects who are replete in iron contain significantly higher amounts. Untreated phenotypic hemochromatosis creates little stainable iron in the enterocyte, similar to iron deficiency. Iron within the enterocyte may operate by up-regulation of a receptor, saturation of an iron-binding protein, or both. [31,32]

In contrast to findings in iron deficiency, enhanced erythropoiesis, or hypoxia, endotoxin rapidly diminishes iron absorption without altering enterocyte iron concentration. This suggests that endotoxin and, perhaps, cytokines alter iron absorption by a different mechanism. This is the effect of hepcidin and the balance of hepcidin versus erythropoietin.

Most iron delivered to nonintestinal cells is bound to transferrin. Transferrin iron is delivered into nonintestinal cells via 2 pathways: the classical transferrin receptor pathway (high affinity, low capacity) and the pathway independent of the transferrin receptor (low affinity, high capacity). Otherwise, the nonsaturability of transferrin binding to cells cannot be explained.

In the classical transferrin pathway, the transferrin iron complex enters the cell within an endosome. Acidification of the endosome releases the iron from transferrin so that it can enter the cell. The apotransferrin is delivered by the endosome to the plasma for reutilization. The method by which the transferrin receptor–independent pathway delivers iron to the cell is not known.

Non-intestinal cells also possess the mobilferrin integrin and DMT-1 pathways. Their function in the absence of an iron-saturated transferrin is uncertain; however, their presence in nonintestinal cells suggests that they may participate in intracellular functions in addition to their capability to facilitate cellular uptake of iron. [32]

Etiology

Dietary factors

Meat provides a source of heme iron, which is less affected by the dietary constituents that markedly diminish bioavailability than nonheme iron is. The prevalence of iron deficiency anemia is low in geographic areas where meat is an important constituent of the diet. In areas where meat is sparse, iron deficiency is commonplace.

Substances that diminish the absorption of ferrous and ferric iron include phytates, oxalates, phosphates, carbonates, and tannates. These substances have little effect upon the absorption of heme iron. Similarly, ascorbic acid increases the absorption of ferric and ferrous iron and has little effect upon the absorption of heme iron.

Purified heme is absorbed poorly because heme polymerizes into macromolecules. Globin degradation products diminish heme polymerization, making it more available for absorption. They also increase the absorption of nonheme iron because the peptides from degraded globin bind the iron to prevent both precipitation and polymerization; thus, absorption of the iron in spinach is increased when the spinach eaten with meat. Heme and nonheme iron uptake by intestinal absorptive cells is noncompetitive.

Hemorrhage

Bleeding for any reason produces iron depletion. If sufficient blood loss occurs, iron deficiency anemia ensues. A single sudden loss of blood produces a posthemorrhagic anemia that is normocytic. The bone marrow is stimulated to increase production of hemoglobin, thereby depleting iron in body stores. Once they are depleted, hemoglobin synthesis is impaired and microcytic hypochromic erythrocytes are produced.

Maximal changes in the red blood cell (RBC) cellular indices occur in approximately 120 days, at a time when all normal erythrocytes produced prior to the hemorrhage are replaced by microcytes. Before this time, the peripheral smear shows a dimorphic population of erythrocytes, normocytic cells produced before bleeding, and microcytic cells produced after bleeding. This is reflected in the red blood cell distribution width (RDW); thus, the earliest evidence of the development of an iron-deficient erythropoiesis is seen in the peripheral smear, in the form of increased RDW. [33,34]

Hemosiderinuria, hemoglobinuria, and pulmonary hemosiderosis

Iron deficiency anemia can occur from loss of body iron in the urine. If a freshly obtained urine specimen appears bloody but contains no red blood cells, suspect hemoglobinuria. Obtain confirmation in the laboratory that the pigment is hemoglobin and not myoglobin. This can be accomplished easily because 60% ammonium sulfate precipitates hemoglobin but not myoglobin.

Hemoglobinuria classically is ascribed to paroxysmal nocturnal hemoglobinuria, but it can occur with any brisk intravascular hemolytic anemia. In the early days of heart surgery with implantation of artificial valves, this mechanism of producing iron deficiency anemia was commonplace in large university hospitals. Today, with better prostheses, it has become a less frequent clinical problem. With less severe hemolytic disorders, there may be no significant hemoglobinuria.

Investigate renal loss of iron by staining the urine sediment for iron. Hemosiderin is detected intracellularly. Most of these patients have a low or absent plasma haptoglobin. Similarly, pulmonary hemosiderosis can result in sufficient loss of iron as hemosiderin from the lungs.

Malabsorption of iron

Prolonged achlorhydria may produce iron deficiency because acidic conditions are required to release ferric iron from food. Then, it can be chelated with mucins and other substances (e.g. amino acids, sugars, amino acids, or amides) to keep it soluble and available for absorption in the more alkaline duodenum.

Starch and clay eating produce malabsorption of iron and iron deficiency anemia. Specific inquiry is required to elicit a history of either starch or clay eating because patients do not volunteer the information.

Extensive surgical removal of the proximal small bowel or chronic diseases (e.g. untreated sprue or celiac syndrome) can diminish iron absorption. Rarely, patients with no history of malabsorption have iron deficiency anemia and fail to respond to oral iron therapy. Most merely are noncompliant with therapy. [34]

Before placing these patients on parenteral therapy, document iron malabsorption either by measuring absorption of radioiron or by obtaining a baseline fasting serum-iron concentration and repeating the test 30 minutes and 1 hour after administration of a freshly prepared oral solution of ferrous sulfate (50-60 mg of iron) under observation. The serum iron should increase by 50% over the fasting specimen.

Genetic abnormalities producing iron deficiency have been shown in rodents (sex-linked anemia [sla] mice, microcytic anemia [mk] mice, Belgrade rat). This phenomenon has not been clearly demonstrated in humans; if it exists, it is probably an uncommon cause of iron deficiency anemia. [35,36]

Clinical Presentation [37,38]
History

Although iron deficiency anemia is a laboratory diagnosis, a carefully obtained history can facilitate its recognition. The history can also be useful in establishing the etiology of the anemia and, perhaps, in estimating its duration.

Iron deficiency in the absence of anemia is asymptomatic. One half of patients with moderate iron deficiency anemia develop pagophagia. Usually, they crave ice to suck or chew. Occasionally, patients are seen who prefer cold celery or other cold vegetables in lieu of ice. Leg cramps, which occur on climbing stairs, also are common in patients deficient in iron.

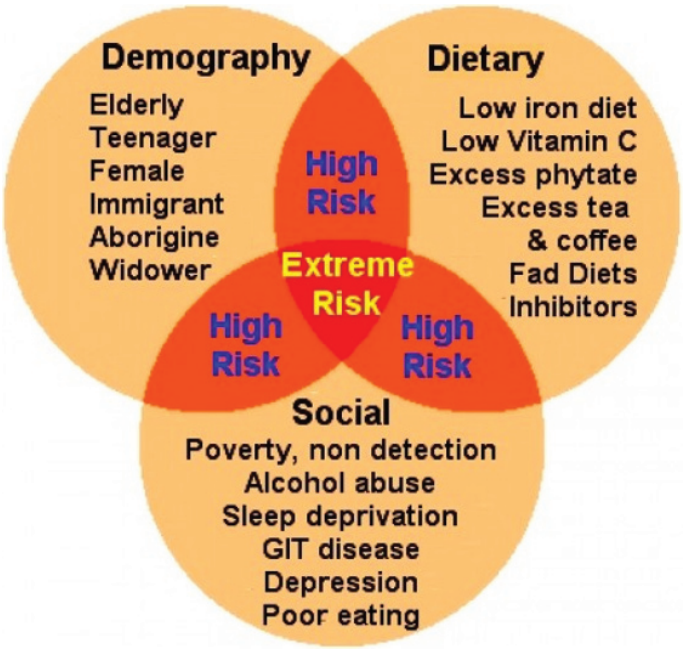


Figure IV: *Etiology of Iron deficiency anemia.*

Often, patients can identify a distinct point in time when these symptoms first occurred, providing an estimate of the duration of the iron deficiency.

