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An update on Anaemia, Iron, Folic acid and Vitamin B 12 in Pregnancy and Postpartum

Obeagu Emmanuel Ifeanyi[1] and Obeagu Getrude Uzoma[2]
[1]Diagnostic Laboratory Unit, Department of University Health Services, Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria.
[2]Department of Nursing Science, Ebonyi State University, Abakaliki, Nigeria.
*Corresponding author: *emmanuelobeagu@yahoo.com*

Abstract

Anaemia is a decrease in number of red blood cell (RBCs) or less than the normal quality of haemoglobin in the blood. However, it can include decreased oxygen-binding ability of each haemoglobin molecule due to deformity or lack of numerical developments as in some other types of haemoglobin deficiency.Iron deficiency anaemia is the common cause of anaemia in women affecting 5-10 of women of child bearing age (20-44 years) and among pregnant women and postpartal, the prevalence of anaemia is up to 20-40%.Anaemia in pregnancy can be defined as haemoglobin concentration below 11g/dL. Anaemia in pregnancy is a common problem in most developing countries and a major cause of mortality and morbidity especially in malaria endemic areas. Low haemoglobin levels in pregnancy may lead to preterm delivery and low birth weight and increase in the risk of maternal mortality. During pregnancy, a woman's iron requirement increase three fold to support the growth of the fetal placental unit and increased red cell mass. After it is absorbed across the maternal gut, iron is carried to the liver in the serum, iron is bound to transferrin. Transferrin has 2 iron binding sites with approximately equal affinities for iron. It is glycossylated and of interest, the glycosylation patterns change during pregnancy.

Keywords: anaemia, ferritin and total iron binding capacity in pregnancy and postpartum

ANAEMIA

Anaemia is a decrease in number of red blood cell (RBCs) or less than the normal quality of haemoglobin in the blood. However, it can include decreased oxygen-binding ability of each haemoglobin molecule due to deformity or lack of numerical developments as in some other types of haemoglobin deficiency. Because haemoglobin normally carries oxygen from the lungs to the capillaries, anaemia leads to hypoxia (Lack of oxygen) in organs since all human cells depends on oxygen for survival, varying degrees of anaemia can have a wide range clinical consequence.

Anaemia is the most common disorder of the body. The several kinds of anaemia are produced by a variety of underlying causes. It can be classified in a variety of ways, based on the morphology of RBCS, underlying etiology mechanisms, and discernible clinical spectra, to mention a few.

TYPES OF ANAEMIA

Macrocytic Anaemia

Macrocytic type of anaemia is an anaemia (defined as blood with an insufficient concentration of haemoglobin) in which the erythrocytes are larger than their normal volume. The normal erythrocyte volume in humans is about 80 to 100 femoliters (GL =10-15). In metric terms, the size is given in equivalent cubic micrometers ($1\mu m^3$ =1L). The condition of having erythrocytes which (on average) are too large is called macrocytosis (weng et al., 2011).

Macrocytic anaemia is not a disease in the sense of having a single pathology, but is rather a condition. As such, it is the class name of a set of pathologies that all produce somewhat the same red blood cell abnormality. In macrocytic associated with insufficient numbers of cells and often also insufficient haemoglobin content per opposite effect of larger cell size, to finally result in a total blood haemoglobin concentration that is less than normal (ie anaemia).

Normocytic Anaemia

Normocytic anaemia is a common issue that occurs in men and women typically over 85 years old. Its prevalence increases with age reaching 44 percent in men older than 85 years old (Weng et al., 2011). Normocytic anaemia is the most frequently encountered type of anaemia (Weng et al., 2011). A normocytic anaemia is defined as anaemia with an MCV of 80-100FL which is the normal range. However, the haemotocrit and haemoblobin is decreased.

Microcytic Anaemia

This is genetic term for any type of anemia characterized by small red blood cells. The normal mean corpuscular volume (MCV) is 76-100FL with smaller cells <76FL described as microcytic and larger cells >100FL as macrocytic. In microcytic anaemia, the red blood cells (erythrocytes) are usually also hypochromic, meaning that the red blood cells are paler usual (Weng et al., 2011).

