INTRODUCTION

Anemia is the most frequent disturbance of physiology in the world throughout the life of a woman. It is a serious condition in the developing countries and also in the developed countries. Most common causes of anemia are malnutrition, iron deficiency, folic acid deficiency, vitamin A deficiency and vitamin B12 deficiency, diseases like malaria, hookworm infestation and schistosomiasis, HIV infection and genetically inherited hemoglobinopathies such as thalassemia ***(Di Renzo et al., 2015).***

Maternal anemia is frequently associated with preterm labor, neonatal low birth weight, infant iron deficiency, neonatal death, and low Apgar scores at 1 min. It is also suspected to reduce the oxygen supply to the growing fetus, leading to the redistribution of fetal blood flow ***(Ali et al., 2016).***

The different adverse effects including low birth weight and preterm labor are depending on the degree and duration of anemia and the age of gestation. Management of mild anemia prevents more severe forms of anemia, which associated with increased risk of fetal-maternal mortality and morbidity ***(Allen, 1997 and Ali et al., 2016).***

In the presence of fetal hypoxemia, fetal blood flow will be centrally distributed to ensure adequate amount of

oxygen to its brain. This redistribution called the brain-sparing reflex, this plays a major role in fetal adaptations to oxygen deprivation ***(Ali et al., 2016).***

Maternal anemia is a hypoxic condition that could be responsible for this redistribution of fetal blood flow ***(Carles et al., 2003).*** The combination of increased placental resistance and decreased cerebral resistance, measured using Doppler ultrasonography, is quantified by calculating the cerebral-to-umbilical artery resistance ratio ***(Ali et al., 2016).***

This Doppler parameter is not affected by the gestational age and is always more than 1.1 during normal pregnancy ***(Adamson et al., 1990)*** and ***(Arbeille et al., 1994).*** However, this ratio is decreased in the presence of hypoxia due to increased placental vasoconstriction and cerebral vasodilatation and correlates closely with fetal growth and hypoxia, especially before 34 weeks of pregnancy ***(Ali et al., 2016).***

The middle cerebral artery is the most accessible fetal cerebral vessel to ultrasound imaging, and it carries more than 80% of cerebral blood flow. The cerebral circulation is normally a high resistant circulation. This is the reverse of flow within the umbilical cord toward the placenta ***(Alfred and Abuhamad, 2016)***.

AIM OF THE WORK

This study aims to assess the changes in fetal cerebral and Umbilical artery resistance index in women with severe iron deficiency anemia using non invasive measurement (colour Doppler ultrasound).

Hypothesis:

In pregnant women with severe anemia Cerebral artery resistance index may be decreased and Umbilical artery resistance index may be increased.

Question:

In pregnant women with severe iron deficiency anemia, does Cerebral artery resistance index decrease and Umbilical artery resistance index increase?

Chapter 1

IRON DEFICIENCY ANEMIA WITH PREGNANCY

Introduction:

Anemia in pregnancy is defined by the World Health Organization (WHO) as a hemoglobin concentration below 11 g/dl. It was further categorized into three levels; mild 9-11 g/dl, moderate 7-9 g/dl and severe < 7 g/dl. Anemia still represents one of the main causes of increased rates of maternal and perinatal mortality, premature delivery, low birth weight and other adverse outcomes ***(Abdel-Aziz et al., 2017).***

Iron deficiency is the most widespread nutritional deficiency in the world. It is the most common cause of anaemia during pregnancy. Other causes include parasitic diseases such as malaria, hookworm infections, and schistosomiasis; micronutrient deficiencies including folic acid, vitamin A, and vitamin B12, and genetically inherited haemoglobinopathies such as thalassaemia ***(Haider et al., 2013).***

The maximum absorption of iron from the diet is less than the body's requirements for iron, resulting in a risk of iron deficiency. In infants and young children (aged 0-15 years), rapid growth consumes the iron stores that accumulate during gestation, which can, in turn, lead to an

absolute deficiency. After childhood, adolescent girls are particularly at risk of iron deficiency anaemia, because of menstrual iron losses. During pregnancy, iron needs are tripled because of expansion of maternal red cell mass and growth of the fetus and placenta. Daily iron supplementation is significantly associated with reduced risk of anaemia at term. Mothers who breastfeed are less likely to be iron deficient than pregnant women because iron concentration in mature breastmilk is only 0.20-0.80 mg/L and most breastfeeders are amenorrhoeic. Regular blood donors are at increased risk of iron deficiency ***(Lopez et al., 2016).***

Iron physiology:

