RESEARCH DISSERTATION

ON

COMPARISON OF CARDIAC FUNCTION BETWEEN PREGNANT WOMEN WITH HBSS AND THOSE WITH HBAA USING ECHOCARDIOGRAPHY AT THE LAGOS UNIVERSITY TEACHING HOSPITAL, LAGOS, NIGERIA.

THIS DISSERTATION IS SUBMITTED TO THE NATIONAL POSTGRADUATE MEDICAL COLLEGE OF NIGERIA IN PART FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF THE FELLOWSHIP OF THE COLLEGE IN OBSTETRICS AND GYNAECOLOGY.

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It is hereby declared that this work is original, unless otherwise acknowledged. It is not presently being submitted wholly or in part by another candidate in another faculty. This work has also not been presented to any other college for a Fellowship Examination, nor has it been published or submitted elsewhere for publication.

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DEDICATION

This work is dedicated to God Almighty who has always been my guide and my strength at all times.
To my parents – ALHAJI ALIYU DOGONDAJI and HAJIYA HAUWAU ALIYU DOGONDAJI who gave me life, taught me the right values and have always supported me in all my endeavours.

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LIST OF ABBREVIATIONS

ANC        Antenatal care
BMI         Body mass index
CO          Cardiac output
EDV         End diastolic volume
ESV         End systolic volume
EF          Ejection fraction
Hb          Haemoglobin
Hb S        Sickle Heamoglobin
Hb A        Adult Heamoglobin
IVS         Interventricular septum
Kg          Kilogramme
LUTH        Lagos University Teaching Hospital
LVDD        Left ventricular diastolic diameter
LVDS        Left ventricular systolic diameter
LV          Left ventricle
Mmhg        Millimetre of mercury
PCV         Packed cell volume
PW          Posterior wall
SCD         Sickle cell disease
SOGON       Society of Obstetricians and Gynaecologists of Nigeria
SPSS        Statistical package for the social sciences
STE         Speckle tracking echocardiography
SV          Stroke volume
2DE         2-Dimensional echocardiography
3D          3-Dimension

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ABSTRACT

Background: Sickle cell anaemia is the commonest haemoglobinopathy in pregnant Nigerian women, and cardiac manifestations are a significant feature of the disease especially in pregnancy. Pregnant women with sickle cell anaemia are at high risk of morbidity and mortality and cardiac dysfunction in them increases this risk and may compromise their post-partum health. Knowledge of optimal cardiac function during pregnancy as well as the post-partum period would help identify and promptly manage cardiac dysfunction in them when it occurs.

Objective: The aim of this study was to assess and compare the cardiac function between pregnant women with HBSS and those with HBAA using echocardiography in LUTH.

Study Design: A longitudinal comparative study.

Study Area: Antenatal clinic, labour ward, and cardiovascular laboratory of LUTH.

Methodology: A total of 40 women were recruited for the study, of which 20 pregnant HBSS were cases and 20 pregnant HBAA women were controls. Echocardiographic studies were performed in the third trimester of pregnancy. They were followed up till delivery, and a follow up Echocardiography was performed after 6 weeks post-partum. Paired t-test, student’s t-test and Pearson’s chi-square were used to respectively compare cardiovascular structure and function during the antepartum and post-partum state and between HBSS and HBAA participants.

RESULTS: There was a statistically significant decrease in the mean left atrial diameter of HBSS women in the post-partum period compared to their antepartum state (3.89 ± 0.40 cm VS 4.31± 0.45cm (t= 4.218, P-value < 0.001). Similarly, there was a statistically significant decrease in the mean left ventricular diameter in systole of HBSS pregnant women in the post-partum period as compared to their antepartum state (3.36 ± 0.42cm VS 3.52 ± 0.41cm
(t- 2.196, P- value- 0.041). In contrast, there was no statistically significant difference in the left atrial diameter in pregnant HBAA women in the antepartum period as compared to their post-partum state (3.69 ± 0.39cm VS 3.58 ± 0.41cm (t- 1.36, P-value- 0.189), but their left ventricular diameter in systole was also significantly higher than during the post-partum period (3.15 ± 0.39cm VS 3.01 ± 0.21cm (t- 2.16, P-value- 0.044). There was negative inverse correlation between haematocrit levels and cardiac size in pregnant HBSS women. Also, there were statistically significant differences in cardiac size but not function between the pregnant HBSS and pregnant HBAA women. (Left atrial diameter P-value- 0.001, left ventricular diameter in diastole P-value- 0.002, left ventricular diameter in systole P-value- 0.006. Ejection fraction P-value- 0.888, fractional shortening P-value- 0.532).

CONCLUSION:

It appears there are significant differences in some of the cardiac size dimensions in both pregnant HbSS women and pregnant HbAA women when comparing their antepartum and post-partum states. HbSS pregnant women also have significantly larger heart sizes than HbAA. However the cardiac left ventricular function did not seem to change both during pregnancy and in the post-partum period. Despite the larger cardiac size dimensions in pregnant HbSS women, they appear to cope during pregnancy in terms of cardiac function.

RECOMMENDATIONS: Pregnant HbSS women can be reassured that their cardiac systolic function remains optimal during uncomplicated pregnancy. Further long term studies to evaluate cardiac changes at 6 months postpartum when cardiovascular changes in pregnancy have fully reversed may further validate these findings.
CHAPTER ONE: INTRODUCTION

The term sickle cell disease (SCD) refers to the inheritance of haemoglobin S, either in the homozygous form (HbSS) or as a compound heterozygote with another haemoglobin variant. HbSS (sickle cell anaemia) is the most common type and often most severe form of sickle cell disease.\textsuperscript{1,2} Sickle cell anaemia is an autosomal recessive disorder in which an abnormal haemoglobin leads to chronic haemolytic anaemia with a variety of severe clinical consequences.\textsuperscript{1}

In the oxygenated state, the solubility of haemoglobin S (HbS) is nearly equal to that of haemoglobin A (HbA), and its oxyhaemoglobin form has the ability to function in a physiological manner. In the deoxygenated state, however, its solubility falls to one-fiftieth of that of HbA, resulting in aggregation to form polymers. This causes the erythrocytes to assume the classical ‘sickle shape’. Re-oxygenation can restore these erythrocytes to their normal shape.\textsuperscript{1,2}

Repetitive cycles of sickling and polymerization however lead to membrane rigidity, and irreversible sickle cells are eventually formed. These permanently damaged erythrocytes are then cleared by the reticulo endothelial system. Thus, the average lifespan of the red blood cells of sickle cell patients is 17 days compared with the 120-day lifespan of normal erythrocytes. This results in a state of chronic haemolytic anaemia (haematocrit usually 20-30\%) as the marrow’s capacity to generate new red blood cells is limited.\textsuperscript{1,2}

Sickle cell anaemia affects millions throughout the world. It is particularly common among people whose ancestors come from sub-Saharan Africa; Spanish-speaking regions (South America, Cuba, Central America); Saudi Arabia; India; and Mediterranean countries such as Turkey, Greece, and Italy.\textsuperscript{3} The highest frequency of sickle cell disease is found in tropical regions, particularly sub-Saharan Africa, India and the Middle-East. Also, about three
quarters of sickle-cell cases occur in Africa. A recent World Health Organization (WHO) report estimated that around 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.\textsuperscript{4,5,6} 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.\textsuperscript{5}

Sickle cell anaemia (SCA) is the commonest inherited haemoglobinopathy in Nigeria with a prevalence of about 2-3\%, and is associated with high morbidity and mortality, particularly in early childhood in most of the affected population.\textsuperscript{6} However, with advances in management, many females with sickle cell disease now survive to have children. The median age at death for women with sickle cell anaemia is 48 years,\textsuperscript{2} though a study described patients followed since childbirth with 40\% still alive at 60 to 68 years.\textsuperscript{7} In women with sickle cell anaemia, the entire pregnancy is a high-risk period that warrants close monitoring. With improved medical care, the frequency of sickle crises in pregnancy has decreased significantly; but they may still occur and constitute an obstetric emergency.\textsuperscript{4} Therefore, it is important for every obstetrician to be familiar with the condition.\textsuperscript{1}

However, there is an increased risk of maternal complications in pregnancies complicated by sickle cell syndromes.\textsuperscript{4} These complications may include sepsis syndromes, pyelonephritis, pneumonia (which manifests by the acute chest syndrome), pulmonary embolism, deep vein thrombosis, cerebral vein thrombosis, gestational hypertension/pre-eclampsia, eclampsia, pseudotoxaemia of pregnancy, placental abruption, preterm delivery and fetal growth restriction.\textsuperscript{2}

Cardiac enlargement especially left ventricular hypertrophy has been found to be a constant feature of sickle cell anaemia,\textsuperscript{6} therefore pregnancy with its additional cardiovascular demands may cause a further left ventricular enlargement. Sickle cell anaemia has also
been thought to be associated with cardiomyopathy.\textsuperscript{2,8} However, echocardiographic studies of ejection phase indices have reported conflicting data in patients with sickle cell anaemia living in America and in Africa.\textsuperscript{9,10}.

