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The Effects of Iron Deficiency Anemia and Iron Supplementation in Pregnancy

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Abstract

Iron deficiency anemia (IDA) is a condition that occurs in both underdeveloped and developed countries worldwide. This disorder is diagnosed in an individual who presents the common signs and symptoms of anemia along with consistently low clinical markers of stored iron. Iron deficiency (ID) usually precedes a diagnosis of IDA as the insufficient amount of iron often goes undetected until one's quality of life is diminished. Certain populations, such as women who are pregnant or of reproductive age, are particularly at risk for ID and the development of IDA. During pregnancy, the recommended dietary allowance (RDA) for iron is greater to assist a woman's body in providing for fetal growth and development. The reticuloendothelial system, as well as iron-rich foods, iron-fortified foods, and iron supplementation are sources necessary to maintain adequate iron levels stored and circulating in the body. Iron supplementation, which comes in various forms, is widely utilized, particularly for pregnant women with IDA. Research has found that fetal growth and newborn development can be negatively affected by ID and IDA, especially without iron supplementation before or during the prenatal period.

Keywords: Iron deficiency anemia (IDA), iron deficiency (ID), pregnancy, prematurity, low birth weight, iron supplementation

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Iron Deficiency Anemia Overview

Iron deficiency anemia (IDA), a type of microcytic and hypochromic anemia, occurs when an individual's iron supply is lower than the physiological amount required for the production of hemoglobin (Hgb). Among other processes, Hgb is a key component of tissue oxygenation, cellular function, and cell development. Hemoglobin (Hgb) level indicates the amount of circulating Hgb proteins, which are attached to red blood cells (RBCs) and make up the body's usable form of iron. As one of the most severe and widespread nutritional deficiencies, IDA typically occurs when an individual's iron intake is insufficient or when there is a complication with absorption. Iron deficiency anemia (IDA) is classified as a hematologic disorder and is multifactorial in nature. Common causes of IDA vary in their potential for modification as they range from population demographics to lack of iron-rich foods (Bánhid, Ács, Puhó, & Czeizel, 2011; Rome, 2014a).

Iron deficiency anemia (IDA) is a specific subtype of anemia, which is the overarching hematological disorder characterized by an insufficient number or malfunctioning of an individual's erythrocytes, or RBCs. Anemia is defined by its cause and particular pathology. For example, vitamin-deficiency anemia, or pernicious anemia, occurs when an individual is lacking adequate amounts of folic acid or vitamin B12 due to insufficient intake or faulty absorption in the gastrointestinal tract. Sickle cell anemia and hemolytic anemia were both appropriately named, as RBCs are sickle-shaped in the first condition and excessively destroyed in the latter. The most common form of anemia

is IDA, as it is frequently found in acute care settings and communities worldwide (American Society of Hematology, 2016).

Iron deficiency (ID) generally precedes a diagnosis of IDA as iron stores are first depleted, iron deficiency (ID) erythropoiesis is established, and a clinical diagnosis of IDA follows as the most prominent display of ID (Breymann, 2013). Babies, women of childbearing age, pregnant women, lactating women, elderly adults, patients with significant blood loss, low socioeconomic classes, and individuals with nutritionally-poor diets, such as alcoholics, are examples of populations most susceptible to IDA (Krafft, Murray-Kolb, & Milman, 2012; Rome, 2014a). Causes of IDA depend on the individual's characteristics, but typical symptoms and diagnostic criteria are consistent in most cases. Iron supplementation is the primary treatment for IDA, but the administration route differs according to individual needs and prevalence of adverse effects. Iron-rich foods and iron-fortified foods are also recommended for patients with ID and especially those with major risk factors for IDA or already diagnosed with IDA. Short and long-term effects of IDA on the development of a fetus or an infant are also being studied in conjunction with prophylactic and therapeutic iron supplementation both before and during pregnancy (Bánhidý et al., 2011).

Pathophysiology of Iron Deficiency Anemia

Iron deficiency anemia (IDA) is a condition characterized by significant and consistent lack of iron storage in the body due to a variety of intrinsic and extrinsic factors. This type of anemia is microcytic and hypochromic in nature, which means the volume of RBCs, or mean corpuscular volume (MCV), is <80 fL and the average concentration of Hgb in a single RBC, or mean corpuscular hemoglobin (MCH), is <27

pg. The lack of or decrease in iron storage is manifested by a lower than normal Hgb level, which denotes the amount of iron bound to heme in erythrocytes, or RBCs.

Hemoglobin (Hgb) is a large molecule on RBCs that is made up of heme, the iron compound, and globin, a simple protein. A major function of Hgb, besides maintaining acid-base balance, is its ability to attract oxygen to the iron it carries. After receiving oxygen from the lungs, Hgb forms what is called oxyhemoglobin. The presence of oxygen on this protein is what makes blood appear bright red. Organs throughout the body receive oxygen as RBCs circulate to body tissues, transported oxygen is released from the Hgb, and the oxygen molecule diffuses into capillaries. The globin section of Hgb then receives carbon dioxide from tissue cells and removes it from the body by respiratory exhalation (Rome, 2014b).

