Chapter one

Introduction and Literature Review

1.1 Introduction

The umbilical cord is a narrow tube-like structure that connects the fetus to the placenta, Umbilical cord consists of one vein, which carries oxygenated, nutrient-rich blood to the fetus and two arteries that carry deoxygenated, nutrient depleted blood away from fetus blood circulation(Sadler, 2000).

The first study on the hematology of the newborns was published in 1924 and since then many studies have been conducted that have examined babies at different gestational age and of varying birth weights (Stanchevavp*et al*., 2002).

Hematology of newborn recently represented as area of study that focusing in study of umbilical cord blood and its elements in general, monitoring early blood disorders possibly occurs within newborn as consequence of complicated or due to uncomplicated pregnancy or results of congenitally formed abnormalities. The umbilical cord blood count at birth shows that there is an increased in hemoglobin, hematocrit, mean corpuscular volume, leukocyte count, reticulocyte count and nucleated red blood cells with presence of occasional immature white blood cells in peripheral blood of healthy infants, with variable degree in immature sick newborns (Mamoury*et al*., 2003).

Various blood indices have been reported to vary in the newborns as compared to older children or adults. It depends on the gestational age, day of life, maternal factors, and mode of delivery and site of blood collection (Siddiqui*et al*., 2002). Hemoglobin and hematocrit have been used routinely in the diagnosis of neonatal anemia and polycythemia; whiteblood cells and platelet count have proved helpful in the assessment of neonatal sepsis and hemostatic status of the infant respectively (Marwaha*et al*., 1992; Mamoury*et al*., 2003).

Hematological values are also frequently determined in newborns for diagnostic purposes in suspected infections and bleeding disorders (Abdurrahman and Adekoje,1993).

Pregnant places extreme stresses on the hematological system and understanding of the physiological changes that result as obligatory in order to interpret any need for therapeutic intervention.(Hoffbrand*et al*., 2001).As consequences various quantitative and qualitative hematological changes occur during pregnancy including cell counts, hemoglobin levels, hematocrit, leucocytes, thrombocytes, red blood cells indices, morphological changes and reticulocyte production index (Lewis *et al*., 2001).

The sole source of nutrients for the growing fetus is the maternal blood (Babay*et al.,* 2002). Anemia is regarded as the most importantpreventable cause of perinatal complications, such as premature delivery, intrauterine growth retardation andneonatal and perinatal death.(Paiva*et al*., 2007). Furthermore, iron deficiency anemia isthe most frequent nutritional deficiency in pregnancy,with an impact on maternal and fetal morbidity andmortality.Furthermore, iron deficiency anemia isthe most frequent nutritional deficiency in pregnancy,with an impact on maternal and fetal morbidity andmortality.Many studies havesupported the belief that iron transport from the motherto their fetus occurs independently of maternal ironlevels,which, might even induce deficiency in themother as a result of fetal "parasitism". However, laterstudies have questioned this belief and no consensus regarding this subject has been reached so far(Paiva*et al*., 2007). A fewstudies have correlated hematological indices ofpregnant mothers with those of their newborns, usinghemoglobin level and iron status, either in anemicpatients or in those who had iron supplementation (Babay*et al*., 2002).

1.2 Literature review

1.2.1 Blood

Blood is a vital fluid of the body and such the life line of human body. It is a red colored viscous fluid slightly salty in taste. It is alkaline in reaction (pH = 7.4) and specific gravity range from 1.052 to 1.060. In adult human, blood volume range between 4.5 to 6.0 litters and approximately about one thirteen of adult human body weight.Temperature of the circulating blood is 37.7˚C(Talib, 1995).

1.2.1.1 Components

Blood has two main components cells and plasma. Cells consists 40% to 45% of total amount of blood, and plasma consists 55% to 60% of total amount of blood; cells are the formed elements and are of three types, red cells (erythrocytes), white blood cells (leukocytes) and platelet (thrombocyte), and each has its own characteristic (Talib, 1995)

1.2.1.2 Functions

1. Oxygen is carried from the lungs to the tissue, this function is performed by hemoglobin which is present in large amount in mature red cell.

2. Transport absorbed nutrients from digestive tract e.g. monosaccharide especially glucose, amino acid and fatty acids to the cell of the body for use or storage.

3. Transport hormones from endocrine glands to the organs where they are needed.

4. Act as a buffer system in the plasma which maintain pH of the blood between 7.35 to 7.45.

5. Assist in regulating the temperature of the body.

6. When blood vessel is damaged, platelets and blood coagulation factors interact to control blood loss by formation of clot.

7. Leukocytes are involved in the body's immune defense (Cheesbrough M, 2006)

1.2.1.3 Hematopoiesis(formation of blood)

Is the process, by which blood cells produced, proliferated, differentiated, and maturated in to different blood cells. All cellular blood components are derived from hematopoietic stem cells. In a healthy adult person, approximately new blood cells are produced daily in order to maintain steady state levels in the peripheral circulation.

Hematopoietic stem cells (HSCs) reside in the medulla of the bone (bone marrow) and have the unique ability to give rise to all of the different mature blood cell types and tissues. HSCs are self-renewing cells (PalisAndSegel, 1998).

1.2.1.3.1 Erythropoiesis(formation of the erythrocytes)

Is the process by which red blood cells are produced, it is stimulated by decreased O_2 in circulation, which is detected by the kidneys, which then secrete the hormone erythropoietin. In the early fetus, erythropoiesis takes place in the mesodermal cells of the yolk sac. By the third or fourth month, erythropoiesis moves to the spleen and liver. After seven months, erythropoiesis occurs in the bone marrow. In humans with certain diseases and in some animals, erythropoiesis also occurs outside the bone marrow, within the spleen or liver, this is termed extra-medullaryerythropoiesis. During maturation, the size of the cell is reduced and the cytoplasmic matrix increases in amount, and the staining reaction of the cytoplasm changes from blue to pinkish red because of the decrease in the amount of RNA and DNA. Initially, the nucleus is large in size and contains open chromatin, but as red blood cells mature the size of the nucleus decreases and finally disappears with the condensation of the chromatin material (Palisand Segel,1998).

1.2.1.4 Erythrocyte (red blood cell):

Erythrocytes have the shape of biconcave disk, thicker at the edges than it the middle like a doughnut with a center depression on each side instead of hole.This shape and their small size (7m in diameter) are important to the erythrocytes, so that oxygen and carbon dioxide can diffuse rapidly to and from the interior of the cell. Erythrocyte plasma membrane contains specific polysaccharides and protein that differ from person to person and these confer upon the blood it's so- called blood type or blood group. The site of erythrocyte production is the soft interior of bones called bonemarrow. With differentiation, the erythrocyte precursors produce hemoglobin, but then they ultimately lose their nuclei and organelles- their machinery for protein synthesis. Young erythrocyte in the bone marrow still contain few ribosomes, which produce aweb like (reticular) appearance when treated with special stains, an appearance that give these young erythrocytes, which have lost this ribosomes, leave the bone and enter the general circulation. The production of the erythrocyte requires the usual nutrient needed to synthesize any cell: amino acid, lipids and carbohydrates. In addition, both iron and certain growth factors, including the vitamins, folic acid and vitamins B12, are essential (Widmaier *et al.,*2006).

Erythrocytes are produced by a process known as erythropoiesis, which is stimulated by the hormone erythropoietin, which is produced by the kidney in response to tissue hypoxia (Hoffbrand*et al.*, 2001).

Erythrocytes lack nuclei and organelles, they can neither reproduce themselves nor maintain their normal structure for very long. The average life span of an erythrocyte is approximately 120 days, which mean that almost 1% of the body Erythrocytes are destroyed and must be replaced every day,erythrocyte destruction normally occurs in the spleen and the liver. The major function of

erythrocyte is to carry oxygen taken in by the lungs and carbon dioxide produced by the cells. Erythrocyte contain large amounts of hemoglobin with which oxygen and a lesser extent, carbon dioxide reversibly combine. Oxygen bind to iron atoms (Fe) in the hemoglobin molecules (Widmaier*et al.,* 2006).