Pregnancy is a serious burden to women with any of the major haemoglobinopathies, particularly those with haemoglobin SS disease (sickle cell anaemia).\textsuperscript{2} Sickle cell disease women have enlarged ventricular heart chambers. This has been seen in those in the third trimester of pregnancy and non-pregnant women. They also have increased cardiac output and supranormal stroke volume which does not rise in pregnancy.\textsuperscript{26} Pregnant women with sickle cell anaemia have been reported to have some degree of cardiac dysfunction from this ventricular hypertrophy.\textsuperscript{39} However, according to Veille and Hanson,\textsuperscript{15} left ventricular systolic function in patients with sickle cell disease was not affected in spite of a marked ventricular hypertrophy and ventricular enlargement. Diastolic function, however, was lower in the sickle cell group, which indicates a decrease in ventricular compliance. These patients had a higher cardiac output than did a normal pregnant group in the third trimester. This was accomplished by increasing ventricular size without increasing heart rate or fractional shortening. Also studies done in children with sickle cell anaemia shows that abnormalities of systolic time intervals became increasingly more pronounced with growth, suggesting that left ventricular function deteriorated with time.\textsuperscript{13}

**JUSTIFICATION OF THE STUDY**

The cardiac manifestations of sickle cell anaemia are a significant feature of the disease but there is paucity of information on the cardiovascular involvement in sickle cell anaemia generally and in Nigeria and Africa, particularly. The size of the sickle cell problem in the country is growing rapidly and there should therefore be a greater awareness of the cardiac problems associated with sickle cell anaemia.\textsuperscript{6} Thus, this study was conducted among
selected HbSS women pregnant in the Lagos University Teaching Hospital, with matched HbAA pregnant women as controls. During pregnancy, there are important hemodynamic variations which result in physiological transient changes in preload and afterload in the maternal heart. Those changes are necessary for the progression of a successful pregnancy, but this may also impose further load on the heart. Moreover, heart disease is the leading cause of non-obstetric mortality during pregnancy, and the number of pregnant women at risk for cardiovascular complications is on the rise. Therefore, identification and understanding maternal cardiac structure and function is of clinical importance. This study is in order to improve the knowledge of the cardiovascular changes of sickle cell anaemia in pregnancy and the management of HbSS patients during pregnancy, intrapartum and the postpartum period. It is hoped that the results of this study will contribute to the existing knowledge about sickle cell anaemia in pregnancy and help to strengthen the monitoring, management and follow-up of sickle cell anaemia in pregnancy in order to reduce maternal morbidity and mortality in this group of women.
CHAPTER 2: LITERATURE REVIEW

Search strategy
The search strategy for the literature review included search terminologies; cardiac function, Sickle cell disease, Sickle cell anaemia, HBSS, pregnancy, echocardiography, cardiac function in normal pregnancy, using PubMed, google search, text books and journal article publications.

2.1 Epidemiology
About 5% of the world’s population carries genes responsible for haemoglobinopathies. In West African countries such as Ghana and Nigeria, the frequency of the trait is 15% to 30%. Each year about 300 000 infants are born with major haemoglobin disorders – including more than 200 000 cases of sickle cell anaemia in Africa. Frequencies of the carrier state determine the prevalence of sickle cell anaemia at birth. For example, in Nigeria, by far the most populous country in the sub region, 24% of the population are carriers of the mutant gene and the prevalence of sickle cell anaemia is about 20 per 1000 births. This means that in Nigeria alone, about 150 000 children are born annually with sickle cell anaemia. 

At least 5.2% of the world population (and over 7% of pregnant women) carry a significant variant. Haemoglobin S accounts for 40% of carriers but causes over 80% of disorders because of localized very high carrier prevalence: around 85% of sickle cell disorders and over 70% of all affected births occur in Africa.

Sickle cell anaemia (HbSS) is the commonest symptomatic haemoglobinopathy in Nigeria with a prevalence of 2-3%. It is also the most troublesome in terms of frequency and severity of clinical manifestations, but the disease is less common in adults and therefore during pregnancy because of earlier mortality especially during early childhood. With the
increased life expectancy and advances in management however, more women now survive to reproductive age. Nevertheless women with sickle cell disease are at greater risk for morbidity and mortality in pregnancy. There is also an increased risk of perinatal morbidity and mortality.\textsuperscript{1,2,6,13}

Cardiac enlargement was one of the earliest cardiovascular features of sickle cell anaemia patients and was found to occur early in childhood with most sickle cell anaemia children developing cardiomegaly in their first 5 years.\textsuperscript{6} In adults, left ventricular hypertrophy (LVH) is almost constant and right ventricular hypertrophy (RVH) is common, depending on the method of detection.\textsuperscript{6}

A study has also shown that pregnant patients with sickle cell disease had a significant enlargement of the left ventricular end-diastolic dimension, posterior wall, interventricular septum, and ventricular mass.\textsuperscript{11}

2.2 Pathophysiology of Sickle Cell Disease

There are over 100 structural haemoglobin variants described in the literature, many of which are not pathological. Haemoglobin S (HbS) is the most common of these variants and results from a single $\beta$- chain substitution of the negatively charged glutamic acid by the neutral amino acid valine because of an adenine for thymine substitution at codon 6 from the N-terminus in the $\beta$-globin gene.\textsuperscript{2} Sickle cell disease include sickle cell anaemia – HbSS, sickle cell haemoglobin C disease - HbSC, sickle cell haemoglobin D disease - HbSD, sickle cell haemoglobin O - Arab disease - HbO-Arab, sickle cell $\beta$- thalassemia disease - either HbS/$\beta$ or HbS/$\beta^+$ and sickle cell haemoglobin E disease - HbSE. These structural changes are inherited as autosomal recessive traits. All are also associated with increased rate of maternal and perinatal morbidity and mortality. HbSS is the most common type of sickle cell disease, followed by HbSC. In West Africa, haemoglobin C and haemoglobin S are both seen in
pregnancy unlike the thalassaemias.\textsuperscript{2,3,14-16} HbSS results from inheritance of the haemoglobin S gene from each parent.

Red blood cells with haemoglobin S undergo sickling when they are deoxygenated and the haemoglobin aggregates to form polymers that damage the red blood cell membrane. Both polymer formation and early membrane damage are reversible, but repeated sickling and desickling cause membrane damage beyond repair, and the red blood cell may become irreversibly sickled. These permanently damaged red blood cells are then cleared by the reticuloendothelial system. Thus, the average lifespan of the red blood cells of sickle cell patients is 16-20 days compared with the 100-120-day lifespan of normal erythrocytes. This results in a chronic haemolytic anaemia (the haemoglobin is usually 6 – 9g/dL in sickle cell anaemia) as the marrow’s capacity to generate new red blood cells is limited.\textsuperscript{1,2}

The basic pathological processes in sickle cell disease are chronic anaemia and blood vessel occlusion leading to acute and chronic organ damage.\textsuperscript{3}

\textbf{2.3 Diagnosis of sickle cell disease}

The sickling test is a solubility test used in screening for sickle cell disease. It is done by adding two drops of 2\% sodium metabisuphate to a drop of blood on a slide and covering the slide with a coverslip and sealing the edges with Vaseline to create deoxygenation. The slide is examined after 20 minutes. This test shows typical sickling in HbSS, HbAS and HbSC patients.\textsuperscript{15,17} Haemoglobin Electrophoresis (diagnostic test) is a method of determining the type and size of haemoglobin molecules in the blood, by observing the rates of transit of these negatively-charged proteins in an electric field medium. It is used to diagnose the haemoglobinopathies. It is a blood test, and requires a few millilitres of blood from a vein.

