Serum Level of FSH and LH among Females with Sickle Cell Anemia in Khartoum State

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قال تعالى:

لا يخلق ما يشاء يبب لم يشاء وإنائنا ويص ولم يشائ الذكور 49 أو يزوجهم ذكرانو وإنائنا ويجعل ومن يشاء عقيما إنه عليم قادر 50

صدق الله العظيم

سورة الشورى الآيات 49-50
Dedication

To my great lovely parents
To my beloved husband
To my brilliant brothers and sister
To my sweetly sons
To my nice flower daughter
To my great teachers
To my awesome friends
To all my family and any person who helped me to fulfill this research
I remember

How you helped me to grow with love, truth and honesty
How to choose the right path with values, morals and self-worth
How you gave me dreams with hope and confidence
Acknowledgment

Thanks you my God, for giving me the ability and courage to bring this research to light.

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Grateful to my beloved friends and colleagues who stood firm behind me and gave me a great push forward.

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**Abstract**

Sickle-cell disease (SCD), also known as sickle-cell anemia (SCA), is a group of genetically passed down blood disorders. It results in an abnormality in the oxygen-carrying protein haemoglobin found in red blood cells.

This is a case control study conducted during the period from February to December 2016, to determine the level of Gonadotropins (follicle stimulating hormone and Luteinizing hormone) among Sudanese female with sickle cell patients, the level of gonadotropin was estimated by using ELISA.

Eighty subjects were included in this study (50 patients {40 sickler, 10 traits} and 30 healthy)

Statistical analysis was done by using SPSS. And the result showed that follicle stimulating hormone level was significantly higher in sickler group when compared to non sickler group (5.82±4.26 Vs 3.80±2.09 p.value = 0.00). And luteinizing hormone did not show significant different in sickler group when compared to non sickler group (4.61±3.23 Vs 4.52±3.43 p.value = 0.947). The study also revealed that a significant positive correlation between follicle stimulating hormone and age. (r = 0.316, p.value = 0.04) and also a significant positive correlation between luteinizing hormone and age. (r = 0.405, p.value = 0.009)

A significant negative correlation between follicle stimulating hormone and duration of treatment by Hydroxyurea (r = -0.447, p.value = 0.045). And also show a significant negative correlation between luteinizing hormone and duration of treatment by Hydroxyurea. (r = -0.538, p.value = 0.039)

In conclusion the serum level of follicle stimulating hormone is increase in patients with sickle cell disease, and luteinizing hormone is not affected.

Also there were relationship between the level of follicle stimulating hormone, luteinizing hormone and duration of treatment, eventually there was association of increasing in age and duration of sickle cell disease in patients with sickle cell disease in the increase level of follicle stimulating hormone, luteinizing hormone.
المتخصّص في الدراسة

مرض الخلية المنجلية أو ما يعرف بمرض الانيميا المنجلية يعتبر من أحد الأمراض الجينية التي تسبب خلل في الدم وتنتج عن اختلال في البروتين الواقف على المريخ (اليهيموغلوبين) في خلايا الدم الحمراء.

أجرت هذه الدراسة للمقارنة بين مجموعتي المرضى والأصحاء في الفترة من فبراير إلى يونيو 2016 تم اختيارهم عشوائياً من مستشفى جعفر بن عوف لتまったく مستوى هرمون FSH لدى مرضى الانيميا المنجلية من فئة الأنثى. تم قياس مستوى LH و FSH باستخدام ELISA.

شملت هذه الدراسة 80 شخص 40 منهم يعانون من مرض الانيميا المنجلية 10 حالات حاملين للمرض (traits) 30 أصحاء ظاهراً كمجموعة تحكم. تم إجراء التحليل الإحصائي باستخدام برنامج SPSS. واظهرت النتائج زيادة بشكل ملمع في متوسط مستوى هرمون FSH لدى المرضى (0.26±0.82) مقارنةً بمتوسط المستوي في المرضى (4.52±3.43) عند مستوى هرمون LH.

بينما لم يظهر أي فرق في متوسط هرمون LH لدى المرضى (0.947) بين مجموعتي المرضى والمkoń. للعلاقة الملمع في مستوى هرمون FSH والوقت المرضي (r=0.316) والعملية المعنوية (p>0.04) أخيراً، و ليس اخبارأ ظهروا النتائج أن هناك علاقة طريقة ملمع في مستوى هرمون LH والوقت المرضي (r=0.405** والعملية المعنوية (p<0.005). أيضاً، وجدنا أن العلاقة القوية بين مستوى هرمون LH والوقت العلاج (R=0.447) والعملية المعنوية (R=0.447).

خلصت الدراسة أن هناك علاقة ملمع في زيادة مستوى هرمون FSH في مصل الدم لدى المرضى المصابون بالانيميا المنجلية بينما لم يظهر أي تغيير في مستوى هرمون LH. وجدنا ان العلاقة القوية بين مستوي هرمون LH، FSH ووقت العلاج، اخيراً لوحظ ان هناك علاقة كلما طالت فترة المرض ارتفع مستوي هرمون LH و FSH.
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<td>DVT</td>
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<td>E6V</td>
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<td>GnRH</td>
<td>Gonadotrobin releasing hormone</td>
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<td>GPCR</td>
<td>G protein coupled receptor</td>
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1. Introduction and Literature review

1.1. Introduction

Sickle cell disease group of haemoglobin disorder in which the sickle B-globin gene is inherited. homozygous sickle cell anaemia (HbSS) is the most common while the doubly heterozygote condition of Hb SC and HbSBthal also cause sickling disease HB S is insoluble and form crystal when exposed to low oxygen tension deoxygenated sickle haemoglobin polymerize in to long fibers each consisting of seven intertwined double strand with cross-linking. The red cells sickle and may block different areas of microcirculation or large vessels causing infacts of various organ. (Hoffbrand et al, 2006)

As of 2013 about 3.2 million people have sickle-cell disease while an additional 43 million have sickle-cell trait. About 80% of sickle-cell disease cases are believed to occur in sub-Saharan Africa. (Rees et al, 2010) It also occurs relatively frequently in parts of India, the Arabian peninsula, and among people of African origin living in other parts of the world. Sickle cell disease is a life-long illness. The severity of the disease varies widely from person to person.

In high-income countries like the United States, the life expectancy of a person with SCD is now about 40–60 years. In 1973, the average lifespan of a person with SCD in the United States was only 14 years. Advances in the diagnosis and care of SCD have made this improvement possible. A sickle cell anemia study has found that the drug Hydroxyurea is as effective as blood transfusions in children to reduce blood flow velocities in the brain, which is a key risk factor for stroke. (Gray, et al 2015).

Sickle-cell anaemia can lead to various complications, including increase risk of severe bacterial infection, priapism, Osteomyelitis, pulmonary hypertension, Growth retardation and chronic kidney failure and endocrine disorder.

Hypogonadism is one of the most prevalent endocrinopathies in subjects with SCD. Male patients with SCD frequently present with eunuchoid body habitus, absent or diminished secondary sexual characteristics, and small testicular size.31 Biochemical
studies have demonstrated low levels of testosterone and dihydrotestosterone and variable levels of follicle-stimulating hormone and luteinizing hormone.\textsuperscript{[10,12,30]}

The etiology for hypogonadism in SCD is unclear; however, several causes have been proposed, including primary testicular failure, hypothalamic and/or pituitary dysfunction, zinc deficiency, and constitutional delay of puberty.\textsuperscript{[18,21,32]} Primary testicular failure due to structural abnormalities has also been suspected as an important cause of gonadal failure and infertility. Episodes of intravascular sickling, vaso-occlusion, and infarction, as well as tissue hypoxia associated with chronic anemia, are responsible for the testicular failure in SCD

**Gonadotropins: luteinizing and follicle stimulating hormone**

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are called Gonadotropins because stimulate the gonads - in males, the testes, and in females, the ovaries. They are not necessary for life, but are essential for reproduction. These two hormones are secreted from cells in the anterior pituitary called gonadotrophs. Most gonadotrophs secrete only LH or FSH, but some appear to secrete both hormones.

As describe for thyroid-simulating hormone, LH and FSH are large glycoproteins composed of alpha and beta subunits. The alpha subunit is identical in all three of these anterior pituitary hormones, while the beta subunit is unique and endows each hormone with the ability to bind its own receptor.(Bowen, 2004)

**Physiologic Effects of Gonadotropins**

Physiologic effects of the Gonadotropins are known only in the ovaries and testes. Together, then regulate many aspects of gonadal function in both males and females.