Fatigue and diminished capability to perform hard labor are attributed to the lack of circulating hemoglobin; however, they occur out of proportion to the degree of anemia and probably are due to a depletion of proteins that require iron as a part of their structure.

Increasing evidence suggests that deficiency or dysfunction of non-hemoglobin proteins has deleterious effects. These include muscle dysfunction, pagophagia, dysphagia with esophageal webbing, poor scholastic performance, altered resistance to infection, and altered behavior.

Dietary history

A dietary history is important. Vegetarians are more likely to develop iron deficiency, unless their diet is supplemented with iron. National programs of dietary iron supplementation are initiated in many portions of the world where meat is sparse in the diet and iron deficiency anemia is prevalent. Unfortunately, affluent nations also supplement iron in foodstuffs and vitamins without recognizing the potential contribution of iron to free radical formation and the prevalence of genetic iron overloading disorders.

Elderly patients who are in poor economic circumstances and do not wish to seek aid may try to survive on a "tea and toast" diet. They may also be hesitant to share this dietary information. This group is far more likely to develop protein-calorie malnutrition before they develop iron deficiency anemia.

A fundamental concept is that after age 1 year, dietary deficiency alone is not sufficient to cause clinically significant iron deficiency, so a source of blood loss should always be sought as part of the management of a patient with iron deficiency anemia. Infants and toddlers are the primary risk groups for dietary iron deficiency anemia. Neonates who double their birthweight are a special risk group.

Pica is not a cause of iron deficiency anemia; pica is a symptom of iron deficiency anemia. It is the link between iron deficiency anemia and lead poisoning, which is why iron deficiency anemia should always be sought when a child is diagnosed with lead poisoning. Hippocrates recognized clay eating; however, modern physicians often do not recognize it unless the patient and family are specifically queried. Both substances decrease the absorption of dietary iron. Clay eating occurs worldwide in all races, though it is more common in Asia Minor. Starch eating is a habit in females of African heritage, and it often is started in pregnancy as a treatment for morning sickness.

History of hemorrhage

Two thirds of body iron is present in circulating red blood cells as hemoglobin. Each gram of hemoglobin contains 3.47 mg of iron; thus, each mL of blood lost from the body (hemoglobin 15 g/dL) results in a loss of 0.5 mg of iron.

Bleeding is the most common cause of iron deficiency, either from parasitic infection (hookworm) or other causes of blood loss. With bleeding from most orifices (hematuria, hematemesis, hemoptysis), patients will present before they develop chronic iron deficiency anemia; however, gastrointestinal bleeding may go unrecognized. Patients often do not understand the significance of a melanotic stool.

Excessive menstrual losses may be overlooked. Unless menstrual flow changes, patients typically do not seek medical attention for menorrhagia. If the clinician asks, these patients generally report that their menses are normal. Because of the marked differences among women with regard to menstrual blood loss (10-250 mL per

menses), query the patient about a specific history of clots, cramps, and the use of multiple tampons and pads.

Physical Examination

Anemia produces nonspecific pallor of the mucous membranes. A number of abnormalities of epithelial tissues are described in association with iron deficiency anemia. These include esophageal webbing, koilonychia, glossitis, angular stomatitis, and gastric atrophy.

The exact relationship of these epithelial abnormalities to iron deficiency is unclear and may involve other factors. For example, in publications from the United Kingdom, esophageal webbing and atrophic changes of the tongue and the corner of the mouth are reported in as many as 15% of patients with iron deficiency; however, they are much less common in the United States and other portions of the world.

Splenomegaly may occur with severe, persistent, untreated iron deficiency anemia. This is uncommon in the United States and Europe.

Diagnosis

Although the history and physical examination can lead to the recognition of the condition and help establish the etiology, iron deficiency anemia is primarily a laboratory diagnosis.

Useful tests include a complete blood count (CBC); a peripheral smear; serum iron, total iron-binding capacity (TIBC), and serum ferritin; evaluation for hemosiderinuria, hemoglobinuria, and pulmonary hemosiderosis; hemoglobin electrophoresis and measurement of hemoglobin A_2 and fetal hemoglobin; and reticulocyte hemoglobin content.

Other laboratory tests (e.g. stool testing, incubated osmotic fragility testing, measurement of lead in tissue, and bone marrow aspiration) are useful for establishing the etiology of iron deficiency anemia and for excluding or establishing a diagnosis of 1 of the other microcytic anemias.

Complete Blood Count

The CBC documents the severity of the anemia. In chronic iron deficiency anemia, the cellular indices show a microcytic and hypochromic erythropoiesis—that is, both the mean corpuscular volume (MCV) and the mean corpuscular hemoglobin concentration (MCHC) have values below the normal range for the laboratory performing the test. Reference range values for MCV and MCHC are 83-97 fL and 32-36 g/dL, respectively.

Often, the platelet count is elevated (>450,000/µL); this elevation normalizes after iron therapy. The white blood cell (WBC) count is usually within reference ranges (4500-11,000/µL), but it may be elevated.

If the CBC is obtained after blood loss, the cellular indices do not enter the abnormal range until most of the erythrocytes produced before the bleed are destroyed at the end of their normal lifespan (120 d).

Peripheral Smear

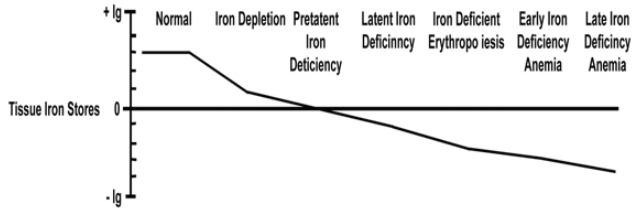
Examination of the peripheral smear is an important part of the workup of patients with anemia. Examination of the erythrocytes shows microcytic and hypochromic red blood cells in chronic iron deficiency anemia. The microcytosis is apparent in the smear long before the MCV is decreased after an event producing iron deficiency. Platelets usually are increased in this disorder.

In iron deficiency anemia, unlike thalassemia, target cells usually are not present, and anisocytosis and poikilocytosis are not marked. This condition lacks the intraerythrocytic crystals seen in hemoglobin C disorders.

Combined folate deficiency and iron deficiency are commonplace in areas of the world with little fresh produce and meat. The peripheral smear reveals a population of macrocytes mixed among the microcytic hypochromic cells. This combination can normalize the MCV.

Serum Iron, Total Iron-Binding Capacity, and Serum Ferritin [39,40]

Low serum iron and ferritin levels with an elevated TIBC are diagnostic of iron deficiency. While a low serum ferritin is virtually diagnostic of iron deficiency, a normal serum ferritin can be seen in patients who are deficient in iron and have coexistent diseases (e.g. hepatitis or anemia of chronic disorders). These test findings are useful in distinguishing iron deficiency anemia from other microcytic anemias (Figure V& VI).



