INTRODUCTION

Iron deficiency anemia and thalassemia minor are among the most frequent hypochromic microcytic anemia in our environment ***(Means, 2013).***

Iron deficiency anemia is the most common nutritional disorder, affecting 30-70% of population in developing countries ***(Means, 2013)***. This type of anemia is the final phase of a process that begins with exhaustion of iron stores and continues with iron depletion from other compartments that contain it compromising normal hematopoiesis ***(Zago et al., 2005).***

In some geographical areas other disorders, such as β-thalassemia trait (β-TT), must be considered ***(Junca et al., 1991; Dugdale, 2001).*** β-thalassemia is genetically determined disorder in which the defect in the β-globin gene results in a decreased production of hemoglobin (Hb) A_1. β-thalassemia is frequently seen in Mediterranean countries in Africa and Asia and it is important public health problem ***(Hermiston et al., 2002).***

β thalassemia-trait is generally asymptomatic; however, in clinical practice, because there is hypochromic microcytic mild anemia and the peripheral smear resembles iron deficiency anemia (IDA), these two disorders must be distinguished from each other ***(Segel et al., 2002).***

The red cell indexes are used in diagnosis of thalassemia trait cases, MCV and MCH are low while MCHC is normal ***(Tatsomi et al., 1989)***. Some differential indexes were defined by calculating red blood cell (RBC) indexes and were used for rapid discrimination between TT and IDA, but there is also some information in the literature about platelet indexes in these two diseases ***(Bessman et al., 1985).***

Frequent occurrence of Iron deficiency anemia in patients with beta thalassemia trait can potentially confound the diagnosis of the later. Hence; iron deficiency should be identified and rectified in patients with suspicion of beta thalassemia trait ***(Sarika et al., 2014).***

AIM OF THE WORK

The aim of this study is to evaluate platelets indexes in differentiation between β-thalassemia trait and iron deficiency anemia to facilitate rapid discrimination between these two common causes of hypochromic microcytic anemia.

IRON DEFICIENCY ANEMIA

Iron is a component of every living cell and has been recognized for centuries as an essential element for the maintenance of health. Iron participates in numerous biochemical reactions primarily involved in oxygen transport and storage, adenosine triphosphate production, deoxyribonucleic acid synthesis, and electron transport ***(Clark, 2008).***

Iron is obtained in the form of non-heme iron from vegetable and as heme iron from meat. A small amount of heme iron in the diet can improve absorption of non– heme iron. The best sources of dietary iron are meat, fish and poultry but their intakes remain low due to multiple reasons ***(Bagchi, 2004)***.

The percentage of iron absorbed (i.e., iron bioavailability) can vary from less than 1% to greater than 50%. The main factor controlling iron absorption is the amount of iron stored in the body. The gastrointestinal tract increases iron absorption when the body's iron stores are low and decreases absorption when stores are sufficient. An increased rate of red blood cell production can also stimulate iron uptake several folds ***(Clark, 2008)***.

Iron absorption is also influenced by the type of dietary iron consumed. Absorption of heme iron ranges from 15% to 35%, and is not significantly affected by diet. In contrast, 2% to

20% of nonheme iron in plant foods such as rice, maize, black beans, soybeans and wheat is absorbed. Nonheme iron absorption is significantly influenced by various food components.

Meat proteins and vitamin C will improve the absorption of nonheme iron. Tannins (found in tea), calcium, polyphenols, and phytates (found in legumes and whole grains) can decrease absorption of nonheme iron. Some proteins found in soybeans also inhibit nonheme iron absorption. It is most important to include foods that enhance nonheme iron absorption when daily iron intake is less than recommended, when iron losses are high (which may occur with heavy menstrual losses), when iron requirements are high, and when only vegetarian nonheme sources of iron are consumed ***(WHO, 2001)***.

I- Definition:

Anemia is one of the most common and intractable nutritional problems in the world today. Approximately two billion people are anemic based on hemoglobin concentrations below recommended thresholds ***(WHO, 2001)***.

Clinically anemia is defined as insufficient mass of Red Blood Cells (RBCs) circulating in the blood; while in public health terms anemia is defined as hemoglobin concentration below normal thresholds, as shown in table 1 ***(WHO, 2001)***.

Table (1): Criteria for Anemia

Classification	Severe	Moderate	Mild	Normal
Hb level (gm/dl), Children 5-11 years	<7	7-9.9	10 – 11.4	›11.5
Hb level, Nonpregnant Women	<7	7-9.9	10- 11.9	›12.0
Hb level, pregnant women	<7	7-9.9	10- 10.9	›11.0

(WHO, 2001)

Iron deficiency is the most common cause of anemia, and is one of the leading risk factors for disability and death worldwide ***(WHO, 2001)***.

