PREVALENCE OF ANAEMIA AMONG PREGNANT EGYPTIAN WOMEN

Thesis

Thesis Submitted as Partial Fulfillment of Master Degree
in Obstetrics and Gynecology

By

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2013

INTRODUCTION

Anemia is a global problem and is associated with maternal morbidity and mortality ***(WHO, 1992).*** Anemia has been considered as the second leading cause of indirect maternal mortality in Egypt ***(Ministry of Health & population– Egypt, 2000).***

Anemia is defined as a clinical condition characterized by reduction in hemoglobin concentration of the blood below the normal for the age, sex, physiological condition and altitude above the sea level of that person ***(Idris and Rehman, 2005).*** Anemia during pregnancy is defined as hemoglobin concentration below 11 g/dl ***(WHO, 2001).***

The World Health Organization (WHO) has reported that 35%-75% (56% on average) of the pregnant women in developing countries and 18% of women in industrialized countries are anemic. However many of these women were already anemic at time of conception with an estimated prevalence of anemia of 43% in non-pregnant women in developing countries and of 12% in women in wealthier region ***(Harris, 1992).***

Anemia can be caused by innumerable factors the most common being deficiency of essential elements for hemoglobin synthesis (iron, vitamin B12 and folic acid). Other causes include blood loss, repeated pregnancy in female of

reproductive age, worm infestation, hemolysis due to known or unknown causes and bone marrow condition causing suppression of red cell synthesis. Chronic diseases like chronic renal failure, rheumatoid arthritis and tuberculosis are also known causes ***(Weissinger, 2008).***

Iron deficiency anemia is the commonest type of anemia throughout the world and in one study it has been reported to affect about 50-60%of young children and pregnant females and 20-30% of non-pregnant females in the developing countries. Adolescents are vulnerable to iron deficiency because of increased iron requirements related to rapid growth ***(Wharton, 2009).***

Women during their reproductive years are at risk of iron deficiency due to blood loss from menstruation in particular that 10% who suffers heavy losses (>80 ml/month). Contraceptive practice also plays separately. The non-medicated intrauterine devices increase menstrual blood loss by 30-50% while oral contraceptives have the opposite effect. Pregnancy is another factor during pregnancy there is significant increase in the amount of iron required to increase in the amount of iron required to increase the red cell mass, expand the plasma volume and to allow for growth of the fetal-placental unit. More importantly is the nutritional deficiency of elements required for red blood cell synthesis, which is probably the commonest cause particularly in developing countries ***(Yip et al., 2001).***

About three-fourths of adolescent females do not meet dietary iron requirement, compared to 17 % of males ***(CDC, 1998).***Anemia during pregnancy is well known and considerable risk factors for both mother and fetus ***(Christian, 2002).***Fetal consequences are increased risk of growth restriction, prematurity, intrauterine fetal death, rupture of membranes and infections. Prematurity is a consequence of early anemia during gestation which lead to release of placental stress hormones (corticosteroid hormones and nor epinephrine) which induce fetal release of adrenocorticotrophic hormone (ACTH) and cortisol, that induce uterine contraction stimulating hormones (estrogen, connexin) and inhibition of insulin like growth factors (IGF) and important anabolic hormones for fetal development.It was also shown that placental development is influenced by anemia and hypoxia ***(Hercberg et al., 2000).***The major concern about the adverse effect of anemia on pregnant women is the significantly greater risk of prenatal mortality and morbidity ***(CDC, 1998; WHO, 2002).***

Maternal consequences of anemia are also well known and include cardiovascular symptoms, reduced physical and mental performance, reduced immunity, tiredness, reduced peripartum blood reserves and finally increased risk for blood transfusion in the postpartum period ***(Baker, 2001).***

According to a study by the Egyptian Nutrition Institute (1993), the prevalence of iron deficiency anemia was between 22 and 30% in rural population groups. The study also found that the population groups that were primarily affected were the children less than 5 years of age and pregnant and lactating women. It is believed that one of the major causes of such a high prevalence rate is insufficient iron intake***(Cairo Nutrition Institute, 1993).***

AIM OF THE WORK

The aim of this study was to determine types of anemia among Egyptian pregnant women attending obstetric outpatient clinic in Ain Shams University Maternity Hospital and to identify the socio-demographic risk factors and underlying causes.