**Luteinizing Hormone**

In both sexes, LH stimulates secretion of sex steroids from the gonads. In the testes, LH binds to receptors on Leydig cells, stimulating synthesis and secretion of testosterone. Theca cells in the ovary respond to LH stimulation by secretion of testosterone, which is converted into estrogen by adjacent granulosa cells. (Mahesh, 2011)
Follicle-Stimulating Hormone

As its name implies, FSH stimulates the maturation of ovarian follicles. Administration of FSH to humans and animals induces "super ovulation", or development of more than the usual number of mature follicles and hence, an increased number of mature gametes.

FSH is also critical for sperm production. It supports the function of Sertoli cells, which in turn support many aspects of sperm cell maturation.
1.2. Literature review

1.2.1. Sicklecellanaemia:

*Sickle-cell disease* (SCD) is a group of genetically passed down blood disorders. The most common type is known as *sickle-cell anaemia* (SCA). It results in an abnormality in the oxygen-carrying protein haemoglobin found in red blood cells. This leads to a rigid, sickle-like shape under certain circumstances. Problems in sickle cell disease typically begin around 5 to 6 months of age. A number of health problems may develop, such as attacks of pain ("sickle-cell crisis"), anemia, bacterial infections, and stroke. chronic pain may develop as people get older. The average life expectancy in the developed world is 40 to 60 years.

Sickle cell disease is a group of haemoglobin disorder in which the sickle B-globin gene is inherited homozygous sickle cellanaemia (HbSS ) is the most common while the doubly heterozygote condition of Hb SC and HbSBthal also cause sickling disease. The sickle B-globin abnormality is caused by substitution of valine for glutamic acid in position 6 in the B chain it is very wide spread and is found in up to one in four west African , maintained at this level because of the protection against malaria that is afforded by the carrier state.(Hoffbrand, et al.2006)

Sickle-cell disease occurs when a person inherits two abnormal copies of the haemoglobin gene, one from each parent. Several subtypes exist, depending on the exact mutation in each haemoglobin gene. An attack can be set off by temperature changes, stress, dehydration, and high altitude A person with a single abnormal copy does not usually have symptoms and is said to have sickle-cell trait Such people are also referred to as carriers. Diagnosis is by a blood test and some countries test all babies at birth for the disease. Diagnosis is also possible during pregnancy.

The care of people with sickle-cell disease may include infection prevention with vaccination and antibiotics, high fluid intake, folic acid supplementation, and pain medication. Other measures may include blood transfusion, and the medication hydroxycarbamide (Hydroxyurea). A small proportion of people can be cured by a transplant of bone marrow cells

Three quarters of sickle-cell cases occur in Africa. A recent WHO report estimated around that 2% of newborns in Nigeria were affected by sickle cell anaemia, giving a total of
150,000 affected children born every year in Nigeria alone. The carrier frequency ranges between 10% and 40% across equatorial Africa, decreasing to 1–2% on the North African coast and <1% in South Africa. There have been studies in Africa that show a significant decrease in infant mortality rate, ages 2–16 months, because of the sickle-cell trait. This happened in predominant areas of malarial cases. (Aidoo, et al., 2002)

1.2.1.1. Homozygous disease

1.2.1.1.1. Clinical features

Clinical features are of a severe anaemia punctuated by crises. The symptoms of anaemia are often mild in relation to the severity of the anaemia because Hb S gives up oxygen (O2) to tissues relatively easily compared with HbA, its O2 dissociation curve being shifted to the right. The clinical expression of Hb SS is very variable, some patients having an almost normal life, free of crises but others develop severe crises but other develop severe crises even as infants and may die in early childhood or in adulthood. Crises may be vaso-occlusive, visceral, a plastic or haemolytic (Hoffbrand, et al. 2004).

Vaso-occlusive crisis

These are the most frequent and are precipitated by such factors as infection, acidosis, dehydration or deoxygenating (e.g. altitude, operation, obstetric, delivery, stasis of the circulation, exposure to cold, violent exercise). Infarcts can occur in a variety of organs including the bones (hips, shoulders and vertebrate are commonly affected) the lung and the spleen. The most serious vaso-occlusive crisis is of the brain or spinal cord (Olujohung & Burnett, 2013).

The vaso-occlusive crisis is caused by sickle-shaped red blood cells that obstruct capillaries and restrict blood flow to an organ resulting in ischaemia, pain, necrosis, and often organ damage. The frequency, severity, and duration of these crises vary considerably. Painful crises are treated with hydration, analgesics, and blood transfusion; pain management requires opioid administration at regular intervals until the crisis has settled. For milder crises, a subgroup of patients manages on NSAIDs (such as diclofenac or naproxen). For more severe crises, most patients require inpatient management for intravenous opioids; patient-controlled analgesia devices are commonly used in this setting. Vaso-occlusive crisis involving organs such as the...
penis or lungs are considered an emergency and treated with red-blood cell transfusions. Incentive spirometry, a technique to encourage deep breathing to minimize the development of atelectasis, is recommended. (Glassberg J, 2011)

· **Splenectomy sequestration crisis**

Because of its narrow vessels and function in clearing defective red blood cells, the spleen is frequently affected. It is usually infarcted before the end of childhood in individuals suffering from sickle-cell anemia. This spleen damage increases the risk of infection from encapsulated organisms; preventive antibiotics and vaccinations are recommended for those lacking proper spleen function. (Anie KA, green et al., 2012)

Splenic sequestration crises are acute, painful enlargements of the spleen, caused by intrasplenic trapping of red cells and resulting in a precipitous fall in hemoglobin levels with the potential for hypovolemic shock. Sequestration crises are considered an emergency. If not treated, patients may die within 1–2 hours due to circulatory failure. Management is supportive, sometimes with blood transfusion. These crises are transient; they continue for 3–4 hours and may last for one day. (Khatib R, et al., 2009)

· **Acute chest syndrome**

Acute chest syndrome (ACS) is defined by at least two of the following signs or symptoms: chest pain, fever, pulmonary infiltrate or focal abnormality, respiratory symptoms, or hypoxemia. (Glassberg J, 2011) It is the second-most common complication and it accounts for about 25% of deaths in patients with SCD, majority of cases present with vaso-occlusive crises then they develop ACS. Nevertheless, about 80% of patients have vaso-occlusive crises during ACS. (MekontsoDessap A, et al., 2008)
· A plastic crisis

A Plastic crisis is acute worsening of the patient's baseline anaemia, producing pale appearance, fast heart rate, and fatigue. This crisis is normally triggered by parvovirus B19, which directly affects production of red blood cells by invading the red cell precursors and multiplying in and destroying them. Parvovirus infection almost completely prevents red blood cell production for two to three days. In normal individuals, this is of little consequence, but the shortened red cell life of SCD patient's results in an abrupt, life-threatening situation. Reticulocytose counts drop dramatically during the disease (causing reticulocytopenia), and the rapid turnover of red cells leads to the drop in haemoglobin. This crisis takes 4 days to one week to disappear. Most patients can be managed supportively; some need blood ‘transfusion.(Slavov, et al 2011)

Visceral sequestration crises ··

These are caused by sickling with in organ and pooling of blood, often with a severe exacerbation of anaemia. The acute sickle chest syndrome is a feared complication and the most common cause of death after puberty. it presents with dyspnoea, falling arterial po2, chest pain and pulmonary infiltrates on chest X-ray. Treatment is with analgesia, oxygen, exchange transfusion and ventilatory support if necessary. Hepatic and girdle sequestration crises and splenic sequestration may lead to sever illness requiring exchange transfusion. Splenic sequestration is typically seen in infant and present with an enlarging spleen, falling haemoglobin and abdominal pain. Treatment is with transfusion and patients must be monitored at regular intervals as progression may be rapid. Attack tends to be recurrent and splenectomy is often needed. (Kumar et al., 2009)

Hemolytic crises·

These are characterized by an increased rate of haemolysis with a fall in haemoglobin but· rise in reticulocytose and usually accompany a painful crisis'

Other clinical features··

Ulcers of the lower leg are common, as a result of vascular stasis and local ischaemia. The spleen is enlarged in infancy and early childhood but later is often reduced in
size as a result of infarcts (autosplenectomy). Pulmonary hypertension detected by Doppler echocardiography and an increased tricuspid regurgitant velocity are common and increases the risk of death. A proliferative retinopathy and priapism are other clinical complications. Chronic damage to liver may occur through microinfarcts. Pigment (bilirubin) gallstones are frequent. The kidney is vulnerable to infarction of medulla with papillary necrosis. Failure to concentrate urine aggravates the tendency to dehydration and crisis, and nocturnal enuresis is common. Osteomyelitis may also occur, usually from salmonella spp.(Hoffbrand et al., 2004)

1.2.1.2. Genetics of sickle cell disease

Normally, humans have haemoglobin A, which consists of two alpha and two beta chains, haemoglobin A₂, which consists of two alpha and two delta chains, and haemoglobin F, consisting of two alpha and two gamma chains in their bodies. Of these, haemoglobin F dominates until about 6 weeks of age. Afterwards, haemoglobin A dominates throughout life.