Serum Ferritin (µg/1)	60	20	<12	<12	<12	<12	<12
Stainable Tissue Iron (0-4+)	2+	1+	0	0	0	0	0
Transferrin Saturation (%)	35	35	35	20	<16	<16	<16
Free Erythrocyle Protoporhyrin (µg/dl)	30	30	30	75	>100	>100	>100
Hemoglobin (g/dl)	14	14	14	14	13	<12	<12
Mean Corpuscular Volume (µ³)	90	90	90	90	88	86	<82
Mean Corpuscular Hemoglobin Concentration (0/0)	33	33	33	33	33	31	<28

Figure V: *Findings in Iron deficiency anemia.*

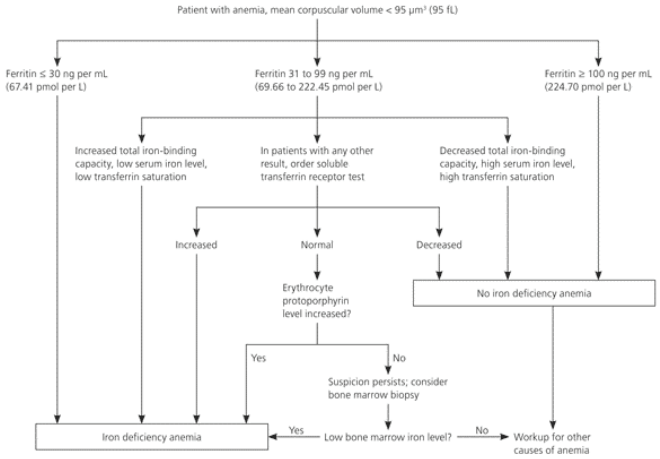


Figure VI: *Diagnostic algorithm for iron deficiency anemia.*

Evaluation for Hemosiderinuria, Hemoglobinuria, and Pulmonary Hemosiderosis

Iron deficiency anemia can occur from loss of body iron in the urine. If a freshly obtained urine specimen appears bloody but contains no red blood cells, suspect hemoglobinuria. Obtain confirmation in the laboratory that the pigment is hemoglobin and not myoglobin. This can be accomplished easily because 60% ammonium sulfate precipitates hemoglobin but not myoglobin.

Hemoglobinuria classically is ascribed to paroxysmal nocturnal hemoglobinuria, but it can occur with any brisk intravascular hemolytic anemia. In the early days of heart surgery with implantation of artificial valves, this mechanism of producing iron deficiency anemia was commonplace in large university hospitals. Today, with better prostheses, it has become a less frequent clinical problem. With less severe hemolytic disorders, there may be no significant hemoglobinuria. [41,42]

Investigate renal loss of iron by staining the urine sediment for iron. Hemosiderin is detected intracellularly. Most of these patients have a low or absent plasma haptoglobin. Similarly, pulmonary hemosiderosis can result in sufficient loss of iron as hemosiderin from the lungs. [43]

Hemoglobin Studies

Hemoglobin electrophoresis and measurement of hemoglobin A_2 and fetal hemoglobin

Hemoglobin electrophoresis and measurement of hemoglobin A_2 and fetal hemoglobin are useful in establishing either beta-thalassemia or hemoglobin C or D as the etiology of the microcytic anemia. Unfortunately, simple tests do not exist for alpha-thalassemia in most laboratories, and it is a diagnosis of exclusion.

Reticulocyte hemoglobin content

Mateos Gonzales et al assessed the diagnostic efficiency of commonly used hematologic and biochemical markers, as well as the reticulocyte hemoglobin content (CHr) in the diagnosis of iron deficiency in children, with or without anemia. [39] The investigators identified CHr and iron serum as the only parameters that were independently associated with iron deficiency (P< .05), and CHr was the strongest predictor of iron deficiency and iron deficiency anemia.

Mateos Gonzalez et al concluded that measurement of CHr may be a reliable method to assess deficiencies in tissue iron supply and, in combination with a CBC, may be an alternative to the traditional biochemical panel for the diagnosis of iron deficiency in children. [39]

Other Laboratory Tests

Stool testing

Testing stool for the presence of hemoglobin is useful in establishing gastrointestinal (GI) bleeding as the etiology of iron deficiency anemia. Usually, chemical testing that detects more than 20 mL of blood loss daily from the upper GI tract is employed. More sensitive tests are available; however, they produce a high incidence of

false-positive results in people who eat meat. Severe iron deficiency anemia can occur in patients with a persistent loss of less than 20 mL/d.

To detect blood loss, the patient can be placed on a strict vegetarian diet for 3-5 days and the stool can be tested for hemoglobin with a benzidine method, or red blood cells (RBCs) can be radiolabeled with radiochromium and retransfused. Stools are collected, and the radioactivity is quantified in a gamma-detector and compared to the radioactivity in a measured quantity of the patient's blood. An immunologic method of detecting human species-specific hemoglobin in stool is under development and could increase specificity and sensitivity.

Incubated osmotic fragility

Incubated osmotic fragility is useful. Microspherocytosis may produce a low-normal or slightly abnormal MCV; however, the MCHC usually is elevated rather than decreased, and the peripheral smear shows a lack of central pallor rather than hypochromia. Spherocytosis can normally be separated from iron deficiency anemia by peripheral blood smear.

Tissue lead concentrations

Measure tissue lead concentrations. Chronic lead poisoning may produce a mild microcytosis. The anemia probably is related to the anemia of chronic disorders. The incidence of lead poisoning is greater in individuals who are iron deficient than in healthy subjects because increased absorption of lead occurs in individuals who are iron deficient. Paint in old houses has been a source of lead poisoning in children and painters.

Bone marrow aspiration

A bone marrow aspirate can be diagnostic of iron deficiency. The absence of stainable iron in a bone marrow aspirate that contains spicules and a simultaneous control specimen containing stainable iron permit establishment of a diagnosis of iron deficiency without other laboratory tests.

A bone marrow aspirate stained for iron (Perls stain) can be diagnostic of iron deficiency, provided that spicules are present in the smear and that a control specimen containing iron is performed at the same time. Although this test has largely been displaced in the diagnosis of iron deficiency by serum iron, TIBC, and serum ferritin testing, the absence of stainable iron in a bone marrow aspirate is the criterion standard for the diagnosis of iron deficiency.

This test is diagnostic in identifying the sideroblastic anemias by showing ringed sideroblasts in the aspirate stained with Perls stain. Occasionally, it is useful in separating patients with the anemia of chronic disorders or alpha-thalassemia from patients with iron deficiency, and it is useful in identifying patients with both iron deficiency and the anemia of chronic disorders. [44]

Histologic Findings

The absence of stainable iron in body tissues, including the bone marrow and liver, is the most useful histologic finding in individuals who are iron deficient. Nonspecific abnormalities of epithelial tissues are reported in iron deficiency. These include gastric atrophy and clubbing of the small intestinal villi. While they suggest that iron deficiency is a pantropic disorder, they have little clinical diagnostic value.

Management

Medical care consists of establishing the diagnosis and reason for the iron deficiency. In most patients, the iron deficiency should be treated with oral iron therapy, and the underlying etiology should be corrected so the deficiency does not recur. However, avoid giving iron to patients who have a microcytic iron-overloading disorder (e.g. thalassemia, sideroblastic anemia). Do not administer parenteral iron therapy to patients who should be treated with oral iron, as anaphylaxis may result.

Transfer of a patient rarely is required for treatment of simple iron deficiency anemia; however, it may be necessary to identify the etiology of the anemia, such as occult blood loss undetected with chemical testing of stool specimens, for identification of a source of bleeding that requires endoscopic examinations or angiography or for treatment of an underlying major illness (e.g. neoplasia, ulcerative colitis).

The British Society of Gastroenterology guidelines suggest that all patients require iron supplementation and that parenteral iron can be used if oral preparations are not well tolerated. The guidelines also state that blood transfusions should be reserved only for patients who are at risk for or who have cardiovascular instability due to their anemia. [39]

Iron Therapy

The most economical and effective medication in the treatment of iron deficiency anemia is the oral administration of ferrous iron salts. Among the various iron salts, ferrous sulfate most commonly

is used. Claims are made that other iron salts are absorbed better and have less morbidity. Generally, the toxicity is proportional to the amount of iron available for absorption. If the quantity of iron in the test dose is decreased, the percentage of the test dose absorbed is increased, but the quantity of iron absorbed is diminished.

Some authors advocate the use of carbonyl iron because of the greater safety for children who ingest their mothers' medication. Decreased gastric toxicity is claimed but not clearly demonstrated in human trials. Bioavailability is approximately 70% of a similar dose of ferrous sulfate.