ERYTHROPOIESIS

Definition:

The term erythropoiesis (erythro = RBC, and poiesis = to make) is used to describe the process of RBC formation or production. In humans, erythropoiesis occurs almost exclusively in the red bone marrow. The yellow bone marrow is primarily composed of fat, but, in response to a greater need for RBC production, the yellow bone marrow can turn to red marrow. The red bone marrow of essentially all bones produces RBCs from birth to about five years of age. Between the ages of 5 to 20, the long bones slowly lose their ability to produce RBCs. Above age 20, most RBCs are produced primarily in the marrow of the vertebrae, the sternum, the ribs, and the pelvis ***(Suda et al., 1984).***

The organ responsible for "turning on the faucet" of RBC production is the kidney (Figure 1). The kidneys can detect low levels of oxygen in the blood and respond by releasing erythropoietin, which then travels to the red bone marrow to stimulate it to begin RBC production ***(Clark and Keating, 1995)***.

Once the erythropoietin stimulates the red bone marrow to begin manufacturing RBCs, a series of events occurs. In the bone marrow there are many special stem cells from which

RBCs can be formed. As these cells mature, they extrude their nucleus as they slowly fill with hemoglobin until they are bright red reticulocytes ready to escape the bone marrow and squeeze into the blood capillaries to begin circulating around the body. In a blood sample, the reticulocytes can be distinguished from RBCs because they still contain some speckles or pieces of their nucleus. Within a few days, this reticulocyte completely loses all its nuclear material and becomes a full-fledged RBC that is ready to serve the oxygen needs of the body. After about three to four months, the RBC has worked so hard that it begins to weaken. The membranes of old RBCs become very fragile and the cells may rupture during passage through some tight spots in the circulation. These old and damaged RBCs are "eaten" primarily by the spleen, and most of the leftover components (especially the iron from the hemoglobin) are recycled to form new RBCs ***(Clark and Keating, 1995)***.

The production of new RBCs occurs as the need arises. At very high altitudes, where the quantity of oxygen in the air is greatly decreased, insufficient oxygen is transported to the tissues, and red cells are produced so rapidly that their number in the blood is considerably increased. Therefore, it is obvious that it is not the concentration of RBC's that controls the rate of red cell production, but instead, it is the functional ability of the RBCs to transport oxygen to the tissues in response to the tissue demand for oxygen that controls the rate of RBC production. In other words, it's just like the economic concept of "supply and

demand." If the supply of oxygen is LESS than what the body demands, the MORE RBCs are produced. If the supply of oxygen is MORE than what the body demands, the FEWER RBCs are produced ***(Rhodes et al., 2008).***

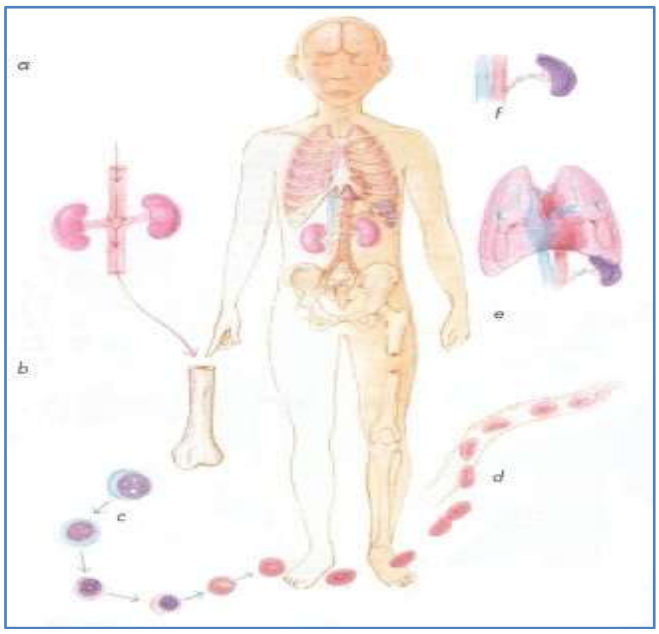

Fig. (1): The life cycle of a red blood cell. a) **Kidneys** respond to a lower than normal oxygen concentration in the blood by releasing the hormone **erythropoietin**. b) Erythropoietin travels to the **red bone marrow** and stimulates an increase in the production of **red blood cells (RBCs)**. c) The red bone marrow manufactures RBCs from **stem cells** that live inside the marrow. d) RBCs squeeze through blood vessel membranes to enter the circulation. e) The **heart** and **lungs** work to supply continuous movement and oxygenation of RBCs. f) Damaged or old RBCs are destroyed primarily by the **spleen**.