Iron is the most abundant essential trace element in the human body ***(Bhattacharya et al., 2016).*** Iron is present in all body cells. As a component of hemoglobin and myoglobin, it functions as a carrier of oxygen in the blood and muscles. Because of iron losses during menstruation, women in their reproductive years require higher iron intakes than men. Therefore, the Recommended Dietary Allowance (RDA) for women 11 to 50 years of age is 18 mg/day, but for men 19 years and older is only 10 mg/day. Women have difficulty achieving this high intake, because they generally have a relatively low caloric intake, and the usual U.S. diet provides only 6 to 7 mg of iron per 1, 000 kcal. Since the need for iron is greater during periods of rapid growth, children from infancy through adolescence, as well as

pregnant women, may fail to consume sufficient iron to meet their needs ***(National Research Council, 1989).***

WHO estimated that Iron Deficiency (ID) occurs in about 66- 80% of the world's population.ID has many negative effects on health, including changes in immune function, cognitive development, temperature regulation, energy metabolism and work performance. It has serious implications in terms of increased morbidity and mortality rates in vulnerable groups, impaired growth and cognitive abilities in children and reduced work capacity and poor obstetric performance in adult women ***(Chandra et al., 2017).***

Normal Iron Homeostasis:

Iron is an essential component of haemoglobin in red blood cells and of myoglobin in muscles, which contain around. 60% of total body iron. It is also necessary for the functioning of various cellular mechanisms, including enzymatic processes, DNA synthesis, and mitochondrial energy generation. In adults, the body contains 3-5 g of iron; 20-25 mg is needed daily for production of red blood cells and cellular metabolism. Because dietary intake is limited (1-2 mg per day), other sources are needed for iron homoeostasis, recycling of ageing erythrocytes in macrophages, exchange of iron in iron-containing enzymes, and iron stores. About 1-2 mg of iron is lost daily as a result of menstrual bleeding, sweating, skin desquamation, and

urinary excretion. Because iron does not have an excretion regulation pathway, dietary intake, intestinal absorption, and iron recycling have to be finely regulated ***(Lopez et al., 2016).***

Iron is absorbed from the diet by duodenal enterocytes and transported into the bloodstream, where it is bound by transferrin. Most iron is incorporated into erythrocytes for heme synthesis. Splenic macrophages recover iron from senescent erythrocytes and release iron into circulation via ferroportin. Smaller amounts of iron are imported into other tissues as needed. Iron loss is not directly regulated and occurs through minor bleeding and shedding of duodenal enterocytes. Approximate iron content of adult human tissues is represented in parentheses ***(Michels et al., 2015)***.