1.2.1.5Hemoglobin

The large complex protein molecule (molecular weight 64.458 g/ mol) consisting of four polypeptide globin chains linked together an iron containing prophyrin called heme which is attached to each polypeptide chain and it's this part of the molecule which is principally responsible for its oxygen – carrying properties. Each Erythrocyte contains approximately 280 million hemoglobin molecules, which give blood its color. The iron group of heme is able to combine with oxygen in the lung and release oxygen in the tissue. The heme iron is recycled from senescent(old) RBCs in the liver and spleen. This iron travels in the blood to the bone marrow attached to protein called transferrin; this recycled hem iron supplies most of the body's need for iron. The balance of the requirements for iron, through relatively small, must be made up for in the diet (Fox, 2006).

In normal human development, several types of hemoglobin are produced, there are hemoglobin A, hemoglobin A2, fetal hemoglobin and embryonic hemoglobin.Each of these hemoglobin types has distinctive composition of polypeptide chains. Many other types of hemoglobin have been identified; these are referred to as variant or abnormal hemoglobin (Turgeon, 2005).

1.2.1.6Hematocrit (HCT)

This is some time also referred to a packed cell volume (PCV) or erythrocyte volume fraction (EVF), it is the proportion of blood volume that is occupied by red cells. For normal subjects it is about 46% for men and 38% for women. Hematocrit measurement is considered an integral part of complete blood count results, along hemoglobin concentration, white blood cell count andplateletcount.Most of the modern automated analyzers have the facility to measure hematocrit. Both elevated and depressed value of hematocrit is suggestive of some malfunctioning on the body (Singh, 2010).

1.2.1.7Red cell indices

From the estimated hemoglobin contains, hematocrit and red cell count, it is possible to drive other values, which indicate the red cell volume. Hemoglobin contain and concentration in the red cells. These values are commonly referred to as the red blood cell indices. They are mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC). The MCV defines the volume or size of the average RBC, the MCH defines the weight of hemoglobin in the average RBC, and MCHC defines the hemoglobin concentration or color of the average RBC (Pal and Pal, 2005).

1.2.1.7.1Mean corpuscular volume

The MCV is average volume of RBCs in femtoliters (fl).RBCs are considered normocytic if the MCV is 80- 100 fl, microcytic if is MCV less than 70 fl , and macrocytic if the MCV is greater than 100 fl , in general microcytic cells are fond in patient with IDA, thalassemia, or other conditions of defective iron utilization. Macrocytic cell are found in patient with liver disease or hypothyroidism, in situations which in there is large increase in young erythrocytes (reticulocyte), in folate and vitamin B12 deficiency, and in patients

undergoing treatment with drugs that interfere with RBCs maturation, such as some chemotherapeutic agents and zidovudine (Hoffbrand and Pettit, 2005).

1.2.1.7.2 Mean corpuscular hemoglobin

The MCH indicates the mean weight of hemoglobin per erythrocyte, expressed in SI units as pictograms (pg).The reference values of 26 to 34 pg are considered normal, those less than 26 decreased, and more than 34 increased. There is a higher MCH in macrocytic anemia's because the erythrocytes are larger and carry more Hb. A lower MCH is found in hypochromic anemia's and in microcytic anemia's unless the erythrocytes are also spherocytic. However, when describing anemia's, MCH is rarely used; MCV and MCHC are more commonly used (Stiene-Martian*et al*., 1998).

1.2.1.7.3 Mean corpuscular hemoglobin concentration

The MCHC indicates the average concentration of Hb in the erythrocytes in specimen. The unit used as gram per deciliter (formerly referred to as percentage). Values of 31 to 37 g/dl, are considered normochromic, those less than 31are hypochromic and those more than 37 are hyperchromic. Hypochromic erythrocytesseen in thalassemia's, IDA and defective iron utilization,hyperchromic erythrocytes are actually caused by a shape change such as that found in spherocytosis(Hoffbrand and Pettit, 2005).

1.2.1.8Red cell distribution width (RDW)

This parameter most commonly used to measurement of red cells distribution. It functions as an index of red cell population heterogeneity and can reflects anisocytosis on the peripheral blood film. It is expressed as the ratio of standard deviation (width of histogram) to the MCV or the coefficient of variation of red cell size within a given red cell population. The RDW has been reported to be increased in iron deficiency but normal in heterozygous thalassemia and

anemia's associated with chronic disease. The RDW has also been reported to be more sensitive than other indicators in detecting early iron deficiency anemia (Stiene-Martian*et al*., 1998).

1.2.2 Anemia

Anemia is present when the hemoglobin concentration in the blood is below the lower extreme of the normal range for the age and sex of the individual (Hoffbrand*etal*., 2006). Also it is defined as qualitative or quantitative deficiency of hemoglobin, which normally carries oxygen from the lung to the tissue (Frank *et al*., 2002).

1.2.2.1 Causes of anemia

Some causes of anemia include: nutritional defect, Genetic abnormality, reduce hemoglobin production, reduce DNA synthesis, reduce stem cell production, bone marrow infiltration, infection, increase red cell destruction and acute or chronic blood loss (Job *et al.,* 2008).

1.2.2.2 Physiological response to anemia

1.2.2.2.1 Chemical and physical response

The first adjustment involves an increase in erythrocyte 2,3- diphosphoglycerate (2,3 DPG), which increases Hb release of oxygen to tissues and is represented by a shift to the right in the oxyghemoglobin dissociation curve. The second response involves the selective re-distribution of blood flow to areas of highest oxygen demand. Finally , cardiac output is increased, and increasing cardiac output (Stiene-Martian*et al*., 1998).

1.2.2.2.2 Hematological response

Tissue hypoxia resulting from anemia normally leads to increase erythropoietin marrow stimulation. The erythropoietin acts on the marrow to increase the number of erythroidprecursors, increase their rate of proliferation and

maturation, and accelerate their release from the bone marrow (Stiene-Martian*et al*., 1998).

1.2.2.3 Clinical feature of anemia

1.2.2.3.1 Symptoms

The symptoms in anemic patient are usually shortness of breath particularly on exercise, weakness, lethargy, palpitation and headaches. In older subjects, symptoms of cardiac failure. Visual disturbances because of retinal hemorrhages may complicate very severe anemia, particularly of rapid onset(Hoffbrand*et al*., 2001).

1.2.2.3.2 Signs

These may be divided into two group general and specific.

❖ **General signs**

Include pallor of mucous membranes which occurs if hemoglobin level less than 9 – 10g/dl. Conversely, skin color is not a reliable sign. Hyperdynamic circulation may be present with tachycardia, abounding pulse, cardiomegaly and a systolic flow murmur especially at the apex. Particularly in the elderly, features of congestive heart failure may present. Retinal hemorrhages are unusual (Hoffbrand*et al*., 2001).

❖ **Specific signs**

Are associated with particular types of anemia, e.g. koilonychias (spoon nails) with IDA, jaundice with hemolytic anemia or megaloblastic anemia's, leg ulcers with sickle cell and other hemolytic anemia bone deformities with thalassemia major and other severe congenital hemolytic anemia's. the   association of features of anemia with excess infections or spontaneous suggest that neutropenia or thrombocytopenia may be present, possibly as a result of bone marrow failure(Hoffbrand*et al*., 2001).

1.2.2.4 Classification of anemia

They are three basic formats are used for classification of anemia, these are etiological, physiological, and morphological.

1.2.2.4.1 Morphological classification

Anemia can be classified as morphological approach by the size of red blood cells; this is either done by automated haematology analyzer based on red cell indices, or on microscopic examination of a peripheral blood smear. The size is reflected in the mean corpuscular volume (MCV). If the cells are smaller than normal (under 80 fl), the anemia is said to be microcytic; if they are normal size (80–110 fl), normocytic; and if they are larger than normal (over 100 fl), the anemia is classified as macrocytic (Halterman *et al*., 2001).

