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"A Thorough Review of Iron Deficiency in Women: Exploring the Diverse Causes, Impacts and Treatment Strategies"

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Abstract:
Iron deficiency is the general micronutrient deficiency around the developing world in the current scenario. More than 20% of women are iron deficient in their reproductive years. Approximately 1.97 billion people worldwide are affected by anemia. From which 50-80% of anemia cases are due to iron deficiency. The major risk factors for iron deficiency for women include high menstrual blood loss, abnormal uterine bleeding, increased iron requirement, and insufficient dietary iron intake. This condition can lead to severe health issues, including maternal and fetal damage, decreased work performance, anemia, and many more. Effective management of disease includes oral iron supplements, IV iron formulation, and blood transfusion. Oral iron supplementation is the majorly preferred treatment for most cases. In cases where oral iron supplementation is not enough or in the presence of severe anemia, IV iron supplementation is the preferred alternative treatment method. Timely diagnosis and suitable treatment are important for managing the iron balance and preventing women from further complications. The objective of this article is to provide a comprehensive review of major causes of iron deficiency and available treatment options. By reviewing the current available strategies and identifying the major causes, this article offers recommendations for effective management of iron deficiency.

Key Words: Iron deficiency, Anemia, Causes, Treatment strategies, Health impacts

1. Introduction:

Iron deficiency is the general micronutrient deficiency around the developing world in the current scenario. This nutritional deficiency affects the women during the different stages of their lives [1]. This condition is primarily because of heavy menstrual blood loss, increased iron requirement, and insufficient dietary iron intake [2]. For women during their reproductive age, the recommended dietary intake (RDA) of iron is 18 mg per day. During pregnancy, the RDA increases to 27 mg per day because of elevated iron requirements for maternal and fetal health [3].

Iron is an essential nutrient for nearly all living organisms. It plays an important role in oxygen carrying capacity and facilitating tissue oxygenation. Furthermore, it is important in oxygen transport and storage and various cellular processes. It is a key component for various enzymatic systems, where it participates in various critical biochemical reactions [4]. It is fundamental in DNA synthesis, influencing cell proliferation and repair [5]. Also, it is an important trace element, involved in various necessary biochemical pathways, and important in tissue metabolism [6]. It also plays a significant role in cell growth, neurotransmission, immune function, and the maintenance of cardiopulmonary health [7].

Iron deficiency in women develops because of several factors, including increased physiological and nutrient iron demands required for growth and pregnancy, heavy menstrual blood loss, chronic blood loss or intestinal blood loss [8]. When iron intake is insufficient to meet the physiological requirements of the body or to compensate for losses due to physiological or pathological conditions, body iron stores simultaneously start decreasing [9].

ID develops through mainly three stages: latent iron deficiency, depletion of iron stores, and iron deficiency anemia [10]. Initially, iron depletion occurs when iron stores start decreasing, as evidenced by low ferritin levels, but serum iron and transferrin levels remain normal. As deficiency advances to iron deficiency without anemia, serum ferritin starts falling below 12 µg/L, serum iron decreases, and transferrin increases, while hemoglobin levels stay normal. In the final stage, iron stores are decreased to very low, leading to insufficient iron for the production of iron-dependent proteins, including hemoglobin, which produces remarkable hematological abnormalities. Simultaneously, erythrocytes become microcytic (smaller in size) and hypochromic (paler), indicating decreased hemoglobin levels and compromised oxygen-carrying capacity [11,3].

During the teenage years, the demand for iron increases. Therefore, Sufficient iron intake is important to meet the increased needs for hemoglobin, myoglobin, and growth-related enzymes and to prevent iron deficiency, anemia, and cognitive disability [12]. In teenage girls, heavy menstrual blood loss is a major factor contributing to iron deficiency and fatigue [13].

Iron deficiency is generally managed with oral iron supplements, which include different formulations of iron salts and ferric compounds. Among those most commonly employed oral iron formulations are ferrous sulfate, ferrous fumarate, ferrous gluconate, and ferrous glycinesulfate [14]. Ferric formulations include ferric protein succinylate, ferric mannitol-ovoalbumin, and ferric polymaltose complexes [15].
Two primary strategies to addressing and preventing iron deficiency are food supplementation and food-based approaches such as food fortification. Among these, food fortification is popular as the most effective strategy for combating iron deficiency [16]. Fortification enhances the content of specific micronutrients in foods [17]. Food fortification involves adding vitamins or minerals to most commonly consumed foods and enhancing their nutritional value [18].