Parenteral iron therapy

Reserve parenteral iron for patients who are either unable to absorb oral iron or who have increasing anemia despite adequate doses of oral iron. It is expensive and has greater morbidity than oral preparations of iron. Parenteral iron has been used safely and effectively in patients with inflammatory bowel disease (e.g. ulcerative colitis, Crohn disease), [45] as the ferrous sulfate preparations may aggravate the intestinal inflammation.

In July 2013, the FDA approved ferric carboxymaltose injection (Injectafer) for the intravenous treatment of iron deficiency anemia in adults who either cannot tolerate or have not responded well to oral iron. The drug is also indicated for the treatment of iron deficiency anemia in adults with non-dialysis dependent chronic kidney disease. Approval was based on 2 clinical studies in which the drug was given at a dose of 15 mg/kg body weight, up to a maximum of 750 mg, on 2 occasions at least 7 days apart, up to a maximum cumulative dose of 1500 mg of iron. [46-48]

Management of Hemorrhage

Surgical treatment consists of stopping hemorrhage and correcting the underlying defect so that it does not recur. This may involve surgery for treatment of either neoplastic or nonneoplastic disease of the gastrointestinal (GI) tract, the genitourinary (GU) tract, the uterus, and the lungs.

Reserve transfusion of packed red blood cells (RBCs) for patients who either are experiencing significant acute bleeding or are in danger of hypoxia and/or coronary insufficiency.

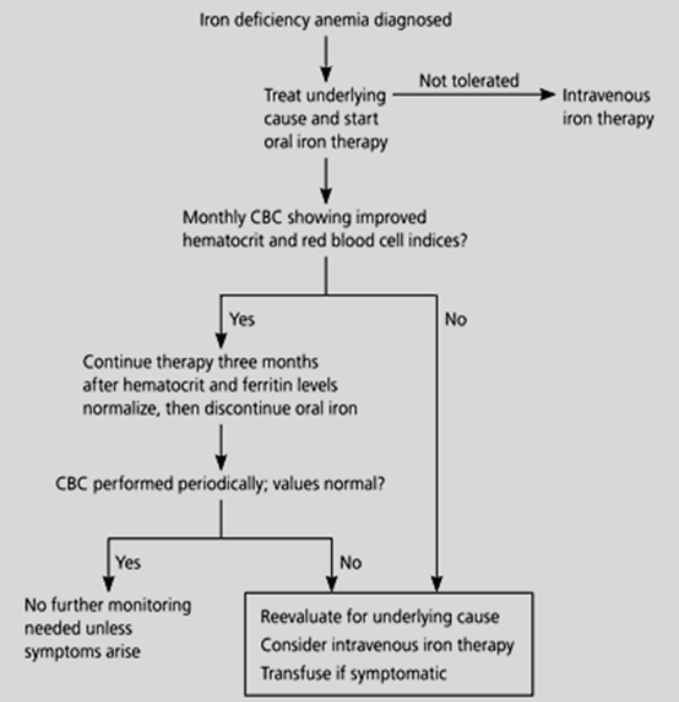


Figure VII: *Management of Iron deficiency anemia*

Dietary Measures

On a worldwide basis, diet is the major cause of iron deficiency. However, to suggest that iron-deficient populations correct the problem by the addition of significant quantities of meat to their diet is unrealistic.

The addition of nonheme iron to national diets has been initiated in some areas of the world. Problems encountered in these enterprises include changes in taste and appearance of food after the addition of iron and the need to supplement foodstuffs that are consumed by most of the population in predictable quantities. In addition, many dietary staples, such as bread, contain iron chelators that markedly diminish the absorption of the iron supplement (phosphates, phytates, carbonates, oxalates, tannates).

In North America and Europe, persons on an iron-poor diet need to be identified and counseled on an individual basis. Educate older individuals on a "tea and toast" diet about the importance of improving their diet, and place them in contact with community agencies that will provide them with at least 1 nutritious meal daily. Patients who have diet-related iron deficiency due to pica need to be identified and counseled to stop their consumption of clay and laundry starch.

Activity Restriction

Restriction of activity is usually not required.

Patients with moderately severe iron deficiency anemia and significant cardiopulmonary disease should limit their activities until the anemia is corrected with iron therapy. If these patients become hypoxic or develop evidence of coronary insufficiency, they should be hospitalized and placed on bed rest until improvement of their anemia can be accomplished by transfusion of packed RBCs. Obviously, such decisions must be made on an individual basis and will depend on the severity of the anemia and the comorbid conditions.

March hemoglobinuria can produce iron deficiency, and its treatment requires modification of activity. Cessation of jogging or wearing sneakers while running usually diminishes the hemoglobinuria.

Prevention

Certain populations are at sufficiently high risk for iron deficiency to warrant consideration for prophylactic iron therapy. These include pregnant women, women with menorrhagia, [49] consumers of a strict vegetarian diet, infants, [50] adolescent females, and regular blood donors.

Pregnant women have been given supplemental iron since World War II, often in the form of all-purpose capsules containing vitamins, calcium, and iron. If the patient is anemic (hemoglobin < 11 g/dL), administer the iron at a different time of day than calcium because calcium inhibits iron absorption.

The practice of routinely administering iron to pregnant females in affluent societies has been challenged; however, it is recommended to provide prophylactic iron therapy during the last half of pregnancy, except in settings where careful follow-up for anemia and methods for measurement of serum iron and ferritin are readily available.

Iron supplementation of the diet of infants is advocated. Premature infants require more iron supplementation than term infants. Infants weaned early and fed bovine milk require more iron because the higher concentration of calcium in cow milk inhibits absorption of iron. Usually, infants receive iron from fortified cereal. Additional iron is present in commercial milk formulas.

Iron supplementation in populations living on a largely vegetarian diet is advisable because of the lower bioavailability of inorganic iron than heme iron.

The addition of iron to basic foodstuffs in affluent nations where meat is an important part of the diet is of questionable value and may be harmful. The gene for familial hemochromatosis (HFe gene) is prevalent (8% of the US white population). Excess body iron is postulated to be important in the etiology of coronary artery disease, strokes, certain carcinomas, and neurodegenerative disorders because iron is important in free radical formation.

Complications

Iron deficiency anemia diminishes work performance by forcing muscles to depend on anaerobic metabolism to a greater extent than they do in healthy individuals. This change is believed to be attributable to deficiency in iron-containing respiratory enzymes rather than to anemia.

Severe anemia due to any cause may produce hypoxemia and enhance the occurrence of coronary insufficiency and myocardial ischemia. Likewise, it can worsen the pulmonary status of patients with chronic pulmonary disease.

Defects in structure and function of epithelial tissues may be observed in iron deficiency. Fingernails may become brittle or longitudinally ridged, with the development of koilonychia (spoon-shaped nails). The tongue may show atrophy of the lingual papillae and develop a glossy appearance. Angular stomatitis may occur with fissures at the corners of the mouth.

Dysphagia may occur with solid foods, with webbing of the mucosa at the junction of the hypopharynx and the esophagus (Plummer-Vinson syndrome); this has been associated with squamous cell carcinoma of the cricoid area. Atrophic gastritis occurs in iron deficiency with progressive loss of acid secretion, pepsin, and intrinsic factor and development of an antibody to gastric parietal cells. Small intestinal villi become blunted.

Cold intolerance develops in one fifth of patients with chronic iron deficiency anemia and is manifested by vasomotor disturbances, neurologic pain, or numbness and tingling.

Rarely, severe iron deficiency anemia is associated with papilledema, increased intracranial pressure, and the clinical picture of pseudotumor cerebri. These manifestations are corrected with iron therapy.

Impaired immune function is reported in subjects who are iron deficient, and there are reports that these patients are prone to infection; however, because of the presence of other factors, the current evidence is insufficient to establish that this impairment is directly due to iron deficiency.