Iron Deficiency Anaemia

This is a common cause of anaemia in women affecting 5-10 of women of child bearing age (20-44 years) and among pregnant women and postpartal, the prevalence of anaemia is up to 20-40%. The extent of which iron deficiency affects maternal and neonatal health is uncertain. Iron deficiency affects two (2) billion people and it is estimated that 50% of pregnant in developing countries and up to 80% in South Asia have iron deficiency anaemia. In U.S, approximately 7-8 million Women and 700, 000 to toddllers have iron deficiency anaemia and 3.2 million women and 240,000 to dillers have iron deficiency anaemia (Hereberg *et al*., 1998). Women who conceive during or shortly after adolescence are likely to enter pregnancy with low or absent iron store and infants born to iron deficient mother also have higher prevalence of anaemia in the first 6 months of life (Preziosi *et al*., 1997). Maternal mortality is increased in women whose haemoglobin levels fall to below 6-7g/dL (Bothwell *et al*., 1979). Iron status influence both human and animal health. Iron deficiency anaemia is a case that normally occurs when iron deficiency sufficiently severe to diminish erythropoesis and cause the development of anaemia. Pregnant women are particularly at high risk for iron deficiency because of increased iron needs during pregnancy (Berymann, 2005).

Iron deficiency is commonly decreased as occurring in three stages, the first stage in iron stores without any effect on essential body iron. The second stage refers to iron deficient erythropoiesis occurs when inadequate iron is available to the erythoid marrow and tissue for normal biochemistry and function. The last and most severe case is iron deficiency anaemia which is identified by a significant reduction in haemoglobin level and decrease in mean corpuscular volume (Bothwell et al., 1979).

Symptoms of iron deficiency anaemia include weakness and fatigue. The symptoms results because of the function of the red blood cell to carry iron to exercising muscles (Waltes *et al*., 1998), this can result to muscular dys-function that impairs muscular work performance (WHO,

2001). The assessment of iron deficiency usually refers to serum ferritin concentration and transferrin saturation.

Signs and Symptoms of Anaemia

Anaemia goes undetermined in many people and symptom can be minor or vague. The signs and symptoms can be related to the underlying cause or the anaemia itself. Most commonly, people with anaemia report feelings of weakness, or fatique, general malaria, and sometimes poor concentration. They may also report dyspnea (shortness of breath) on exertion. In very severe anaemia, the body may compensate of the blood by increasing cardiac output. The patient may have symptoms related to this such as palpitation, agina (if pre-existing heart disease is present), intermittent claudication of legs and symptoms of heart failure on examination, the sign exhibited may include pallor (pale skin, mucosal linking), but this is not a reliable sign, there may be signs of specific causes of anaemia. Restless syndrome is more common in those with iron deficiency anaemia.

CAUSES OF ANAEMIA

Iron Deficiency

Iron deficiency is a common cause of anaemia in women, affecting 5-10% of women of child bearing age (20-44 years) and among pregnancy women, the prevalence of anaemia is up to 20-40%. The extent to which iron deficiency affects maternal and neonatal health is uncertain-iron deficiency affects >2 billion people and it is estimated that 50% of pregnant women in developing countries and up to 80% in South Asia have iron deficiency anaemia. In approximately 7-8 million women and 700,000 toddlers have iron deficiency anaemia and 3-2 million women and 240,000 toddlers have iron deficiency anaemia (Hereberg, 1998, Viteri, 1998). Women who conceive during or shortly after adolescence are likely to enter pregnancy with low or absent iron stores and infant born to iron deficient mother also have a higher prevalence of anaemia in the first six (6) months of life (Preziosi *et al*., 1997). Maternal mortality is increased in women whose haemoglobin levels fall to below 6-7g/dL (Bothwell *et al.*, 1979). Iron status influence both human and animal health. Iron deficiency anaemia is a case that normally occurs when iron deficiency is sufficiently severe to diminish erythropoiesis and cause the development of anaemia. Pregnant women are particularly at high risk for iron deficiency because of increased iron needs during pregnancy (Berymann, 2005). Iron deficiency is commonly described as occurring in three stages, the first stage of iron depletion refers to a decrease in iron stores without any effect on essential body iron. The second stage refers to iron deficient erythropoiesis. This occurs when inadequate iron is available to the erythoid marrow and tissue for normal biochemistry and function. The last and most severe case of iron deficiency anaemia which is identified by a significant reduction in haemoglobin level and dexrease in mean corpuscular volume (Bothwell *et al.*, 1979).