The sickling test differentiates between Haemoglobin S and other Haemoglobin types that travel with it but which do not sickle (and therefore cause pathology). It doesn't quantify the percentage of each haemoglobin type. Haemoglobin electrophoresis however confirms the
presence of HbS and also quantifies it, and is also used to differentiate sickle cell disease (SS) from sickle trait (AS) and from SC disease. Furthermore it can show if there are concurrent alpha-chain abnormalities (thalassaemias). However, since it divides molecules by weight and charge, there are some variants of haemoglobin that can travel with HbS on electrophoresis. For example Hb D, Hb G or Philadelphia.17,54

The normal adult haemoglobin is Haemoglobin A (HbA, 95-97%), but people with normal genotype also have a small amount of HbA₂ (2%) and Fetal Haemoglobin (HbF, <1.5%).18 In sickle cell anaemia, there is no haemoglobin A (HbA, 0%), haemoglobin S is 86 – 98%; there is also a small amount of HbA₂ (1 – 3%), and HbF is 5 – 15%.1 The peripheral blood smear is characteristically abnormal, with irreversibly sickled cells comprising 5 – 50% of red blood cells. Other findings include reticulocytosis(10 – 25%), nucleated red blood cells, and hallmarks of hyposplenism such as Howell-Jolly bodies and target cells. The white blood cell count is characteristically elevated to 12,000 – 15,000/μL (even in the non-pregnant state), and thrombocytosis may occur. Indirect bilirubin levels are high.1

2.4 Sickle cell disease in pregnancy

Constant sickling and desickling of red blood cells cause membrane damage, and the cell becomes irreversibly damaged. Clinically, the hallmark of sickling episodes is periods during which there is ischaemia and infarction in various organs. Precipitating factors to vaso-occlusion include processes that slow red blood cell transit through the microcirculation like endothelial cell adhesion, red cell dehydration, vasomotor dysregulation.2

These produce clinical symptoms predominantly pain, which is often severe. The most common manifestation of sickle cell disease is this acute painful crisis which occurs secondary to vaso-occlusion. These painful crises can be precipitated by infection, stress,
dehydration and cold conditions. There is an increased risk of painful crisis during pregnancy, especially in the latter half of pregnancy and the puerperium (particularly the last month of pregnancy, just before and during labour and immediately after delivery), and may even occur in women who have previously had very few episodes of sickle pain. At this time marrow embolism is likely to complicate infarction of the bone marrow. There may also be haemolytic, sequestration and aplastic crisis.\textsuperscript{1,2,15} The phenomenon of systolic hypertension and albuminuria in a pregnant sickle cell anaemia patient with bone pain crisis should not be misdiagnosed as pre-eclampsia. This is rather pseudotoxaemia of pregnancy and it indicates imminent marrow embolism.\textsuperscript{15}

Chronic and other acute changes from sickling that may also occur in pregnancy include bony abnormalities such as osteonecrosis of the femoral and humeral heads, renal medullary damage, autosplenectomy in HbSS and splenomegaly in other variants, hepatomegaly, ventricular hypertrophy, pulmonary infarction, pulmonary hypertension, cerebrovascular accidents, leg ulcers and an increase predisposition to infection and sepsis, especially due to encapsulated organisms such as \textit{Streptococcus pneumoniae} and \textit{Haemophilus influenzae}.\textsuperscript{1,12,16} Pregnancy is a serious burden in any of the major haemoglobinopathies especially sickle cell anaemia. The study done by Villers and colleagues showed increased rates of maternal complications in pregnancies complicated by sickle cell syndromes.\textsuperscript{15} The complications include those due to pre-existing medical disorders like cardiomyopathy, pulmonary hypertension and renal failure; pregnancy complications like cerebral vein thrombosis, pneumonia, pyelonephritis, deep vein thrombosis, pulmonary embolism, sepsis syndrome; and antepartum complications like gestational hypertension/pre-eclampsia, eclampsia, placental abruption, preterm delivery and fetal growth restriction.\textsuperscript{14,15}
Another morbidity includes acute chest syndrome which is a life-threatening complication that presents with cough, chest pain, dyspnoea, fever, worsening anaemia, leucocytosis, audible crackles and/or bronchial breathing on examination, and a new and florid pulmonary infiltrate on the chest X-ray. The patient may need assisted or mechanical ventilation. This is among the most common causes of maternal death. The syndrome arises due to sickling in the lungs, possibly combined with precipitants like infection, marrow emboli, thromboembolism, or atelectasis. Although there are thought to be many causes, the underlying features are not totally understood.5

Pregnancy outcomes in women with sickle cell disease have improved substantially in the last 25-30 years, The initiation of early aggressive prenatal care has dramatically improved perinatal outcome and reduced maternal mortality to less than 1% in the developed world1,4 but maternal mortality in this group of patients is still relatively high in developing countries like Nigeria.

2.5 Cardiovascular Changes in Sickle Cell Anaemia

The cardiac manifestations of sickle cell anaemia are a significant feature of the disease. Cardiac signs and symptoms were prominent in many of the early cases of sickle cell anaemia described. Sickle cell anaemia has been thought to be associated with cardiomyopathy and cardiac dysfunction. However, echocardiographic studies of ejection phase indices have reported conflicting data in patients with sickle cell anaemia living in America and in Africa.8-11

A systemic review of the cardiovascular findings in this disorder in an attempt to detect distinguishing features which could be attributed to the chronic anaemic state, it was concluded that the cardiac changes seen in sickle cell anaemia were more marked than the changes found in other anaemias because of the long duration of the severe
anaemia.\textsuperscript{21} The reduced oxygen carrying capacity due to anaemia increases demand on the heart with an increase in cardiac output.\textsuperscript{20,21} Complaints of dyspnoea on exertion and easy fatigability are frequent in sickle cell anaemia, and these may mimic those of heart failure. Physical examination may reveal prominent pulsations in the neck, a thrill in the suprasternal notch and at the base of the right side of the neck. There is a high output state in sickle cell anaemia which will be revealed by a collapsing pulse with tachycardia as well as a visible precordial and apical impulse that is not easily located, although forceful in character when located. \textsuperscript{25} Blood pressure in the steady state is lower than normal. A left parasternal heave is common and a pulsation may be palpated over the pulmonary artery in the second left intercostal space. An accompanying loud pulmonary component of the second sound suggests a diagnosis of pulmonary hypertension, but pulmonary artery pressures are usually normal in such cases.\textsuperscript{8,12.}

On auscultation, the first and second heart sounds are loud and frequently split more widely than normal, consistent with the increased haemodynamic load. A loud third heart sound and mid systolic (ejection type) murmurs are common. Diastolic flow murmurs, are also heard frequently. Patients without audible murmurs tend to be those without cardiomegaly and with high haemoglobin levels.\textsuperscript{9,10}

The changes in cardiac structure are age dependent. Cardiac enlargement was one of the earliest cardiovascular features of sickle cell anaemia patients and was found to occur early in childhood with most sickle cell anaemia children developing cardiomegaly in their first 5 years. Echocardiographic studies of cardiac structure and size in children and adults with sickle cell anaemia confirmed left chamber enlargement; and in addition myocardial hypertrophy with increased left ventricular mass (LVM) were common.\textsuperscript{31,32,33}

In adults, left ventricular hypertrophy (LVH) is almost constant and right ventricular hypertrophy (RVH) is common, depending on the method of detection.\textsuperscript{6,8,13,21}
Akinola and Balogun, radiologically using cardiothoracic ratio, assessed the cardiovascular status of 22 adult Nigerians with sickle cell anaemia and 22 controls and found that sickle cell anaemia patients had significantly larger hearts than HbAA controls.\textsuperscript{28} These radiological studies will have clear limitations if used in a pregnant population, due to risk of radiation exposure to the fetus. Also, as a result of the diaphragmatic elevation that occurs in pregnancy, the rotation of the heart on its longitudinal axis and anatomical and physiological alteration of the thoracic wall in pregnancy, using the cardiothoracic ratio will not give an accurate estimation of heart size. Typically, there is cardiomegaly with left ventricular hypertrophy and right ventricular hypertrophy. The heart valves and pericardium are usually normal.\textsuperscript{25}

Gerry et al studied 52 autopsy patients with sickle cell anaemia and noted no evidence of recent or remote myocardial infarction, coronary thrombosis or arteritis in any of them. Renal failure and infection were the most common causes of death, with 17 patients having clinical evidence of congestive cardiac failure before death.\textsuperscript{13} Also in a study of 23 adult sickle cell anaemia patients and 9 normal controls, Gerry and colleagues also observed that sickle cell anaemia patients had significantly greater mean left ventricular (LV) systolic and diastolic dimension indices, left ventricular mass, stroke volume index, interventricular septal width, aortic root index and left atrial (LA) index.\textsuperscript{13,31} The clinical features of sickle cell disease such as intermittent fever, joint pains, cardiomegaly and heart murmurs may mimic acute rheumatic fever with cardiac involvement and this leads to diagnostic difficulties. Meanwhile it is essential that patients with atypical cardiac features be investigated for associated RHD since surgery may offer striking benefits in such patients.\textsuperscript{29}
Simmon et al. found that pulmonary hypertension, which was present in two thirds of their 40 sickle cell anaemia patients, was minimal to moderate as assessed by passive Doppler technique. They concluded that passive elevation of pulmonary pressure was one of the cardiac effects of sickle cell anaemia. Simmon et al also noted that abnormalities were found more frequently in the left than the right heart of the adult sickle cell anaemia patients studied, as manifested primarily by increased left ventricular mass, and left ventricular and left atrial dilatation.31