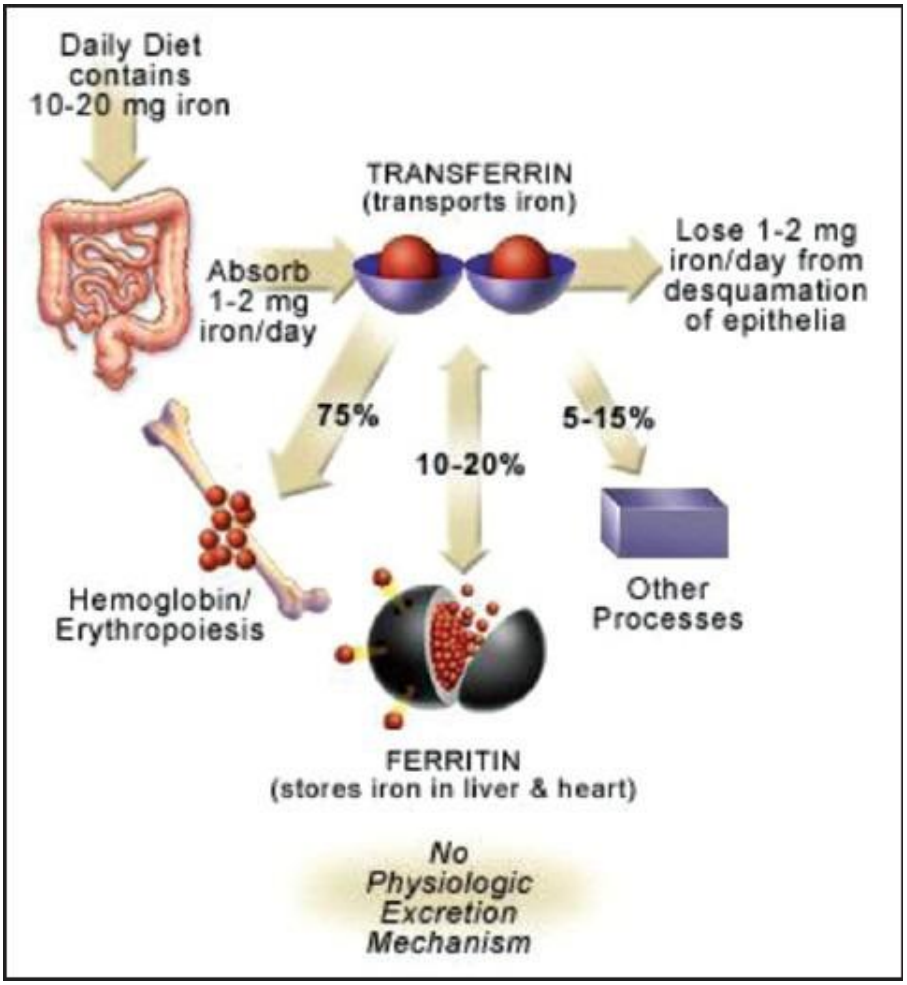

Fig. (1): Iron homeostasis: Iron is bound and transported in the body via transferrin and stored in ferritin molecules. Once iron is absorbed, there is no physiologic mechanism for excretion of excess iron from the body other than blood loss, that is, pregnancy, menstruation, or other bleeding ***(Abbaspour et al., 2014).***

Iron is transported around the body bound to the abundant plasma protein transferrin (TF). TF accepts iron from the small intestine and iron storage sites and delivers it to cells where it is required. TF can bind two atoms of iron and it is this diferric TF that is most efficiently delivered to cells via its interaction with transferrin receptor 1 (TFR1) on

the plasma membrane. Cells with particularly high iron requirements, such as developing erythroid cells (which require iron for hemoglobin synthesis) and rapidly dividing cells (e.g., the enterocytes of the intestinal crypts), express particularly high levels of TFR1. Under normal physiological conditions, circulating TF is only approximately 30% saturated with iron, so there is a considerable reserve capacity to sequester any large amounts of potentially toxic iron that enter the plasma. In certain pathological situations, the capacity of TF to bind iron is exceeded and non-transferrin-bound iron may appear in the circulation. This form of iron can very rapidly enter cells, and is potentially highly cytotoxic. Small amounts of ferritin iron can also be found in the circulation and these can be delivered to certain cell types via receptors ***(Anderson and Vulpe, 2009).***

Iron Deficiency:

A normal adult human has a significant reserve of stored iron that can be drawn upon in times of need. As body iron levels decline, these stores are eroded. Iron depletion is the situation where little stored iron remains but hematopoiesis remains unaffected and plasma iron indices are only slightly reduced. With further declines in iron content, the condition of iron deficient erythropoiesis is reached where iron supply to the marrow is impaired. This stage is associated with significant declines in plasma iron levels and impaired red cell production, but red cell morphology is usually normal. As body iron levels decline

further, erythropoiesis becomes more severely impaired and iron deficiency anemia results. At this stage frank decreases in the hemoglobin level and a reduction in red cell size are evident. Although it is changes in the erythroid compartment that are most apparent, iron supply to all body cells becomes limiting. The consequences of anemia and tissue iron deficiency include lethargy, reduced work and exercise performance, defective immune function, impaired motor and intellectual development in infants, and adverse outcomes in pregnancy.The main cause of iron deficiency globally is inadequate iron intake. In general, women are more prone to iron deficiency than men as they have lower basal iron stores and regularly lose blood through menstruation ***(Lopez et al., 2016)***.

Iron deficiency occurs in two main forms: absolute or functional. Absolute iron deficiency arises when total body iron stores are low or exhausted; functional iron deficiency is a disorder in which total body iron stores are normal or increased, but the iron supply to the bone marrow is inadequate. Absolute and functional deficiencies can coexist. Functional iron deficiency can be present in many acute and chronic inflammatory states ***(Lopez et al., 2016)***.

The nature of the diet can have a significant influence on iron status. People consuming diets rich in protein-bound iron (heme and ferritin iron), and in substances that promote the absorption of elemental iron (e.g., ascorbic acid) are less

prone to iron deficiency than those with minimal protein-bound iron intake consuming diets rich in inhibitors of elemental iron absorption. Phytates, fiber, polyphenols, and tannins (rich in plant-based diets) as well as calcium can greatly inhibit the absorption of elemental iron but appear to have limited effect on the absorption of protein-bound iron.Iron deficiency can also result from a range of pathological conditions. Most iron deficiency in adults in developed countries is the result of blood loss. This could reflect bleeding through gastrointestinal malignancies, ulcers, or from the prolonged consumption of aspirin or nonsteroidal anti-inflammatory drugs, or intravascular hemolysis. In developing countries, parasitic infections, particularly hookworm, can make a significant contribution to gastrointestinal blood loss. Conditions that limit iron absorption, either through a reduction in the absorptive surface area of the small intestine or through impaired gastric acid secretion, can also lead to iron deficiency. These include celiac disease, autoimmune gastritis, and Helicobacter pylori infection. Inherited disorders leading to reduced iron intake are rare, but it has been recognized recently that many cases of iron deficiency anemia that are refractory to iron therapy result from mutations of the TMPRSS6 gene, which encodes the upstream regulator of hepcidin matriptase-2. In affected individuals, hepcidin levels are unusually high, and this leads to reduced iron absorption ***(Camaschella and Poggiali, 2011).***

Iron needs during pregnancy:

Iron requirements increase significantly (near 10-fold) over gestation; therefore, pregnant women are particularly at risk of developing iron deficiency anemia. The prevalence of anemia is dependent on nutritional status and use of sufficient prenatal supplements and ranges from 14 to 52% women who are not taking prenatal supplements, to 0-25% among pregnant women receiving regular multivitamin (containing iron and folic acid) preparation ***(Peña-Rosas et al., 2012)***.