The first erythrocytes contain nuclei and derive from stem cells (BFU/CFU-E) that arise in the blood islands of the umbilical vesicle. Centrally lying cells of these blood islands join up thereby into nucleus-containing, large erythroblasts, whereas

those peripherally located become endothelial cells. One also calls this extraembryonic phase of the blood formation megaloblastic erythropoiesis. This extraembryonic erythropoiesis is supplanted by the embryonic erythropoiesis, which arises in the liver. These stem cells have their origin in the aorto-gonado-mesonephros region. The erythrocytes that arise in the liver are nucleus-free - in contrast to those formed outside the embryo - and are produced there up to the 28th week of pregnancy ***(Rhodes et al., 2008).***

A small portion is also formed in the spleen (green in Figure 2). This hepatolienal phase dominates the second trimenon of the pregnancy. In the last trimenon the bone marrow is the most important hematopoietic organ (myeloid phase of the erythropoiesis) ***(Finch et al., 1999)***.

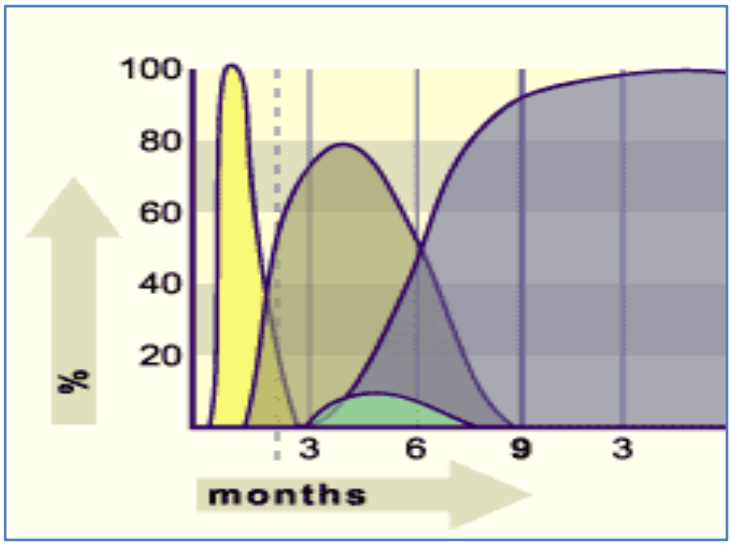

Fig. (2): This diagram shows the approximate contributions of the various blood forming organs during pregnancy ***(Finch et al., 1999)***.