Adebiyi et al. found that there were significant differences between the Nigerian sickle cell anaemia patients and controls in the estimate of right ventricular (RV), left ventricular, aortic root and left atrial dimensions, and left ventricular mass indices, with the left ventricular posterior wall thickness in systole being significantly larger in the patients.11 Left ventricular dimensions were also increased in sickle cell anaemia patients in the study by Braden and colleagues, but they had normal septal and posterior wall thickness.32

The Cooperative Study of Sickle Cell Disease by Covitz et al. showed that stable sickle cell anaemia patients had dilated chambers and septal hypertrophy.33 In another study on 22 adolescents and young adults with sickle cell anaemia, Covitz and Colleagues revealed left ventricular hypertrophy in all the patients, with resulting high stroke volume and cardiac output.32,33 Lewis et al. found that left ventricular transverse end-diastolic dimension was greater in 30 sickle cell anaemia patients compared to 30 controls, and that calculated left ventricular mass and left ventricular mass index was also increased in the patients than the control.34 The above studies have a mixed gender population, and therefore do not put into consideration the subtle differences that may be present between the heart of the male and female sickle cell anaemia patient. A previous study also showed left ventricular size to be inversely
related to Haemoglobin level, and age (duration of illness) was an important factor in that relationship.\textsuperscript{35}

**2.6 Cardiovascular physiology in Normal Pregnancy**

Uterine enlargement and diaphragmatic elevation causes a longitudinal cardiac rotation in a left-upward displacement. This causes a lateral shift of the apex beat. Overall, the heart size increases by about 12\% due to both an increase in myocardial mass and intracardiac volume (about 80mls). Vascular changes include hypertrophy of smooth muscle and a reduction in collagen content.\textsuperscript{37}

Blood volume expansion beginning in the early first trimester includes about 50\% increase in plasma volume and about 30\% increase in red cell mass, which plateaus at about the 30\textsuperscript{th} week. Cardiac output increases approximately 40\% during pregnancy, with maximum values achieved at 20-24 weeks’ gestation. Stroke volume increases 25-30\% reaching peak values at 12-24 weeks’ gestation.\textsuperscript{36}

In normal pregnancies, there is an increase in the left ventricular end-diastolic dimensions (assessed echocardiographically), which can be noted by 10 weeks’ gestation and peaks during the third trimester. There are also increases in the left atrial, right atrial and right ventricular diastolic dimensions. The physiological changes in preload and afterload are accompanied by remodelling of the ventricles and atria. All four cardiac chambers increase in size from the first trimester to the end of the third trimester. The dimensions decrease to baseline levels in the postpartum period. Left ventricular remodelling also manifests as increases in left ventricular wall thickness and mass.\textsuperscript{39,40}

Left ventricular end diastolic dimensions (measured by echocardiography) during pregnancy and postpartum are 43.6±2.5mm and 41.8±1.8mm in the third trimester and puerperium respectively; with controls being 40.1±3.0mm. Left atrial dimensions (measured by
echocardiography) during pregnancy and postpartum are 32.8±3.0mm and 29.9±1.8mm in the third trimester and puerperium respectively; with controls being 27.9±2.4mm. Right ventricular diastolic dimensions (measured by echocardiography) during pregnancy and postpartum are 35.5±2.3mm and 31.1±2.1mm in the third trimester and puerperium respectively; with controls being 28.5±3.0mm. Right atrial dimensions (measured by echocardiography) during pregnancy and postpartum are 50.9±2.8mm and 46.6±3.3mm in the third trimester and puerperium respectively; with controls being 43.7±4.4mm.54,55,56

2.7 Cardiovascular physiology in Sickle Cell Anaemia in Pregnancy

From the study done by Veille and Hanson using a two-dimensional M-mode echocardiography, pregnant patients with sickle cell disease had a significant enlargement of the left ventricular end-diastolic dimension, posterior wall, interventricular septum, and ventricular mass than the HbAA control group.26 Although heart rate and fractional shortening were not different between the two groups, stroke volume and cardiac output were higher in patients with sickle cell disease. This was mostly because of enlargement of left end-diastolic dimension. Ventricular diastolic function was different in patients with sickle cell disease, resulting in an increase in the duration of the rapid filling. They concluded that left ventricular systolic function in patients with sickle cell disease was not affected in spite of a marked ventricular hypertrophy and ventricular enlargement. Diastolic function, however, was lower in the sickle cell group, which indicates a decrease in ventricular compliance. These patients had a higher cardiac output than did a normal pregnant group in the third trimester. This was accomplished by increasing ventricular size without increasing heart rate or fractional shortening.24,26

With regard to the vascular compartment, the plasma volume in HbSS pregnant women was found not to rise during pregnancy compared to HbAA pregnant women who showed normal
plasma volume expansion in pregnancy. This was postulated to be due to vasoconstriction or inadequate vasodilator activity in pregnancy.

2.8 Echocardiography

Echocardiography is one of the most versatile non-invasive imaging techniques in clinical cardiology, it is also known as the cardiac ultrasound. Because it does not use ionizing radiation, known risk is minimal and can be employed safely throughout pregnancy. It uses standard ultrasound techniques to image two-dimensional slices of the heart. The latest ultrasound systems now employ 3D real-time imaging. Further technological advance of three dimensional (3D) speckle-tracking echocardiography (STE) has developed to obtain all components of myocardial displacement vectors, which could detect 3D cardiac motion that has been ignored in current 2D. 3D STE is more representative of the morphological state of the heart and provides a new opportunity to further understanding of myocardial deformation. There are basically two imaging approaches in echocardiography: the transthoracic and transoesophageal imaging approaches. In the transthoracic or standard imaging the transducer is applied to the chest wall, and is usually satisfactory. However, better-quality information is obtained via the transoesophageal approach, in which the transducer is mounted on a special probe and positioned in the oesophagus, directly behind the heart. The patient swallows the probe under light sedation with an anaesthetic spray to the posterior pharynx to prevent gagging. This provides better quality images because there are no intervening ribs or lung tissue and the probe is closely applied to the posterior aspect of the heart. It is particularly useful in imaging the left atrium, the aorta and prosthetic heart valves.
2.8.1 Principles

A transducer containing piezoelectric crystals converts electrical energy into high frequency ultrasound waves that can be directed towards the heart. The beam is reflected when it strikes an interface between tissues of different densities. The reflected ultrasound or echo, is converted back to electrical energy by the piezoelectric element, which permits the construction of an image using two basic units of information: The intensity of the echoes, which defines the density difference at tissue interface within the heart and the time taken for echoes to arrive back at the transducer, which defines the distance of the cardiac structures from the transducer.

Density differences within the heart are greatest between the blood-filled chambers and the myocardial and valvular tissues, all of which are clearly visible on the echocardiogram. Because the depth of the myocardial and valvular tissues with respect to the transducer changes constantly throughout the cardiac cycle, the time taken for echo reflection changes accordingly. Thus, real-time imaging throughout the cardiac cycle provides a dynamic record of cardiac function.\(^{44,46,50}\)

2.8.2 Technique

Techniques in echocardiography include the M-mode, the two-dimensional and three-dimensional echocardiogram. The M-mode echocardiogram provides a unidimensional ‘ice-pick’ view through the heart. The two-dimensional echocardiogram provides more detailed information about morphology and the M-mode traces are used to measure the movement of fast moving structures. Typically M-mode traces are taken of the aortic valve, mitral valve and the left ventricle (for systolic and diastolic measurements). There is also the 3-dimensional technique which views in all three planes, it is more recent and sophisticated and therefore not readily available in all centres in the developing world. Continuous recording on
photographic paper provides an additional time dimension, thereby permitting appreciation of the dynamic component of the cardiac image.\textsuperscript{34,35,38}

In addition to creating two-dimensional pictures of the cardiovascular system, an echocardiogram can also produce accurate assessment of the velocity of blood and cardiac tissue at any arbitrary point using pulsed or continuous wave Doppler ultrasound. This allows assessment of cardiac valve areas and function, any abnormal communications between the left and right side of the heart, any leaking of blood through the valves (valvular regurgitation), and calculation of the cardiac output as well as the ejection fraction.\textsuperscript{21,29} Other parameters measured include cardiac dimensions (luminal diameters and septal thickness).