Sickle-cell conditions have an autosomal recessive pattern of inheritance from parents. The types of haemoglobin a person makes in the red blood cells depend on what haemoglobin genes are inherited from her or his parents. If one parent has sickle-cell anaemia and the other has sickle-cell trait, then the child has a 50% chance of having sickle-cell disease and a 50% chance of having sickle-cell trait. When both parents have sickle-cell trait, a child has a 25% chance of sickle-cell disease, 25% do not carry any sickle-cell alleles, and 50% have the heterozygous condition.

Sickle-cell gene mutation probably arose spontaneously in different geographic areas, as suggested by restriction endonuclease analysis. These variants are known as Cameroon, Senegal, Benin, Bantu, and Saudi-Asian. Their clinical importance is because some are associated with higher HbF levels, e.g., Senegal and Saudi-Asian variants, and tend to have milder disease.(Green, et al, 1993)

In people heterozygous for HgbS (carriers of sickling haemoglobin), the polymerization problems are minor, because the normal allele is able to produce over 50% of the haemoglobin. In people homozygous for HgbS, the presence of long-chain polymers of HbS distort the shape of the red blood cell from a smooth doughnut-like shape to ragged and full of spikes, making it fragile and susceptible to breaking within
Capillaries. Carriers have symptoms only if they are deprived of oxygen (for example, while climbing a mountain) or while severely dehydrated. The sickle-cell disease occurs when the sixth amino acid, glutamic acid, is replaced by valine to change its structure and function; as such, sickle-cell anemia is also known as E6V. Valine is hydrophobic, causing the haemoglobin to collapse on itself occasionally. The structure is not changed otherwise. When enough haemoglobin collapses on itself the red blood cells become sickle-shaped. (Alison, 2009)

The gene defect is a known mutation of a single nucleotide (see single-nucleotide polymorphism - SNP) (A to T) of the β-globin gene, which results in glutamic acid (E/Glu) being substituted by valine (V/Val) at position 6. Note, historic numbering put this glutamic acid residue at position 6 due to skipping the methionine (M/Met) start codon in protein amino acid position numbering. Current nomenclature calls for counting the methionine as the first amino acid, resulting in the glutamic acid residue falling at position 7. Many references still refer to position 6 and both should likely be referenced for clarity. Haemoglobin S with this mutation is referred to as HbS, as opposed to the normal adult HbA. The genetic disorder is due to the mutation of a single nucleotide, from a GAG to GTG codon on the coding strand, which is transcribed from the template strand into a GUG codon. Based on genetic code, GAG codon translates to glutamic acid (E/Glu) while GUG codon translates to valine (V/Val) amino acid at position 6. This is normally a benign mutation, causing no apparent effects on the secondary, tertiary, or quaternary structures of haemoglobin in conditions of normal oxygen concentration. What it does allow for, under conditions of low oxygen concentration, is the polymerization of the HbS itself. The deoxy form of haemoglobin exposes a hydrophobic patch on the protein between the E and F helices. The hydrophobic side chain of the valine residue at position 6 of the beta chain in haemoglobin is able to associate with the hydrophobic patch, causing haemoglobin S molecules to aggregate and form fibrous precipitates.

HBB gene (responsible for sickle-cell anaemia) is located on the short (p) arm of chromosome 11 at position 15.5

The allele responsible for sickle-cell anaemia can be found on the short arm of chromosome 11, more specifically 11p15.5. A person who receives the defective gene from both father and mother develops the disease; a person who receives one
defective and one healthy allele remains healthy, but can pass on the disease and is known as a carrier or heterozygote. Heterozygotes are still able to contract malaria, but their symptoms are generally less severe. (Kwiatkowski, 2005)

Due to the adaptive advantage of the heterozygote, the disease is still prevalent, especially among people with recent ancestry in malaria-stricken areas, such as Africa, the Mediterranean, India, and the Middle East. Malaria was historically endemic to southern Europe, but it was declared eradicated in the mid-20th century, with the exception of rare sporadic cases.

The malaria parasite has a complex lifecycle and spends part of it in red blood cells. In a carrier, the presence of the malaria parasite causes the red blood cells with defective haemoglobin to rupture prematurely, making the Plasmodium parasite unable to reproduce. Further, the polymerization of Hb affects the ability of the parasite to digest Hb in the first place. Therefore, in areas where malaria is a problem, people's chances of survival actually increase if they carry sickle-cell trait (selection for the heterozygote). (Poncon, et al, 2007)

In the USA, with no endemic malaria, the prevalence of sickle-cell anaemia among African Americans is lower (about 0.25%) than in West Africa (about 4.0%) and is falling. Without endemic malaria, the sickle-cell mutation is purely disadvantageous, and tends to decline in the affected population by natural selection, and now artificially through prenatal genetic screening. However, the African American community descends from a significant admixture of several African and non-African ethnic groups, and also represents the descendants of survivors of slavery and the slave trade. Thus, a lower degree of endogamy and, particularly, abnormally high health-selective pressure through slavery may be the most plausible explanations for the lower prevalence of sickle-cell anaemia (and, possibly, other genetic diseases) among African Americans compared to West Africans. Another factor that limits the spread of sickle-cell genes in North America is the absence of cultural proclivities to polygamy, which allows affected males to continue to seek unaffected children with multiple partners. (Lesi, Bassey, 1972)
1.2.1.3. **Labrotary Diagnosis**

In HbSS, the complete blood count reveals haemoglobin levels in the range of 6–8 g/dl with a high reticulocyte count (as the bone marrow compensates for the destruction of sickled cells by producing more red blood cells). In other forms of sickle-cell disease, Hb levels tend to be higher. A blood film may show features of hyposplenism (target cells and Howell-Jolly bodies).

Sickling of the red blood cells, on a blood film, can be induced by the addition of sodium metabisulfite. The presence of sickle haemoglobin can also be demonstrated with the "sickle solubility test". A mixture of haemoglobin S (Hb S) in a reducing solution (such as sodium dithionite) gives a turbid appearance, whereas normal Hb gives a clear solution.

Abnormal haemoglobin forms can be detected on haemoglobin electrophoresis, a form of gel electrophoresis on which the various types of haemoglobin move at varying speeds. Sickle-cell haemoglobin (HgbS) and haemoglobin C with sickling (HgbSC)—the two most common forms—can be identified from there. The diagnosis can be confirmed with high-performance liquid chromatography. Genetic testing is rarely performed, as other investigations are highly specific for HbS and HbC. (Clarke, Higgins .2000)

An acute sickle-cell crisis is often precipitated by infection. Therefore, a urinalysis to detect an occult urinary tract infection, and chest X-ray to look for occult pneumonia, should be routinely performed. (Lee C, et al. 2000)

People who are known carriers of the disease often undergo genetic counseling before they have a child. A test to see if an unborn child has the disease takes either a blood sample from the fetus or a sample of amniotic fluid. Since taking a blood sample from a fetus has greater risks, the latter test is usually used. Neonatal screening provides not only a method of early detection for individuals with sickle-cell disease, but also allows for identification of the groups of people that carry the sickle cell trait.(Oniyangi&Omari. 2006)
1.2.1.4. Management of sickle cell disease

Prophylactic – avoid these factor known to precipitate crises, especially dehydration, anoxia, infection, stasis of circulation and cooling of the skin surface. Folic acid (5mg once weekly) daily for life is recommended. From birth to five years of age, penicillin daily due to the immature immune system that makes them more prone to early childhood illnesses is also recommended.

Good general nutrition and hygiene

Pneumococcal, haemophilis and meningococcal vaccination and regular oral penicillin are effective to reduce infection rate with these organisms.

Crises - treat by, warmth, rehydration by oral fluid or intravenous normal saline and antibiotic if infection is present. Analgesia should be given.

Particular care is needed in pregnancy and anesthesia.