Children deficient in iron may exhibit behavioral disturbances. Neurologic development is impaired in infants and scholastic performance is reduced in children of school age. The intelligence quotients (IQs) of schoolchildren deficient in iron are reported to be significantly lower than those of their nonanemic peers. Behavioral disturbances may manifest as an attention deficit disorder. Growth is impaired in infants with iron deficiency. The neurologic damage to an iron-deficient fetus results in permanent neurologic injury and typically does not resolve on its own. Iron repletion stabilizes the patient so that his or her status does not further decline.

A case-control study of 2957 children and adolescents with iron deficiency anemia and 11,828 healthy controls from the Taiwan National Health Insurance Database found that iron deficiency anemia is associated with an increased risk for psychiatric disorders. After adjusting for demographic data and risk factors for iron deficiency anemia, children and adolescents with iron deficiency anemia were at higher risk for the following [51,52]:

- Unipolar depressive disorder
- Bipolar disorder
- Anxiety disorder
- Autism spectrum disorder
- Attention-deficit/hyperactivity disorder
- Tic disorder
- Delayed development
- Mental retardation

Prognosis

Iron deficiency anemia is an easily treated disorder with an excellent outcome; however, it may be caused by an underlying condition with a poor prognosis, such as neoplasia. Similarly, the prognosis may be altered by a comorbid condition such as coronary artery disease. Promptly and adequately treat a patient with iron deficiency anemia who is symptomatic with such comorbid conditions.

Chronic iron deficiency anemia is seldom a direct cause of death; however, moderate or severe iron deficiency anemia can produce sufficient hypoxia to aggravate underlying pulmonary and cardiovascular disorders. Hypoxic deaths have been observed in patients who refuse blood transfusions for religious reasons. Obviously, with brisk hemorrhage, patients may die from hypoxia related to posthemorrhagic anemia.

Whereas a number of symptoms, such as ice chewing and leg cramps, occur with iron deficiency, the major debility of moderately severe iron deficiency is fatigue and muscular dysfunction that impairs muscular work performance.

In children, the growth rate may be slowed, and a decreased capability to learn is reported. In young children, severe iron deficiency anemia is associated with a lower intelligence quotient (IQ), a diminished capability to learn, and a suboptimal growth rate.

Hypothesis & Objectives

Objectives

The objective of the study was:

- "To determine the frequency of pregnant women non-adherent to iron supplements in gestational age 16-34 weeks attending antenatal OPD in Holy Family Hospital.
- To determine the factors responsible for non-adherence as perceived by patients."

Operational Definitions

Non-adherence

It is skipping iron tablets more than 3 days in last 1 month.

Iron supplements

Iron supplements are available in various forms of ferrous salts with different iron content as follows
Ferrous fumarate 65mg/200mg tablet
Ferrous sulphate 60mg/300mg tablet
Ferrous gluconate 35mg/300mg tablet

Gestational Age

Weeks in pregnancy calculated from earliest scan. Gestational age included in this study is 16-34 weeks.

First and Second Antenatal Visits

Gestational age at booking and second visit to antenatal OPD in Holy Family Hospital

Factors Responsible

Poor Knowledge

Patient is unaware of iron supplements intake and importance.

Poor Counselling

Either doctor has not prescribed it or has written it down on antenatal card but not explained it to patient.

Gastrointestinal Disturbances

They include nausea, vomiting, abdominal cramps, diarrhoea.

Materials & Methods

Study Design

Descriptive, cross-sectional study.

Setting

OPD of Obstetrics & Gynecology, Holy Family Hospital, Rawalpindi.

Duration of Study

4th August 2018 to 3rd February 2019.

Sample Size

- Using WHO sample size calculator with
- Confidence interval = 95%
- Absolute precision = 5%
- [Anticipated proposed population] = 35.3%18
- Sample size = 351

Sample Technique

Non-probability, consecutive sampling.

Sample Selection

a. Inclusion Criteria:

1. Age 18-40 years
2. Obstetric patients
3. Gestational age 16-34 weeks.

b. Exclusion Criteria:

1. Patients with Hb < 10.5
2. Patients with known hemoglobinopathies
3. Patients with psychiatric disorders.

Data Collection Procedure

Prior approval from Institutional Research and Ethics Forum of Rawalpindi Medical University was taken.

Patients' were selected from antenatal clinic of Gynaecology/Obstetrics department Holy Family Hospital.

Written informed consent was taken.

Interview of patients' was carried out by the investigator using structured questionnaire attached as annex including information regarding socio-demographic details, parity, gestational age, antenatal visits, status of adherence or non-adherence to iron supplements during last month and reasons for non-adherence.

Statistical Analysis

The data on categorical variables like non-adherence, factors for non-adherence, education and SES was reported as frequency or percentages. Numerical variables including age, parity, and gestational age were reported as Mean and Standard Deviation of Mean.

Effect modifiers like age, gestational age, parity, education and SES were controlled through stratification. Post-stratification chi square was applied and p-value ≤0.05 was taken as significant.

Results

Age range in this study was from 18 to 40 years with mean age of 30.50 ± 4.21 years. Majority of the patients 196 (55.80%) were between 31 to 40 years of age as shown in Table I. Mean gestational age was 24.78 ± 3.98 weeks (Table II). Distribution of patients according to parity is shown in Table III.

Distribution of patients according to monthly income and education level are shown in Table IV and V respectively.

In this study, frequency of pregnant women non-adherent to iron supplements was found in 147 (41.88%) women as shown in Figure VIII. Frequency of factors responsible for non-adherence as perceived by patients were as follows; Poor knowledge in 59 (40.14%), Poor counselling in 35 (23.81%) and Gastrointestinal Disturbances in 53 (36.05%) women as shown in Table VI.

Stratification of non-adherent to iron supplements with respect to age groups, gestational age and parity is shown in Table VII, VIII & IX respectively. Stratification of non-adherent to iron supplements with respect to monthly income and education is shown in Table X & XI respectively.

Age (in years)	No. of Patients	%age
18-30	155	44.16
31-40	196	55.80
Total	351	100.0

• Mean ± SD = 30.50 ± 4.21 years

Table I: *Age distribution of patients (n=351).*

Gestational Age (in weeks)	No. of Patients	%age
16-24	166	47.29
25-34	185	52.71
Total	351	100.0

• Mean ± SD = 24.78 ± 3.98 weeks

Table II: *Distribution of patients according to gestational age (n=351).*

Parity	No. of Patients	%age
Primiparous	75	21.37
Multiparous	276	78.63
Total	351	100.0

Table III: *Distribution of patients according to parity (n=351).*

Monthly income	No. of Patients	%age
<20000	163	46.44
20001-40000	135	38.46
>40000	53	15.10
Total	351	100.0

Table IV: *Distribution of patients according to monthly income (n=351).*

Education	No. of Patients	%age
Illiterate	36	10.26
Primary	60	17.09
Middle	79	22.51
Matric	85	24.22
Graduate	91	25.93

Table V: *Distribution of patients with respect to education.*

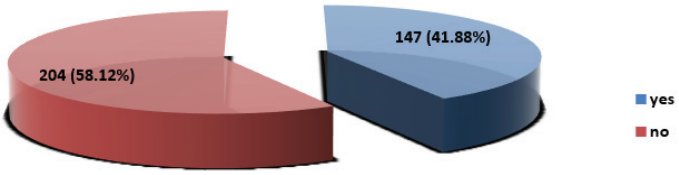


Figure VIII: *Frequency of pregnant women non-adherent to iron supplements (n=351).*

Factors	No. of Patients	%age
Poor knowledge	59	40.14
Poor counselling	35	23.81
Gastrointestinal Disturbances	53	36.05

Table VI: *Frequency of factors responsible for non-adherence as perceived by patients (n=147).*

Age (years)	non-adherent to iron supplements		p-value
	Yes	No	
18-30	76	79	0.016
31-40	71	125	

Table VII: *Stratification of non-adherent to iron supplements with respect to age groups.*

GA (weeks)	Non-adherent to iron supplements		p-value
	Yes	No	
16-24	72	94	0.591
25-34	75	110	