**2.9 Summary of literature**

With the global quest to reduce maternal mortality especially in Sub-Saharan Africa, coupled with improving cardiac diagnostic facilities, there should therefore be a greater awareness of the cardiac problems associated with sickle cell anaemia in pregnancy. This will help guide in the antepartum, intrapartum and postpartum management of this group of obstetric patients among whom maternal morbidity and mortality is significantly high especially in the developing countries.
CHAPTER 3: AIM AND OBJECTIVES

3.1 Aim
The aim of this study was to evaluate the cardiac size and function in women with sickle cell anaemia during pregnancy in the third trimester and in the postpartum period with a view to improving management options in this group of patients.

3.2 Statement of Objectives
1. To determine if cardiac size and function in sickle cell anaemia in pregnancy improve after delivery.
2. To determine the correlation between the degree of cardiomegaly and the haematocrit level in pregnant women with sickle cell anaemia.
3. To compare the cardiac size and function in both pregnant and postpartum HbSS and HbAA women.
4. To evaluate maternal and fetal outcomes among the study participants.

3.3 Null Hypotheses
1. The enlarged ventricular chambers are not reversible by 6 weeks postpartum.
2. There is no relationship between the degree of cardiomegaly and haematocrit level in pregnant women with sickle cell anaemia.
3. There is no difference in the heart size of pregnant and postpartum HBSS women and HBAA women.

3.4 Working Hypotheses
1. The enlarged ventricular chambers are reversible by 6 weeks postpartum.
2. The degree of cardiomegaly is inversely proportional to the haematocrit level in pregnant women with sickle cell anaemia.
3. The heart is larger in pregnant and postpartum HbSS patients than in pregnant HbAA patients.
CHAPTER 4: METHODOLOGY

4.1 Study Area

This study was carried out at the antenatal clinic, labour ward and cardiovascular laboratory of the Lagos University Teaching Hospital. The Lagos University Teaching Hospital (LUTH) is the teaching hospital of the College of Medicine, University of Lagos. It acts mainly as a referral centre for other government owned and private hospitals in the state. It is on the mainland of Lagos which has a population of over 9 million inhabitants. The antenatal clinic in LUTH has a capacity of between 1300 and 1500 registered patients annually.

4.2 Study Population

There were two study populations. The first group consists of haemoglobin SS pregnant participants in their third trimester (≥ 30 weeks gestational age) with no clinical cardiovascular or other chronic medical diseases or obstetric complications. The second group were matched (for age (± 2years), parity (± 1) and gestational age (± 1 week) apparently healthy pregnant haemoglobin AA patients in their third trimester.

4.3.1 Eligibility criteria for the first group:

1. The patient is haemoglobin SS and is pregnant in the third trimester (≥ 30 weeks).
2. The patient must be booked for antenatal care in LUTH and consequently has an antenatal record.
3. The patient has no known cardiovascular disease or obstetric complication.
4. Informed written consent has been obtained.

4.3.2 Eligibility criteria for the second group:

1. The patient is haemoglobin AA and is pregnant in the third trimester (≥ 30 weeks).
2. The patient must be booked for antenatal care in LUTH and consequently has an antenatal record.
3. The patient has no known cardiovascular disease or obstetric complication.

4. Informed written consent has been obtained.

4.3.3 Exclusion criteria:

1. Presence of a history of or clinical cardiovascular disease.

2. Presence of multiple gestation.

3. Women who had received or donated blood or with a history of sickle cell crises in the three months prior to the study.

4. Patients with conditions that may predispose to chronic anaemia such as Human Immunodeficiency Virus (HIV) infection.

4.3 Study Design

This was a longitudinal study that was conducted among patients attending the antenatal clinic of the Lagos University Teaching Hospital. This study was conducted from 15th July 2016 to 31st March 2017. The annual delivery rate in the hospital was 1500. The number of HbSS attending the antenatal clinic annually was 40-50, with annual delivery rate of HbSS of 35-40 women per annum.

Women recruited into the study were pregnant haemoglobin SS in their third trimester attending the antenatal clinic, with matched pregnant normal haemoglobin AA women in their third trimester attending the antenatal clinic (they were matched for age (± 2 years), parity (± 1) and gestational age (± 1 week). Twenty (20) patients were recruited into each of the two groups, giving a total of 40 participants. A 2-dimensional transthoracic echocardiogram was performed to measure the sizes of the heart chambers and to identify enlarged chambers. They were followed up till delivery, and at 6 weeks postpartum, at which time another 2-dimensional transthoracic echocardiogram was performed. Haematocrit levels were estimated in all the haemoglobin SS patients. All the information were recorded in a proforma (Appendix 1).
4.4 Determination of sample size

This study took into account the mean ventricular size in women with SCA (primary outcome variable). Two groups of patients were then ultimately compared. This is considered in calculating the sample size. In calculating the sample size the following formula was used:

\[
 n = \frac{(u+v)^2(\sigma_1^2 + \sigma_0^2)}{(\mu_1-\mu_0)^2}
\]

Where:

- \( n \) = desired sample size.
- \( u \) = one-sided percentage point of the normal distribution corresponding to 100% - the power.
  - When power = 90%, \( u = 1.28 \).
- \( v \) = percentage point of the normal distribution corresponding to the (two-sided) significance level. When significance level = 5%, \( v = 2.56 \).
- \( \mu_1-\mu_0 \) = difference between the means of left ventricular size in the HbSS and HbAA pregnant women.
- \( \sigma_1, \sigma_0 \) = standard deviations of the left ventricular size in these group of women.

Thus, the minimum sample size \( n = (1.28+2.56)^2(7^2+2.5^2) = 11.55 \)

\[
(52-43.6)^2
\]

This is approximated to 14 after adding the 20% attrition and then rounded off to 20 for each group.

The sample size was, 20 pregnant HbSS women and 20 pregnant HbAA women as matched controls making a total of 40 women. Thus, 80 echocardiography studies were done (40 studies during the antenatal period and 40 at the 6\textsuperscript{th} week post-partum visit).

Furthermore, sample population were consecutive patients as cases, applying the already defined eligibility criteria.
4.5 Recruitment and Data collection

A detailed review as well as clinical assessment of the patient’s case and antenatal records was done in order to recognize patients that were to be excluded from the study. The purpose of the study was explained to the women and informed written consent was obtained from each participant. The women were then scanned at the echocardiography unit of LUTH with the necessary measurements made and entered into the proforma for each woman. The pregnant haemoglobin SS and AA women were then seen at 6 weeks after delivery and all haematocrit levels were obtained in the haemoglobin SS groups.

4.5.1 Cardiomegaly

This is enlargement of the heart, which is assessed in terms of chamber enlargement.

4.5.2 Left ventricular enlargement

This was detected and measured from the left ventricular dimensions at diastole and at systole, that is the diameter across the left ventricle at the end of diastole (left ventricular end diastolic diameter - LVEDD) and at systole. Normal values in an adult is about 48mm with a range of 36-56mm. It is specified with which plane the distance is measured in. For example, the dimension of the longitudinal plane. Left ventricular end diastolic dimensions (measured by echocardiography) during pregnancy and postpartum are 43.6±2.5mm and 41.8±1.8mm in the third trimester and puerperium respectively.

4.5.3 Cardiac function

Systolic function was measured in terms of ejection fraction and fractional shortening.

4.5.4 M-mode Echocardiogram

It is useful and easily used in the estimation of dimensions and detect motion. By convention, cardiac structures closest to the transducer are displayed at the top of the record and more distant structures are displayed below. Thus, on the transthoracic M-mode echocardiogram,
anteriorly located (‘right-sided’) structures lie above the posteriorly located (‘left-sided’) structures.\textsuperscript{39,44}

4.5.5 Two–dimensional Echocardiogram

This provides more detailed information about morphology than the M-mode recording. By projecting a fan of echoes in an arc of up to 80° a two-dimensional ‘slice’ through the heart can be obtained, coupled with the precise view depending on the location and angulation of the transducer.\textsuperscript{38}

4.5.6 Haemoglobin level

This is the concentration of the iron-binding pigment (haemoglobin) in blood. This determines the level of anaemia and its value is a third of the haematocrit value. Normal adult female value is 11g/dl or above (33% haematocrit).\textsuperscript{37} Any value below 10g/dl is considered anaemia in this environment.\textsuperscript{27} The haematocrit is routinely done for all pregnant HbSS patients at every antenatal clinic visit.