Iron metabolism, which is the breakdown of stored iron in the body, is the necessary process for the production of Hgb and synthesis of enzymes required for systemic oxygenation and cellular energy (Bánhidly et al., 2011). The body's major source of iron comes from the reticuloendothelial system, in which macrophages from the liver and spleen phagocytize old or damaged RBCs (Rome, 2014b). Enzymes, such as heme oxygenase-1 (HO-1), play a role in the breakdown of heme that is released from phagocytized RBCs. This process is done to create a form of usable iron throughout the body. The resulting iron, which is either stored or quickly utilized by proteins, such as transferrin, is the form necessary for energy as well as oxygenation of cells, tissues, and organ systems (Chung, Chen, & Paw, 2012; Khalafallah & Dennis, 2012; Rome, 2014b).

Transferrin is a carrier plasma protein that is synthesized in the liver and known to be an acceptable indicator of iron supply within the body (Rome, 2014b). Transferrin has

a high affinity for iron and is referred to as ferrotransferrin when attached to an iron molecule during transport (Winter, Bazydlo, & Harris, 2014). Storage of iron occurs mostly in the spleen, bone marrow, and cytoplasm of macrophages. This iron storage is noted as ferritin or hemosiderin, a broken-down form of ferritin. The production of Hgb is slowed when iron storage is not replaced in these reservoirs, resulting in ID and a coinciding low Hgb level (Rome, 2014b; Winter et al., 2014). However, very little iron stays in circulation compared to that which is utilized intracellularly for erythropoiesis, or the production of RBCs, as well as for other cellular functions (Chung et al., 2012; Winter et al., 2014).

Hepcidin, a hepatic hormone secreted into the ferroportin plasma to regulate iron, is indirectly proportional to iron stores and serum iron. To specify, when hepcidin levels are low in the plasma, iron is released into the blood at a high rate. When levels of hepcidin are high, iron is kept intracellularly and used for cellular energy and erythropoiesis (Khalafallah & Dennis, 2012; Rome, 2014b). Hepcidin regulation is also known to be affected by erythropoietic activity, oxygen tension within hepatocytes, transferrin saturation (TS), inflammation, and the iron content of hepatocytes. These physiological components directly alter iron storage and serum iron levels, which in turn affects hepcidin (Winter et al., 2014). Overall, hepcidin works to maintain homeostasis as it controls iron transporters, including ferroportin and DMT1 (Liu & Kaffes, 2012).

Intestinal enterocytes and hepatocytes are proteins that act as negative feedback indicators for iron levels. These proteins maintain a sufficient serum iron level as they detect the ever-changing iron level in the blood and other organ tissues. Iron can be harmful to cells if not properly stored by proteins, such as ferritin, and used for cellular

function and energy (Kurniawan, 2011). Extrinsic sources of iron, or the iron that is ingested through food, drink and supplements, alter one's serum iron level, as these sources indirectly increase the total iron in circulation (Khalafallah & Dennis, 2012; Winter et al., 2014).

Iron is a micronutrient required for oxygenation within the body and is a major component for energy production on the cellular and systemic levels. Therefore, an individual's serum iron and iron storage level not only affect cellular functions, but the individual as a whole. This is evident by the systemic signs and symptoms associated with iron depletion and their negative impact on an individual's quality of life. Cognitive development has also been found to be associated with one's iron supply. A literature review found that 8-10 year-old children diagnosed with IDA demonstrated slower reaction times and abnormal electroencephalogram (EEG) results, as compared with children of the same age without IDA. Similar results, with the addition of poor object permanence, were also documented for infants with IDA who were 3-15 months of age (Jáuregui-Lobera, 2014).

Data suggest the strong likelihood of a link between hematological status and an individual's cognitive behavior due to the role of the central nervous system in cognitive functioning. More specifically, research shows that Hgb levels are directly correlated with the central nervous system. This conclusion can also be readily assumed due to the importance of oxygen, transported by RBCs, within the brain. However, there is debate as to whether the true cause of this abnormal cognitive functioning is solely the ID or anemia, not to discount the possible combination of both elements (Jáuregui-Lobera, 2014).

Loss of iron naturally occurs through various physiological processes in both men and women. One of the most notable processes that causes a drop in iron is the naturally occurring menstrual cycle in premenopausal women. This fact, in conjunction with other physiological elements, makes women of reproductive age one of the populations more susceptible to IDA than others (Rome, 2014a; Winter et al., 2014). Despite this normal occurrence, supplements are usually unnecessary, as the recommended dietary allowance (RDA) can be achieved through a standard diet that includes iron-rich foods (Rome, 2014a).

On the contrary, even if a non-pregnant woman of reproductive age is meeting her RDA for iron, studies have pointed to the benefits prophylactic iron supplementation has on a future pregnancy. In most cases, women in this population with ID do not see distinguishable differences in quality of life with or without iron supplementation. Prophylactic iron is largely intended to benefit the woman's possible future pregnancy and prevent the development of IDA. With IDA, supplementation, most often in the form of an oral tablet or liquid, is considered to be the first-line treatment option for IDA, particularly in pregnancy (Falahi, Akbari, Ebrahimzade, & Gargari, 2011; Rome, 2014a).