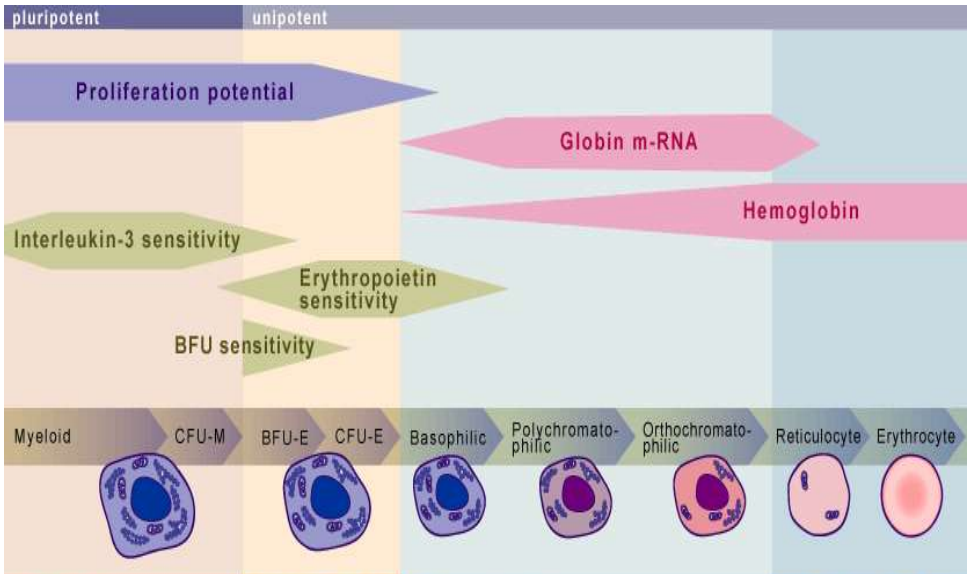

Fig. (3): This diagram provides an overview of the morphological stages during the differentiation of the erythrocytes from the pluripotent stem cells to the mature, differentiated erythrocytes. The purple bar shows the proliferation potential of the various pre-steps and pink the increasing formation of globin mRNA and hemoglobin, respectively. The reactivity to the growth factors in the various phases is shown with green bars ***(Kaushansky, 2006).***

The production of erythrocytes is a tightly regulated process. During steady state hematopoiesis, approximately 10^{10} red blood cells are produced per hour in the bone marrow to maintain the hemoglobin level within fairly narrow limits. Production can be rapidly increased in the setting of ongoing blood loss or hemolysis ***(Suda et al., 1984).***

Erythropoiesis begins with the differentiation of a small pool of pluripotent stem cells into the most primitive erythroid progenitors. These progenitors develop into recognizable

erythroid precursors, which subsequently follow a specific differentiation program that culminates in the emergence of mature erythrocytes. This process is probably driven by successive combinations of transcription factors which dictate the expression of adhesion and hematopoietic growth factor receptors (HGFRs) ***(Clark and Keating, 1995)***:

- Adhesion receptors play an important role in the localization and release of maturing cells from specific niches in bone marrow.
- Hematopoietic growth factors (HGFs), such as those for interleukin 3 (IL-3), granulocyte-macrophage colony-stimulating factor (GM-CSF), and Steel factor (SF, also called c-kit ligand), are important for the amplification of progenitor cells.

Erythropoietin (EPO) is a growth factor essential for the amplification and terminal differentiation of erythroid progenitors and precursors. Recent data concerning the control of EPO expression by hypoxia have provided new insight into the regulation of erythropoiesis ***(Rhodes et al., 2008).***

Erythroid progenitor cells:

These committed single lineage progenitors are derived from the stochastic differentiation of bipotential or multipotential progenitors, which emerged from a tiny population of stem cells ***(Suda et al., 1984)***.

In humans, the most primitive single lineage committed erythroid progenitor is the erythroid burst-forming unit (BFU-E). These cellular clusters are so named because they have the following characteristics in semisolid in vitro cultures:

In response to the combination of EPO and one of SF, IL-3, or GM-CSF, the progeny of the first few cellular divisions are motile and form subpopulations of erythroid colony-forming units (CFU-E). Each of these units subsequently forms a large colony of proerythroblasts, which become more mature erythroblasts and a few enucleated reticulocytes (***Axelrad et al., 1984)***.

The entire process requires approximately two weeks in vitro.

Bone marrow also contains the more mature CFU-E that, under the influence of EPO, form small colonies of erythroblasts in seven days. These erythroid progenitors (BFU-E and CFU-E) cannot be identified by specific morphological features. Current evidence suggests that all hematopoietic progenitors or stem cells resemble lymphoblasts (***Rosse, 1996).***

Precursors and mature cells:

The erythroid precursor or erythroblast pool represents about one-third of the marrow cell population in the normal child (above the age of three) and the adult. Proerythroblasts are the earliest recognizable forms. These cells divide and mature

through basophilic, polychromatic, and orthochromatic normoblast cells to form the reticulocyte; this process involves a reduction in cell size, nuclear condensation and extrusion, and hemoglobin accumulation ***(Clark and Keating, 1995)***.