4.5.7 Procedure

The echocardiography was conducted in the cardiovascular laboratory of the Lagos University Teaching Hospital using Sonoscape SSI-8000 machine with a 3.5Mhz transducer probes used to perform the 2-D echocardiographic studies. A Senior Registrar in cardiology who is under training with the co-supervising cardiology consultant performed the echo studies in conjunction with the researcher who recruited the women and performed clinical assessment involving the weight, height, blood pressure and pulse rate measurements which were taken prior to the commencement of the scanning session. The anthropometric indices, the weight measurement was done with a digital weighing scale, with subjects wearing light clothes and no foot wears. Measurements were taken to the nearest 0.1kg. A stadiometer was employed for height measurement with the women standing erect, back against the height
meter rule such that the occiput, back and heels made contact with the height meter rule without footwear.

The body mass index was calculated using the formula below:

\[
\text{BMI} = \frac{\text{Weight (Kg)}}{\text{Height (m}^2\text{)}}
\]

The Blood pressure was measured using the standard auscultatory method with the help of pneumatically operated mecurial type random-zero sphygmomanometer. Blood pressure was measured in the left arm in sitting position with the arm at the level of the heart. While recording blood pressure, appearance of sound (phase I korottkoff) and disappearance of sound (phase V) were recorded as systolic and diastolic blood pressures respectively\textsuperscript{53,54}. 2D examinations included imaging a number of cross-sectional planes through the heart. Parasternal long axis and short axis views and apical four and two chamber views of the heart were obtained with standard transducer positions.\textsuperscript{47} Echocardiographic studies were done with patients in the left lateral decubitus position after the procedure was explained to them. The women were positioned and screened before the sonographer arrived to avoid bias.

M-mode echocardiograms were derived from the 2-D images under direct anatomic visualization. Cardiac dimensions were measured from M-mode echocardiograms directly from the monitor according to the recommendations of the American Society of Echocardiography using the leading edge to leading edge methodology.\textsuperscript{48} Left ventricular dimensions were taken with the M-mode line perpendicular to the long axis of the heart and immediately distal to the tips of the mitral valve leaflets in the parasternal long-axis view. Measurements were taken at end-diastole and at end-systole.

The diastolic measurements that were obtained include the left ventricular internal diameter (LVIDD). In systole, left ventricular internal diameter (LVIDS) was also obtained. The ejection fraction (EF) and fractional shortening (FS) were obtained.
Systolic function was determined using left ventricular ejection fraction and fractional shortening formulae. 50,51

Left ventricular ejection fraction: \[ \text{EDV} - \text{ESV} \times 100 \ (\%) \]

\[ \text{EDV} \]

\[ \text{EDV} = \text{End-diastolic volume}, \text{ESV} = \text{End-systolic volume} \]

Fractional shortening: \[ \frac{\text{LVIDD} - \text{LVIDS}}{\text{LVIDD}} \times 100 \ (\%) \]

Systolic dysfunction was defined as ejection fraction <55% and fractional Shortening <28%. 47

4.6 Data analysis

Data from the proforma was entered into Excel spreadsheet and exported to an electronic data base designed on SPSS Version 17. Data analysis was carried out using this same statistical package.

Descriptive continuous data were shown as means ± Standard Deviation for normally distributed data and median (interquartile range) for non-normally distributed variables. Categorical variables were expressed as frequencies and percentages. Paired t test for repeated measures was used to compare cardiac structural and functional data that were obtained antenatally among the participants to similar data that was obtained at the post-partum visit. Pregnancy data of the HBSS patients were compared with controls using independent sample Student’s t tests. Pearson correlation coefficient was used to assess the linear relationship between two continuous parameters. Chi-square and Mann-Whitney U were used to compare the categorical birth outcomes between HBSS and HBAA women. P-value<0.05 was considered to indicate statistical significance.

Primary outcome variable

The primary outcome variable was ventricular size.
Secondary outcome variable

Secondary variables included ejection fraction, fractional shortening, and haemoglobin levels.

4.7 Ethical consideration

The study was conducted after obtaining approval from the Ethics Committee of the Health Research and Ethics Committee (HREC) of the Lagos University Teaching Hospital, (Ethics Assigned No: ADM/DCST/HREC/APP/428). Informed consent was also obtained from the women prior to recruitment. The procedure of scanning the women is non-invasive and not harmful to the women and their babies. The haemoglobin concentration results that were used in the study were obtained from routine free haemoglobin level checks done by HbSS patients at every clinic visit. The assessment was carried out at no extra cost to the participants. Also the six weeks postpartum echocardiography timing coincided with the women’s routine postnatal visit hence at no additional cost or inconvenience. The participants were assured of this and their identity was protected throughout the study.

4.8 Beneficence of the study to participants

The expected benefits of this study to the participants are that by undergoing this echocardiographic examination, features that could be pointers of cardiovascular compromise could be highlighted and this information passed to the managing doctors. This can positively impact on the outcome of pregnancy in them since insidious findings can help improve the monitoring and care received from the managing doctors.

4.9 Non maleficence

The study evaluates HbSS women who are already having routine haemoglobin level checks and they are not financially liable for the echocardiographic examinations. In the event of obvious deranged parameters, the attention of the managing doctors is drawn and she is further evaluated according to hospital protocol. The process of scanning is not invasive, harmful, uncomfortable or embarrassing. The results of the echocardiographic examination is
immediately made known and explained to the participant and further counselling offered as appropriate.

4.10 Justice

Recruitment into the study arms was scientifically conducted. The study also aimed to gather evidence that could support or change the current guidelines on management of HbSS pregnant patients with respect to echocardiographic findings (so as to improve morbidity and mortality in them). Also the findings could add to information on how to counsel SCD women on family size, that is, if there is deterioration in cardiac function that is not reversible, it would add to the reasons they should limit their family size.
CHAPTER FIVE: RESULTS

5.1 Clinical characteristics of the study women.

This study was conducted over the period of 8 months from 14th July 2016 to 31st March 2017.

Forty (40) pregnant women were recruited. Twenty (20) pregnant women with Heamoglobin SS and 20 matched HbAA pregnant women as controls. The mean age was 30.1 ± 4.4 years for the HbSS women and the mean age of the HbAA women was 31.4 ± 5.3 years and there was no statistically significant difference in the mean ages of the two groups P= 0.387. The mean body mass index (BMI) of the HbSS cohort was lower, 23.9 ± 3.7 kg/m² as compared to the mean BMI of HbAA women 29.6 ± 4.1 kg/m², P < 0.001. Furthermore, there was no statistically significant difference in the mean gestational age at echocardiography in pregnancy of HbSS women as compared to HbAA women, 33.6 ± 2.3 weeks Vs 32.5 ± 3.4 weeks P= 0.325.

**TABLE 1**: Clinical and hemodynamic characteristics of the study population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HbSS Pregnant (n= 20) Mean ± SD</th>
<th>HbAA Pregnant (n= 20) Mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.1 ± 4.4</td>
<td>31.4 ± 5.3</td>
<td>0.387</td>
</tr>
<tr>
<td>Parity (Median , interquartile range)</td>
<td>1 (0, 1)</td>
<td>2 (0, 1)</td>
<td>0.623</td>
</tr>
<tr>
<td>Gestational age at echo (weeks)</td>
<td>33.6 ± 2.3</td>
<td>32.5 ±3.4</td>
<td>0.325</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.1 ± 8.1</td>
<td>75.4 ± 6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>23.9 ± 3.7</td>
<td>29.6 ±4.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>87 ± 9.3</td>
<td>89 ± 7.8</td>
<td>0.245</td>
</tr>
<tr>
<td>Systolic blood pressure (mmhg)</td>
<td>107.9 ± 9.6</td>
<td>110 ±8.5</td>
<td>0.375</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmhg)</td>
<td>63 ± 11.1</td>
<td>72 ± 9.3</td>
<td>0.169</td>
</tr>
</tbody>
</table>
5.2 Echocardiographic parameters of HbSS women during pregnancy and postpartum.

The mean left atrial diameter in pregnant HbSS was 4.31 ± 0.45 cm, and a statistically significant reduction was observed postpartum 3.89 ± 0.40 cm, p= <0.001 (Table 2). There was no statistically significant difference in the left ventricular diameter in diastole, ejection fraction and fractional shortening between ante-partum and postpartum periods, p >0.05. The left ventricular mass index and left ventricular systolic diameter both showed a statistically significant reduction in the postpartum period, p= <0.05.