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Folate and Vitamin B12 Deficiency

Folate deficiency is a lack of folic acid in the body and the signs are often subtle. Folate deficiency anaemia is the medical name given for the condition (Hurther *et al.*, 2004). Symptoms include loss of appetite and weight loss. Additional signs are weakness, sore tongue, headaches, heart palpitations, irritability and behavioural disorders (Haslam *et al.*, 1998). In adults, anaemia (macrocyte megaloblastic anaemia) can be a sign of advanced folate deficient. If infants and children folate deficiency can slow growth rate, women with folate deficiency who become pregnant are mostly more likely to give birth to low birth weight and premature infants and infants with neural tube defects.

A deficiency of folate can occur when the body's need for folate is increased, when dietary intake of folate is inadequate, or when the body excretes more interfere with the body's ability to use folate may also increase the need for those vitamins (Pietrzit *et al.*, 1997). Some research indicates that exposure to ultraviolent light includes the use of tanning beds can lead to a folic acid deficiency (Hurther *et al.*, 2004).

Malaria

Anaemia is a major health problem in many developing countries where malaria and other infections contribute to increase maternal and prenatal mortality and morbidity (Meuris et al, 1993). Malaria has been known to alter haematological and biochemical parameters during pregnancy and is one of the causes of anaemia in pregnancy. Pregnant women are more susceptible than general population to malaria; they are more likely to become infected, suffer a recurrence, and develop severe complications and to die from the disease. Malaria contributes very significantly to maternal and fetal mortality with at least 10,000 maternal deaths per annum attributable in subsahara Africa. Regardless of symptoms, the presence of plasmodial parasites in a pregnant woman's body will have a negative impact on her own health and that of the foetus. In areas endemic for malaria, it is estimated that at least 25% of pregnant women are infected with malaria, with the highest risk for infection and morbidity in primigrivadas, adolescent and those co-infected with HIV (Desai *et al.*, 2007). Adults who live in malaria endemic region generally have some acquired immunity to malaria infection as a result of immunoglobulin production during prior infections in childhood. This immunity diminishes significantly in pregnancy, particularly in primigravidas. A recent study of 300 women delivery in rural area showed higher rates of anaemia, the study also noted that babies born to mother with placental malaria infection were more than twice as likely to be underweight at birth (Ofori *et al.*, 2009). In Africa, it has been estimated that malaria is responsible for 25% of severe anaemia during pregnancy, defined as haemoglobulin less than 7µg/dL (Desai *et al.*, 2007). Both plasmodium falciparium and plasmodium vivax can cause complications that affect the foetus. Fetal mortality is estimated at 15% for P-vivax and around 30% for P. falciparium (Centers for Disease control and prevention, 2012).

PREGNANCY

Pregnancy is the fertilization and development of one or more offspring, known as an embryo or foetus in a woman's uterus (Weng *et al.*, 2011). It is the common name for gestation in humans. A multiple pregnancy involves more than one embryo or foetus in a single pregnancy, such as with twins children usually occurs about 38 weeks after conception in women who have a menstrual cycle length of four weeks, this is approximately 40 weeks from the start of the last normal menstrual period (LNMP). Conception can be achieved through sexual intercourse or assisted reproductive technology. An embryo is the developing offspring during the first eight (8) weeks following conception, and subsequently the term foetus is used until birth (Weng *et al*., 2011). In many societies medical or legal definitions human pregnancy is somewhat arbitrarily divided into three trimester period, as a means to simplify reference to the different stages of prenatal development (Weng *et al.*, 2011). The first trimester carries the high risk of miscarriage (natural death of embryo or foetus). During the second trimester, the development of the foetus can be more easily monitored and diagnosed. The third is marked by further growth of the foetus and the development of fetal fat stores (Weng *et al.*, 2011). The point of fetal viability or the point in time at which fetal life outside the uterus is possible, usually coincides with the late second or early third trimesters, babies born as this early point in development are at high risk for having medical conditions and dying (AGOG, 2002).