❖ **Microcytic anemia**

It is primarily a result of hemoglobin synthesis failure or insufficiency, which could be caused by several etiologies:

- **Heme synthesis defect:** Iron deficiency anemiaand anemia of chronic disease (more commonly presenting as normocytic anemia).

- **Globin synthesis defect:** Alpha and beta-thalassemia, HbE and HbC syndrome and various other unstable hemoglobin diseases (Halterman*et al.,* 2001).

❖ **Macrocytic anemia**

The most common cause of macrocytic anemia is the deficiency of either vitamin B12 or folic acid or both. Deficiency in folate and/or vitamin B12 can be due to either inadequate intake or insufficient absorption.Folate deficiency normally does not produce neurological symptoms, while B12 deficiency does. Pernicious anemia is caused by a lack of intrinsic factor, which is required to absorb vitamin B12 from food. A lack of intrinsic factor

may arise from an autoimmune condition targeting the parietal cells (atrophic gastritis) that produce intrinsic factor or against intrinsic factor itself. These lead to poor absorption of vitamin B12 (Halterman*et al*., 2001).

❖ **Normocytic anemia**

Occurs when the overall hemoglobin levels are decreased, but the red blood cell size (mean corpuscular volume) remains normal. Causes include acute blood loss, Anemia of chronic diseases, aplastic anemia (bone marrow failure) and hemolytic anemia (Halterman*et al.,* 2001).

1.2.2.4.2 The etiological classifications of anemia

This based on underlying pathological process; the cause of anemia in a particular patient is determined from consideration of the type of anemia indicated by examination of the blood, the clinical features, and results of further investigations when these are necessary(Frank *et al*, 2002).

The etiological classification include:

- **Relative anemia:**pregnancy, hyperproteinemia and intravenous fluids**.**

- **Anemia associated with defective hemoglobin synthesis:** IDA, sideroblastic, anemia of chronic disease and thalassemia syndromes.

- **Anemia associated with vitamin B$_{12}$ or Folatedeficiency:**megaloblastic anemia

- **Anemia associated withimpaired bone marrow or stem cell function:**bone marrow injury, decreased marrow stimulation, bone marrow replacement and ineffective hematopoiesis.

- **Anemia associated with decreased red cell survival and increased red cell destruction:** intrinsic red cell defect (membrane defect, enzyme defect and hemoglobinopathies) and extrinsic red cell defect (immune and non-immune).

- **Anemia associated to blood loss:** acute and chronic (Stiene-Martian*etal*., 1998**).**

1.2.2.4.3 Physiological classification

This based on the ability of the bone marrow to respond to anemia with increased erythropoiesis. It involves assessing erythrocyte production using the reticulocyte count and calculated reticulocyte production index(RPI). When anemia occurs, the bone marrow is capable of responding increased number of young nucleated red cells enter the circulation The physiological classification include:

1. **RPI< 2.0 (ineffective erythropoiesis):** hypo proliferative anemia and maturation disorders.

2. **RPI> 3.0 (effective erythropoiesis):** hemolytic anemia and blood loss anemia's (Frank *et al*., 2002).

1.2.2.5 Diagnosis of anemia

Physical examination and medical history play a crucial role in diagnosis of anemia. Some of the important features in medical history cover question about family history, previous personal history of anemia or other chronic condition, medication, color of stool and urine, bleeding problems, and occupation and social habits (such as alcohol intake). While performing a complete physical examination, the physician may particularly focus on general appearance (signs of fatigue, paleness) or liver (hepatomegaly), heart sound, and lymph nodes.

Laboratory tests for anemia may include the following :

1. Complete blood count(CBC): Determines the severity and morphological type of anemia and is typically the first test ordered.

2. Peripheral blood smear: looks at the red blood cells under a microscope to determine the size, shape, number, and color as well as evaluate other cells in the blood (Lewis*et al*., 2001).

3. Iron level: an iron level may tell the doctor whether anemia maybe related to iron deficiency or not. This test is usually accompanied by other tests that measure the body's iron storage capacity, such as transferrin level and ferritin level.

4. FolatelevelandVitamin B_{12} level: this test is essential to the diagnosis of megaloblastic anemia (Hoffbrand*et al*., 2001).

5. Bilirubin level: Useful to determine if the red cells are being destroyed within the body which may be a sign of hemolytic anemia.

6. Hemoglobin electrophoresis: sometime used when a person has a family history of anemia, this test provides information on haemoglobinopathies.

7. Reticulocyte count : A measure of new red blood cells produced by the bone marrow

8. Stool hemoglobin test: tests for blood in stool which may detect bleeding from the stomach or the intestines (stool occult test).

9. Liver function tests: a common test to determine how the liver is working, which may

give a clue to otherunderlying disease causing anemia.

10. Kidney function test: A test that is very routine and can help determine whether any kidney dysfunction exists

11. Bone marrow biopsy: Evaluation of red cells production and may be done when bone marrow problem is suspected(Lewis *et al.,* 2001).

1.2.3 Pregnancy

When the ovum becomes fertilized, a new sequence of event called gestation or pregnancy takes place, and the fertilized ovum eventually develops into a full term fetus. The pregnancy includes changes in cardio vascular system develops primarily to meet the increased metabolic demands of the mother and fetus. The increases in plasma volume (40% - 50%) is relatively greater than that of red cell mass (20%- 30%) resulting in haematodilutionand decrease in hemoglobin concentration. The mean hemoglobin concentration falls from 13.3g/dl in non-pregnant state to 10.9 g/dl at the thirty six weeks of the normal pregnancy, (Steer, 2000).

1.2.3.1 Physiological change during pregnancy

Physiological and anatomical alterations develop in many organ systems during the course of pregnancy and delivery early changes are due, in part to the metabolic demands brought on by the fetus, placenta and uterus and in part to the increasing levels of pregnancy hormones, particularly those of progesterone and estrogen, later changes, starting in mid-pregnancy, are anatomical in nature and are caused by mechanical pressure from the expanding uterus, these alterations create unique requirements for the anesthetic management of the pregnant women, this physiological change has been mistaken in the part for the development of pathological anemia (Steer, 2000).

1.2.3.2 Anemia in pregnancy

Pregnancy places extreme stresses on the hematological system and an understanding of the physiological changes that result is obligatory in order to interpret any need for therapeutic intervention (Hoffbrand*et al*, 2001).Women often become anemic during pregnancy because the demand for iron and other vitamin is increased.The mother must increase her production of red cells and

in addition, the fetus and placenta need their own supply of iron, which can only be obtained from the mother(Frank, 2002).

Maternal plasma volume increases by approximately 50% during the first and second trimesters of pregnancy, whereas the corresponding increase in red cell mass is only 20 – 30%. A dilutional anemia results, so that the lower limit of normal hemoglobin concentration is approximately 10.5 g/dl between 16 and 40 weeks of pregnancy.Aplastic anemia has an increased incidence during pregnancy and the condition may worsen in patient with pre-existing aplasia. Auto-immune hemolytic anemia occurring during pregnancy is typically severe and refractory to therapy. Elevated erythropoietin levels increase the total red cell mass by the end of the second trimester but hemoglobin concentrations never reach pre– pregnancy level(Hoffbrand*etal*., 2005).

1.2.3.3 Types of anemia during pregnancy

1.2.3.3.1 The Physiologicalanemia of pregnancy

Beginning in the week of pregnancy, the plasma volume increases disproportionately to the red cell mass. The plasma volume may reach a maximum value at 24 weeks or continue increasing until as late as the 37th week. At its peak, the average plasma volume is about 45% greater in the pregnant women than in non-pregnant women. A reduction in hematocrit and hemoglobin concentration is evident by the sixth to eight week of normal pregnancy and progresses until the 16 to 20 weeks when anew equilibrium is established; these values usually stabilize the hematocrit at 0.33l/l and the hemoglobin at 11g/dl (Hoffbrand*et al.,* 2006).