**TABLE 2:** Comparison of the two-dimensional echocardiographic parameters of cardiac size and function in HbSS women during pregnancy and post-partum.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pregnant HbSS Mean ± SD</th>
<th>Post-partum HbSS Mean ± SD</th>
<th>T-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Atrial Diameter (cm)</td>
<td>4.31 ± 0.45</td>
<td>3.89 ± 0.40</td>
<td>4.218</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Left Ventricular Diameter in Diastole (cm)</td>
<td>5.09 ± 0.37</td>
<td>4.97 ± 0.43</td>
<td>1.389</td>
<td>0.181</td>
</tr>
<tr>
<td>Left Ventricular Diameter in Systole (cm)</td>
<td>3.52 ± 0.41</td>
<td>3.36 ± 0.42</td>
<td>2.196</td>
<td>0.041</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>118.27 ± 28.44</td>
<td>100.19 ± 20.89</td>
<td>3.230</td>
<td>0.004</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>61.34 ± 7.33</td>
<td>62.45 ± 5.84</td>
<td>0.706</td>
<td>0.489</td>
</tr>
<tr>
<td>Fractional Shortening (%)</td>
<td>30.88 ± 5.29</td>
<td>32.24 ± 7.47</td>
<td>0.919</td>
<td>0.370</td>
</tr>
</tbody>
</table>
5.3 Echocardiographic parameters of HbAA women during pregnancy and postpartum.

Most parameters of cardiac size and function remained within normal values both during pregnancy and post-partum in the HbAA women. However, there was a statistically significant reduction in the left ventricular diameter during systole in the postpartum period compared to the antepartum value, $3.01 \pm 0.21\text{cm} \text{Vs} \ 3.15 \pm 0.39\text{cm}$, $P = 0.044$, and the left ventricular mass index $p<0.05$. The observed slight reduction in the other parameters (left atrial diameter, left ventricular diameter in diastole, ejection fraction and fractional shortening) during the post-partum period were not statistically significant, $p>0.05$.

**TABLE 3:** Comparison of the two-dimensional echocardiographic parameters of cardiac size and function in HbAA women during pregnancy and post-partum.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pregnant HbAA Mean ± SD</th>
<th>Post-partum HbAA Mean ± SD</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Atrial diameter (cm)</td>
<td>3.69 ± 0.39</td>
<td>3.58 ± 0.41</td>
<td>1.36</td>
<td>0.189</td>
</tr>
<tr>
<td>Left Ventricular diameter in diastole (cm)</td>
<td>4.66 ± 0.46</td>
<td>4.55 ± 0.38</td>
<td>1.41</td>
<td>0.174</td>
</tr>
<tr>
<td>Left Ventricular diameter in systole (cm)</td>
<td>3.15 ± 0.39</td>
<td>3.01 ± 0.21</td>
<td>2.16</td>
<td>0.044</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>84.84 ± 15.19</td>
<td>73.96 ± 12.54</td>
<td>2.564</td>
<td>0.016</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>61.67 ± 7.45</td>
<td>63.42 ± 5.45</td>
<td>1.01</td>
<td>0.322</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>31.77 ± 7.03</td>
<td>31.81 ± 3.93</td>
<td>0.02</td>
<td>0.983</td>
</tr>
</tbody>
</table>
5.4 Echocardiographic parameters comparing cardiac size and function between pregnant HbSS and HbAA women.

The left atrial diameter, left ventricular diameter in diastole and left ventricular diameter in systole and the left ventricular mass index were statistically significantly larger in the pregnant HbSS group, p <0.05. However, the systolic function observed using ejection fraction and fractional shortening was similar in both groups. (Table 4).

5.4.1 Left atrial parameters

The pregnant HbSS women had significantly higher left atrial diameter compared with the pregnant HbAA group with a p value 0.001 for the comparison.

5.4.2 LV chamber parameters

The comparison of ventricular parameters of both study groups yielded the results as shown in table 4. HbSS pregnant women group had significantly higher mean LV diastolic diameter, LV systolic diameters and LV mass index compared with the HbAA pregnant group (p < 0.05 for all comparisons).

5.4.3 LV systolic function

The HbSS pregnant women had no statistically significant difference in both mean fractional shortening and ejection fraction compared with the HbAA pregnant group (30.88 ± 5.29% vs 32.11 ± 6.96%, p 0.532 and 61.34 ± 7.33% vs 61.67 ± 7.45%, p 0.888 respectively).
**TABLE 4**: Comparison of cardiac size and function between pregnant HbSS versus HbAA women.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HbSS Pregnant</th>
<th>HbAA Pregnant</th>
<th>t- value</th>
<th>p- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Atrial Diameter (cm)</td>
<td>4.31 ± 0.45</td>
<td>3.69 ± 0.39</td>
<td>4.61</td>
<td>0.001</td>
</tr>
<tr>
<td>Left Ventricular Diameter in Diastole (cm)</td>
<td>5.09 ± 0.37</td>
<td>4.66 ± 0.46</td>
<td>3.25</td>
<td>0.002</td>
</tr>
<tr>
<td>Left Ventricular Diameter in Systole (cm)</td>
<td>3.52 ± 0.41</td>
<td>3.15 ± 0.39</td>
<td>2.92</td>
<td>0.006</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>118.27 ± 28.44</td>
<td>84.84 ± 15.19</td>
<td>4.64</td>
<td>0.001</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>61.34 ± 7.33</td>
<td>61.67 ± 7.45</td>
<td>0.14</td>
<td>0.888</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>30.88 ± 5.29</td>
<td>32.11 ± 6.96</td>
<td>0.63</td>
<td>0.532</td>
</tr>
</tbody>
</table>

**5.5 Echocardiographic parameters comparing cardiac size and function between HbSS and HbAA women in the postpartum period.**

The left atrial diameter, left ventricular diameter in diastole and left ventricular diameter in systole and the left ventricular mass index were still statistically significantly larger in the postpartum HbSS group, p<0.05. However, the systolic function observed using ejection fraction and fractional shortening was similar in both groups in the postpartum period.

**5.5.1 Left atrial parameters**

The postpartum HbSS women had significantly higher left atrial diameter compared with the postpartum HbAA group with a p value 0.019 for the comparison.
5.5.2 LV chamber parameters

The comparison of ventricular parameters of both study groups yielded the results as shown in table 5. HbSS postpartum women group had significantly higher mean LV diastolic diameter, LV systolic diameters and LV mass index compared with the HbAA postpartum group (p < 0.05 for all comparisons).

5.5.3 LV systolic function

The HbSS postpartum women had no statistically significant difference in both mean fractional shortening and ejection fraction compared with the HbAA postpartum group p>0.05 (Table 5).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HbSS</th>
<th>HbAA</th>
<th>t- value</th>
<th>p- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Atrial Diameter (cm)</td>
<td>3.89 ± 0.40</td>
<td>3.58 ± 0.41</td>
<td>2.45</td>
<td>0.019</td>
</tr>
<tr>
<td>Left Ventricular Diameter in Diastole (cm)</td>
<td>4.97 ± 0.43</td>
<td>4.55 ± 0.38</td>
<td>3.26</td>
<td>0.002</td>
</tr>
<tr>
<td>Left Ventricular Diameter in Systole (cm)</td>
<td>3.36 ± 0.42</td>
<td>3.01 ± 0.21</td>
<td>3.29</td>
<td>0.002</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>100.19 ± 20.89</td>
<td>73.96 ± 12.54</td>
<td>3.14</td>
<td>0.001</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>62.45 ± 5.84</td>
<td>63.42 ± 5.45</td>
<td>0.63</td>
<td>0.550</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>32.24 ± 7.47</td>
<td>31.81 ± 3.93</td>
<td>0.11</td>
<td>0.920</td>
</tr>
</tbody>
</table>
5.6 Correlation between haematocrit and cardiomegaly in HbSS pregnant women

There was a negative linear relationship between haematocrit and left ventricular diameter in systole and left ventricular mass index \( p < 0.05 \). However, the correlation between left atrial diameter, left ventricular diameter in diastole and haematocrit were not statistically significant. (Table 6, Fig 1).