Iron Deficiency Anemia in Pregnancy

Pregnant women are more susceptible to IDA, as their need for iron increases to three times the amount needed in all other populations, including both men and women. The increase in red cell mass, as well as growth of the fetal placenta, are major factors within pregnancy that lend to an increased demand for more iron to sustain normal growth of the fetus (Krafft et al., 2012). The RDA for iron in the typical nonpregnant woman of at least 14 years or older is 8-18 mg. In comparison, the RDA for a pregnant

woman is increased to 27 mg. The RDA for iron decreases somewhat again during lactation in the postpartum period to 9-10 mg for women above 14 years-old (National Institutes of Health, 2015). Although the primary source of iron for humans is the internal recycling of destructed RBCs, an external source is highly recommended to make up for the iron deficit created in the prenatal period. Furthermore, pregnant women with multiple risk factors for IDA are strongly encouraged to use iron supplements throughout their pregnancy as their babies have an even greater risk for complications associated with IDA (Khalafallah & Dennis, 2012).

A study was done in Spain to determine the effects of IDA on neonatal behavior in different stages of pregnancy. This study followed a population of low-risk pregnant women from week 13 of gestation to childbirth. This group of women began receiving iron supplements starting in the second trimester of pregnancy. Researchers evaluated maternal iron levels throughout each woman's pregnancy by regularly drawing blood samples to measure serum ferritin (SF), serum iron, and serum transferrin. In each woman's case, these levels were used to calculate the percentage of TS and determine her severity of ID. These blood markers help to determine serum iron levels in accordance with World Health Organization (WHO) recommendations. Results of this study reported that the prevalence of ID increased from 8.3% in the first trimester, to 42.6% in the second trimester, and 62.5% in the third trimester. Furthermore, TS and SF levels also increased as the duration of the pregnancy increased. The researchers claim that prenatal ID and neonatal behavior are closely associated and the trimester in which IDA is most severe does alter neonatal behavior (Hernandez-Martinez et al., 2011).

Although ID was found to be a greater indicator than SF and ST measurements alone, TS was found to be related to the robustness and motor performance of the neonate during the third trimester. In addition, distinguishable ID at the beginning of pregnancy is associated with indications of brain immaturity, exemplified by responses such as jumpiness and trembling in newborns. Abnormal motor development and self-regulation can be found when maternal ID is present in the third trimester of pregnancy. However, more longitudinal research is needed to assess the long-term behavioral, cognitive, and psychosocial development of children born to mothers with prenatal ID or IDA (Hernandez-Martinez et al., 2011).

Statistics

Iron Deficiency Anemia

There is a high number of ID and IDA cases in all types of countries across the world. It is estimated that upwards of 4-5 billion people are iron deficient and about half of those people are clinically anemic (Lokeshwar, Mehta, Mehta, Shelke, & Babar, 2011). Researchers have performed a plethora of studies in underdeveloped countries in particular, due to their increased risk of ID resulting from lack of widespread iron-rich foods and iron supplements. Lack of access to healthcare that could treat parasitic and chronic diseases known to create ID or IDA is a common occurrence in underdeveloped nations. In these cases, ID can go untreated and lead to more complicated issues that could have been prevented or addressed early on. Infant mortality can also be higher in underdeveloped countries as a result of nutritional deficiencies, namely ID. Even if a baby is born at term and without complications, the newborn has a high risk for death when maternal ID or IDA causes insufficient lactation. Without an adequate supply of

iron-rich breast milk, infants can suffer from malnutrition, dehydration, and hypoglycemia, amongst other nutritional-related difficulties (Mala, Tuitoek, & Odhiambo, 2012).

The global percentage of children with anemia due to insufficient nutrition is 44% to 74%, with the highest rates being amongst preschool-aged children and infants. Children ages 2-11 years-old take in on average 11.5-13.7 mg/day of iron through food alone (Lokeshwar et al., 2011; National Institutes of Health, 2015). Iron deficiency anemia (IDA) makes up a large percentage of the 79% anemic children in India between the ages of 6 months and 5 years. In addition, 50% of 10-19 year-old adolescents in India are anemic, with ID being the most prevalent cause (Chandra & Sahi, 2015). About half of all women aged 15-49 years are suspected to have ID and IDA. The average daily intake of iron through food and supplementation for men and women over 19 years of age ranges from 17.0-20.5 mg/day, with the largest amount taken in by men. Studies show that women who become pregnant within four years after menarche have even greater nutritional needs than adult women because of the significant growth that occurs in adolescence (Lokeshwar et al., 2011; National Institutes of Health, 2015).

Iron Deficiency Anemia in Pregnancy

As a population with greater physiological demands to support the growth of a life, as well as hormonal changes and increased nutritional needs, pregnant women are already at a higher risk for nutritional deficiencies. According to McMahon (2010), ID and IDA appear in almost equal pervasiveness across all populations in both developed and underdeveloped countries. De Benoist, another researcher referenced by McMahon, claimed the prevalence of anemia in pregnant women worldwide increases almost 20%

compared to the population of anemic women who are not pregnant. McMahon also cited a study of pregnant women from China, India, Zimbabwe, and Mexico, which found that ID and IDA is higher in the third trimester of pregnancy. This author also found that 43% to 73% of typical pregnant women have ID. Ferritin concentration, which drops below 15 mg/L in notable iron depletion during all stages of pregnancy, is the diagnostic tool utilized within this study and throughout McMahon's article (McMahon, 2010; Vandevijvere, Amsalkhir, Van Oyen, Ines, & Moreno-Reyes, 2013).