Iron-deficiency anemia (IDA) is defined as a disease of the reduced erythrocyte production with low content of hemoglobin, resulting in red blood cells that are abnormally small (microcytic) and contain a decreased amount of hemoglobin (hypochromic) ***(Kanamaru, 2008)***.

II- Epidemiology:

Epidemiology of iron deficiency:

Estimates of occurrence of iron deficiency in industrialized countries are usually derived from nationally representative samples with specific indicators of iron status. By contrast, estimates from developing countries are often based only on haemoglobin measurements from restricted regions or target populations, and should be interpreted with

caution. Prevalence estimates of iron deficiency anemia based on hemoglobin alone are overestimations because they fail to account for other causes of anemia, such as nutritional deficiencies (e.g. vitamin A deficiency), infectious disorders (particularly malaria, HIV disease, and tuberculosis), hemoglobinopathies, and ethnic differences in normal hemoglobin distributions ***(Lynch, 2005)***.

WHO (2001) estimated that 39% of children younger than 5 years and 48% of children between 5 and 14 years in developing countries are anemic, with half having iron deficiency anemia. According to WHO, the frequency of iron deficiency in developing countries is about 2.5 times that of iron deficiency anemia in developed countries. In France, iron deficiency and iron deficiency anemia affect 29% and 4% of children younger than 2 years respectively; in the USA, 2% of children between one and 2 years have iron deficiency anemia ***(Center of Disease Control and Prevention (CDC), 2002)***.

In the Eastern Mediterranean region, anemia is particularly attributed to iron deficiency among infants, preschool children and remained a widespread public health problem, The Prevalence of anemia vary from 17% to over 70% among preschool children; 14% to 42% among adolescents and from 11% to over 40% among women of childbearing age. The prevalence of anemia has often been used as a proxy indicator for iron deficiency anemia ***(Bagchi, 2004)***.

In Palestine, the prevalence of iron deficiency in the preschool children 48-59 months old is high, it was reported that 19.8% of these were iron deficient. In Jordan, high prevalence of anemia was reported affecting women of childbearing age and infants/preschool children. The prevalence of anemia in children aged 6-59 months was 20.1% and the prevalence of IDA was 10.1%.

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 ***(Gonzalez et al., 2009).***

Age-related demographics:

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 what is lost in order to maintain a normal body concentration of 60 ppm.

Race-related demographics:

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 is more frequently is observed in children of various racial backgrounds living in poorer areas of the world ***(Goddard et al., 2011)***.

Screening recommendation:

Analysis of the National Health and Nutrition Examination Survey (NHANES) III database demonstrated that anemia (hemoglobin level < 11 gm/dl) is neither a sensitive nor a specific screen for iron deficiency ***(White, 2005)***.

Dietary history may be suggestive of iron deficiency and has been studied as a possible marker for microcytic anemia. In one study of healthy inner-city children between the ages of 15 and 60 months, dietary iron deficiency was defined as: fewer than 5 servings per week each of meat, cereals or bread, vegetables, and fruit; more than 16 oz per day of milk; or daily intake of fatty snacks or sweets or greater than 16 oz of soda. As a screening test for microcytic anemia, the study found that diet history had 71% sensitivity, 79% specificity, and 97% negative predictive value. Similarly, low specificity was

demonstrated in another prospective study that used a questionnaire to assess diet, Women, Infant and Children (WIC) participation, and medical and family history. Response to a clinical trial of iron therapy is used by most clinicians as a practical method of diagnosing iron deficiency anemia ***(Boutry and Needlham, 1996)***.

These data provide a framework for whom should be screened for iron deficiency and includes the following screening recommendations by the American Academy of Pediatrics in infants and young children ***(American Academy of Pediatrics (AAP), 2008)*:**

- In normal healthy infants, risk assessment for iron deficiency is recommended at 4, 18, and 24 months of age, and annually thereafter. A hemoglobin or hematocrit is recommended at 12 months of age.
- Children with special health needs (chronic infection, inflammatory disorders, chronic gastrointestinal dysfunction, restricted diets).
- Children two to five years with increased (dietary) risk factors for IDA.

In the United States, screening for anemia is generally performed by measuring hemoglobin/hematocrit between 9 and 12 months. For high risk groups (e.g. those who receive women, infant and children support), blood screening is

"mandatory". Follow-up testing is then mandated at later time periods for those with abnormal results ***(American Academy of Pediatrics (AAP), 2008)***.

III- Etiology:

Iron deficiency results due to several causes but to be more specific causes that fall into four main categories.