1.2.3.3.2 Iron deficiency anemia

about 95% of anemia cases during pregnancy are due to iron deficiency or inadequate intake Up to 600mg of iron required for the increase the mass of red cell; A further300mg for the fetus despite an increase in iron

absorption.Fewwomen avoided severe depletion of iron reserves by the end of pregnancy.In uncomplicated pregnancy the mean corpuscular volume typically rises by around 4fl. A fall in red cell MCV is the earliest sing of iron deficiency, Later the mean corpuscular hemoglobin MCH fall and finally is below 15mg/l together with serum iron <10 mole/l and should be treated with oral iron supplements. The useof routine iron supplementation in pregnancy is often debated but iron is probably better avoided until unit Hb falls below 10g/dl or MCV below 82 ft in the third trimester (Hoffbrand*et al*., 2005).

1.2.3.3.3 Folate deficiency anemia

Folate requirements are increased approximately twofold in pregnancy and serum folate levels fall to about half the normal range with aless dramatic fall in red cell folate. Insome parts of the worldmegaloblastic anemia during pregnancy is common because of a combination of poor diet and exaggerated folate requirements(Hoffbrand*et al*., 2001).

1.2.3.3.4 Vitamin B_{12}deficiencyanemia

It is rare during pregnancy, although serum vitamin B_{12} levels fall to below normal in 20 – 30% of pregnancies and low values are sometimes the cause of diagnostic confusion (Hoffbrand*et al*., 2001).

1.2.4 The umbilical cord

1.2.4 .1 Definition

The umbilical cord (also called the birth cord) is the tube that connects developing embryo of fetus to the placenta. It normally contains two arteries and one vein embedded in gelatinous material called Wharton's jelly.The umbilical vein supplies the fetus with oxygenated, nutrient- rich blood from the placenta. Conversely, the umbilical arteries return the deoxygenated, nutrient – depleted blood, also anther definition the umbilical cord is pathway which connects the placenta with the ventral aspect of the embryo (Sadler, 2006).

1.2.4 .2 Development

The umbilical cord develops from the same sperm and ovum from which the placenta and fetus develop, and contain remnants of yolk sac and allantoises. It forms by the fifth week of   fetal development, replacing the yolk sac as the source of nutrients for the fetus . In humans, the umbilical cord in a full term neonate is usually about 50 centimeter long and 2 centimeter diameter, shrink rapidly in diameter after birth.

The umbilical cord passes through 3 stages of development: -

A) Primitive umbilical ring.

B) Primitive umbilical cord.

C) Fully developed umbilical cord.

Some details four structures which lie inside the primitive umbilical cord although four structures are known to lie in the primitive umbilical cord, the umbilical cord can be said to develop from main elements (Rakhawy, 1981).

1.2.4 .3Vascular development

Umbilical cord arteries:-initially paired ventral branches of the dorsal aorta, course to the placenta in close association with the allantois during the fourth

week, however, each artery acquires, secondary connection with the dorsal branch of the aorta, the common iliac artery, and loses its earliest origin. After birth the a proximal, portions of the umbilical arteries persist as the internal iliac and superior vesicle arteries, and the distal parts are obliterated to form the medical ligaments.

Umbilical veins:- initially the umbilical veins pass on each side of the liver, but some connect to the hepatic sinusoids. The proximal part of both umbilical veins and the remainder of the right umbilical vein then disappear, so that the life vein is the only one to carry blood from the placenta to the liver, with the increase of the placental to the liver. With the increase of the placental circulation, a direct communication forms between the left umbilical vein and the right hepatocardiac channel. The duct us venous(Sadler, 2000).

1.2.4 .4Connection to fetal circulatory system

The umbilical cord veins continues to words the transverse fissures of the liver, where it splits into two, one of these branches joins with hepatic portal vein which carries blood into the liver. The second branch allow the majority of the incoming blood (approximately 80%) to bypass the liver and flow directly into the interior vein which carries blood towards the heart.

The tow arteries branch from the internal iliac arteries, and pass on either side of the urinary bladder before joining the umbilical cord (Rakhawy, 1981).

1.2.4 .5Function of umbilical cord

The umbilical cord is attached to the placenta which transfers oxygen, nutrients, electrolytes, such as amino acid, free fatty acids, carbohydrates, and vitamins, and waste product such as carbon dioxide (Co_2) to and from the maternal blood circulatory system without any direct contact between fetal and maternal blood the blood vessels in the umbilical cord operate differently from what would normally be expected, with the umbilical vein providing the fetus with a supply

of oxygenated blood and nutrients, which(it carries to the fetal heart), and the umbilical arteries carrying away the deoxygenate and nutrient depleted blood In the full- term healthy neonate the cord has a spiral twist and is normally around 50- 60 cm in length, with a diameter of approximately 1- 2 cm. the length of the umbilical cord enables the baby to pass down the birth canal and deliver vaginal without any tractions being applied to the placenta. Where the umbilical is of an above average length, although not of clinical significance, there is an increased risk that it could become wrapped around the fetal body/ neck, prolapsed, or become knotted known as a true knot (Rakhawy, 1981).

1.2.4 .6 Cord blood

Cord blood,is found in the umbilical cord of newborn babies, after baby is born, and the umbilical cord cut, the baby has no more use for the blood remains in these organs. The cord blood contains all the normal elements of blood, red blood cells, white blood cells, platelets and plasma; it is also rich in hematopoietic stem cells.Until a few years ago, it was believed that only cord blood contained hematopoietic stem cells; medical science now knows that venous blood and menstrual blood also contains some blood forming cells that can be used as stem cell sources, but cord blood remains the best option (Querol*etal*., 2009).

1.2.4 .7 Cord blood collection

Umbilical cord blood is up to 180 ml of blood from a newborn baby that is returned to the neonatal circulation if the umbilical cord is not prematurely clamped. In some obstetric and midwifery practices, extended- delayed cord clamped protocol, allows for blood to pulse into the neonate for 5-20 minutes after delivery. If the umbilical cord is not clamped, a physiological clamping occurs upon interaction with cold air and internal gelatinous substance, called Wharton's jells around the umbilical artery and veins. The cord blood collection process is simple safe, and painless. It is usually completed in less than five

minutes by health care provider.Cord blood dose not interfere with delivery and is possible with vaginal or cesarean deliveries. Midwives will use one of two options for cord blood collection: syringe method or bag method. A syringe is used to draw blood from the umbilical cord shortly after the umbilical cord has been cut. The process is basically the same as drawing blood for blood test. In a bag method the umbilical cord is elevated to cause the blood to drain into a bag. The syringe or bag should be labeled with a unique number that represents your baby. Cord blood may only be collected during few minutes following the birth, and should be processed by the laboratory within 48 hours. After umbilical cord blood has been collected, it is placed into sterile bags or syringes and quickly transported to laboratory or cord blood bank (Iannelli, 2009).

1.2.5 Neonatal Hematology

Hematology of newborn recently represented as area of study that focusing in the study of umbilical cord and its elements in general, monitoring early blood disorders possibly occurs within newborn as consequence of complicated or due to uncomplicated pregnancy or result of congenitally formed abnormalities. Identification of expected values associated with hematological parameters essentially requires giving accurate and precise baseline assessment that facilitate the final diagnosis of any abnormalities occur within new at time of birth (purves*etal*., 2000).

The cord blood Hb varies between around16.5and17.1g/ dl and is influenced by the timing of cord clamping.MCV averages 119 fl but falls to adult levels by around 9 weeks. The reticulocyte count is initially high (2-6%) but falls to below 0.5% at 1 week.This is associated with a progressive fall in Hb to around 10-11g /dl at 8 weeks from which point it recovers to 12.5g / dl at around 6 months. In the blood film nucleated red cell will be seen for the first 4days and for up to 1week in preterm infants. Number is increased in cases of hypoxia, hemorrhage or hemolytic disease of the newborn (HDN). Neutrophils are

initially high at birth and fall to plateau at days from this point on the lymphocyte count is higher than neutrophils throughout childhood (Hoffbrand*etal.*, 2001).MCH is also increased in newborn, MCH values ranging from 33.5 to 41.4 pg as compared to adult values 27 to 31 pg; MCHC in the newborn period is quite similar to that in adult, ranging from 30 to 35 percent (Lewis*et al.,* 2006).