Transfusions - Blood transfusions are often used in the management of sickle-cell disease in acute cases and to prevent complications by decreasing the number of red blood cells (RBC) that can sickle by adding normal red blood cells. (Drasar, et al, 2011) In children preventative red blood cell (RBC) transfusion therapy has been shown to reduce the risk of first stroke or silent stroke when transcranial Doppler (TCD) ultrasonography shows abnormal cerebral blood flow. In those who have sustained a prior stroke event it also reduces the risk of recurrent stroke and additional silent strokes. These are also given repeatedly as prophylaxis to patient having frequent crises or who had major organ damage. The aim is to suppress Hb S production over a period of several months or years. Iron over load, which may need iron chelation (Gyang, et al.2011)

Hydroxyurea(15—20 mg/ kg) The first approved drug for the causative treatment of sickle-cell anaemia, Hydroxyurea, was shown to decrease the number and severity of attacks in a study in 1995 (Characheet al, 1995.) and shown to possibly increase survival time in a study in 2003 (Steinberg et al, 2003). This is achieved, in part, by reactivating fetal haemoglobin production in place of the haemoglobin S that causes sickle-cell anaemia. Hydroxyurea had previously been used as a chemotherapy agent, and there is some concern that long-term use may be harmful, but this risk has been shown to be either absent or very small and it is likely that the benefits outweigh the risks. (Platt, 2008)
can increase Hb F level and improve the clinical course of children or adult

Stem cell transplantation can cure the disease and many patient have now been successfully treated. Bone marrow transplants have proven effective in children. Bone marrow transplants are the only known cure for SCD. However, bone marrow transplants are difficult to obtain because of the specific HLA typing necessary. Ideally, a close relative (allogeneic) would donate the bone marrow necessary for transplantation. (Walters, et al. 1996.)

Other drugs (e.g. butyrates) to enhance Hb F synthesis or to increase the solubility of Hb

**Modern treatment is omega 3**

Omega-3 (n-23) fatty acids (DHA And EPA) are significantly reduced in patients with the disease. Objective: The aim was to investigate the therapeutic potential of Omega-3 fatty acids for patients with homozygous sickle cell disease in a randomized, placebo-controlled, double-blind trial. Omega-3 capsule contained 277.8 mg DHA and 39.0 mg EPA. And the placebo capsule contained high oleic acid (41%) oil Blend. The omega-3 fatty acid dose was calculated by multiplying the median weight of each age group by 25 mg/kg body wt. Vitamin E (1.5 mg/capsule) was added to both types of capsules to prevent peroxidation. Both types of capsules were carefully matched in appearance and flavor to prevent treatment unmasking. Enrollment identification number, sex, residence, ethnicity, Weight, height

**Sickle cell trait.1.2.1.5**

This is benign condition with no anaemia and normal appearance of red cells on a blood film. Haematuria is the most common symptom and is thought to be caused by minor infarcts of the renal papillae. Hb S varies from 25 to 45% of the total haemoglobin. Care must be taken with anaesthesia, pregnancy and high altitudes. (Hoffbrand, et al. 2004)

Sickle cell trait means having one gene for a condition called sickle cell disease (SCD). This in itself does not normally cause problems and sickle cell trait is not considered as a disease. It is extremely rare for it to cause problems or complications,
which mainly occur under conditions of severe physical stress (explained below) (Eichner, 2007).

Sickle cell trait is important because your children can inherit the sickle cell gene. If BOTH parents have sickle cell trait, their children could get a double dose of the sickle cell gene, which would give them the serious condition called SCD (Roach, 2005).

Sickle cell disease is a blood disorder in which there is a single amino acid substitution in the hemoglobin protein of the red blood cells, which causes these cells to assume a sickle shape, especially when under low oxygen tension. Sickling and sickle cell disease also confer some resistance to malaria parasitization of red blood cells, so that individuals with sickle-cell trait (heterozygotes) have a Sickle cell trait is a hemoglobin genotype AS and is generally regarded as a benign condition However, individuals with sickle cell trait may have rare complication selective advantage in environments where malaria is present (Eichner, 2007).

1.2.1.6. Complications of sickle cell disease

Sickle-cell anaemia can lead to various complications, including:

Increased risk of severe bacterial infections due to loss of functioning spleen tissue (and comparable to the risk of infections after having the spleen removed surgically). These infections are typically caused by encapsulated organisms such as *Streptococcus pneumonia* and *Haemophilus influenza*. Daily penicillin prophylaxis is the most commonly used treatment during childhood, with some haematologists continuing treatment indefinitely. Patients benefit today from routine vaccination for *S. pneumoniae*. (Kavanagh, et al. 2011)

Stroke, which can result from a progressive narrowing of blood vessels, prevents oxygen from reaching the brain. Cerebral infarction occurs in children and cerebral haemorrhage in adults.

Silent stroke causes no immediate symptoms, but is associated with damage to the brain. Silent stroke is probably five times as common as symptomatic stroke. About 10–15% of children with SCD suffer strokes, with silent strokes predominating in the younger patients. (Adams, 2007)
Cholelithiasis (gallstones) and cholecystitis may result from excessive bilirubin production and precipitation due to prolonged haemolysis.

A vascular necrosis (aseptic bone necrosis) of the hip and other major joints may occur as a result of ischaemia. (Marti-Carvajal, et al. 2004)

Decreased immune reactions due to hyposplenism (malfuinctioning of the spleen)

Priapism and infarction of the penis.

Osteomyelitis (bacterial bone infection), the most common cause of Osteomyelitis in SCD is Salmonella (especially the atypical serotypes Salmonella typhimurium, Salmonella enteritidis, Salmonella choleraesuis and Salmonella paratyphi B), followed by Staphylococcus aureus and Gram-negative enteric bacilli perhaps because intravascular sickling of the bowel leads to patchy ischaemic infarction. (Almeida, Robert. 2005)

Opioid tolerance can occur as a normal, physiologic response to the therapeutic use of opiates. Addiction to opiates occurs no more commonly among individuals with sickle-cell disease than among other individuals treated with opiates for other reasons.

Acute papillary necrosis in the kidneys

Leg ulcers. (Rudge, 2011)

In eyes, background retinopathy, proliferative retinopathy, vitreous haemorrhages, and retinaldetachments can result in blindness. Regular annual eye checks are recommended.

During pregnancy, intrauterine growth retardation, spontaneous abortion, and pre-eclampsia (Elagouz, et al. 2010)

Chronic pain: Even in the absence of acute vaso-occlusive pain, many patients have unreported chronic pain.

Pulmonary hypertension (increased pressure on the pulmonary artery) can lead to strain on the right ventricle and a risk of heart failure; typical symptoms are shortness of breath, decreased exercise tolerance, and episodes of syncope. 21% of children and
30% of adults have evidence of pulmonary hypertension when tested; this is associated with reduced walking distance and increased mortality. (Caughey, et al. 2015)

Chronic kidney failure due to sickle-cell nephropathy manifests itself with hypertension, protein loss in the urine, loss of red blood cells in urine and worsened anaemia. If it progresses to end-stage renal failure, it carries a poor prognosis. (Powers, et al.1991)

1.2.1.7. Epidemiology of Sickle cell Disease
The highest frequency of sickle cell disease is found in tropical regions, particularly sub-Saharan Africa, tribal regions of India and the Middle-East. (Weatherall and Clegg, 2001) Migration of substantial populations from these high prevalence areas to low prevalence countries in Europe has dramatically increased in recent decades and in some European countries sickle-cell disease has now overtaken more familiar genetic conditions such as haemophilia and cystic fibrosis (Roberts and Montalembert, 2007). In 2013 it resulted in 176,000 deaths due to SCD up from 113,000 deaths in 1990.

Sickle-cell disease occurs more commonly among people whose ancestors lived in tropical and sub-tropical sub-Saharan regions where malaria is or was common. Where malaria is common, carrying a single sickle-cell allele (trait) confers a selective advantage in other words, being a heterozygote is advantageous. Specifically, humans with one of the two alleles of sickle-cell disease show less severe symptoms when infected with malaria (Wellems et al., 2009).

1.2.2. Gonadotropins: Luteinizing and Follicle Stimulating Hormone
Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are called Gonadotropins because stimulate the gonads - in males, the testes, and in females, the ovaries. They are not necessary for life, but are essential for reproduction. These two hormones are secreted from cells in the anterior pituitary called gonadotrophs. Most gonadotrophs secrete only LH or FSH, but some appear to secrete both hormones.
As describe for thyroid-simulating hormone, LH and FSH are large glycoproteins composed of alpha and beta subunits. The alpha subunit is identical in all three of these anterior pituitary hormones, while the beta subunit is unique and endows each hormone with the ability to bind its own receptor.