Risk Factors for IDA

Numerous causes and factors contribute to ID and a subsequent diagnosis of IDA in both pregnant and non-pregnant populations. Causative factors vary in severity and are influenced by the environment as well as the individual patient's circumstance. People of all backgrounds and demographics can develop IDA, but particular populations and those who possess certain characteristics or lifestyle habits have a higher likelihood of diagnosis.

Age

Babies, women in their reproductive years, and elderly adults are the age-specific populations with the largest percentages of IDA cases worldwide. The very old and very young are exceptionally prone to ID and IDA as upheld by the results of a National Health and Nutrition study performed in 2012 on Mexican men and women over the age of 60. Statistical data gathered from this survey, which included participants in both urban and rural settings, showed that the number of men and women, at least 70 years or older with IDA, was markedly greater than those who were under age 70. For example, the percentage of those diagnosed with IDA was 8.7% in populations younger than age

70, but jumped to 23.6% in the population older than 70. It is supposed that the effects of increased age, such as a slowed immune response, increased prevalence of gastrointestinal disorders due to slowed peristalsis, and decreased function in senses and other physiological processes, are what make older adults more prone to this micronutrient deficiency. However, anemia, and IDA most specifically, is not an expected or normal phenomenon of aging. Often times, other factors that are associated with increased age, such as chronic disease and imbalanced nutrition, add to an elderly adult's likelihood of ID (American Society of Hematology, 2016; Conteras-Manzano, de la Cruz, Villalpando, Rebollar, & Shamah-Levy, 2015; Kurniawan, 2011).

Nutrition

Iron deficiency (ID) and IDA are directly affected by one's diet, as iron is typically ingested through iron-rich and nutrient-dense foods. Furthermore, dietary iron is absorbed in the gastrointestinal tract. When an individual's diet lacks one of these two criteria, the result is ID and then possibly IDA over time. These conditions depend on the severity of deficiency as well as other factors. Dietary iron is found in a variety of foods, but is particularly greatest in red meats, seafood, green leafy vegetables, dark chocolate, beef liver, and nuts. Iron-fortified foods include cereal and most other grain products, although these have been artificially altered by the government in order to meet regulations implemented by the Food and Drug Administration (FDA). People who consume diets with little to no intake of meats or iron-fortified foods, such as vegans and vegetarians, have a great need for other sources of iron (National Institutes of Health, 2015).

As quoted by the National Institutes of Health, Office of Dietary Supplements (2015), “the RDAs for vegetarians are 1.8 times higher than for people who eat meat” (p. 1). The nonheme iron in plant-based foods is not as readily absorbed as the heme iron in meats. However, ascorbic acid, or Vitamin C, meats, and seafood are all known to augment the bioavailability of nonheme iron. This gives reason as to why iron supplementation is most effective when administered with products high in Vitamin C, such as orange juice. In contrast, foods with phytate and polyphenols, such as legumes and certain grain products, can hinder the absorption of iron to some extent (National Institutes of Health, 2015).

A group of women and girls in their reproductive years from India were studied to compare the nutritional status and sociobiological aspects of their most recent child since the time of the study. This study’s data were collected from national surveys provided by the country. The nutritional status of these women depended on nourishment, clean water, smoking, drugs, and other lifestyle choices. Nutritional status of the mother before and during pregnancy was found to be a strong contributing factor in the size of the baby, if not the most prominent factor in determining a newborn’s birth weight (Dharmalingam, Navaneetham, & Krishnakumar, 2010). Iron deficiency (ID) and IDA are very common in India, which undoubtedly affects future generations of India, as babies are continuously born to women with IDA. Abnormal cognitive or physical development in these newborns might have been prevented with proper iron intake in the prenatal period.

Blood Loss

Individuals with an unusually large amount of blood loss may or may not show immediate signs and symptoms of ID with a progression to IDA. For example, some

patients who are losing up to 100 mL of blood per day may not have bloody stools, as evidenced by a negative fecal occult blood test (FOBT). However, daily loss greater than 5-10 mL is more than the gastrointestinal system can absorb through dietary iron (Liu & Kaffes, 2012).

A significant loss of blood in any population can cause an individual to have ID or IDA, particularly in severe or traumatically acute situations. Most research points to blood loss as the chief cause of IDA, which is the initiating factor in most acute care-related cases of IDA (American Society of Hematology, 2016). Frequent blood donors, women with abnormally heavy menstrual cycles, and patients who have lost abnormally large amounts of blood during or after surgery or trauma can develop acute IDA. Chronic blood loss can also result from lesions of the gastrointestinal tract in both inpatient and outpatient populations. Various types of ulcers, polyps, and cancers that range from benign to malignant can be found in the upper and lower gastrointestinal tract. Besides the potential pain and malabsorption often associated with these lesions, overt or occult bleeding can create a negative iron balance in the body, manifested as IDA. Blood loss can also occur apart from the gastrointestinal tract through the renal or pulmonary systems. However, blood loss through these systems is much less common (Liu & Kaffes, 2012).

Chronic Comorbidities

Since IDA is not a disease process in itself, it is often accompanied by or a result of various diseases. These comorbidities can be acute, but are often chronic or developed over time, such as inflammatory bowel disease (IBD). Iron deficiency (ID) is present in 36%-76% of the populations with IBD. In these patients, all or parts of the digestive tract,

specifically the intestines, are chronically inflamed. Crohn's disease and ulcerative colitis are the two most severe and prominent subtypes of IBD. If one of these pathologies is present, there is an increased risk for developing IDA. Malnutrition, including nutrient deficiencies like ID, is the major complication of IBD that impacts all bodily functions. Nutrients are not properly absorbed in the intestines because of ulcers and occasional fistulas within these pathologies (Goldberg, 2013; Mayo Clinic, 2016a).