1.2.5.1Neonatal Erythrocytes

Fetal erythrocytes are larger and have more variation in shape than those of adult,thecells in the peripheral blood smears of neonates show greater numbers of acanthocytes, target cells, stomatocytes, immature erythrocyte than peripheral blood smear of adult and also shows decreased deformability and increased osmatic resistance during the frits 4 – 6 weeks of life. Red cell count shows a great variability at the time of birth and ranges from 4.6 to 5.2 X 10^{12}/l; the diameter about 8.5 to 9.3µm at birth reaching the adult value of 7.5µm around 6 months of age; relative macrocytosis is observed in the new born(Lewis*et al.,* 2006).

1.2.5.2 Neonatal Hemoglobin

Embryonic hemoglobin referred to as hemoglobin Gower-1($\delta_2\varepsilon_2$) which is seen at less than 5 weeks gestation, followed by hemoglobin Gower-2 ($\alpha_2\varepsilon_2$) and hemoglobin Portland ($\delta_2\gamma_2$) which are seen between 5 to 12 weeks of gestation. Fetal hemoglobin (Hb F- $\alpha_2\gamma_2$) is the predominant hemoglobin of fetal life and comprises the major proportion of hemoglobin found at birth which is seen from 12 weeks to term. HbA ($\alpha_2\beta_2$) is the major hemoglobin found in adult and children. Hb A_2 ($\alpha_2\delta_2$)**,**andHb F are found in small quantities in adult life(Susan, 2007).

1.2.5 .3 Neonatal packed cell volume (PCV)

The average hematocrit level approximately 0.55L/L at birth, both Hb and PCV increase sharply during the first few hours then slowly decrease, by the end of the first week they approximate the initial cord blood valuesIn healthy new born the cord blood hematocrit is around 65% and decreases by ten days of life, then gradually decreases to achieve normal adult values of about 0.45 L/L for males, and 0.42 L/L for females in adolescence (Firkin, 1996).

1.2.5.4 Anemia inthe neonate

Generally anemia at birth is usually secondary to immune hemolysis. Non-immune causes of hemolysis appearing within 24h after birth. Impaired red cell production is usually not apparent for at last 3 weeks. Hemolysis is often associated with serves jaundice, and the causes include HDN, autoimmune Hemolyticanemia(AIHA) in the mother and congenital disorders of red cell membrane or metabolism.Red cell transfusion may be needed for symptomatic anemiawithHb<10.5g /dl or a higher threshold if there is serves cardiac or respiratory disease (Hoffbrand*et al.,* 2001).

1.3 Previous studies

Many studies has been conducted to correlate the hematological parameters of normal maternal blood with the cord blood of healthy newborns. Cross sectional study was conducted at four public and private hospitals of Karachi including Sindh Government Qatar Hospital, Sindh Government Hospital, Liaquatabad, Ziauddin University Hospital, and Chinniot Maternity and Child Hospital, in the period from July 2006 to April 2008. A total of 404 maternal and umbilical cord blood samples were analyzed. Except for MCHCthere was no correlation between all the routine hematological parameters (including hemoglobin,RBCs count, HCT, MCV, MCH, white blood cell count,differential leukocyte count and platelet count). They concluded that, routine hematological parameters of

newbornsare independent of maternal routine hematological parameters (Qaiser*et al*., 2013).

Another study conducted on two hundred (200) apparently healthy pregnant women at term, aged 18–42 years in Nigeria, in which, the result of the cord blood hemoglobin concentration and packed cell volume were significantly higher than the maternal values. However, there were no significant differences between cord blood and maternal MCHC. Furthermore, a positive linear Pearson's correlation was observed between the mean Hb and PCV of cord blood and maternal blood(Nneli*et al.,* 2011).

Also another study was conducted in northeastern Iran to correlate hemoglobin between maternal and cord blood. The result showedno significant correlation between cord Hb and maternal Hb , (Mamoury*etal*., 2003).

Chapter two

Rationale and objectives

2.1Rationale

The study of the umbilical cord blood parameters will give important information about hematological aspects of the neonates .

Umbilical cord blood samples are usually used for diagnosis of hematological disease in neonates.

It is debatable whether the fetus blood is formed independently of the mother or not, and whether the mother iron status has an effect on fetus red blood cell parameters or not; while some researcher reported a correlation between maternal and cord blood parameters, others were not.

To our knowledge there is no study in Sudan addressing the correlation between maternal and cord blood red cell parameters. This study stand as baseline data for hematological parameters of pregnant women and neonatal cord blood in Sudan.

2.2 Objectives

2.2.1 General Objective

To investigate whether there is a correlation between maternal and cord blood red cell parametersor not.

2.2.2 Specific Objectives

1. To measure hemoglobin, RBCs, PCV, red cell indices, RDW-SD and RDW-CV in the mother and cord blood using automated hematology analyzer.

2. To correlate the mother hematological findings with the cord blood findings.

3. To compare red blood cells parameters of neonates according to gender.

4. To study the effect of mother's age on cord blood findings.

Chapter three

Materials and Methods

3.1 Study design

This is a descriptive cross sectional study, carried out during January to March 2015 to study the correlation between the maternal and cord blood red cell parameters.

3.2 Study area

The study was conductedat Alfasher teaching hospital, North Darfur, Sudan.

3.3 Study population and sample size

Two hundred blood Samples were collected, 100 from pregnant Sudanese ladies immediately before delivery and 100 from cord blood during delivery .

3.4 Inclusion Criteria

Pregnant Sudanese ladies without any complications and apparently healthy neonates.

3.5 Exclusion Criteria

Pregnant ladies with known hematological disorders rather than those knownto be associated with pregnancy were excluded from the study.

3.6 Collection and handling of blood Samples

Blood samples were collected from the umbilical cord immediately after delivery by clamping and cutting the babies end of the cord. The blood samples were also collected from the antecubital fossa of the mothers by venipuncture inside the labour room immediately before delivery. These process were done under high aseptic conditions. Blood samples were collected into sample bottles containing EDTA anticoagulant adequate for 3 milliliter (ml) of blood. Each

sample was mixed gently and thoroughly to prevent cell lysis and clotting of blood.

3.7 Hematological investigations

Completeblood count (CBC) was performed within two hours of collection using automated hematology analyzer (Sysmex K-21N, Japan).

3.8 Data Collection tools and analysis

Data was collected by proper personal interview questionnaire to the pregnant ladies, including gender of baby, type of delivery and history of diseases. Data was analyzed by statistical package for social sciences (SPSS, version 11.5). Qualitative data was represented as frequency and percentage; quantitative data was represented as Mean±SD; means of quantitative variables were compared using independent 2- sample T-test. Correlation between maternal and cord blood parameters was tested by Pearson correlation.

3.9 Ethical Consideration

The mothers were informed about the research objectives and procedures during the interview period, and vebral consent was obtained from all participants.

Chapter four

Results

A total of 100 maternal blood samples and 100 umbilical cord blood samples were analyzed. 40(40%) of the mothers were delivered by spontaneous vaginal delivery and 60(60%) by caesarean section. Mothers' ages ranged from 15 to 40 years (Mean ± SD: 26±4.9).

Table (4.I) shows the mean values and standard deviation of the mothers' and cord blood red cell parameters. Except for MCHC all the red blood cell parameters were found to be higher in the cord blood samples than the maternal blood samples. The difference was statistically significant .

