CHAPTER II

BACKGROUND

1. IRON DEFICIENCY

Iron deficiency denotes a deficit in total body iron resulting from iron requirement exceeding iron supply. There are three levels of iron deficiency.

1.1 Storage iron depletion :

A decrement in storage iron with a decline in the level of functional iron compounds leads to iron depletion. The patients are not anemic with no clinical manifestation. Hemoglobin level, hematocrit, serum iron and transferrin saturation including erythrocyte protoporphyrin are within normal value limits. Only serum ferritin is lower than 25 ng/ml.

1.2 Iron deficient erythropoiesis :

This is due to insufficient iron much enough to limit the production of hemoglobin and other metabolically active compound that requires iron as a cofactor. At this stage the patients still have no anemia. Hemoglobin and hematocrit are within normal limits but serum iron, transferrin saturation and serum ferritin are decreased. Serum ferritin is lower than 20 ng/ml at this level.

1.3 Iron deficiency anemia :

When the insufficiency of iron goes down further until there are not enough iron to produce new heme, the patients begin to have anemia. Hemoglobin and hematocrit are decreased. Serum ferritin, serum iron and transferrin saturation are also decreased. At this level the peripheral blood smear of the patients show hypochromic microcytic cells.

2. IRON ABSORBTION , TRANSPORTATION AND STORAGE

Iron. is absorbed as both heme and non-heme. The site of absorption is the upper part of the small intestine. Heme iron is highly available for absorption (20-30 percent or more absorbable) and little affected by other component in the diet, but usually it is only a small portion of the diet especially in the northeastern Thai food. Nonheme iron is less absorbable. The absorption of nonheme iron is determined by the balance between inhibitors (phytates, tannates, phosphates) and enhancers (amino acids, ascorbic acid). For the people in the North-east whose sticky rice is the main food which contain high phytates, iron absorption may be inhibited. Fortunately lime juice which contains plenty of ascorbic acid is also commonly used in cooking their food.

Iron availability is also influenced by gastrointestinal factors such as gastric secretion, intestinal motility and the consequences of surgery or bowel disease. Absorption of iron increases with diminished storage iron and increased erythropoietic activity.

After the iron is absorbed, it will be transported by transferrin, the transport protein. In normal situation, only about 35 percent of transferrin bind with iron. The iron will be transported to storage site. There are two storage iron compounds, ferritin and hemosiderin. Most of them are stored in the reticuloendothelial cells in the bone marrow, liver and spleen.

2.1 Distribution of iron in the body

About two thirds of total iron in the body are in red blood cells in the form of hemoglobin. The concentration of iron in human body is normally about 40 to 50 mg/kg body weight; women typically have lower iron than men. About 6-7 mg of iron per kg are the component of myoglobin, heme enzymes (cytochrome, catalase, peroxidase) and nonheme enzymes (ribonucleotide reductase, metalloflavoproteins, iron sulfur proteins). Iron in the transport compartment is bound to the protein transferrin in the plasma and extracellular fluid. The remainder of iron is in the form of ferritin and hemosiderin contained in hepatocyte and macrophage in the liver, bone marrow and spleen.

2.2 Iron requirement

Over all iron requirement for an individual includes the iron needed to replenish physiologic losses; the demands of growth and pregnancy and the amounts needed to replace pathologic losses.

Physiologic losses of iron are generally due to shedding of iron contained cells from the intestine, urinary tract, and skin. In women, blood losses during menstruation and pregnancy increase the iron requirement. In normal men, the daily basal iron loss is about 1.0 mg/day. In normal menstruating women, the basal iron loss is about 1.5 mg/day. The median total iron loss with pregnancy is about 500 mg or about 2 mg/day over the 280 days of gestation.

3. ETIOLOGY OF IRON DFEFICIENCY

3.1 Chronic blood loss

This is very common in Thailand due to the high prevalence of hook worm infestation (Butaraj et.al.,1982 ; Chularerk and Luangpirom,1988; Dulyapiree,1990 ; Vajrasthira and Harinasuta , 1957). The most prevalent species in Thailand is Necator Americanus which can cause blood loss of about 0.03-0.08 ml per worm per day (Areekul et.al. , 1970). The other sources of blood loss in the gastrointestinal tract are gastritis and peptic ulcer. The popularity of aspirin analgesic which is freely sold in drugs stores is high among Thai farmers. They get it to relieve muscle pain after work and finally some get addicted to it. Incessant aspirin use can cause gastritis and gastro-intestinal blood loss becomes frequent.

Among females during menstrual period, hypermenorrhea may be the cause of iron deficiency especially when iron intake is just enough and there are few iron stored.

3.2 Inadequate iron intake

Iron intake depends on iron content and bioavailability of food, inhibitors and enhancers of iron absorption and intestinal absorption ability. Iron content and bioavailability of food including inhibitors and enhancers of iron absorption depend on eating habit, available food, culture and belief and socioeconomic status.

Increased iron requirement during pregnancy, lactation, growth spurt in teens and children and menstruating women can cause iron deficiency even though they eat ordinary diet.

The vegetarian is another group at risk for iron deficiency because most of the iron content in their food is non heme iron which is much less absorbable than heme iron.