Besides gastrointestinal diseases, such as Crohn's disease, IDA can also develop with chronic obstructive pulmonary disease (COPD). Although the specific links between the two conditions are still being researched, it has been shown that a percentage of TS and serum iron is directly associated with forced expiratory volume (FEV) levels. Other variables common in populations with COPD and IDA are also to be considered, such as the large number of geriatric individuals, nicotine users, postmenopausal women, and individuals with cardiovascular complications. Most cases of IDA associated with COPD are severe and the individuals are in acute care settings with significantly reduced lung function. Furthermore, inflammation, the chief characteristic of COPD, is correlated to higher levels of cytokines, which can decrease the production of erythropoietin (EPO) and alter the function of hepcidin. Erythropoietin (EPO) helps regulate the rate of erythropoiesis relevant to the oxygenation status of body tissues. Therefore, serum iron and RBC count can indirectly be reduced, to a certain degree, in the presence of extensive inflammation. Unfortunately, IDA is not currently assessed for or specifically treated in COPD patients within the acute care setting (Silverberg et al., 2014).

Signs and Symptoms

Iron deficiency anemia (IDA) is a type of anemia, which is an expression of a disease process brought about by various causes and aforementioned risk factors. Therefore, IDA can be manifested by general signs and symptoms that range in severity and depend on the significance of an individual's condition. Since some symptoms are nonspecific, general, and easily confused as resulting from another health condition or everyday cause, IDA can go unnoticed and undiagnosed for an extended period of time. Pallor, loss of energy, or weakness, and exertional dyspnea are cardinal signs and symptoms of IDA across all populations. These signs and symptoms are a result of the abnormally low amount of oxygen circulating to body tissues. This low oxygen level is represented by a reduced Hgb level as well as other diagnostic lab values (American Society of Hematology, 2016; Bánhidý, Ács, Puhó, & Czeizel, 2011).

Not only can signs and symptoms of IDA often be non-specific and general, but symptoms can also lack consistency in their presentation. Tachycardia, palpitations, and cardiac hypertrophy are a few cardiovascular symptoms that can be exhibited in chronic cases of IDA; these have particularly been noted by pregnant women with IDA (Breymann, 2013). Fatigue, or lethargy is the chief complaint by an individual with IDA, while irritability and impaired regulation of temperature are other symptoms most specifically exhibited by pregnant women (Pavord et al., 2012). Some patients also report having pica, or an unusual craving to eat or chew on non-food items, such as ice and dirt. These substances, if toxic when ingested, can indirectly damage a developing fetus. Headache, sore or smooth tongue, referred to as glossitis, and loss of hair or nail strength can also suggest IDA. Most of these signs and symptoms arise when IDA has

become severe enough to be diagnosed. Other underlying causes, such as acutely severe blood loss or chronic comorbidities, need to be treated. Often times, signs and symptoms of ID or IDA will disappear or become less prominent as the risk factors or underlying causes are ruled out or well-managed (American Society of Hematology, 2016).

There are multiple stages of ID that occur before a diagnosis of IDA is established. Iron deficiency (ID) can appear without having a complete diagnosis of IDA where one's iron storage is low, yet the functional and transport amounts remain unaffected. Iron deficiency (ID) can be temporary or short-term, as factors such as a female's menstrual cycle and acute blood loss can foster symptoms of ID. General fatigue and lethargy are commonly observed in patients who have ID and are more pronounced as iron depletion escalates. When erythropoiesis is affected by the body's inability to absorb dietary iron, ID progresses to IDA. When there is a significantly reduced number of RBCs, depletion of iron stores, and consistently low serum iron, pervasive tissue hypoxia and issues with cellular function can result. These physiological occurrences then lead to the signs and symptoms experienced by the typical individual with IDA (Liu & Kaffes, 2012; Pavord et al., 2012; Zariwala, Somavarapu, Farnaud, & Renshaw, 2013).

Diagnostics

Iron deficiency anemia (IDA) is diagnosed when a patient's Hgb level is consistently less than his or her normal range in conjunction with a low hematocrit (HCT) and other clinical signs and symptoms. Women of all ages tend to naturally have lower Hgb and HCT levels due to a slightly lower blood volume and other gender-related factors. A normal Hgb range for women is generally accepted to be 12-16 g/dL, while the normal range for men is 14-18 g/dL (National Institutes of Health, 2015; Pagana &

Pagana, 2013; Rome, 2014b). Factors such as pregnancy and comorbidities do alter these normal ranges and manifest a greater requirement of iron. Hematocrit (HCT) is a volume-based measurement indicating the proportion of erythrocytes in the blood at a given time. A normal HCT for women is considered to be around 36%-44%, while males have a higher HCT at 41%-50%. Hemoglobin (Hgb) and HCT are accurate measures of blood content and indices of anemia or IDA, but both are considered non-specific and non-sensitive in pinpointing pathology (National Institutes of Health, 2015).