**Physiologic Effects of Gonadotropins**

Physiologic effects of the Gonadotropins are known only in the ovaries and testes. Together, then regulate many aspects of gonadal function in both males and females

1.2.2.1. **Follicle-stimulating hormone**

**Follicle-stimulating hormone (FSH)** is a gonadotropin, a glycoproteinpolypeptidehormone. FSH is synthesized and secreted by the gonadotropic cells of the anterior pituitary gland, and regulates the development, growth, pubertal maturation, and reproductive processes of the body. FSH and luteinizing hormone (LH) work together in the reproductive system.

1.2.2.1.1. **Structure of follicle stimulating hormone**

FSH is a 35.5 kDa glycoproteinhetrodimer, consisting of two polypeptide units, alpha and beta. Its structure is similar to those of luteinizing hormone (LH), thyroid-stimulating hormone (TSH), and human chorionic gonadotropin (HCG). The alpha subunits of the glycoproteins LH, FSH, TSH, and hCG are identical and consist of about 96 amino acids, while the beta subunits vary.(Pierce & Parsons ,1981) Both subunits are required for biological activity. FSH has a beta subunit of 111 amino acids (FSH β), which confers its specific biologic action, and is responsible for interaction with the follicle-stimulating hormone receptor. The sugar portion of the hormone is covalently bonded to asparagine, and is composed of N-acetylgalactosamine, mannose, N-acetyl glucosamine, galactose, and sialic acid. (Jiang , et al.2012)
1.2.2.1.2. Genes of FSH

In humans, the gene for the alpha subunit is located at cytogenetic location 6q14.3.[5] It is expressed in different cell types, most notably the basophiles of the anterior pituitary. The gene for the FSH beta subunit is located on chromosome 11p13, and is expressed in gonadotropes of the pituitary cells, controlled by GnRH, inhibited by inhibin, and enhanced by activin.

1.2.2.1.3. Activity of FSH

As its name implies, FSH stimulates the maturation of ovarian follicles. Administration of FSH to humans and animals induces "super ovulation", or development of more than the usual number of mature follicles and hence, an increased number of mature gametes.

FSH is also critical for sperm production. It supports the function of Sertoli cells, which in turn support many aspects of sperm cell maturation. (Bowen, 2004)

FSH regulates the development, growth, pubertal maturation and reproductive processes of the human body.

- In both males and females, FSH stimulates the maturation of germ cells.
- In males, FSH induces Sertoli cells to secrete androgen-binding proteins (ABPs), regulated by inhibin's negative feedback mechanism on the anterior pituitary.
- In females, FSH initiates follicular growth, specifically affecting granulosa cells. With the concomitant rise in inhibin B, FSH levels then decline in the late follicular phase. This seems to be critical in selecting only the most advanced follicle to proceed to ovulation. At the end of the luteal phase, there is a slight rise in FSH that seems to be of importance to start the next ovulatory cycle.

Control of FSH release from the pituitary gland is unknown. Low frequency gonadotropin-releasing hormone (GnRH) pulses increase FSH mRNA levels in the rat, but is not directly correlated with an increase in circulating FSH. GnRH has been shown to play an important role in the secretion of FSH, with hypothalamic-pituitary disconnection leading to a cessation of FSH. GnRH administration leads to a return of
FSH secretion. FSH is subject to oestrogen feed-back from the gonads via the hypothalamic pituitary gonadal axis.

Reference ranges for the blood content of follicle-stimulating hormone levels during the menstrual cycle.
- The ranges denoted by biological stage may be used in closely monitored menstrual cycles in regard to other markers of its biological progression, with the time scale being compressed or stretched to how much faster or slower, respectively, the cycle progresses compared to an average cycle.
- The ranges denoted Inter-cycle variability are more appropriate to use in non-monitored cycles with only the beginning of menstruation known, but where the woman accurately knows her average cycle lengths and time of ovulation, and that they are somewhat averagely regular, with the time scale being compressed or stretched to how much a woman's average cycle length is shorter or longer, respectively, than the average of the population.
- The ranges denoted Inter-woman variability are more appropriate to use when the average cycle lengths and time of ovulation are unknown, but only the beginning of menstruation is given.

**Effects in females**

FSH stimulates the growth and recruitment of immature ovarian follicles in the ovary. In early (small) antral follicles, FSH is the major survival factor that rescues the small antral follicles (2–5 mm in diameter for humans) from apoptosis (programmed death of the somatic cells of the follicle and oocyte). In the luteal-follicle phase transition period the serum levels of progesterone and estrogen (primarily estradiol) decrease and no longer suppress the release of FSH, consequently FSH peaks at about day three (day one is the first day of menstrual flow). The cohort of small antral follicles is normally sufficiently in number to produce enough Inhibin B to lower FSH serum levels.

In addition, there is evidence that gonadotropin surge-attenuating factor produced by small follicles during the first half of the follicle phase also exerts a negative feedback on pulsatile luteinizing hormone (LH) secretion amplitude, thus allowing a more
favorable environment for follicle growth and preventing premature
luteinization. (Fowler, et al. 2003)

As a woman nears perimenopause, the number of small antral follicles recruited in
each cycle diminishes and consequently insufficient Inhibin B is produced to fully
lower FSH and the serum level of FSH begins to rise. Eventually the FSH level
becomes so high that down regulation of FSH receptors occurs and by post
menopause any remaining small secondary follicles no longer have FSH nor LH
receptors. (Vihko kk. 1996)

When the follicle matures and reaches 8–10 mm in diameter it starts to secrete
significant amounts of estradiol. Normally in humans only one follicle becomes
dominant and survives to grow to 18–30 mm in size and ovulate, the remaining
follicles in the cohort undergo atresia. The sharp increase in estradiol production by
the dominant follicle (possibly along with a decrease in gonadotropin surge-
attenuating factor) cause a positive effect on the hypothalamus and pituitary and rapid
GnRH pulses occur and an LH surge results.

The increase in serum estradiol levels cause a decrease in FSH production by
inhibiting GnRH production in the hypothalamus.

The decrease in serum FSH level causes the smaller follicles in the current cohort to
undergo atresia as they lack sufficient sensitivity to FSH to survive. Occasionally two
follicles reach the 10 mm stage at the same time by chance and as both are equally
sensitive to FSH both survive and grow in the low FSH environment and thus two
ovulations can occur in one cycle possibly leading to non identical (dizygotic) twins.
(Dickerson, et al. 2008)

· Effects in males

FSH stimulates primary spermatocytes to undergo the first division of meiosis, to
form secondary spermatocytes.

FSH enhances the production of androgen-binding protein by the Sertoli cells of the
testes by binding to FSH receptors on their basolateral membranes, and is critical for
initiation the of spermatogenesis. (Boulpaep & Boron, 2005)
1.2.2.1.4. Abnormality of FSH hormone

· High FSH levels

The most common reason for high serum FSH concentration is in a female who is undergoing or has recently undergone menopause. High levels of Follicle-Stimulating Hormone indicate that the normal restricting feedback from the gonad is absent, leading to an unrestricted pituitary FSH production.

If high FSH levels occur during the reproductive years, it is abnormal. Conditions with high FSH levels include:

1. Premature menopause also known as Premature Ovarian Failure
2. Poor ovarian reserve also known as Premature Ovarian Aging
3. Gonadal dysgenesis, Turner syndrome
4. Castration
5. Swyer syndrome
6. Certain forms of CAH
7. Testicular failure.
8. Klinefelter syndrome
9. Systemic Lupus Erythematosus also known as Lupus [14]

Most of these conditions are associated with subfertility and/or infertility. Therefore, high FSH levels are an indication of subfertility and/or infertility.

· Low FSH levels

FSH levels are normally low during childhood and, in females, high after menopause.

Diminished secretion of FSH can result in failure of gonadal function (hypogonadism). This condition is typically manifested in males as failure in production of normal numbers of sperm. In females, cessation of reproductive cycles is commonly observed. Conditions with very low FSH secretions are:

1. Polycystic Ovarian Syndrome
2. Polycystic Ovarian Syndrome + Obesity + Hirsutism + Infertility
3. Kallmann syndrome
4. Hypothalamic suppression
5. Hypopituitarism
6. Hyperprolactinemia
7. Gonadotropin deficiency
8. Gonadal suppression therapy
1. GnRH antagonist
2. GnRH agonist (down regulation).