Table 4.1: Red blood cell parameters of the maternal and cord blood

Parameters	Maternal N: 100 Mean ± SD	Cord blood N: 100 Mean ± SD	*P.value*
Hb(g/dl)	11.4 ± 1.4	14.6 ± 1.6	0.000
RBCs (X 10^{12}/L)	4.0 ± 0.7	4.2 ± 0.7	0.005
PCV(%)	36.2 ± 5.6	42 ± 7.3	0.000
MCV (fl)	84.7± 8.2	106 ± 8.1	0.000
MCH (pg)	28.1± 2.7	34.8 ± 3.7	0.000
MCHC (g/dl)	32.3± 2.2	31 ± 1.8	0.010
RDW- SD (fl)	56.9± 13.7	63.3 ± 7.5	0.000
RDW-CV (%)	16.2 ± 2.9	17.1 ± 1.9	0.007

p. values considered significant ≤ 0.05

Forty one (41%) of the mothers were anemic, while 59(59%) were found to have normal red blood cell parameters. Of the anemic mothers, 29(29%) were found to have microcytic hypochromic anemia, 9(9%) have normocytic normochromic anemia, and 3(3%) had macrocytic normochromic anemia. Comparison of red blood cell parameters of the neonates born to anemic mothers and those born to normal mothers showed no statistically significant differences (Table 4.2).

Table (4.2): Comparison of red blood cell parameters in neonates born to anemic and non-anemic mothers

Parameters	Anemic mothers (n=41)	Non anemic mothers (n=59)	*P. value*
Hb (g/dl)	14.3 ± 1.6	14.7 ± 1.2	0.20
PVC (%)	41.4± 7.4	41.7 ± 7.1	0.85
RBCs $(X10^{12}/l)$	4.1± 0.7	4.3 ± 0.6	0.22
MCV (fl)	105.7 ± 10.8	106 ± 5.7	0.83
MCH (pg)	32.4± 3.8	35.1 ± 3.5	0.38
MCHC (g/dl)	31.9 ± 2.2	31.5 ± 1.5	0.27
RDW-SD (fl)	63.5 ± 7.3	63.2 ± 7.6	0.82
RDW-CV(%)	17.2 ± 1.9	17.1 ± 2	0.86

p. values considered significant ≤ 0.05

As shown in table (4.3) the red blood cell parameters of male neonates 46(46%) and female neonates 54(54%) were not significantly different.

Table (4 .3): Comparison of red blood cells parameters in umbilical cord blood with correlation to gender

Parameter	Male	Female	*P.Value*
Hb(g/dl)	14.6 ± 1.4	14.5 ± 1.8	0.55
PVC(%)	42.4± 6.6	40.8 ± 7.7	0.26
RBCs (10^{12}/l)	4.26± 0.7	4.23 ± 0.6	0.84
MCV (fl)	107 ± 9.4	105 ± 6.7	0.23
MCH (pg)	34.5± 3.6	35 ± 3.8	0.47
MCHC (g/dl)	31.9 ± 2.2	31.3 ± 1.2	0.15
RDW-SD (fl)	63.6 ± 6.9	63 ± 8.2	0.35
RDW-CV(%)	17.4 ± 2.2	16.7 ±1.5	0.08

p. values considered significant ≤ 0.05

Table (4.4) shows the correlation between red blood cell parameters of cord blood and mothers ages, the result showed no statistically significant correlation.

Table (4.4)Red blood cells parameters in correlation to mothers ages

Parameter	Pearson correlation (r)	P.Value
Hb(g/dl)	0.15	0.13
PVC(%)	0.01	0.88
RBCs (10^{12}/l)	0.009	0.93
MCV (fl)	0.01	0.92
MCH (pg)	0.04	0.64
MCHC (g/dl)	0.15	0.12
RDW-SD (fl)	0.003	0.97
RDW-CV(%)	0.09	0.33

p. values considered significant ≤ 0.05

No statistically significant correlation was found between mothers' and neonates' red cell parameters, including Hb (r= 0.13 , P.value: 0.2), HCT (r= 0.1, P.value: 0.24), RBCs (r= 0.1 , P.value: 0.29), MCV (r= 0.06 , P.value: 0.54), MCH (r= 0.07 , P.value: 0.48), MCHC(r= 0.09 , P.value: 0.36) , RDW-SD (r=   0.09 , P.value: 0.32   ) and RDW-CV (r= 0.08 , P.value: 0.46) shows (figures 4.1 – 4.8).
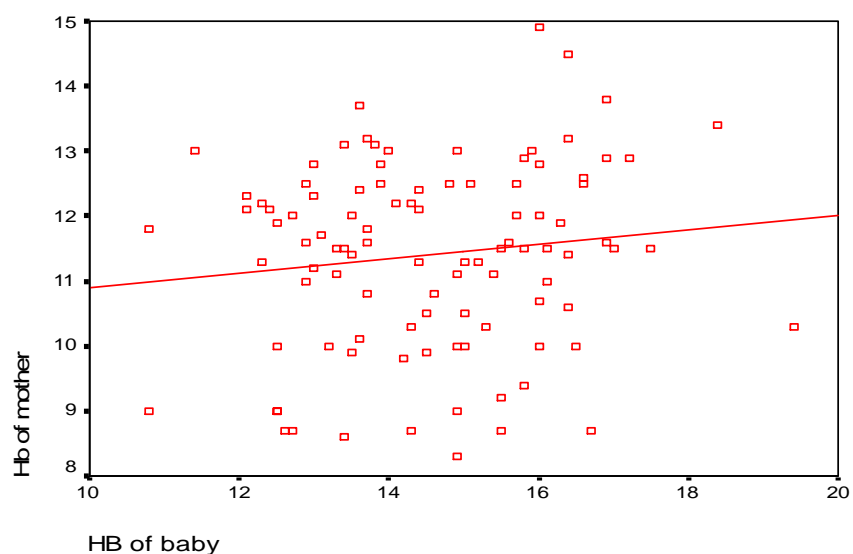
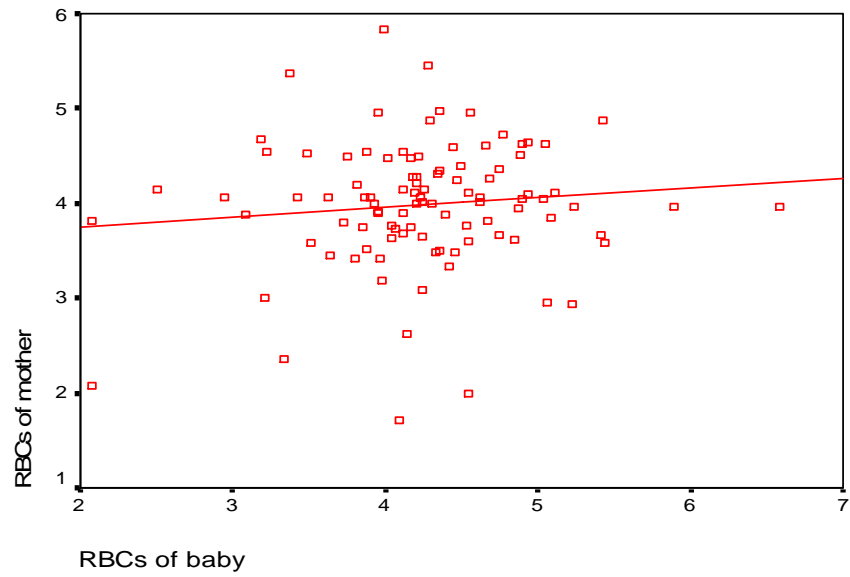