2. Causes of Iron Deficiency:

Nutrition is very essential for the survival of humans, general health, and development during different stages of life. From birth to old age, sufficient nutrition requirements are important for meeting physical growth, mental development, overall health, productivity, and well-being [19]. Nutritional iron deficiency majorly happens when the dietary intake is insufficient to provide bioavailable iron to meet the body's requirement for growth or replacement of iron lost due to any reason [20].
Iron deficiency happens due to several reasons. These include insufficient dietary intake, malabsorption conditions such as gastritis, celiac disease, gastrointestinal resection, or iron refractory anemia. Additionally, increased physiological demands during growth, menstruation, and pregnancy, as well as pathological blood loss from internal bleeding, menorrhagia, or intravascular hemolysis, contribute to the development of ID [21].

Table 1. Causes of Iron deficiency [22,1]

Type of cause	Condition	Pathophysiological mechanism
Increased iron requirements	Infants, adolescent	Growth
	Pregnancy	Fetal development
Inadequate iron uptake	Malnutrition	Insufficient dietary Iron
Decreased intestinal iron absorption	Gastrectomy	Reduce the absorptive surface
	Helicobacter pylori infection	Increased pH and blood loss
	proton pump inhibitors, H2 Blocker	Blocking of gastric acid secretion
Chronic blood loss	Gastrointestinal Bleeding	Bleeding from gastrointestinal tract
	Hematuria, Heavy menstrual bleeding	Bleeding from genitourinary system
	Hemostasis defects	Systemic bleeding
Multiple Causes	Chronic kidney disease	Decreased iron absorption, increased blood loss, reduced hepcidin excretion
	Chronic systolic heart failure	Decreased iron absorption, increased inflammation, blood loss
	Inflammatory bowel diseases	Decreased iron absorption, increased blood loss, high hepcidin

2.1. Inadequate iron uptake:

Iron deficiency majorly occurs in the absence of anemia when there is insufficient iron intake. Because the absorption of dietary iron is insufficient to compensate for the losses of iron from the body [23]. Dietary iron recommendations for women during the reproductive age are approximately 18 mg per day to meet their nutritional requirements. During pregnancy, these iron requirements typically increase to meet their demands for fetal development and expanded maternal blood volume. As a result, the recommended dietary iron requirements for pregnant women are increased to 27 mg per day to support these physiological changes and prevent further complications [24,3].

2.2. Increased iron requirements:

Increased iron requirements majorly develop from several physiological and therapeutic conditions such as growth or pregnancy, blood loss, and improper dietary intake of iron [8]. Furthermore, therapy with erythropoiesis-stimulating agents increases iron requirements by stimulating RBC production, which requires additional iron to support the enhanced erythropoiesis [9].

Pregnancy further increases iron requirements because of increased blood volume and fetal development [22]. It is generally recognized that a typical singleton pregnancy carried the transfer of approximately 500–800 mg of maternal iron. This iron transfer supports fetal development and prepares the newborn for antepartum iron requirements [25].

2.3. Blood loss:
Blood loss is the most common physiological occurrence in women during their reproductive age. Although excessive menstrual blood loss can lead to severe iron deficiency and likely progress to iron deficiency anemia if not properly diagnosed and managed. A blood loss of 35 ml during 28 days of the menstrual cycle results in daily iron loss of approximately 0.5 to 0.68 ml, in addition to the body's other iron losses [26,8].

2.4. Decreased intestinal iron absorption:
Decreased intestinal iron absorption occurs due to several reasons. This majorly includes surgical procedures such as gastrectomy, duodenal bypass, and bariatric surgery, which significantly reduce the total absorptive surface of the intestine, which results in decreasing intestinal iron absorption. Helicobacter pylori infection reduces gastric acid secretion and also increases gastric pH levels, which results in defective or insufficient iron absorption. Also, some medications, such as proton pump inhibitors and H2 blockers, inhibit gastric acid secretion, which reduces iron solubility and absorption [22,9].

2.5. Menstruation:
Menstruation in teenage girls is associated with a decrease in iron stores. It is a significant reason in a population for low dietary iron intake. This menstrual-associated iron loss significantly increases the risk of iron deficiency [27]. Menstrual blood loss plays a major role in creating a negative iron balance in women during their childbearing age, as the regular shedding of the endometrial lining during menstruation results in a loss of iron. Consequently, these women are at higher risk due to the increased iron demands [28].