It is widely accepted that IDA is diagnosed when a woman manifests signs and symptoms of ID or IDA, as well as multiple Hgb levels less than or equal to 10.5-12 g/dL, depending on what is considered normal for the individual (Breyman, 2013; Khalafallah & Dennis, 2012). Serum ferritin (SF) levels are also measured for a diagnosis of IDA and considered to be one of the most accurate determinants of this condition. This indicator specifically represents how much iron is stored in the body (Iron Disorders Institute, 2016). Severe ID, which has usually reached the point of diagnostic IDA, is determined by SF levels that are continually below 20-30 mg/L, while moderate ID is established when SF levels are below 70-100 mg/L (Khalafallah & Dennis, 2012; Reveiz, Gyte, Cuervo, & Casasbuenas, 2011).

Effects on Infants

Infants are directly affected by a lack of iron at birth and on into their first year of life. This population has a critical need for sufficient nutrients in order to meet developmental milestones, both physically and cognitively. Infants born to women with prenatal IDA have even more pronounced adverse physiological and cognitive

developmental effects compared to infants born with low iron, yet without a maternal cause.

Prematurity

Prematurity is defined as a fetus being born before coming to the full gestational term of 38-40 weeks, or at any point less than 37 weeks (Heaman et al., 2012). The shorter the gestational age of the baby, the more complications the newborn will suffer outside the womb, as development is not complete and viability may or may not have been reached. Viability, although it has various interpretations in regards to medical support and other ethical criteria, is generally the point during the pregnancy that a fetus is able to survive on its own outside the womb (Gatti et al., 2012).

It is important to note that the efficacy of iron supplementation in women with ID and diagnosed IDA varies. Often times, it depends on the individual's demographic characteristics and the timing of treatment initiation. Research on the benefits of supplementation during pregnancy is often associated with the frequency of pregnancy complications and abnormal birth outcomes. An increased risk of preterm births and significantly shorter gestational age at delivery have been found when IDA was present at some point during the pregnancy, particularly during the first and third trimesters. The first trimester is when the fetus is growing and developing cognitively with great speed and cellular detail. Without sufficient micronutrients, such as iron, the fetus cannot develop the way it was intended. Harm to fetal development can occur even before signs and symptoms of IDA are present in the mother, which is why, in most cases, prophylactic supplementation is recommended. Furthermore, as the severity of a mother's

nutritional deficiency increases, the risk of both cognitive and physical harm to the fetus increases (Gambling, Kennedy, & McArdle, 2011).

Prematurity is a pregnancy outcome closely associated with prenatal IDA. Gambling, Kennedy, and McArdle (2011) claim there is an increased risk for premature birth when maternal IDA occurs during pregnancy. When a fetus is born before coming to term, and is therefore small for gestational age (SGA), the shorter gestational timeframe results in a below average level of stored iron in the newborn. Furthermore, the child's total iron storage is likely to be insufficient, regardless of gestational age, if the pregnant mother has a low amount of stored iron and cannot adequately transport enough iron to her child. Therefore, daily iron supplementation after birth is fundamental for the infant's survival and improved quality of life when born to a woman with prenatal IDA (Bánhidly et al., 2011; Gambling et al., 2011; Mala et al., 2012; Pavord et al., 2012).

Supplementation is especially important for premature newborns. Premature infants have an even greater risk for infection and long-term complications due to factors such as their immature immune system and underdeveloped integumentary system. Select research shows that congenital defects tend to be absent in pregnant women who had IDA and used iron supplementation at some point during the pregnancy. Even if a woman with prenatal IDA did not start iron supplementation until her third trimester, her baby's wellbeing is better than a baby born to a woman who did not use any supplementation throughout the pregnancy. Therefore, it is clear that prematurity is linked, to some degree, with prenatal IDA and associated risks can be reduced with iron supplementation during pregnancy (Bánhidly et al., 2011; Gambling et al., 2011; Mala et al., 2012; Pavord et al., 2012).

Low Birth Weight

Research shows that the risk for having a newborn with a low birth weight is at least doubled in women with Hgb levels greater than 11 g/dL or less than 9 g/dL during the prenatal period. Low birth weight is often correlated with other neonatal complications like intrauterine growth restriction (IUGR), which occurs when a fetus does not develop at a normal rate. Factors that are known to thwart normal fetal development include maternal use of drugs or alcohol, preeclampsia, and various nutritional deficiencies, such as ID. Besides a mother's iron levels, her SF levels have been shown to indirectly lead to IDA and cause the newborn to have a low birth weight (Breyman, 2013).

The infant mortality rate within a population is measured more accurately and frequently than the population's record of low birth weights. A low birth weight can be caused by a variety of both extrinsic and intrinsic factors, besides IDA, that are modifiable and unmodifiable (McMahon, 2010; Pavord et al., 2012). Low birth weight babies, like premature infants, are at an increased risk for IDA if born to a mother with prenatal IDA. Newborn infants of low birth weight are in a critical period where iron needs to be supplemented in order to prevent long-term complications or immediate death (Heaman et al., 2012; National Institutes of Health, 2015).

Iron deficiency (ID) can negatively affect a child's future development as much as it impacts a fetus or premature infant. Research shows that postnatal development of cognitive and immunological function can be greatly inhibited when ID is present before birth. Even more concerning are the results from studies that show an increased risk of early disease onset for adults who had low birth weights. Early onset of diabetes mellitus

(DM), obesity, and cardiovascular disease (CVD) has been linked to ID during the prenatal period as well as low birth weight (Gambling et al., 2011; Heaman et al., 2012).