1.2.2.1.5 Measurement of FSH hormone

Follicle stimulating hormone is typically measured in the early follicular phase of the menstrual cycle, typically day three to five, counted from last menstruation. At this time, the levels of estradiol (E2) and progesterone are at the lowest point of the menstrual cycle. FSH levels in this time is often called *basal FSH* levels, to distinguish from the increased levels when approaching ovulation.

9. FSH is measured in International Units (IU). For Human Urinary FSH, one IU is defined as the amount of FSH that has an activity corresponding to 0.11388 mg of pure Human Urinary FSH.\(^\text{[12]}\) For recombinant FSH, one IU corresponds to approximately 0.065 to 0.075 µg of a "fill-by-mass" product.\(^\text{[13]}\)

1.2.2.1.6. follicle-stimulating hormone receptor

The *follicle-stimulating hormone receptor* FSH receptor (FSHR) is a transmembrane receptor that interacts with the follicle-stimulating hormone (FSH) and represents a G protein-coupled receptor (GPCR). Its activation is necessary for the hormonal functioning of FSH. FSHRs are found in the ovary, testis, and uterus.

**Ligand binding and signal transduction**
Upon initial binding to the LRR region of FSHR, FSH reshapes its conformation to form a new pocket. FSHR then inserts its sulfotyrosine from the hinge loop into the pockets and activates the 7-helical transmembrane domain. This event leads to a transduction of the signal that activates the G protein that is bound to the receptor internally. With FSH attached, the receptor shifts conformation and, thus, mechanically activates the G protein, which detaches from the receptor and activates the cAMP system.

It is believed that a receptor molecule exists in a conformational equilibrium between active and inactive states. The binding of FSH to the receptor shifts the equilibrium between active and inactive receptors. FSH and FSH-agonists shift the equilibrium in favor of active states; FSH antagonists shift the equilibrium in favor of inactive states. For a cell to respond to FSH, only a small percentage (~1%) of receptor sites need to be activated.

**Phosphorylation by cAMP-dependent protein kinases**

Cyclic AMP-dependent protein kinases (protein kinase A) are activated by the signal chain coming from the G protein (that was activated by the FSH-receptor) via adenylyl cyclase and cyclic AMP (cAMP). These protein kinases are present as tetramers with two regulatory units and two catalytic units. Upon binding of cAMP to the regulatory units, the catalytic units are released and initiate the phosphorylation of proteins, leading to the physiologic action. The cyclic AMP-regulatory dimers are degraded by phosphodiesterase and release 5’AMP. DNA in the cell nucleus binds to phosphorylated proteins through the cyclic AMP response element (CRE), which results in the activation of genes.(Simoni M, et al; 1997)

The signal is amplified by the involvement of cAMP and the resulting phosphorylation. The process is modified by prostaglandins. Other cellular regulators that participate are the intracellular calcium concentration modified by phospholipase,

The FSH receptor can also activate the extracellular signal-regulated kinases (ERK). In a *feedback mechanism*, these activated kinases phosphorylate the receptor. The
longer the receptor remains active, the more kinases are activated, the more receptors are phosphorylated. (Piketty, et al; 2006)

**Action of FSH**

In the ovary, the FSH receptor is necessary for follicular development and expressed on the granulosa cells. (Simoni M, et al; 1997)

In the male, the FSH receptor has been identified on the Sertoli cells that are critical for spermatogenesis. (Asatiani K et al., 2002)

The FSHR is expressed during the luteal phase in the secretory endometrium of the uterus. (La Marco A et al., 2005)

FSH receptor is selectively expressed on the surface of the blood vessels of a wide range of carcinogenic tumors. (Radu A et al., 2010)

**Receptor regulation**

**Upregulation**

Upregulation refers to the increase in the number of receptor site on the membrane. Estrogen upregulates FSH receptor sites. In turn, FSH stimulates granulosa cells to produce estrogens. This synergistic activity of estrogen and FSH allows for follicle growth and development in the ovary.

**Desensitization**

The FSHR become desensitized when exposed to FSH for some time. A key reaction of this down regulation is the phosphorylation of the intracellular (or cytoplasmic) receptor domain by protein kinases. This process uncouples Gs protein from the FSHR. Another way to desensitize is to uncouple the regulatory and catalytic units of the cAMP system.
Down regulation

Down regulation refers to the decrease in the number of receptor sites. This can be accomplished by metabolizing bound FSHR sites. The bound FSH-receptor complex is brought by lateral migration to a "coated pit," where such units are concentrated and then stabilized by a framework of clathrins. A pinched-off coated pit is internalized and degraded by lysosomes. Proteins may be metabolized or the receptor can be recycled. Use of long-acting agonists will downregulate the receptor population. (Del baere A et al., 2005)

1.2.2.2 Luteinizing hormone

Luteinizing hormone (LH, also known as lutropin and sometimes lutrophin) is a hormone produced by gonadotropic cells in the anterior pituitary gland. In females, an acute rise of LH ("LH surge") triggers ovulation. (Ujihara Makoto et al., 1992) and development of the corpus luteum. In males, where LH had also been called interstitial cell–stimulating hormone (ICSH), it stimulates Leydig cell production of testosterone. It acts synergistically with FSH. (Louvet jean-pierre et al., 1975)

1.2.2.2.1. Structure of Luteinizing hormone

LH is a heterodimeric glycoprotein. Each monomeric unit is a glycoprotein molecule; one alpha and one beta subunit make the full, functional protein.

Its structure is similar to that of the other glycoprotein hormones, follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and human chorionic gonadotropin (hCG). The protein dimer contains 2 glycopeptidic subunits, labeled alpha and beta subunits, that are non-covalently associated (i.e., without any disulfide bridge linking them). (Jiang et al., 2014)

- The alpha subunits of LH, FSH, TSH, and hCG are identical, and contain 92 amino acids in human but 96 amino acids in almost all other vertebrate species (glycoprotein hormones do not exist in invertebrates).
- The beta subunits vary. LH has a beta subunit of 120 amino acids (LHB) that confers its specific biologic action and is responsible for the specificity of the interaction with the LH receptor. This beta subunit contains an amino acid sequence
that exhibits large homologies with that of the beta subunit of hCG and both stimulate the same receptor. However, the hCG beta subunit contains an additional 24 amino acids, and the two hormones differ in the composition of their sugar moieties.

The different composition of these oligosaccharides affects bioactivity and speed of degradation. The biologic half-life of LH is 20 minutes, shorter than that of FSH (3–4 hours) and hCG (24 hours)

1.2.2.2. Activity of LH

In both males and females, LH is essential for reproduction.(Bowen R, 2012)

1.2.2.3. Abnormality of LH Hormone

Effects in females

LH supports theca cells in the ovaries that provide androgens and hormonal precursors for estradiol production. At the time of menstruation, FSH initiates follicular growth, specifically affecting granulosa cells. With the rise in estrogens, LH receptors are also expressed on the maturing follicle, which causes it to produce more estradiol. Eventually, when the follicle has fully matured, a spike in 17-hydroxyprogesterone production by the follicle inhibits the production of estrogens, leading to a decrease in estrogen-mediated negative feedback of GnRH in the hypothalamus, which then stimulates the release of LH from the anterior pituitary.(Maheh, 2011)

However another theory of the LH peak is a positive feedback mechanism from estradiol. The levels keep rising through the follicular phase and when they reach an unknown threshold, this results in the peak of the LH. This effect is opposite from the usual negative feedback mechanism presented at lower levels. In other words, the mechanism(s) are not yet clear. The increase in LH production only lasts for 24 to 48 hours. This "LH surge" triggers ovulation, thereby not only releasing the egg from the follicle, but also initiating the conversion of the residual follicle into a corpus luteum that, in turn, produces progesterone to prepare the endometrium for a possible implantation. LH is necessary to maintain luteal function for the second two weeks of the menstrual cycle. If pregnancy occurs, LH levels will decrease, and luteal function
will instead be maintained by the action of hCG (human chorionic gonadotropin), a hormone very similar to LH but secreted from the new placenta. (John Hall & Arthuerguyton, 2011)

**Effects in males**

LH acts upon the Leydig cells of the testis and is regulated by GnRH. The Leydig cells produce testosterone (T) under the control of LH, which regulates the expression of the enzyme 17-β hydroxysteroid dehydrogenase that is used to convert androstenedione, the hormone produced by the gonads, to testosterone, an androgen that exerts both endocrine activity and intratesticular activity on spermatogenesis.