2.6. Chronic blood loss:
Chronic blood loss is a major contributor to iron deficiency and can develop from various conditions. Such as Hookworm infestations that contribute to gastrointestinal bleeding, which simultaneously results in loss of iron [9]. Taking medications such as anticoagulants, antiplatelets, salicylates, corticosteroids, and nonsteroidal anti-inflammatory drugs leads to increases in gastrointestinal blood loss and systemic bleeding [29]. In the genitourinary system, heavy menstrual blood loss and hematuria conditions contribute to major iron losses [30]. Conditions such as paroxysmal nocturnal hemoglobinuria (PNH) and march hemoglobinuria cause intravascular hemolysis and result in urinary loss of hemoglobin and consequently iron loss [31].

2.7. Multiple causes:
Iron deficiency can develop from multiple causes, each one impacting iron metabolism and absorption in different ways. Chronic infections and malnutrition result in reduced dietary iron intake, increase proinflammatory cytokines, and decrease iron metabolism [22]. Chronic kidney increases blood loss, and elevates hepcidin levels, which negatively affects iron utilization. Furthermore, Postoperative anemia, following major surgery, results from blood loss and an increased systemic inflammatory response, both of which disrupt iron metabolism and reduce iron availability [29]. In individuals with inflammatory bowel disease (IBD), iron deficiency majorly results from chronic inflammation and its effects on gastrointestinal iron absorption [32].

3. Consequences:

Iron deficiency anemia significantly affects women of all ages. When the dietary iron absorption is typically insufficient to meet the body's total iron demands, leading to an increased risk of iron deficiency [33]. Iron deficiency anemia is associated with increased fatigue, diminished work performance, cardiovascular stress, reduced tolerance to cold, and compromised resilience to significant blood loss, particularly in pregnant women [34]. Iron deficiency can directly or indirectly affect the activity and function of osteoblasts and osteoclasts by inducing hypoxia and disrupting vitamin D metabolism. These disturbances can ultimately lead to the disruption of bone homeostasis [35]. Iron deficiency can lead to various behavioural and functional consequences, including pica, restless leg syndrome, dysphagia with oesophageal webs, functional deterioration, and reduced cognitive function, particularly in older adults [36].
Timely diagnosis is required to prevent such negative outcomes and increase overall wellbeing. Additionally, individuals may experience muscle aches, restless legs, reduced exercise tolerance, increased anxiety, low mood or depression, and a decrease in work performance. These symptoms collectively produce a broad impact of iron deficiency on physical performance, psychological condition, and general health [37,7].
Iron deficiency during pregnancy is a major health problem associated with various maternal, fetal, and neonatal complications. Maternal outcomes may include increased susceptibility to anemia, higher risks of preterm delivery, and reduced postpartum recovery. These include an increased risk of low birth weight, preterm birth, perinatal mortality, elevated susceptibility to maternal infections, and reduced tolerance to blood loss and infections [38]. Iron deficiency during pregnancy produces significant risks for both the mother and fetal development. In pregnant women, iron deficiency has a significant risk of hemorrhage, highlighting the serious implications of insufficient iron levels for maternal health [39]. Significant research in both humans and animal models provides evidence that

early iron deficiency (ID) can result in long lasting neurobehavioral issues, even if the condition is diagnosed and treated [40].

4. Treatment:

Increasing dietary iron intake alone is insufficient for the effective management of iron deficiency. Comprehensive treatment requires not only correcting the anemia but also recovering the decreased iron stores. The management of iron deficiency involves three primary approaches: oral iron supplementation, parenteral iron administration, and blood transfusion.

For the treatment of iron deficiency, it is recommended that an adult, including pregnant women, consume a sufficient amount of elemental iron daily, divided into 2 to 3 doses. This aims to address the early signs of anemia and restore iron levels. For individuals who are at risk of ID, a lower dosage of 65 mg of elemental iron daily is advised to prevent further complications. This approach ensures both the correction of existing anemia and the prevention of future iron deficiency [41]. A diet rich in folate has potential therapeutic benefits for the prevention and treatment of iron deficiency in patients with heart failure [42].