Table VIII: *Stratification of non-adherent to iron supplements with respect to gestational age.*

Parity	Non-adherent to iron supplements		p-value
	Yes	No	
Primiparous	20	55	0.003
Multiparous	127	149	

Table IX: *Stratification of non-adherent to iron supplements with respect to parity.*

Monthly income	Non-adherent to iron supplements		p-value
	Yes	No	
<20000	99	64	0.0001
20001-40000	18	117	
>40000	30	23	

Table X: *Stratification of non-adherent to iron supplements with respect to monthly income.*

Education	Non-adherent to iron supplements		p-value
	Yes	No	
Illiterate	02	34	0.0001
Primary	19	41	
Middle	11	68	
Matric	64	21	
Graduate	51	40	

Table XI: *Stratification of non-adherent to iron supplements with respect to education.*

Discussion

Physiological changes during pregnancy, foetal growth and development increase the requirement for Iron and Folic Acid. The increased demand for these nutrients is not meet through diet alone due to decreased bioavailability of nutrients among pregnant women. The likelihood of presenting Iron deficiency and Folate deficiency is high if diet is not supplemented with Iron and Folic Acid tablets during pregnancy. [53] Pregnant women are among the risk groups for anemia due to low Iron stores in their body. This is supported by reports from the World Health Organization (WHO), indicating that anemia affected 38.2% of pregnant women globally and 46.3% in African. [54] Concerning the prevalence of anemia among Ethiopian reproductive age women, it is estimated that 24% of them are anemic. [55]

In order to reduce the risk of maternal Iron-deficiency anemia, the WHO recommended a daily oral dose of 60 mg Iron and 400 µg Folic Acid (IFA) supplements throughout pregnancy, to begin as early as possible as a routine part of antenatal care. [56,57] Several studies have reported that the use of any antenatal Iron and Folic Acid supplementation during pregnancy reduces the risk of early neonatal and childhood mortality by preventing maternal anemia, low birth weight, and preterm delivery. [58]

Even though, WHO recommends giving all pregnant women a standard dose of 60 mg Iron and 400 µg Folic Acid supplementation for 6 months on a daily basis to prevent maternal anemia and neonatal neural tube defects [56], adherence to IFA supplement during pregnancy is poor and has not improved significantly in the last decades among low and middle income countries. A study done in South Australia showed that 23% of pregnant mothers adhered to IFA supplementation. [59] In Malawi 37% of the pregnant mothers consumed the ideal minimum of 180 IFA tablets. [60,61] Another study done at the University of Gondar, in Northwest, Ethiopia, reported that 55% of pregnant women adhered to the recommended Iron and Folic Acid supplementation. [61]

Lack of Iron and Folic Acid (IFA) supplementation and poor adherence to the supplement during pregnancy is associated with anaemia. Maternal anemia is also associated with low weight gain, congestive heart failure, preterm labour, bleeding, lower resistance to infection, poor cognitive development and reduced work capacity. Likewise, Folic Acid deficiency during pregnancy is also associated with increased risk of neural tube defect, preeclampsia, foetal malformations and preterm delivery. [62]

In 2004, Ethiopia adopted the global Iron and Folic Acid supplementation targeting to reduce the prevalence of Iron deficiency anemia in women of reproductive age and children under five, by one third which is expected to be achieved through distributing IFA supplement during ANC visits. [63] However, increases were observed in anemia prevalence from 17 to 24% in the last 5 years among women and the coverage of IFA supplementation during pregnancy has improved from 1 to 5%, but remains at substandard level as only 5% of pregnant women took Iron and Folic Acid tablets for 90 days or more during their most recent pregnancy in Ethiopia. [55] Reasons for poor adherence to IFA supplementation arises from pregnant women's behaviour such as misunderstanding of instructions, side effects, frustration about the frequency and number of pills taken, nausea and constipation which might make the intervention inadequate to reduce anaemia among pregnant women. [56]

I have conducted this study to determine the frequency of pregnant women non-adherent to iron supplements in gestational age 14-32 weeks attending antenatal OPD in Holy Family Hospital and to determine the factors responsible for non-adherence as perceived by patients. Age range in this study was from 18 to 40 years with mean age of 30.50 ± 4.21 years. Majority of the patients 196 (55.80%)

were between 31 to 40 years of age.In this study, frequency of pregnant women non-adherent to iron supplements was found in 147 (41.88%) women. Frequency of factors responsible for non-adherence as perceived by patients were as follows; Poor knowledge in 59 (40.14%), Poor counselling in 35 (23.81%) and Gastrointestinal Disturbances in 53 (36.05%) women. A study conducted in South Ethiopia showed compliance of 39.2%. [16] Another study in South-eastern Nigeria showed compliance of 65.9%. [17] A study in South India showed compliance of 64.7% and non-adherence in 35.3%. [18] A study in 2 provinces in Cambodia showed adherence of 47%. [19]

A study done in eight rural districts of Ethiopia showed 25.1% non-adherence rate, 38.3% non adherence rate in western India [64], 33% non-adherence in Mozambique [65], and 41.1% non-adherence rate reported by WHO. [66] However, our study reported relatively lower level of nonadherence compared to in a study done in Tigray (62.8%). [67] Looking for factors associated with non-adherence, age, income, knowledge about hemoglobin status, knowledge about anemia and nutritional counseling were significant predictors for non-adherence to iron supplementation. Pregnant women with in age group of 25-34 years and above 35 years had a 4.48 times and 4.16 times higher non adherence to iron folic supplementation compared to women aging 18-24 years old that is in agreement with a study done in North Western Zone of Tigray. [67] In contrast, a study done in mozampique reported that increasing maternal age increased the likelihood of having had a regular intake of tablets. [65] HLs might be due to the fact that our study used a cross sectional study including 18 years old and above ages who have better access for education.

This study revealed that maternal education status had a significant association with adherence to iron and folic acid supplementation. Pregnant women who had secondary and above education were nearly 2.5 times more likely to adhere to iron supplements than those pregnant women who had primary education. The finding is supported by other studies done in Mecha district, Northwest Ethiopia, Nepal, and Indonesia. [68-70] This might be associated with educated women who are likely to have better knowledge and access to information about iron deficiency anemia and therapy, the benefits of supplements, and pregnancy in general. Secondly, it might be due to the fact that education would increase the women's access to information through reading and understanding the benefit of the supplement. Third, it might be associated with the notion that education is more likely to enhance female awareness of micronutrient deficiency and ways to overcome these deficiencies. And it might be associated with the fact that educated women have greater ability to stick to health care inputs such as IFA which offer better care for both the infant and the mother.

Another factor that had a significant association with iron and folic acid supplementation adherence in this study was knowledge of iron and folic acid supplementation. Pregnant women who had good knowledge were nearly 2 times more likely to adhere to iron supplements than those who had poor knowledge. This finding is supported by other studies done in eight rural districts of Ethiopia and India. [71,72] The possible reason is that those pregnant women who had good knowledge of iron and folic acid supplementation were aware of the tablets importance, side effect, how it is taken, and complication if missed. Secondly, this might be associated with the fact that knowledge helps women to have a good perception of the benefits of taking iron tablets.

Forgetfulness and fear of side effect were the leading reason of pregnant women for nonadherence to iron and folic acid supplementation. The finding of this study is supported by studies done in Ethiopia. [73-75] A possible explanation for forgetfulness was because most pregnant women in a rural part of Pakistan were tired at night time because they spent the daytime with different activities. The majority of women have a misunderstanding about taking the tablets due to inadequate counseling because most of the community in rural part believes that consuming medications during pregnancy may make delivery more difficult. So better counseling might decrease the high occurrence of side effects by increasing the psychological tolerance of women to side effects of the tablet.