Figure 4.1 Correlation between maternal and cord blood Hb

Figure 4.2 Correlation between maternal and cord blood RBCs.
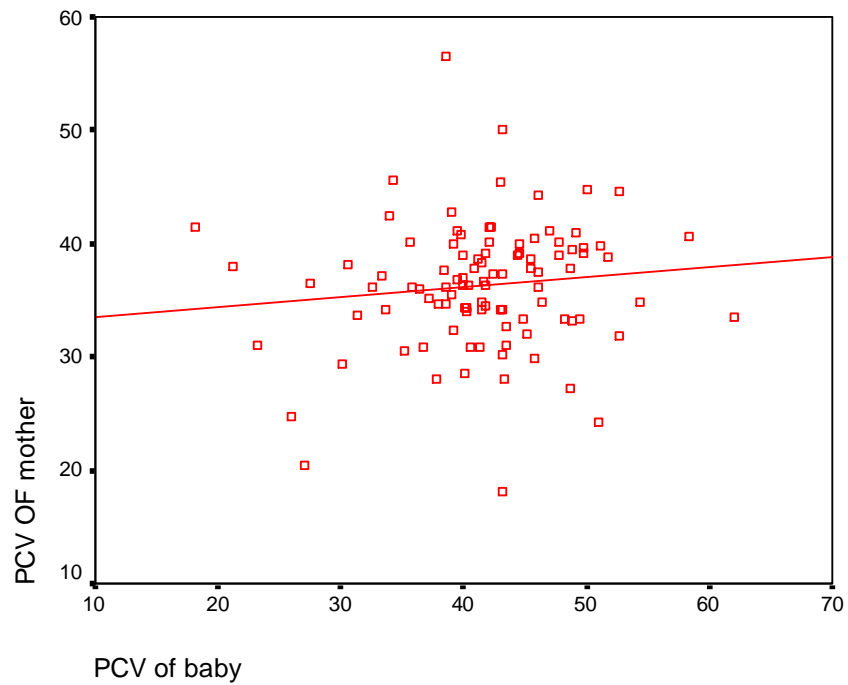
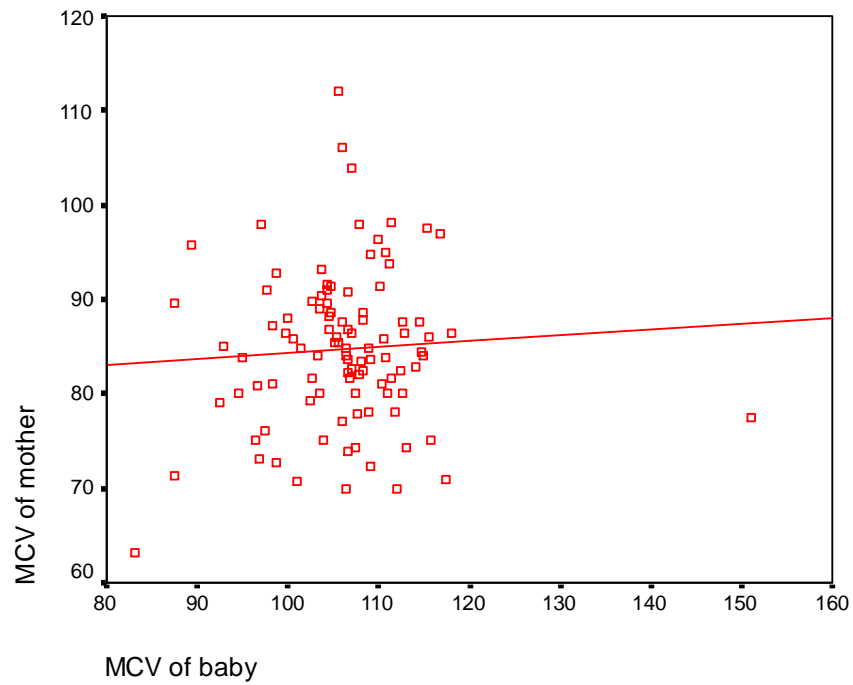**Figure 4.3** Correlation between maternal and cord bloodPCV.

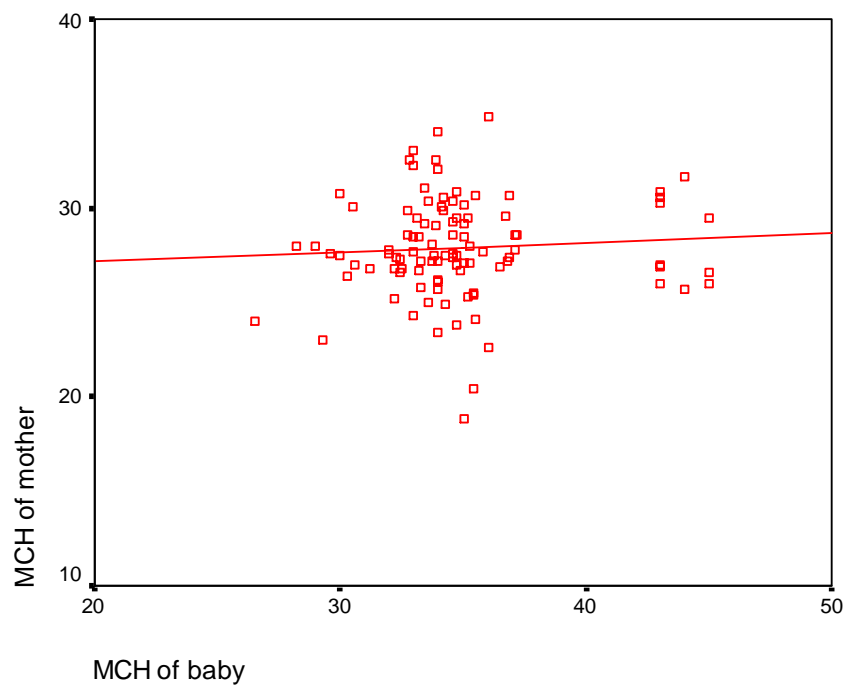**Figure 4.4** Correlation between maternal and cord blood MCV.

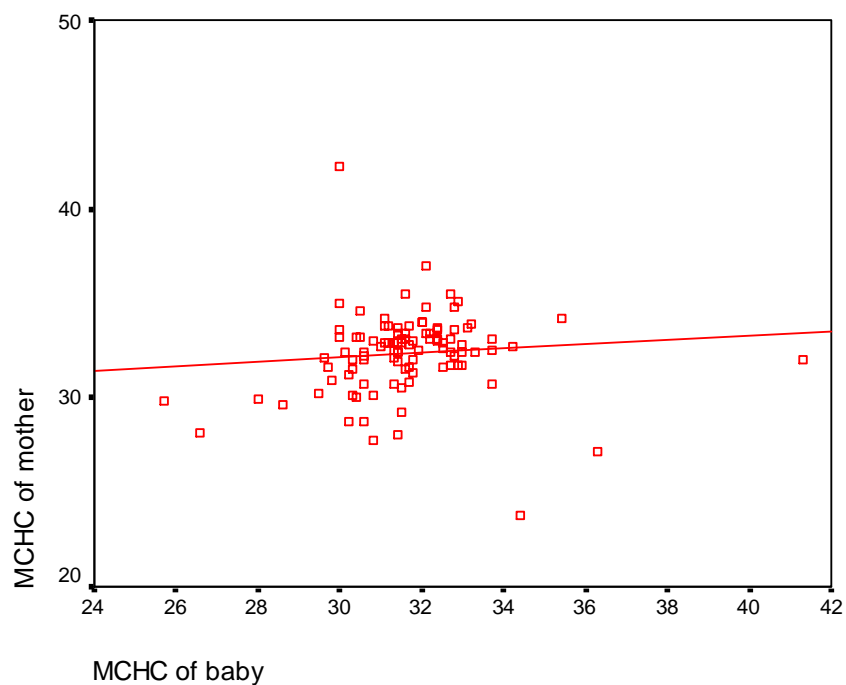**Figure 4.5** Correlation between maternal and cord blood MCH.