In the united states and united Kingdom, 40% of pregnancies are unplanned, and between a quarter and half of those unplanned pregnancies were unwanted pregnancies (Jayson et al., 2011) of those unintended pregnancies that occurred in the U.S, 60% of the women used birth control to some extent during the month pregnancy occurred (Joseph *et al.*, 2011).

Development of Embryo and Foetus

After about 10 weeks of gestational age, the embryo becomes known as a foetus instead. At the beginning of the fetal stage, the risk of miscarriage decreases sharply (Lennart, 1990). When the fetal stage commences, a foetus is typically about 30mm (12 inches) in length , and the heart can be seen beating via ultrasound, the foetus can be seen making various involuntary motions at this stage (Kalverboer, 2011). During continued feta development, the early body systems and structures that were established in the embryonic stage continue to develop. Sex organ s begins to appear during the third month of gestation. The foetus continues to grow in both weight and length, although the majority of the physical growth occurs in the last weeks of pregnancy. Electrical brain activity is first defected between the 5^{th} and 6^{th} weeks of gestation, through this is still considered primitive neural activity rather than the beginning of conscious thought, something that develop much later in fetation, synapses begin forming at 17 weeks, and as about week 28 begin to multiply at a rapid pace which continues until 3 to 4 months after birth (Judy, 2008).

MATERNAL CHANGES

During pregnancy, the women undergoes many physiological changes, which are entirely normal, including cardiovascular, haematologic, metabolic, renal and respiratory changes that becomes very important in the event of complications. The body must change its physiological and homeostatic mechanisms in pregnancy to ensure the foetus is provided for the foetus inside a pregnant women may be viewed as an unusual successful allograft, since it genetically differs from the women (Clark *et al*., 1986). This increase immune tolerance in pregnancy can also cause an increased susceptibility to and severity of some infectious diseases.

Pregnancy is typical broken into three period or trimesters, each of about three months (Collins Dictionary, 2012). Obstetricians define each trimester as lasting for 14 weeks, resulting in a total duration of 42 weeks, although the average 40 weeks. While there are no hard and fast rules, these destinations are useful in describing the changes that take place over time.

First Trimester

Minute ventilation is increased by 40% in first trimester. The womb will grow to the size of a lemon by eight weeks. Many symptoms and is comfort of pregnancy appear in the first trimester (Stacey *et al.*, 2011). In the first trimester, iron requirements are partially met through the cessation of menstruation, saving 0.56mg iron per day (WHO, 2001).

Second Trimester

Week 13 to 28 of the pregnancy are called the second trimester, most women feel more energized in this period, and begin to put on weight as the symptom of morning sickness subside and eventually fade away. The uterus, the muscular organ that holds the developing foetus can expand up to 20 times its normal size during pregnancy. In the second trimester iron demand increases significantly (WHO, 2001), to a maximum of 90% at 30 weeks.

Third Trimester

Final weight gain takes place, which is the most weight gain throughout the pregnancy. The woman’s abdomen will transform in shape as it drop due to the foetus turning in a downward position ready for birth. The foetus begins to move regularly, and is felt by the woman. It is also during the third trimester that maternal activity and sleep may affect fetal development due to restricted blood flow for instance, the enlarged uterus may need blood flow by compressing the lower pressured vena cava, with the left lateral positions appearing to providing better oxygenation to the infant (Stacey *et al*., 2011).