Conclusion

- This study concluded that frequency of pregnant women non-adherent to iron supplements was found in 41.88% women with poor knowledge and Gastrointestinal Disturbances as the common factors for non-adherence. So, we recommend that some practical recommendations should be made for decreasing the non-adherence to iron supplements and preventing the factors for non-adherence in order to reduce the complications.
- Non-adherence to iron supplements is mainly due to poor counselling of patients by doctors as patients have poor education status. Mere documentation on antenatal card is not enough. Patients need to be explained its regular intake and importance by overcoming communication barrier.

- Awareness regarding iron supplements can be raised by handing them pamphlets in local language about its importance, anemia and consequences of anemia. Same knowledge can be conveyed by television advertisements on screens being displayed in OPD corridors and on national television.
- To avoid GIT issues, health care providers need to advice intake of iron pills with meals along with water and drinks containing vitamin C (for better absorption).Moreover, change the brand of drug or reduce the dose of drug or give in divided doses.
- At the end I recommend use of modern technology such as gadgets to mark reminders in order to avoid forgetfulness.

References

1. Vijayasree M. (2013). Study of Efficacy of intravenous iron sucrose therapy in iron deficiency anemia of pregnancy. Health Renaiss. 11(2): 107-10.
2. Janz TG, Johnson RL, Rubenstein SD. (2013). Anemia in the emergency department: evaluation and treatment. Emergency Med Practice. 15(11): 1–15.
3. Smith RE. (2010). The clinical and economic burden of anemia. Am J Managed Care. 16 Suppl Issues: S59–66.
4. Kalaivani K. (2009). Prevalence & consequences of anaemia in pregnancy. Indian J Med Res. 130(5): 627-33.
5. Bhargava R, Maheshwari M. (2013). Evaluation of intravenous iron versus oral iron in management of iron deficiency anemia in pregnancy with specific refrence to body iron store. J Evolut Med Dental Sci. 2(16): 2750-55.
6. Sarin A. (1995). Severe anaemia of pregnancy, recent experience. Intl J Gynaecol Obstet. 2: 43-9.
7. McDermott J, Slutsker L, Steketee R, Wirima J, Breman J, Heymann D. (1996). Prospective assessment of mortality among a cohort of pregnant women in rural Malawi. Am J Trop Med Hyg. 55:66-70.
8. Scholl TO, Hediger ML, Fischer RL, Shearer JW. (1992). Anemia vs iron deficiency: increased risk of preterm delivery in a prospective study. Am J Clin Nutr. 55:985-8.
9. Murphy J, O'Riordan J, Newcombe R, Coles E, Pearson J. (1986). Relation of haemoglobin levels in first and second trimesters to outcome of pregnancy. Lancet. 1: 992-5.
10. Imdad A, Bhutta ZA. (2012). Routine iron/folate supplementation during pregnancy: effect on maternal anaemia and birth outcomes. Paediatric and perinatal epidemiology. 26(s1): 168-77.
11. Benoist BD, McLean E, Egll I, Cogswell M. (2008). Worldwide prevalence of anaemia 1993-2005: WHO global database on anaemia. Worldwide prevalence of anaemia 1993-2005: WHO global database on anaemia.
12. World Health Organization. (2012). Guideline: daily iron and folic acid supplementation in pregnant women. World Health Organization.
13. .Pavord S, Myers B, Robinson S, Allard S, Strong J, Oppenheimer C, (2012). British Committee for Standards in Haematology. UK guidelines on the management of iron deficiency in pregnancy. British journal of haematology. 156(5): 588-600.
14. Peña-Rosas JP, De-Regil LM, Garcia-Casal MN, Dowswell T. (2015). Daily oral iron supplementation during pregnancy. The Cochrane Library. Jul 22.
15. Alikari V, Zyga S. (2014). Conceptual analysis of patient compliance in treatment. Health Science Journal. Apr 1; 8(2).
16. Arega Sadore A, Abebe Gebretsadik L, Aman Hussen M. (2015). Compliance with iron-folate supplement and associated factors among antenatal care attendant mothers in Misha district, south Ethiopia: community based cross-sectional study. Journal of environmental and public health. 2015.
17. Ugwu EO, Olibe AO, Obi SN, Ugwu AO. (2014). Determinants of compliance to iron supplementation among pregnant women in Enugu, Southeastern Nigeria. Nigerian journal of clinical practice. 17(5): 608-12.
18. Mithra P, Unnikrishnan B, Rekha T, Nithin K, Mohan K, Kulkarni V, Agarwal D. (2013). Compliance with iron-folic acid (IFA) therapy among pregnant women in an urban area of south India. African health sciences. 13(4): 880-5.
19. Lacerte P, Pradipasen M, Temcharoen P, Imamee N, Vorapongsathorn T. (2011). Determinants of adherence to iron/folate supplementation during pregnancy in two provinces in Cambodia. Asia Pacific Journal of Public Health. 23(3): 315-23.
20. Breymann C. (2015). Iron deficiency anemia in pregnancy. In Seminars in hematology Oct 1 (Vol. 52, No. 4, pp. 339-347). Elsevier.
21. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 380(9859): 2163–96.

22. Servilla KS, Singh AK, Hunt WC. (2009). Anemia management and association of race with mortality and hospitalization in a large not-for-profit dialysis organization. Am J Kidney Dis. 54(3):498-510.
23. Adebisi OY, Strayhorn G. (2005). Anemia in pregnancy and race in the United States: blacks at risk. Fam Med. 37(9): 655-62.
24. Silva DG, Priore SE, Franceschini Sdo C. (2007). Risk factors for anemia in infants assisted by public health services: the importance of feeding practices and iron supplementation. J Pediatr (Rio J). 83(2): 149-56.
25. Oliveira MA, Osorio MM, Raposo MC. (2007). Socioeconomic and dietary risk factors for anemia in children aged 6 to 59 months. J Pediatr (Rio J). 83(1): 39-46.
26. Borgna-Pignatti C, Rugolotto S, De Stefano P. (2004). Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica. 89(10): 1187-93.
27. Halterman JS, Kaczorowski JM, Aligne CA, Auinger P, Szilagyi PG. (2001). Iron Deficiency and Cognitive Achievement Among School-Aged Children and Adolescents in the United States. Pediatrics. 107(6): 1381–6.
28. Grantham-McGregor S, Ani C. (2001). Iron-Deficiency Anemia: Reexamining the Nature and Magnitude of the Public Health Problem. J Nutr. 131(2): 649S–668S.
29. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 380(9859): 2163–96.
30. Brady PG. (2007). Iron deficiency anemia: a call for. Southern Med J. 100(10): 966–7.
31. Mazza J, Barr RM, McDonald JW, Valberg LS. (1978). Usefulness of the serum ferritin concentration in the detection of iron deficiency in a general hospital. Canadian Med Assoc J. 119(8): 884–6.
32. Conrad ME, Umbreit JN. (2000). Iron absorption and transport-an update. Am J Hematol. 64(4): 287-98.
33. Dreyfuss ML, Stoltzfus RJ, Shrestha JB. (2000). Hookworms, malaria and vitamin A deficiency contribute to anemia and iron deficiency among pregnant women in the plains of Nepal. J Nutr. 130(10): 2527–36.
34. Calis JC, Phiri KS, Faragher EB. (2008). Severe anemia in Malawian children. N Engl J Med. 358(9):888–99.
35. Chen MH, Su TP, Chen YS, Hsu JW, Huang KL, Chang WH, et al. (2013). Association between psychiatric disorders and iron deficiency anemia among children and adolescents: a nationwide population-based study. BMC Psychiatry. 13: 161.
36. Mazza J, Barr RM, McDonald JW, Valberg LS. (1978). Usefulness of the serum ferritin concentration in the detection of iron deficiency in a general hospital. Canadian Med Assoc J. 119(8): 884–6.
37. Rangarajan S, D'Souza GA. (2007). Restless legs syndrome in Indian patients having iron deficiency anemia in a tertiary care hospital. Sleep Med. 8(3): 247–51.
38. Kis AM, Carnes M. (1998). Detecting Iron Deficiency in Anemic Patients with Concomitant Medical Problems. J Gen Intern Med. 13(7): 455–61.
39. Mateos GME, de la Cruz BJ, Lopez LE, Valdes SMD, Nogales EA. (2009). Review of haematology and biochemistry parameters to identify iron deficiency. An Pediatr (Barc). 71(2): 95-102.
40. Hoffman R, Benz EJ Jr, Shattil SJ. (1998). Hematology: Basic Principles and Practice. Vol 3. New York, NY: Churchill Livingston. 397-427.
41. Lee GR, Foerster J, Lukens J. (1999). Wintrobe's Clinical Hematology. Vol 10. 10th ed. Baltimore, Md: Williams & Wilkins. 979-1011.
42. McLoughlin MT, Tham TC. (2009). Long-term follow-up of patients with iron deficiency anaemia after a negative gastrointestinal evaluation. Eur J Gastroenterol Hepatol. 21(8): 872-6.
43. Goddard AF, James MW, McIntyre AS, Scott BB. (2011). Guidelines for the management of iron deficiency anaemia. Gut. 60(10): 1309-16.
44. Thomason RW, Almiski MS. (2009). Evidence That Stainable Bone Marrow Iron Following Parenteral Iron Therapy Does Not Correlate With Serum Iron Studies and May Not Represent Readily Available Storage Iron. Am J Clin Pathol. 131(4): 580–5.
45. Koutroubakis IE, Oustamanolakis P, Karakoidas C, Mantzaris GJ, Kouroumalis EA. (2010). Safety and efficacy of total-dose infusion of low molecular weight iron dextran for iron deficiency anemia in patients with inflammatory bowel disease. Dig Dis Sci. 55(8):2327-31.
46. Onken JE, Bregman DB, Harrington RA, Morris D, Buerkert J, Hamerski D, et al. (2013). Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: the REPAIR-IDA trial. Nephrol Dial Transplant.