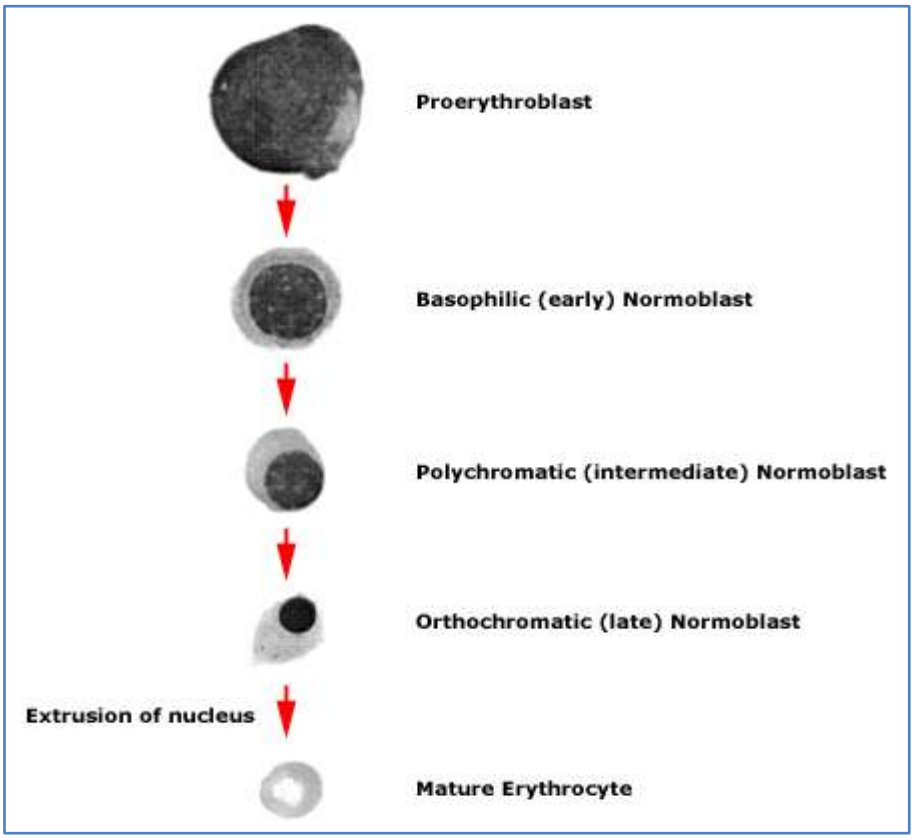

Fig. (4): Cells involved in erythropoiesis ***(Clark and Keating, 1995)***

The proerythroblast, the first identifiable erythroid precursor, has a diameter of 14 to 19 µM, a large, oval homogenously-staining nucleus, indistinct nucleoli, and darkly basophilic cytoplasm. The basophilic normoblast is 12 to 17 µM in diameter with basophilic cytoplasm, and coarsening and

prominent clumping of the nuclear chromatin (spoked wheel or cartwheel appearance). Nucleoli are generally not seen. Accumulation of hemoglobin is seen in the polychromatic normoblast by the presence of less basophilic and muddy gray cytoplasm. The last nucleated RBC precursor, the orthochromatic normoblast approaches the diameter of a reticulocyte (8 to 12 µM); the eosinophilic staining cytoplasm contains nearly a full amount of hemoglobin, with a condensed pyknotic nucleus. Extrusion of the nucleus results in the reticulocyte (not shown), a cell slightly larger than a fully mature erythrocyte. The reticulocyte has a fine granular or reticular network of ribosomal RNA observed with supravital stains, such as cresyl blue or methylene blue. Such cells are present in small quantities in the peripheral blood of normal persons (1 to 2 percent), but are increased in response to stress on the erythroid lineage (eg, hemolysis, blood loss, hypoxia) ***(Clark and Keating, 1995)***.

On average, each proerythroblast can form approximately eight reticulocytes. The mean transit time from proerythroblast to the emergence of the reticulocyte into the circulation is approximately five days ***(Finch et al., 1999)***.

In acute anemia, the length of this period may decrease to as little as one or two days because of skipped divisions. In this setting, the red cells that emerge are macrocytic; they may also bear surface antigen and other fetal characteristics because they have had insufficient time to have converted i antigen to I