In addition, many studies state the evidence-based importance of exclusively breastfeeding an infant born to a mother with prenatal IDA. Although the iron concentration in breast milk varies, it is believed to decline over time. This is why the habit of breastfeeding is particularly vital in the first six months of an infant's life. Glucose tolerance and blood pressure can also be negatively impacted in infants with low birth weights, who are exceptionally vulnerable and often in neonatal care facilities. Management of systemic homeostasis is challenged and infection rates increase, due to the unstable glucose levels and blood pressure. Without proper treatment, long-term physiological or mental problems can result (Breyman, 2013; Gambling et al., 2011; Heaman et al., 2012).

Treatment

A treatment plan for IDA is initiated after a true diagnosis has been made, usually based on the diagnosis criteria previously mentioned. Besides raising one's Hgb levels, RBC count, and heme carrying capacity within the blood, treatment is aimed to help improve quality of life by reducing the symptoms associated with IDA. Whether it is a prescription for a daily oral iron supplement or an order to increase one's intake of iron-rich or iron-fortified foods in the diet, treatment takes on different forms and is patient-specific. Studies have monitored the Hgb levels of children with IDA after they were treated with either iron supplements or iron-fortified food for an extended period of time. Disputes in the healthcare realm surround whether iron-fortified foods or iron supplementation leads to more success and patient compliance in IDA management,

usually because of the variation in these studies. However, iron supplementation continues to be the first-line treatment option, as it is more easily regulated with a prescription (Chandra & Sahi, 2015).

Iron Supplementation

Non-pregnant populations. Women with IDA who are not pregnant, as well as other populations such as newborns, the elderly, and alcoholics, are commonly prescribed a form of iron to treat their clinically-diagnosed iron deficit. An iron-rich diet and other non-pharmacological considerations are useful for treatment in these populations as well. Yet, iron supplementation is often easiest to regulate and prescribe in countries with accessible healthcare and financial resources for this treatment. Countries without accessible healthcare and financial resources for this treatment often have a higher infant mortality rate and death rate associated with nutrient deficiencies. Furthermore, education is necessary for people in these areas as to the importance of iron-rich foods and utilization of any available sources of iron. Supplementation, particularly by the oral route, is widely accepted and encouraged when individuals have multiple risk factors for IDA or are already diagnosed with IDA (Taylor & Rampton, 2015).

Oral supplements, in which a ferrous product such as ferrous sulfate is utilized, are taken as a tablet or a liquid. The prescription is usually dependent on the patient's recommended dose and individual clinical circumstance. Some patients dislike taking iron supplements orally, not because of inconvenience or adverse effects, but because of unpleasant side effects that accompany the supplement. It is the healthcare team's responsibility to educate individuals receiving long-acting or enteric-coated oral iron supplements about the expected side effects. For example, gastrointestinal side effects

can include black tarry stool or constipation. These effects should not be reported to a physician because they are benign and a result of iron absorption within the gastrointestinal tract. It is concerning only when complications such as nausea and vomiting, severe or prolonged constipation, and signs of infection occur in conjunction with the supplements (Gupta, Manaktala, & Rathore, 2013; Mayo Clinic, 2016b; Taylor & Rampton, 2015).

Intravenous therapy is the most common route of parenteral iron supplementation, as research discourages the administration of intramuscular iron dextran due to complications including pain and adverse reactions at the site of injection (Gupta et al., 2013). Intravenous iron supplementation, or iron sucrose, is often utilized when patients are unable to tolerate the adverse effects of oral iron supplements, such as gastrointestinal distress, or when there is an issue with patient compliance. Intravenous therapy can be argued as a more effective option due to fewer times of administration and higher dosages. In order to prepare an intravenous dose of iron, an individual's body weight and Hgb or iron levels are put into a formula to determine a dose appropriate for the iron shortage. Intravenous treatment is best administered by health care providers within facilities that can quickly respond to hypersensitivity reactions (HSRs) that sometimes result from infusions. This mode of treatment tends to create fewer adverse reactions, HSRs are rare, though this depends on the patient's history and clinical picture. Health care providers are required to evaluate patient response to each treatment by monitoring laboratory values such as ferritin level, TS, and Hgb concentration (Gupta et al., 2013; Taylor & Rampton, 2015).

Pregnant population. Various treatment options are available for ID and IDA, but effectiveness during pregnancy is widely debated. Supplementary intake is needed due to the significant consumption of iron during pregnancy, especially during the first trimester. Iron supplements are also strongly advocated for throughout the third trimester and into the postpartum period because of blood loss during the birthing process (Khalafallah & Dennis, 2012).

Part of the debate on iron supplementation during pregnancy concerns patient compliance. Providing detailed education on daily administration of oral iron supplements should be given to pregnant women, women in the postpartum period, or women who may soon become pregnant. Oral iron supplementation is the most common form of treatment due to its ease of administration and how it primarily uses the body's natural route for iron absorption. Iron is naturally received and absorbed by the gastrointestinal system first, as opposed to the bloodstream. Researchers have also endorsed intravenous iron therapy, despite its known disadvantages and pharmacological considerations, such as potential for severe systemic reactions (Berger, Wieringa, Lacroux, & Dijkhuizen, 2011; Gupta et al., 2013; Khalafallah & Dennis, 2012; Krafft et al., 2012; Pavord et al., 2012).