Complications of pregnancy

Each year according to the WHO, ill-health as a result of pregnancy is experienced (sometimes permanently) by more than 20 million women around the world. Furthermore, the lives of eight million women are threatened, and more than 500,000 women are estimated to have died in 1995 as a result of causes related to pregnancy and childbirth (WHO, 2009).

The following are some example of pregnancy complications:-

a. Pregnancy include hypertension
b. Anaemia (Merck, 2008)
c. Postpartum depression
d. Postpartum psychosis
e. Thromboembolic disorders.The death in pregnant women in the U.S.
f. Pupp skin disease. This develops around the 32nd week, red plagues, papules, itchiness around the belly button that spread all over the body except for the inside of hands and face.
g. Ectopic pregnancy. Importation of the embryo outside the uterus
h. Hyperemesis gravidarum, excessive nausea that is more severe than morning sickness.

ANAEMIA IN PREGNANCY

Anaemia in pregnancy can be defined as haemoglobin concentration below 11g/dL. Anaemia in pregnancy is a common problem in most developing countries and a major cause of mortality and morbidity especially in malaria endemic areas (Bertman, 2005, Obeagu *et al.*,2016; Obeagu, 2016; Obeagu *et al.*,2016, Obeagu and Obeagu, 2018). In sub-Saharan Africa, anaemia in pregnancy is highly prevalent (WHO, 1992). Low haemoglobin levels in pregnancy may lead to preterm delivery and low birth weight (Klebanoff *et al.,* 1991, Meuris *et al.,* 1993) and increase in the risk of maternal mortality. Due to the complex aetiology of anaemia in pregnancy in tropical Africa, the relative role of risk factors is difficult to estimate. However, it is estimated that the anaemia cases of pregnancy are related to iron deficiency (Berymann, 2005). Women are particularly at risk of iron deficiency due to blood loss during menstruation and increased demand for iron during pregnancy (Michael *et al.*, 2008).

During pregnancy, a woman's iron requirement increase three fold to support the growth of the fetal placental unit and increased red cell mass (Michael *et al.*, 2008). Meeting this demand requires a diet high in bioavailable iron during pregnancy, but also stored iron levels of at least 300mg before pregnancy (WHO, 2001). Unfortunately, this pre-pregnancy level of iron stores is often not reached with approximately 40% of women entering pregnancy with small body iron reserves and an unfavourable iron status. This leads to around 25% of pregnant women in Western Society having iron deficiency anaemia. Iron deficiency anaemia during pregnancy and post partum can lead to serious consequences for both mother and child (Schumann *et al.*, 1998, Hurrell *et al.*, 2010). It is therefore essential that iron deficiency is identified early and adequately treated before resulting in iron deficiency anaemia.

ANAEMIA IN POSTPARTUM

Anamie caused by iron deficiency in postpartum has been linked with the following consequences; fatigue and exhaustion (Warsh *et al.*, 2013). Beyond the normal tiredness expected of a mother with a new born, are clinical symptoms of anaemia (Warsh *et al*., 2013). Fatigue also impact upon milk supply (Warsh *et al.*, 2013). Breast feeding for both mother and infant depends on varieties of factors. One of the important roles of breast milk is the transfer of antibodies which help protect the infant against gastrointestinal and respiratory infection (Rimon et al., 2005). Maternal anaemia is associated with reduced level of antibodies and complement protein, and difference in the fat and calorie content at different milk maturation stage (Rimon *et al.*, 2005).

Iron Requirement

Iron absorption is regulated by the size of body iron stores (Tapiero, 2001). Virtually all of the iron derived from absorption and it increased markedly only after most of the storage iron had

been used. The diets of women in developing countries do not contain sufficient bioavailable iron to meet these needs during the second and third trimester even if iron stores are adequate at the beginning of pregnancy. The size of iron stores is best measured by the serum ferritin level (1mg/L serum ferritin = 5mg storage iron in an adult) (Bothwell *et al.*, 1979) (Tapiero *et al*., 2001). The serum ferritin concentration for women aged between 20 and 44 years in the United States is 36µg/L (Looker, 1991) (Tapiero *et al.*, 2001).