1. Deficient intake:

One of its possible causes is a poor dietary iron intake, which is infrequent in developed countries, but quite common in developing areas. In these countries, dietary ID is highly prevalent and comprises a real public health problem and a challenge for health authorities. ID, with or without anemia, can cause important symptoms that are not only physical, but can also include a decreased intellectual performanc ***(Kattalin et al., 2011).***

2. Increased demand:

In infancy, childhood, and adolescence, the requirements for iron are relatively great because of the increased needs of rapidly growing tissues. The most rapid relative growth rates in human development occur in the first year of life. Body weight and blood volume approximately triple, and the circulating hemoglobin mass nearly doubles. Still greater relative growth occurs in premature and low-birth-weight infants. Premature infants weighing 1.5 kg may increase their weight and blood

volume six fold and may triple the circulating hemoglobin mass in 1 year ***(Ferrara et al., 2006)***.

The relatively slower rates of growth in children through the remainder of the first decade require a positive iron balance of 0.2 to 0.3 mg/day. The growth spurt that occurs in the early teens requires a positive balance of 0.5 mg/day in girls and 0.6 mg/day in boys. Toward the end of this period, the onset of menstruation occurs in girls, and their requirements then equal those of adult women ***(Ferrara et al., 2006)***.

3. Blood loss:

Iron deficiency by itself, irrespective of its cause, may result in occult blood loss from the gut. More than 50% of iron-deficient infants have guaiac-positive stools. This blood loss is due to the effects of iron deficiency on the mucosal lining (e.g. deficiency of iron-containing enzymes in the gut), leading to mucosal blood loss. This sets up a vicious cycle in which iron deficiency results in mucosal change, which leads to blood loss and further aggravates the anemia. The bleeding due to iron deficiency is corrected with iron treatment. In addition to iron deficiency per se causing blood loss, it may also induce an enteropathy, or leaky gut syndrome. In this condition, a number of blood constituents, in addition to red cells, are lost in the gut ***(Ferrara et al., 2006)***.

A. Perinatal:

1. Placental:

a. Transplacental bleeding into maternal circulation.

b. Retroplacental (e.g. premature placental separation).

c. Intraplacental.

d. Fetal blood loss at or before birth (e.g. placenta previa).

e. Fetofetal bleeding in monochorionic twins.

f. Placental abnormalities.

2. Umbilicus:

a. Ruptured umbilical cord (e.g. vasa previa) and other umbilical cord abnormalities.

b. Inadequate cord tying.

c. Post exchange transfusion.

B. Postnatal:

1. Gastrointestinal tract:

a. ***Primary iron-deficiency anemia*** resulting in gut alteration with blood loss aggravating existing iron deficiency. 50% of iron-deficient children have guaiac-positive stools.

b. ***Hypersensitivity to whole cow's milk:*** Ingestion of whole cow's milk may induce protein-losing enteropathy and gastrointestinal bleeding in infants, probably on the basis of hypersensitivity or allergy.

Cow's milk can result in an exudative enteropathy associated with chronic Gastrointestinal (GI) blood loss resulting in iron deficiency. Whole cow's milk should be considered the cause of iron-deficiency anemia under the following clinical circumstances:

- One quart or more of whole cow's milk consumed per day.
- Iron deficiency accompanied by hypoproteinemia (with or without edema) and hypocupremia (dietary iron-deficiency anemia unassociated with exudative enteropathy is usually associated with an elevated serum copper level). It is also associated with hypocalcemia, hypotransferrinemia, and low serum immunoglobulins due to the leakage of these substances from the gut.
- Iron-deficiency anemia unexplained by low birth weight, poor iron intake, or excessively rapid growth.
- Iron-deficiency anemia that recurs after a satisfactory hematologic response following iron therapy.
- Rapidly developing or severe iron-deficiency anemia.
- Suboptimal response to oral iron in iron-deficiency anemia.

- Consistently guaiac-positive stool tests in the absence of gross bleeding and other evidence of organic lesions in the gut.

- Return of GI function and prompt correction of anemia on cessation of cow's milk and substitution by formula.

c. ***Anatomic gut lesions*** (e.g. varices, hiatus hernia, ulcer, leiomyomata, ileitis, Meckel's diverticulum and duplication of gut) may be associated with significant blood loss leading to IDA ***(Ferrara et al., 2006).***

d. ***Gastritis*** as a result of drug ingestion is another common cause of bleeding. Aspirin ingestion is as likely to cause bleeding in patients without preexisting ulcer as in those with peptic ulcer. Other medications (such as glucocorticoids, indomethacin, ibuprofen, or other nonsteroidal anti inflammatory drugs) may also cause bleeding by inducing gastric or duodenal ulcers or colitis ***(Faucheron and Parc, 1996).***

e. ***Intestinal parasitic infestations*** particularly by hookworms, is a major cause of gastrointestinal blood loss in many parts of the world ***(Mahadeva et al., 2007)***.

2. **Lung:** Pulmonary hemosiderosis, Goodpasture syndrome, defective iron mobilization with IgA deficiency ***(Hudson et al., 2003)***.