4. LABORATORY MEASURMENT OF IRON STATUS

4.1 Bone marrow iron

This technique is the time honored method for assessing storage iron. The presence of marrow iron in a patient with significant anemia excludes iron deficiency with two possible exceptions :

a) In patients with a recent massive hemorrhage, large particles of iron may occasionally persist during the period mobilization of iron reserves

b) In patients recently given parenteral iron which may be seen histologically weeks or even months in the face of continued iron deficiency.

Although this method is very sensitive for measuring iron status ,this technique is not suitable for survey study because of its invasiveness.

4.2 Serum ferritin

There is sample evidence that in normal subjects serum ferritin is directly proportional to body iron stores. In several surveys of normal adult women , the median or geometric mean ferritin varied from 23-34 ng/ml.(Srotongkul and Naksukskul , 1986)

Serum ferritin measurement has a complex methodology. Many laboratory methods are available, including immuno radiometric assays (IRMA) using labeled antibody, radio immunoassay (RIA) using labeled antigen, and enzyme linked immunosorbent assays (ELISA) which eliminate the need for radioisotopes. Despite the wide range of techniques, the difference between ferritin value measured by different method is not so high. Commercially available ferritin assay kits have made the cost of serum ferritin measurements comparable to other iron measurements.

An important advantage of the serum ferritin is its relative stability with repeated measurements in the same subject. The serum ferritin level does not have diurnal variation.

In this study, serum ferritin was chosen to be the measurement for iron status of the subjects because it is more sensitive to determine iron status and more stable than serum iron, total iron binding capacity (TIBC), transferrin saturation or red cell indices. It has less variability related to physiologic factors. The only factor that can interfere with measurement of serum ferritin is inflammatory process from infection.

ELISA method is chosen because it is easier to perform, less risk of contamination to radioisotope of the technician, and sensitivity and specificity of the test is not much different from other methods.(Srotongkul and Naksukskul ,1986)

4.3 Serum iron (SI), TIBC and Transferrin Saturation (TS)

The iron transport parameters (SI, TIBC, TS) usually do not change until storage iron is completely exhausted. It is less sensitive to changes in iron stores than the serum ferritin. Laboratory errors in measuring SI and TS are common. The main clinical disadvantage of the TS is that it is highly labile. Diurnal variation in serum iron and TS is high which can result in jerked difference within the same individual over 24 hours. Inflammation and infection can also alter the ST and TS levels.

4.4 Free Erythrocyte Protoporphyrin (FEP)

The FEP provides about the same information as the TS but is more stable. It is useful in recognizing iron deficiency in infants. The problem of FEP is that the level is increased in lead poisoning which is often an important differential diagnosis in children.

4.5 Red Cell indices

The most reliable Red cell index now is mean corpuscular volume (MCV). It is useful for diagnosis of iron deficiency anemia only in the area that thalassemia is rarely seen because both iron deficiency anemia and thalassemic cases have low MCV.

4.6 Hemoglobin / hematocrit

The final stage of iron deficiency is associated with a significant decrease in circulating hemoglobin. The main limitation of hemoglobin and hematocrit as a measure of iron deficiency is the marked overlap in frequency distribution curves in anemic and normal individuals. In the area where thalassemia is prevalence hemoglobin and hematocrit alone can not determine iron deficiency anemia because thalassemic patients also have low hemoglobin and hematocrit level . The other causes of anemia can decrease hemoglobin and hematocrit also.

5. MANIFESTATIONS OF IRON DEFICIENCY

5.1 Anemia :

Usually, iron deficiency anemia is a chronic disease with gradual onset. The patients have very few symptoms. Even with severe anemia, fatigue and shortness of breath may escape notice if the iron deficiency is very gradual.

5.2 Decreasing exercise tolerance and work performance :

When anemic individuals are evaluated at rest there is unlikely to be any obvious impairment of cardiovascular function unless the anemia is severe. In contrast, even mild anemia may result in decreased performance under a standard work load. Iron deficiency in man results in an impairment of work which can be rapidly reversed by iron treatment.The impairment has economic relevance and is evident even when iron deficiency is mild especially if the prevalence in population is high.

5.3 Behavior & Development in Children :

Severely iron deficient infants have been characterized as irritable and uninterested in their surroundings. Within days of iron treatment, there had been an impression that the infants became calmer yet more alert. There are several studies about impairment of mental and physical development among iron deficient children.(Chwang et.al.,1988; Pollit et.al.,1989 ; Oski et.al.,1983)

5.4 Complication of pregnancy :

Iron deficiency anemic mothers have higher mortality rate than normal mothers because they can not tolerate blood loss during delivery (Danfort ,1982). The perinatal death rate of infant and incidence of premature labour are also increased in iron deficiency anemic mothers (Barns , 1979)

5.5. Infection

There were evidences that iron deficiency decreased immune mechanism. T-lymphocyte, lymphocyte transformation, myeloperoxidase in white blood cells and lactoferin are decreased in iron deficiency patients.

However there is no clear demonstration of clinical significance (Dallman , 1982).

6. SOCIOECONOMIC EFFECTS OF IRON DEFICIENCY ANEMIA

Decreased work performance and productivity in iron deficiency anemic person lead to economic loss. Whenever the symptoms of anemia are severe, the patients seek for help. Increasing demand of health & service in severe anemia cases, complicated pregnancy can cause more economic loss.

The effect of iron deficiency anemia in infants and children is also serious. Since it can cause retardation in both physical and mental development of a child, the quality of future adult population will be poor if the prevalence of iron deficiency is high.