A daily supplements containing 16 to 20mg of iron is recommended during pregnancy and postpartum. Based on the results of the modelling process, it was concluded that a supplement of 16mg per day throughout pregnancy would be effective and safe for pregnant women who are in good health. When added to the iron they get from a mixed diet, these women would have all they need for pregnancy.

FERRITIN, TIBC AND IRON METABOLISM IN PREGNANCY

After it is absorbed across the maternal gut, iron is carried to the liver in the serum, iron is bound to transferrin. Transferrin has 2 iron binding sites with approximately equal affinities for iron. It is glycossylated and of interest, the glycosylation patterns change during pregnancy.

The functional consequences of these alterations in unknown (Jeschke *et al*., 2003), but the liver still plays an important role in iron homeostasis. How the iron stored in the liver is passed to the foetus has not been studied directly. Concentration decrease significantly during pregnancy, the process does occur, and presumably it is mediated by signals from the developing foetus. The nature of those signals is not yet known (Gambling *et al*., 2009). Although the release of iron from ferritin has been studied extensively, the underlying mechanism is still a matter of discussion. However, that is beyond the scope of this review. After it is released, the iron [Fe (ii)] is oxidized by ceruloplasmin to fe (iii) and this interaction is also not clear, but presumably it occurs at the hepatocyte cell surface (Obeagu, 2018; Obeagu, 2018)

The transferrin binds to the transferrin receptor on the placental microvillar membrane surface. The binding has very high affinity (= 10-9mol/<-1). After binding is completed, the complex is incorporated into clathrin-coated vesicles and internalized. The P.H inside the vesicle is reduced, probably by an H+-AT phase. The iron is released from the transferrin. At P.H 7.4, apo-transferrin (transferrin with no iron on it) has a relatively low affinity for the receptor, therefore apo-transferrin will not bind on the cell surface. At P.H 5.5, the affinity of transferring for Fe is greatly decreased, consequently, the iron is released from the protein and the protein becomes apo-transferrin.

Inside the vesicle, iron (as Fe (ii)] moves through a channel known as divalent metal transporter, (DMTI) into the cytoplasm.

The iron is released from the cell through a protein called ferroportin, fetal transferrin bind Fe as Fe (iii), and hence it must be oxidized once it is released in other for it to bind to it carrier protein. This is carried out by a protein called Zyklopen, a copper Ferroxidase from a family of Ferroxidases that are central to iron release. When a cell accumulates excess iron, it stores it in ferritin. Ferritin and transferrin are regulated in an exceedingly elegant manner. Each of the two (2) MRNAs has an iron regulatory element (IRE) at either the 5 (Ferritin) or 3 (transferrin receptor) end (Rouault *et al.*, 2006). This is a loop of RNA to which the iron regulatory protein (IRP) binds. When iron is present, it binds to the IRP and causes its release from the IRE. This release has different effects depending on where the IRP binds. Increased iron means increase iron stores, and releasing the IRP from transferring receptor (TFR)mRNA destabilizes it so that it is degraded, whereas removing the IRP from ferritin mRNA releases it from being blocked from translation, so that ferritin protein is produced (Rouault *et al.*, 2006).

Conclusion

Anaemia is a decrease in number of red blood cell (RBCs) or less than the normal quality of haemoglobin in the blood. However, it can include decreased oxygen-binding ability of each haemoglobin molecule due to deformity or lack of numerical developments as in some other types of haemoglobin deficiency.Iron deficiency anaemia is the common cause of anaemia in women affecting 5-10 of women of child bearing age (20-44 years) and among pregnant women and postpartal, the prevalence of anaemia is up to 20-40%. Anaemia in pregnancy is a common problem in most developing countries and a major cause of mortality and morbidity especially in malaria endemic areas. Low haemoglobin levels in pregnancy may lead to preterm delivery and low birth weight and increase in the risk of maternal mortality.

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