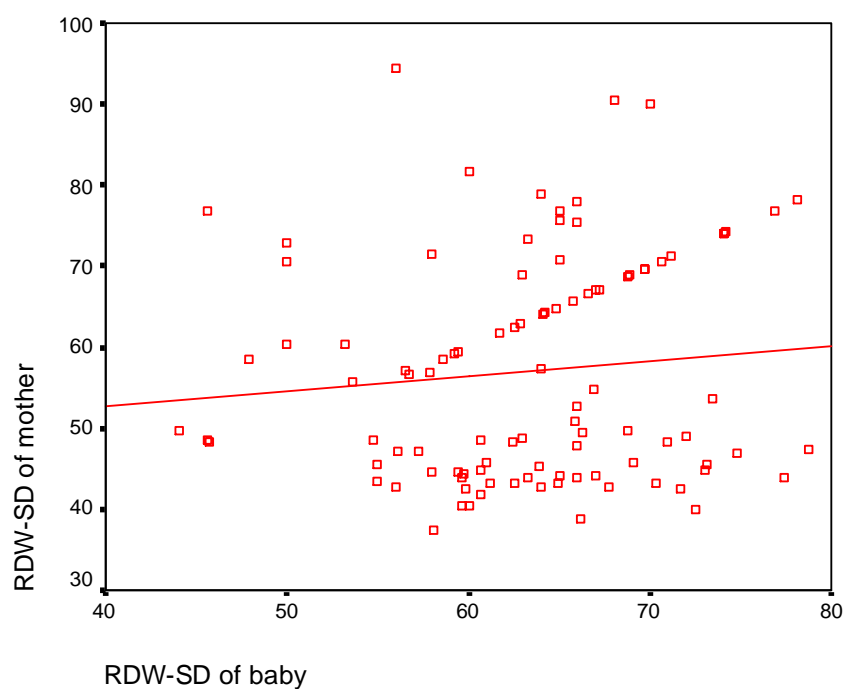**Figure 4.6** Correlation between maternal and cord blood MCHC.

Figure 4.7 Correlation between maternal and cord bloodRDW-SD.
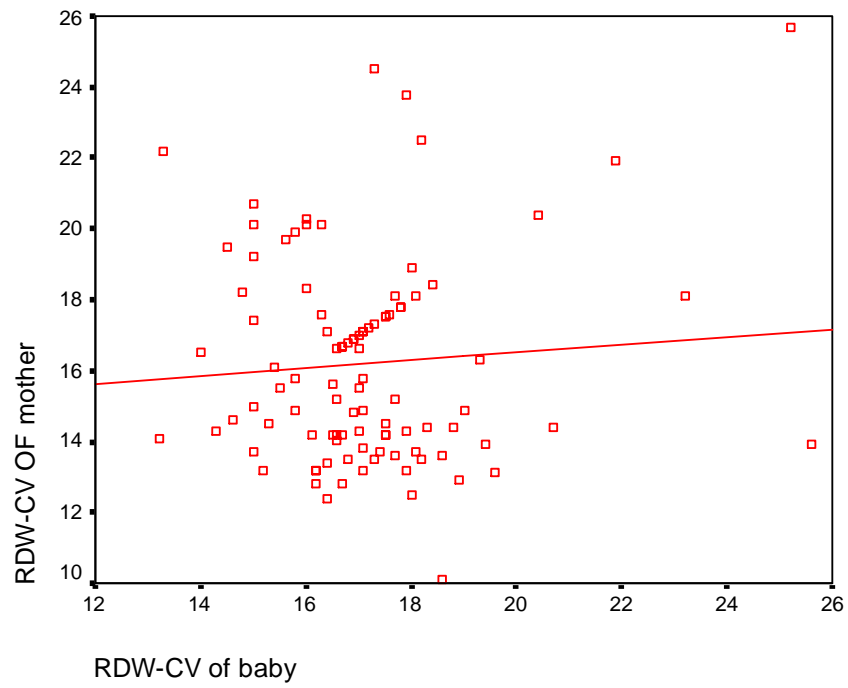
Figure 4.8 Correlation between maternal and cord bloodRDW-CV.

Discussion

This study was conducted at Alfasher teaching hospital, North Darfur, Sudan, to investigate the correlation between maternal and cord blood red cell parameters.

To our knowledge very few studies have shown positive correlation in hematological parameters between mother and cord blood whereas many studies have shown no correlation between these two groups(Qaiser*et al*., 2013).

 The results of the present study showed that, except for MCHC all the red blood cell parameters were higher in cord blood than maternal blood, this could be due to increased number and size of red blood cells in cord blood (Odey and Ibu,2003). On the other hand, the lower red cell parameter's observed in the maternal blood can also be related to increased plasma volume during pregnancy which lead to haemodilution(Nneli*et al*., 2011). In addition, physiological changes in pregnancy, which modifies the chemical constitution of blood, amplifies transfer of some hematopoietic micronutrients, and increased utilization of some of these micronutrients as defense mechanisms against pregnancy induced oxidative stress may lead to maternal depletion and low hematological values(Qaiser*et al*., 2013).

This study revealed that, mean Hb values of healthy Sudanese newborn cord blood and mothers was 14.6 and 11.4 g/dl respectively; both were slightly higher than results obtained in Nigerian (14.2±1.5 and 11.2±0.9 g/dl) (Nneli .*et al*., 2011). Our results were lower than the results obtained in Pakistan (15±1.5 and 11.5±1.9 g/dl) (Qaiser*et al*., 2013). The suggested reasons for the differences observed in the previous studies in various locations were environmental and dietary factors. other factor could be the time of clamping of the umbilical cord before blood samples were collected (Ezeilo, 1972).

The present study showed that, mean values of MCV, MCH and MCHC of healthy Sudanese newborn cord blood and mothers were 106 fl, 34.8 pg, and 31 g/dl respectively for cord blood and 84 fl, 28 pg and 32.3 g/dl respectively for the mothers. The results were comparable to that obtained in Pakistan (means: 106 fl, 35.8 pg, and 32 g/dl respectively for cord blood and 84.9 fl, 27.9 pg and 32.4 g/dl respectively for the mothers (Qaiser*et al*., 2013).

In the current study there was no statistically significant correlation between mothers' and cord blood red cell parameters, this finding was similar to that obtained in Pakistan (Qaiser*et al*., 2013), Nigeria (Nneli*et al*., 2011), North eastern Iran (Mamoury, *et al*., 2003) and Manipuri (Devi *et al*., 1989. The lack of correlation may be because the iron storage in the fetus and mother is not directly related and it is under the control of an independent systems (Nneli*et al*., 2011), this in addition to the physiological changes occur during pregnancy.

In this study, maternal age had no significant effect on the red blood cell parameters and this agrees with similar results observations in Nigeria (Nneli*et al*., 2011) and Pakistan (Qaiser*et al*., 2013).

Also, our study explained that, there was no statistically significant difference in red blood cell parameters between male and female newborns; this agrees to the result done in Nigeria (Qaiser*et al*., 2013), and disagree to result obtained in Northeastern Iran (Mamoury*et al*., 2003). However, it is known that. in this age gender has no effect on red cell parameters.
Comparison of red cell parameters in cord blood of neonates born to anemic mothers and those born to non-anemia mothers showed no statistically significant variation. This finding agrees with the result obtained by Elgari&Waggialla(2013), and this support the above mentioned fact that, red cell production in the fetus are under the control of an independent mechanism.

Conclusion

1. There was no significant correlation between maternal and cord blood red cell parameters.

2. There was no statistical significant difference in red blood cells parameters of neonates according to gender.

3. No statistically significant difference was found in red cell parameters of neonates born to anemic mothers when compared with those born to non-anemic mothers.

4. Mother age has no effect on neonatal red cell parameters.

Recommendation

- Cord blood sample can be used for evaluation of red cell parameters in neonate regardless of the mothers red cell parameters.

- Further study should be conducted in the future taking in consideration the hematological parameters other than red cell parameters.

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Appendix (1)

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Colleg of post graduate studies

Questionnaire

Measurment of red blood cell parameters of maternal and umbilical cord blood in Alfasher teaching hospital, North Darfur, Sudan.

Serial number: ……..

Age of mother : …..

Gender of baby:

Male   (   )

Female (   )

Type of delivery:

Normal vaginal   (   )

Caesarean section   (   )

State of pregnancy :

Normal (   )

Known disorders (   )