A patient's Hgb level does not show significant increase as a result of oral iron supplements until about 4-6 weeks after treatment is initiated. Furthermore, it is an additional 2-3 months until stores of iron are built up as a result of iron supplementation. Research studies have compared the safety and effectiveness of intravenous iron sucrose to oral elemental iron, or ferrous sulfate. Results of these studies claim an overall larger mean increase in Hgb levels for groups receiving intravenous iron sucrose as opposed to

oral supplements. In addition, 76% of study participants who received iron intravenously reached a Hgb level of at least 11 gm/dL compared to a lesser 54% of participants receiving oral iron therapy. Participants who received the oral iron supplement also experienced more adverse effects than the group who received intravenous therapy, although all effects were reported to be mild and manageable over time (Gupta et al., 2013).

Prenatal iron RDA, treatment dosages, and adverse effects of supplements during pregnancy are variables that continue to be researched for the betterment of IDA treatment in all clinical arenas. For example, the prevalence of ID and prenatal IDA in a group of Danish women was studied in 2012 by assessing a population's intake of iron supplements throughout their pregnancy. This study found there is a variety of consensus across countries, but the increase in iron demand during pregnancy cannot be met solely by internal sources or dietary iron. Besides a low-dose oral iron supplementation, individualized iron prophylaxis is highly recommended when accessible for women in their reproductive years. The immediate and long-term effects of iron supplementation on babies born to women with prenatal IDA are still being researched to make adequate conclusions (Chang, Zeng, Brouwer, Kok, Yan, 2013; Gupta et al., 2013; Krafft et al., 2012; Milman, 2012; Pavord et al., 2012).

Other studies give evidence that iron supplementation during prenatal IDA reduces birth complications. Congenital abnormalities, preterm births, low birth weights, and other fetal or postpartum health concerns are common when women with prenatal IDA do not take iron supplements. For example, one study performed in Hungary in 2011 using the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA)

found that the rate of preterm births was higher and the gestational age at delivery was shorter for women with prenatal IDA who did not utilize iron supplementation for treatment. Maternal health and wellbeing were also concluded to be improved as a result of oral iron supplements during pregnancy. A newborn's cognitive ability and physical condition as well as psychosocial development and emotional stability are greatly affected by iron supplementation and the presence of prenatal IDA, particularly in the third trimester. Iron deficiency anemia (IDA) in the third trimester typically occurs in pregnant women with a high-risk for IDA paired with a lack of iron supplementation throughout the entire pregnancy (Khalafallah & Dennis, 2012; Milman, 2012).

Implications for Practice

The conclusions drawn from this peer-reviewed information will be applicable in the health care realm and in the lives of all patients with IDA, particularly those who are pregnant or considering becoming pregnant. This research will benefit all women of childbearing age since they have a higher risk for IDA and the consequences can affect their unborn child. Research on this topic also increases long-term health in the general population since premature and low birth weight babies are more susceptible to long-term health conditions and infant mortality.

This research compilation was limited to peer-reviewed or professional studies done within the past five years, studies that used participants with ID or IDA established by various diagnostic criteria, and studies that concerned ID, IDA, IDA in pregnancy, or the effects of IDA on infants. More comprehensive research should be performed to study women of various ages with IDA before and during pregnancy. Research should also be focused on the prenatal and postnatal development of babies born to women with prenatal

IDA. Case studies and longitudinal studies of patients with IDA in various countries would benefit the research and health care communities as dietary recommendations, ID prevention, and IDA treatment could become more evidence-based.

Conclusion

The prevalence of IDA and amount of information available regarding the condition is substantial. Iron deficiency anemia (IDA) is not a disease, but a collection of signs and symptoms that are displayed according to an insufficient amount of iron in the body. Iron supplies rise when a dietary form is ingested or it accumulates by the reticuloendothelial system, when RBCs are broken down by hepatocytes and intestinal enterocytes. Iron is then transported via transferrin and stored throughout the body. For example, the spleen, bone marrow, and cytoplasm of macrophages are major storehouses for iron, which is kept as ferritin or hemosiderin. Hemoglobin level is another accurate measure of serum iron. This erythrocyte protein transports iron through the bloodstream and aids in oxygenation as well as various cellular and systemic physiological functions, such as energy or metabolism. Individuals can experience fatigue, or significant lack of energy, in the presence of ID. Iron deficiency (ID) leads to an insufficient supply of oxygen and proteins needed for adequate cellular functioning (American Society of Hematology, 2016).

The harmful impact of IDA on fetal and newborn development is a global issue. Recent research indicates that adequate prophylaxis and treatment of IDA stems from standardized iron supplementation regulations and education of iron-rich foods. IDA is a global issue that should be addressed by the federal government as well as state organizations with the consideration of local communities. Select research lends to the

assumption that negative developmental effects on newborns, prematurity and low birth weights, and debilitating anemia-related symptoms can be prevented. This prevention is dependent on the early and successful utilization of diagnostic tools and treatment options for IDA. Treatment comes in different forms and is determined on a case-by-case basis. Further research and individualized education in clinical settings is necessary as this condition increases in prevalence and severity (Gupta et al., 2013).

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