During pregnancy, the increase in plasma volume exceeds the increase in red cell volume; this causes a physiological hem dilution resulting in reduced hemoglobin (Hb) concentration. In a normal pregnancy without iron supplementation, maternal Hb has been found to fall from an average of between 12.5 - 13.0 g/dL to an average of 11.0 - 11.5 g/dL. Based on the world health organization (WHO) documents, it is estimated that more than 40% of pregnant women suffer from anemia, which is due to iron deficiency anemia about half of the time. Thus, in the recently published guidelines by the WHO, 30-60 mg of elemental iron supplementation is advised for all pregnant women ***(Alizadeh and Salehi, 2016)***.

The transfer from the maternal compartment to the fetus isregulated by a complex mechanism of transport that include: release from maternal liver-in which it is stored as

ferritin-into circulation as Fe2+, uptake by the placenta, transfer to the fetus (by a specific protein), oxidation to Fe3+, storage (as ferritin) or transport into the fetal circulation (still bound to transferrin) ***(Cetin et al., 2016).***

Effect of iron deficiency anemia on pregnancy:

Whatever its cause, anaemia can negatively affect physical performance, particularly work productivity, in adults, as a result of both the reduced oxygen transport associated with anaemia and the reduced cellular oxidative capacity associated with iron deficiency ***(Lopez, 2016).***

In pregnancy, profound changes occur in several laboratory parameters used for the assessment of immune status. Studies undertaken by the National Institute of Nutrition, Hyderabad, showed that there was a fall in T and B cell count with fall in hemoglobin levels below 11 g/dl. The fall in T and B cells was statistically significant in women with hemoglobin levels below 8 g/dl. Immunoglobin levels showed a progressive rise with decreasing Hb levels ***(Prema et al., 1982).***

Available data indicated that humoral immunity as assessed by response to immunogens including tetanus toxoid remains unimpaired. The changes in T and B cells and immunoglobulin were reversed within 6-12 wk by parenteral iron therapy and improvement in hemoglobin levels, indicating that these alterations are due to anemia per se and

not due to co-existent undernutrition. Investigations carried out indicated that the prevalence of morbidity due to infections was doubled in women with hemoglobin levels below 8.0 g/dl ***(Prema et al., 1992).***

Data from both the developed and the developing countries have documented the association between asymptomatic bacteriuria and anemia, often refractory to treatment, poor intrauterine growth, prematurity and low birth weight. It is possible that immuno-depression in anemic women renders them more susceptible to infection, and increased morbidity due to infection, might be one of the factors responsible for the adverse effect of anemia on the course and outcome of pregnancy ***(Prema et al., 1992).***

Maternal effects according to severity of anemia:

Mild anemia

Women with mild anemia in pregnancy have decreased work capacity. They may be unable to earn their livelihood of the work involves normal labor. Women with chronic mild anemia may go through pregnancy and labor without any adverse consequences, because they are well compensated ***(Prema, 1981).***

Moderate anemia

Women with moderate anemia have substantial reduction in work capacity and may find it difficult to cope with household chores and child care. Available data from

India and elsewhere indicate that maternal morbidity rates are higher in women with Hb below 8gm/dl ***(Prema, 1981).***

They are more susceptible to infections and recovery from infections may be prolonged. Premature births are more common in women with moderate anemia. They deliver infants with lower birth weight and perinatal mortality is higher in these babies ***(Prema, 1981).*** They may not be able to bear blood loss prior to or during labor and may succumb to infections more readily. Substantial proportion of maternal deaths due to ante-partum and post-partum hemorrhage, pregnancy induced hypertension and sepsis occur in women with moderate anemia.

Severe anemia

Three distinct stages of severe anemia have been recognized - compensated, decompensated, and that associated with circulatory failure. Cardiac decomposition usually occurs when Hb falls below 5.0 g/dl. The cardiac output is raised even at rest, the stroke volume is larger and the heart rate is increased. Palpitation and breathlessness even at rest are symptoms of these changes. These compensatory mechanisms are inadequate to deal with the decrease in Hb levels. Oxygen lack results in anaerobic metabolism and lactic acid accumulation occurs. Eventually circulatory failure occurs further restricting work output. Untreated, it leads to pulmonary oedema and death. When