47. Brooks M. (2013). FDA Approves Injectafer for Iron Deficiency Anemia. Medscape Medical News. Available at http://www.medscape.com/viewarticle/808800.
48. Grogan K. (2013). Vifor gets FDA approval for Injectafer. PharmaTimes. Available at http://www.pharmatimes.com/Article/13-07-26/Vifor_gets_FDA_approval_for_Injectafer.aspx.
49. Fernandez-Gaxiola AC, De-Regil LM. (2011). Intermittent iron supplementation for reducing anaemia and its associated impairments in menstruating women. Cochrane Database Syst Rev. 12:CD009218.
50. De-Regil LM, Jefferds ME, Sylvetsky AC, Dowswell T. (2011). Intermittent iron supplementation for improving nutrition and development in children under 12 years of age. Cochrane Database Syst Rev. 12:CD009085.
51. Brooks M. (2013). Iron Deficiency Linked to Psychiatric Disorders in Kids. Medscape Medical News. Available at http://www.medscape.com/viewarticle/806778.
52. Chen MH, Su TP, Chen YS, Hsu JW, Huang KL, Chang WH, et al. (2013). Association between psychiatric disorders and iron deficiency anemia among children and adolescents: a nationwide population-based study. BMC Psychiatry. 13: 161.
53. Marti-Carvaja AL. (2002). Prevalence of anemia during pregnancy: results of Valencia (Venezuela) anemia during pregnancy study.
54. World Health Organization. The global prevalence of anaemia in 2011. Geneva: World Health Organization; (2015).
55. Central Statistical Agency, AA, Ethiopia. Ethiopian Demographic and Health Survey. Rockville: The DHS Program ICF; (2016). Key Indicators Report
56. WHO. Guideline: Daily iron and folic acid supplementation in pregnant women. Geneva: World Health Organization; (2012).
57. World Health Organization, World Health Organization Guideline: Iron supplementation in postpartum women. Library cataloguing-in-publication data, (2016).
58. Alam M. (2017). A Qualitative Assessment of Supply and Demand of Maternal Iron-Folic Acid Supplementation and Infant and Young Child Feeding Counseling in Jamshoro and Thatta Districts, Pakistan. Maternal and child survival program: USAID. https://www.mcsprogram.org/wp-content/uploads/.../IFA-Study-Pakistan-Report.pdf.
59. Malek L, Makrides W, Zhou M, Shao J. (2016). Poor adherence to folic acid and iodine supplement recommendations in preconception and pregnancy: a cross-sectional analysis. Aust N Z J Public Health. 40(5): 424–9.
60. Titilayo. (2016). Sociodemographic factors influencing adherence to antenatal iron supplementation recommendations among pregnant women in Malawi: analysis of data from the 2010 Malawi demographic and health survey. Malawi Med J. 28(1):1–5.
61. Birhanu TM. (2018). Compliance to iron and folic acid supplementation in pregnancy, Northwest Ethiopia. BMC Res Notes. 11: 345.
62. Organization: W.H. Global nutrition targets 2025: anaemia policy brief. Geneva: World Health Organization; (2014).
63. Federal Ministry of Health of Ethiopia, A.A., Ethiopia, National guideline for control and prevention of micronutrient deficiencies. (2004).
64. Dutta AJ, Patel P, Bansal RK. (2014). Compliance to Iron Supplementation Among Pregnant Women: A Cross Sectonal Study in Urban Slum Natl J Community Med 5: 457-462.
65. Nwaru BI, Salome G, Abacassamo F, Augusto O, ClL' J, Sousa C, et al. (2014). Adherence in a pragmatic randomized controlled trial on prophylactic iron supplementation during pregnancy in Maputo, Mozambique. Public Health Nutrition. 18: 1127-1134.
66. WHO (1992). He prevalence of anemia in women. Geneva.
67. Gebre A, Mulugeta A, Etana B. (2015). Assessment of Factors Associated with Adherence to Iron-Folic Acid Supplementation Among Urban and Rural Pregnant Women in North Western Zone of Tigray, Ethiopia: Comparative Study. Int J Nutrition and Food Sci. 42: 161-168.
68. Titaley CR, Dibley MJ. (2015). Factors associated with not using antenatal iron/folic acid supplements in Indonesia: The 2002/2003 and 2007 Indonesia Demographic and Health Survey. Asia Pacific J Clin Nutr 24: 162–176.
69. Begum S. (2012). Factors associated with adherence to Iron Folic acid supplementations during Pregnancy in Uttar Pradesh. Indian J Maternal Child Health. 14(2).
70. Arega Sadore A, Abebe Gebretsadik L, Aman Hussen M. (2015). Compliance with iron-folate supplement and associated factors among antenatal care attendant mothers in Misha District, South Ethiopia: Community based cross-sectional study. J Environment Public Health. 2015.
71. Gebremedhin S, Samuel A, Mamo G, Moges T, Assefa T. (2014). Coverage, compliance and factors associated with utilization of iron supplementation during pregnancy in eight rural districts of Ethiopia: a cross-sectional study. BMC Public Health, 14: 607.

72. Mithra P, Unnikrishnan B, Rekha T. (2014). Compliance with iron-folic acid (IFA) therapy among pregnant women in an urban area of South India. Afr Health Sci. 1.
73. Shewasinad S, Negash S. (2017). Adherence and Associated Factors of Prenatal Iron Folic Acid Supplementation among Pregnant Women Who Attend Ante Natal Care in Health Facility at Mizan-Aman Town, Bench Maji Zone, Ethiopia, 2015. J Pregnancy Child Health 04.
74. Brhanie TW, Sisay H. (2016). Prevalence of Iron Deficiency Anemia and Determinants among Pregnant Women Attending Prevalence of Iron Deficiency Anemia and Determinants among Pregnant Women Attending Antenatal Care at Woldia Hospital, Ethiopia. J Nutr Disord Therap. 6.
75. Haidar J. (2010). Prevalence of anemia, deficiencies of iron and folic acid and their determinants in Ethiopian women. Int Centr Diarrhoeal Dis Res Bangladesh. 28: 359–368.