4.1. Oral iron supplementation:

It is the primary and cost-effective method for management of iron deficiency ID and iron deficiency anemia IDA [43]. It involves administration of oral iron salts, mostly ferrous ions, which are effective in recovering iron stores and treating anemia [44].

Ferrous iron salts are preferred more because of their better solubility and absorption in the duodenum and jejunum. Standard treatment for iron deficiency anemia in adults majorly involves oral administration of ferrous sulfate tablets (containing 60 mg of elemental iron) three to four times daily [45]. Iron supplements containing iron in its ferrous form are more rapidly absorbed as compared to other forms [46].

To increase the absorption of iron, it is recommended that iron tablets be taken at night or at least before one hour of the meals. Additionally, substances that may decrease iron absorption, such as tannins and dairy products, should be avoided to increase the efficacy of supplementation and improve overall iron status and iron stores. Also, consuming iron supplements with fruit juice containing ascorbic acid increases their absorption [47,1].

Alternative dosing of supplements increases iron absorption by 34-50% as compared to administering the same dose on continuous days. This approach not only increases the efficiency of iron absorption but also helps to reduce the amount of unabsorbed iron in the gastrointestinal tract. Additionally, it also helps to minimize gastrointestinal side effects and improve patient compliance with supplementation [48].

Oral iron supplements have several limitations, including limited gastrointestinal absorption of iron, an unpleasant taste, patient compliance, and some side effects such as nausea, vomiting, diarrhoea, and constipation. For the patients who experience intolerance or insufficient response to traditional iron salts, are suggested non-salt-based oral iron formulations, such as ferric maltol or sucrosomial iron, that serve as suitable alternative treatments. These formulations are designed to improve the efficacy of supplementation [49,15].

Undiagnosed iron deficiency is very common in women of childbearing age, particularly those with a history of intolerance to oral iron supplements. The use of iron-whey protein microspheres shows an increase in compliance to iron therapy, an increase in gastrointestinal tolerability, and an increase in iron stores, hemoglobin levels, and energy in this population [50].

4.2. Parenteral iron:

Intravenous iron is considered an effective treatment for the management of anemia caused by iron deficiency. It is important and very effective for various clinical conditions such as chronic kidney disease, inflammatory bowel disease, heart failure, and pregnancy [7].

When oral iron supplementation is ineffective, intravenous iron supplementation offers a safe and efficient alternative treatment. It is particularly employed for patients when oral iron is insufficient and ineffective, such as in the presence of inflammation, the need for rapid iron replacement, or ongoing blood loss. Parenteral iron is the preferred treatment for the patients with inflammatory bowel disease who present with moderate to severe anemia, especially in the circumstance of active disease or when oral iron is intolerable or ineffective [51,36].

In clinical practice, six different parenteral iron preparations are mainly used, which are ferric carboxymaltose, ferric gluconate, ferumoxytol, iron isomaltoside, iron sucrose, and lowmolecular-weight iron dextran. The benefit of iron dextran is that it can be administered in large doses at a time [52,15].

New intravenous iron formulations are developed to offer a wide dosing range and facilitate effective iron balance in one or few sessions. These IV preparations increase rapid infusion, decrease side effects, increase patient compliance, and reduce the risk of anaphylaxis. Additionally, the treatment should be convenient for patients and healthcare professionals, and it should be cost-effective for the healthcare system [53].

4.3. Transfusion:

Transfusion is considered as a final treatment option, which is reserved for cases of major conditions such as hemorrhage or for patients who are hemodynamically unstable with endogen dysfunction. Its use should be limited

for some critical situations. The requirement for further iron should be assessed after the patient has achieved stabilization [1].

5. Conclusion:

Iron plays a very important role in various biochemical and physiological processes, including the synthesis of red blood cells. The main risk factors for iron deficiency in women mainly include insufficient dietary intake, heavy menstrual blood loss, abnormal uterine bleeding, and pregnancy. These conditions can cause extremely severe fatigue and decreased physical capacity and work performance. Increasing dietary iron intake is not enough to effectively manage iron deficiency. The management of iron deficiency mainly involves three main approaches to prevent the condition: oral iron supplementation, parenteral iron administration, and blood transfusion. Understanding the various causes and spread of iron deficiency (ID) can help prevent and treat iron deficiency in a number of ways. To improve results, future research and policy should focus on improved strategies for ID prevention and management. This includes creating specialized solutions for those most at risk and ensuring that health professionals receive ongoing education to process ID more effectively.

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