LH is released from the pituitary gland, and is controlled by pulses of gonadotropin-releasing hormone (GnRH). When T levels are low, GnRH is released by the hypothalamus, stimulating the pituitary gland to release LH. As the levels of T increase, it will act on the hypothalamus and pituitary through a negative feedback loop and inhibit the release of GnRH and LH consequently. Androgens (T, DHT) inhibit monoamine oxidase (MAO) in pineal, leading to increased melatonin and reduced LH and FSH by melatonin-induced increase of GnIH synthesis and secretion. T can also be aromatized into estradiol (E2) to inhibit LH. E2 decreases pulse amplitude and responsiveness to GnRH from the hypothalamus onto the pituitary. (Pittlou et al, 2008)

Gonadal steroids (estrogens and androgens) generally have negative feedback effects on GnRH-1 release at the level of the hypothalamus and at the gonadotropes, reducing their sensitivity to GnRH. Positive feedback by estrogens also occurs in the gonadal axis of female mammals and is responsible for the midcycle surge of LH that stimulates ovulation. Although estrogens inhibit kisspeptin (Kp) release from kiss1 neurons in the ARC, estrogens stimulate Kp release from the Kp neurons in the AVPV. As estrogens' levels gradually increase the positive effect predominates, leading to the LH surge. GABA-secreting neurons that innervate GnRH-1 neurons also can stimulate GnRH-1 release. These GABA neurons also possess ERs and may be responsible for the GnRH-1 surge. Part of the inhibitory action of endorphins on GnRH-1 release is through inhibition of these GABA neurons. Rupture of the ovarian follicle at ovulation causes a drastic reduction in estrogen synthesis and a marked
increase in secretion of progesterone by the corpus luteum in the ovary, reinstating a predominantly negative feedback on hypothalamic secretion of GnRH-1. (Norris Do & Carr JA 2013)

Changes in LH and testosterone (T) blood levels and pulse secretions are induced by changes in sexual arousal in human males. (Stoleru et al., 1993)

1.2.2.4. Normal LH levels...

The ranges denoted by biological stage may be used in closely monitored menstrual cycles in regard to other markers of its biological progression, with the time scale being compressed or stretched to how much faster or slower, respectively, the cycle progresses compared to an average cycle.

The ranges denoted Inter-cycle variability are more appropriate to use in non-monitored cycles with only the beginning of menstruation known, but where the woman accurately knows her average cycle lengths and time of ovulation, and that they are somewhat averagely regular, with the time scale being compressed or stretched to how much a woman's average cycle length is shorter or longer, respectively, than the average of the population.

The ranges denoted Inter-woman variability are more appropriate to use when the average cycle lengths and time of ovulation are unknown, but only the beginning of menstruation is given.

LH levels are normally low during childhood and, in women, high after menopause. As LH is secreted as pulses, it is necessary to follow its concentration over a sufficient period of time to get proper information about its blood level.

During the reproductive years, typical levels are between 1-20 IU/L. Physiologic high LH levels are seen during the LH surge (v.s.); typically they last 48 hours.

In males over 18 years of age, reference ranges have been estimated to be 1.8-8.6 IU/L.
LH is measured in international units (IU). For human urinary LH, one IU is defined as the amount of LH that has an activity corresponding to 0.13369 mg of pure human urinary LH.

**High LH Level.1.2.2.2.5.**

In children with precocious puberty of pituitary or central origin, LH and FSH levels may be in the reproductive range instead of the low levels typical for their age.

During the reproductive years, relatively elevated LH is frequently seen in patients with polycystic ovary syndrome; however, it would be unusual for them to have LH levels outside of the normal reproductive range.

Persistently high LH levels are indicative of situations where the normal restricting feedback from the gonad is absent, leading to a pituitary production of both LH and FSH. While this is typical in menopause, it is abnormal in the reproductive years. There it may be a sign of:

1. Premature menopause
2. Gonadal dysgenesis, Turner syndrome
3. Castration
4. Swyer syndrome
5. Polycystic ovary syndrome
6. Certain forms of congenital adrenal hyperplasia
7. Testicular failure
8. Pregnancy - BetaHCG can mimic LH so tests may show elevated LH

**1.2.2.6. Low LH level**

Diminished secretion of LH can result in failure of gonadal function (hypogonadism). This condition is typically manifest in males as failure in production of normal numbers of sperm. In females, amenorrhea is commonly observed. Conditions with very low LH secretions include:

1. Pasqualini syndrome[19]
2. Kallmann syndrome
3. Hypothalamic suppression  
4. Hypopituitarism  
5. Eating disorder  
6. Female athlete triad  
7. Hyperprolactinemia  
8. Hypogonadism  
9. Gonadal suppression therapy
1. GnRH antagonist
2. GnRH agonist (inducing an initial stimulation (flare up) followed by permanent blockage of the GnRH pituitary receptor). (Weiss et al., 1992)
1.3. Rationale

Sickle cell anemia is a public health problem in the Western part of Sudan (Vella, 1966). The years 1984-85 showed massive influx of migrants from the West to the capital, Khartoum due to the draught and dissertation. Among these migrant were tribes in whom sickle cell anemia is prevalent. And study done in children from these population show growth retardation and delayed sexual maturation. (Sayyid et al., 1989).

The sickle cell blocks the flow of the blood through vessel resulting in lung tissue damage (acute chest syndrome) pain episodes (arm, legs, chest, chest, and abdomen) stroke and priapism painful prolonged erection. It also cause damage to most organ including spleen, kidney, liver, sexual organs and easily infected by certain bacterial (Baltimore, Maryland. 2015). Sickle cell is destroyed rapidly in the body people with disease causing anemia jaundice and the formation of gall stone.

Number of study done in male with sickle cell anaemia showed growth retardation and hypogonadism.

No studies were found in measured gonadotropin (FSH, LH) among Sudanese female with sickle cell anaemia

This study aimed to evaluate (FSH and LH in Sudanese female with sickle anemia in Khartoum State.
1.4. Objective

1.4.1. General objective:

To study the level of serum follicle stimulating hormone and luteinizing hormone in Sudanese females with sickle cell anemia.

1.4.2. Specific objective:

- To measure serum follicle stimulating hormone and luteinizing hormone in Sudanese female with sickle cell anemia in comparisons to healthy female.
- To compare mean concentration of Follicle stimulating hormone and luteinizing hormone in case and control.
- To estimate Follicle stimulating hormone and luteinizing hormone level in patients with Sickle Cell Disease SCD and traits study group.
- To correlate between level of gonadotropin (Follicle stimulating hormone and luteinizing hormone), age and duration of treatment.
Chapter two

Materials and methods
MATERIALS AND METHOD2.

Materials2.1.

2.1.1. Study design:
This is a descriptive analytical case control study.

2.1.2. Study area:
The study was conducted in Sudanese sickle cell anemic female in JaaferEbnOaf hospital in Khartoum state.

2.1.3. Study period:
The study done during February to December 2016.

2.1.4. Study population:
This study included 50 sickle cell anemic females and 30 healthy individuals as control.

2.1.5. Inclusion Criteria:
Sudanese females with sickle cell anemia were included.

2.1.6. Exclusion criteria:
Hemolyze and icteric samples as well as individuals with hyperlipidemia, hypertension, Hyper or hypothyroidism, renal disease, bone diseases or any other disorders that may affect the levels of FSH, LH, were excluded.

2.1.7. Sample size and sampling technique:
About 5ml of venous blood was collected from each patient at the plane containers, after clotting it was centrifuged for 3 minutes at 3000 RPM to obtain serum and analyzed.

2.1.8. Ethical consideration:
patients who voluntarily accepted to participate in this study were included. All participants were told about the research importance during interview, data collected by quatianair. (Appendix 1)

2.1.9. Statistical analysis
Mean and standard deviation were used to describe the groups, independent T test was employed to compare mean concentration of study parameter, person correlation was used to compare between study parameter and variables, significant difference consider as p value ≤ or = 0.05 , all this was analyzed by using the computer (SPSS) programmer.

2.1.10. Quality control
For quality control, calibrators are used, the reagents must be mixed before use, The control intervals and limits should be adapted to each laboratory’s individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the limits.

2.2. Methodology
Estimation of serum FSH & LH concentration By using ELISA Immunotribidimetry technique.

• Principle: The Fortress (LH & FSH) ELISA assays were used a monoclonal antibody and (LH & FSH) HRP conjugate in anti (LH & FSH) coated plates. After incubation and subsequent washing the wells were incubated with a substrate solution. Measurements were performed after stopping the reaction used an acidic stop solution.
Chapter Three

Results
3.1. Results

In this study, 50 female with sickle cell disease and 30 healthy female served as control, (Aged was matched from 2—38 years), were enrolled in this study to assess effect of sickle cell anaemia on gonadotropin (Fsh,LH) among Sudanese female.

Mindary MR-96A auto analyzer was used for estimation follicle stimulating hormone and luteinizing hormone levels

Statistical analysis was done by using SPSS computer program and the result were as follow:

**Table 3.1** Shows the comparison of mean of follicle stimulating hormone, (5.82±4.26) and luteinizing hormone, (4.61±3.23) in female with sickle cell anaemia and control group {FSH (3.80±2.09), LH(4.52±3.43) }.

**Table 3.2** Shows the Comparison between means of serum FSH (5.54±2.39) and LH (4.24±4.18) levels in Sudanese females with sickle cell disease, sickle cell trait {FSH (6.87±3.75),LH(3.04±1.86) } and non-sickle cell disease {FSH(3.80±2.09) , LH(3.83±2.62)}.

**Figure 3.3** a scatter plot shows a significant positive correlation between FSH and age among Sudanese female with sickle cell disease(r= 0.316, p.value =0.047).

**Figure 3.4** a scatter plot shows a significant positive correlation between LH and age among Sudanese female with sickle cell disease,(r=0.405, p.value =0.009).

**Figure 3.5** a scatter plot shows a significant negative correlation between FSH and duration of treatment by Hydroxyurea.(r =-0.447, p.value =0.045)

**Figure 3.6** a scatter plot show a significant positive correlation between LH and duration of treatment by Hydroxyurea. (r =-0.538, p.value =0.039,)
Table 3.1. Comparison of mean of follicle stimulating hormone and luteinizing hormone in female with sickle cell anaemia and control group:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Case (Mean ±SD)</th>
<th>Control (Mean ±SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH</td>
<td>4.61±3.23</td>
<td>4.52±3.43</td>
<td>0.947</td>
</tr>
<tr>
<td>FSH</td>
<td>5.82±4.26</td>
<td>3.80±2.09</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Independent sample T test was used for comparison, P value consider significant at level <= 0.05
Table 3.2. Comparison between means of serum FSH & LH levels in Sudanese females with sickle cell disease, sickle cell trait and non-sickle cell disease.

ANOVA test was used for comparison P value consider significant at level \( \leq 0.05 \)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean±Std. Deviation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>5.541±2.394</td>
<td>0.044</td>
</tr>
<tr>
<td>Cases2</td>
<td>6.871±3.751</td>
<td>0.032</td>
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<tr>
<td>Control</td>
<td>3.800±2.093</td>
<td></td>
</tr>
<tr>
<td>LH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>4.244±4.189</td>
<td>0.916</td>
</tr>
<tr>
<td>Cases2</td>
<td>3.046±1.865</td>
<td>0.865</td>
</tr>
<tr>
<td>Control</td>
<td>3.833±2.628</td>
<td></td>
</tr>
</tbody>
</table>
Figure 3.3: correlation between follicle stimulating hormone and age among Sudanese female with sickle cell anemia. (p value= 0.04, r=0.316)
Figure 3.4: correlation between luteinizing hormone and age among Sudanese female with sickle cell anemia. ($r = 0.405$, p.value = 0.009)
Figure 3.5: correlation between follicle stimulating hormone and duration of treatment by Hydroxyurea among Sudanese female with sickle cell anemia. (r = -0.447, p.value = 0.045.)
Figure 3.6: correlation between luteinizing hormone and duration of treatment by Hydroxyurea among Sudanese female with sickle cell anemia. ($r = -0.538$, p.value = 0.039.)
Chapter Four

Discussion, conclusion and recommendations
4. Discussion, conclusion and recommendations

4.1. Discussion

Endocrine disorders in sickle cell disease have multifarious causes: tissue hypoxia, chronic anemia, iron overload, high energy demand, genetic influence and malnourishment. Slow speed of growth and delayed puberty are frequent. (ALves&Cresio. 2011)

This is a case control study aimed to study the effect of sickle cell disease on gonadotrobin (follicle stimulating hormone and luteinizing hormones). Eighty Sudanese female (50 female with sickle cell disease and 30 healthy female with out sickle cell disease) were enrolled in this study. After evaluation of follicle stimulating hormone and luteinizing hormone by Elisa, statistical analysis was done by using SPSS computer program and the result showed that follicle stimulating hormone level was significantly increase in females with sickle cell disease when compared to females with out sickle cell disease (5.82±4.26 Vs 3.80±2.09, Pvalue = 0.00). And luteinizing hormone did not show significant different in sickler group when compared to non sickler group (4.61±3.23 Vs 4.52±3.43, p.value = 0.947)(Table 3-1).

This result disagreed with result done in Saudiaarabia. By Nashwa and her team showed that.

Female patients with SCD (Group 2) have a significant lower level of LH than the control group (8.72±5.44 Vs 16.2±2.74; respectively, p=0.001).

There was no significant difference between the level of FSH among Group 2 and the control group (6.19±3.60 Vs 6.4±1.3; respectively, p= 0.05). (Nashwaet al., 2009).

Other study also disagreed with this result done by Alhazmi and his team, to show endocrine disorder in patient with sickle cell anaemia in female human volunteers, showed that the FSH and LH had significantly lower in sickler than non sickler. and also show that Patients with the severe form of the sickle cell disease showed more frequent abnormalities of LH, FSH, cortisol and testosterone in comparison with the patients with a mild disease (Alhazmima, et al. 2013)
This different from another study result from different of population the populations in this study take the omega3 Supplementation of patients with HbSS with the omega-3 fatty acids DHA and EPA was effective at reducing the frequency and severity of vaso-occlusive episodes, severe anemia if use as treatment for long time it have strong affect on endocrine

Also in this study, the subjects of diseased group were divided into two sub groups, sickle cell disease and sickle cell trait groups according to the electrophoresis bands, the results found that there were a significant differences in means concentration of FSH between sickle cell disease, sickle cell trait and control groups with p-value of (0.044 and 0.032) respectively, which indicates that the sickle cell disease is strong affect on the FSH level. Also found that there were in significant differences in means concentration of LH between sickle cell disease, sickle cell trait and control groups with p-value of (0.916 and 0.865) respectively, which indicates that the sickle cell disease is not affect on the LH level. (Table 3.1)

Result of this study revealed that. Increase in follicle stimulating hormone is proportional with age. (P value = 0.04, r = 0.316) and revealed also increase in luteinizing hormone is proportional with age. (p.value = 0.009, r =0.405**). This result agree with study done by ALHAZMi and her team showed that Patients with the severe long form of the sickle cell disease showed more frequent abnormalities of LH, FSH. (ELhazmi, et a.1992)

This study showed that decrease in follicle stimulating hormone is inversely relation with duration of treatment by Hydroxyurea. (p.value =0.045, r =0.447*) and revealed that luteinizing hormone decrease inversely relation with duration of treatment by hydroxyurea. (p.value =0.039, r =0.538*)
4.2 conclusion

The study result concluded that:

1. There was difference between level of follicle stimulating hormone among Sudanese female with sickle cell disease compared to control group (healthy female). And level of luteinizing hormone did not show different in patient with sickle cell disease compared with control group.

2. The level of follicle stimulating hormone and luteinizing hormone was correlated with age among Sudanese female with sickle cell disease.

3. The level of follicle stimulating hormone and luteinizing hormone was correlated with duration of treatment by Hydroxyurea.
4.3. Recommendations

- From the result of this study it is recommended that:

  • FSH & LH hormone should be measured monthly in female with sickle cell anemia to monitor the effect of disease and treat this complication marker profile like recent laboratory diagnosis should be done to monitor the patient (Anti mullarian hormone, inhibin b) and ultra sound also can done (antral follicle count)

  • Also the study recommended Omega-3, vitamin E and folic acid protocol supplements continuously for females with sickle cell anemia who received Hydroxyurea doses, to decrease Hydroxyurea side effects on reproductive system, improve egg quality and prolong the female's reproductive lifespan

  • should be evaluate zinc, feritin and vitamin D in female with sickle cell anaemia and supplement when decrease to avoid hypogonadism and infertility
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Appendices
Serum Level of FSH and LH among Females with Sickle Cell Anemia in Khartoum State

Questionnaire

Name: ..............................................................................................

Age: ..............................................................................................

Gender: ............................................................................................

History and Duration of disease: ...................................................

Type and Duration of treatment:
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