**TABLE 6**: Correlation between haematocrit and selected echo parameters during pregnancy in HbSS women.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pearson’s correlation coefficient ( r )</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Atrial Diameter (cm)</td>
<td>-0.242</td>
<td>0.152</td>
</tr>
<tr>
<td>Left Ventricular Diameter in Diastole (cm)</td>
<td>-0.316</td>
<td>0.087</td>
</tr>
<tr>
<td>Left Ventricular Diameter in Systole (cm)</td>
<td>-0.424</td>
<td>0.031</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>-0.430</td>
<td>0.029</td>
</tr>
</tbody>
</table>
FIGURE 1: Pearson’s correlation between haematocrit level and left ventricular mass index.

This shows a negative linear correlation between haematocrit level and left ventricular mass index, $p=0.029$. 

$$r = 0.430, \ p = 0.029$$
5.7 Comparison of maternal and perinatal outcome of the study groups

HbSS women delivered earlier than the HbAA women (37 ± 0.3 vs 39.2 ± 0.4, P-value <0.001) table 7. Four HbSS women (20%), and 2 (10%), had instrumental vaginal delivery with forceps and vacuum respectively, while none of the HbAA control group women had assisted vaginal delivery. The mean birth weight of babies born to HBAA women was higher than that of the HBSS women, p<0.05.

**TABLE 7:** Maternal and perinatal outcomes in HbSS and HbAA women.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>HbSS ± SD/ n (%)</th>
<th>HbAA ± SD / n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at delivery(weeks) (Mean ± SD)</td>
<td>37.5 ± 0.3</td>
<td>39.2 ± 0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live births (n %)</td>
<td>19 (95%)</td>
<td>20 (100%)</td>
<td></td>
</tr>
<tr>
<td>Mode of delivery</td>
<td>0.723</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>14 (70%)</td>
<td>15 (75%)</td>
<td></td>
</tr>
<tr>
<td>Caesearean</td>
<td>6 (30%)</td>
<td>5 (25%)</td>
<td></td>
</tr>
<tr>
<td>Birth weight (kg) (Mean ± SD)</td>
<td>2.61± 0.32</td>
<td>3.4 ± 1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apgar score at 1’ median (IQR)</td>
<td>7 (6, 8)</td>
<td>8 (7, 9)</td>
<td>0.634</td>
</tr>
<tr>
<td>Apgar score at 5’ median (IQR)</td>
<td>8 (7, 9)</td>
<td>10 (8,10)</td>
<td>0.642</td>
</tr>
</tbody>
</table>

SD= Standard deviation, IQR= Inter quartile range.
CHAPTER SIX: DISCUSSION

This study aimed to evaluate the echocardiographic structure and function of the heart in HbSS pregnant women in comparison to HbAA women so as to document any impact of pregnancy on cardiac function in HbSS women in our environment. The exhaustive literature search suggest that this is the first study to use echocardiography to evaluate cardiac function and structure in HBSS women in comparison to HBAA women with apparently normal pregnancies in Nigeria and is the first study ever to compare post-partum echocardiography values with ante-natal ones in HbSS women, to the best of my knowledge.

The study was conducted in the 3rd trimester as it is expected that the physiological changes of the cardiovascular system plateau at about this time.\(^{54}\)

The mean age of the women in both groups is similar to previous studies.\(^{52,60}\) Also, the mean gestational age at echocardiography in the third trimester of pregnancy was synonymous with previous study.\(^{24}\)

The cardiac size parameters for the HBAA women in pregnancy (LAD, LVDD & LVDS) were comparable to previous findings in studies done in Nigeria and Turkey.\(^{25,61}\) However the values of the ejection fraction in the HBAA pregnant women (which assesses left ventricular function), were lower than what was obtained by the previous Nigerian study that performed echocardiography on 100 normal pregnant women. The inconsistencies in prior studies evaluating maternal cardiac function may reflect assessment at different gestational ages during the third trimester. The difference in sample size among the studies could have contributed to the difference. In contrast, the cardiac dimensions in the pregnant HBSS women in this study were larger than those in the HbAA group. The increase in cardiac chambers might be due to structural remodelling as a compensatory mechanism for chronic volume overload state seen in this category of women.\(^{60}\) The values of Ejection fraction &
Fractional shortening in the pregnant and postpartum HBSS women group observed from this study are comparable to previous findings. However, no significant change was observed post-partum in the HBSS women. In current clinical practice, 2DE is the first-choice technique to diagnose changes of LV dimensions, and Left Ventricular Ejection Fraction is a widely used and prognostic important indicator of Left Ventricular systolic function. Furthermore, in this present study, ejection fraction and fractional shortening values were observed to be within normal limits in the pregnant HBSS in spite of marked ventricular enlargement, and in HBAA women too. Therefore, there seems to be preservation of the left ventricular systolic function in this study. This suggests some adjustments to cardiovascular stress of pregnancy.

In this study, the left atrial size in the HbSS pregnant women were larger than in the HbAA pregnant women. This finding differed from the finding in the study by Vielle’s et al though only 10 HbSS pregnant Afro Caribbean women were included in that study. The smaller sample size of pregnant HbSS women in that study and also inclusion of other haemoglobinopathies other than HbSS like HbSC into their study may have accounted for this observed difference.

As expected, the heart chambers were found to be significantly larger in the pregnant HbSS women than HbAA women. There was some improvement in cardiac size, although function was not significantly affected in the pregnant versus post-partum state in HbSS women. It appears that the increase in cardiac size compensates sufficiently to maintain cardiac function in steady state pregnant HbSS women. Perhaps these findings in this current study could be due to the fact that the women were selected (based on exclusion criteria) from a population of patients who are assumed to be better motivated for regular follow-up in a tertiary hospital and in a commercial centre of the country.
The mean left ventricular mass indexed to the body surface area, in the pregnant HBAA women from this study was within normal limits both during pregnancy and postpartum and did not show significant alteration. This finding is similar to a previous Nigerian study within similar gestational ages in the third trimester of apparently healthy women. In contrast, the pregnant HbSS women had left ventricular hypertrophy with statistically significant reduction observed during the postpartum period. There was also a statistically significant difference in the mean left ventricular mass between the pregnant HBSS and HBAA women. An increment in left ventricular mass may reduce ventricular compliance, necessitating increased atrial pressure and volume with the need for more forceful contraction for emptying. An explanation for this hypertrophy could be as a result of local ischaemic changes secondary to either chronic anaemia with attendant volume overload, which is worsened by pregnancy, repeated sickling, or obstruction of the microcirculation, rather than in response to an increased systemic vascular resistance.

Further analysis comparing cardiac size and function in the postpartum state between HbSS and HbAA women showed that despite significant reduction in postpartum values in HbSS women, the indices of cardiac size (LA, LVDD, LVDS, LVMass index) were still significantly larger in the postpartum HbSS women compared to the HbAA women. Even though cardiac function still remained optimal both during pregnancy and postpartum period in these study women, the persistent significantly larger size observed in the postpartum period in HbSS women might lead to long term deterioration in function.

There was an inverse correlation between the haematocrit values and the left ventricular systolic diameter among the HBSS participants. The inverse relationship between
haematocrit and left ventricular systolic diameter in HbSS pregnant women suggests that the worse the anaemia, the larger the left ventricular size. Thus, this study supports the hypothesis that an inverse relationship exists between cardiomegaly and haematocrit. This may suggest the need for optimal haematocrit values especially during pregnancy to improve cardiac size and possibly function.

HBSS women delivered earlier than HBAA women as shown in table 6. Furthermore, the mean birthweight of babies born to HBAA women was higher than that of the HBSS women. The earlier gestational age at delivery and the lower birth weight of the HbSS women is similar to previous findings.\textsuperscript{26,58}

Surprisingly, there was no statistically significant difference between the birth outcome in HBSS and HBAA women in this study, despite a higher preponderance of vaginal operative deliveries in them. This differed from findings in a previous study conducted eight years ago in the same institution as this study\textsuperscript{4} which found pregnancy in women with sickle cell disease still fraught with maternal and fetal complications. That study was a retrospective case controlled study where all HBSS women (75) delivering within the study period were included. Furthermore, the time gap between that study and the present one, and the likelihood of advancement in clinical practice management of pregnant HbSS women may account for the difference. Furthermore, apparently healthy HbSS participants with no known co-morbidities were recruited into this study. Nevertheless, this study still suggests that HBSS women can still have a reasonably good birth outcome if impeccable multi-disciplinary obstetric care as offered in LUTH is made available to them. The good outcome among this cohort may also be related to the fact that most HBSS pregnant women are managed by an obstetric unit in LUTH with special interest in HBSS care and research.
This study demonstrates that HBSS pregnant women’s adaptation to pregnancy is comparable to that in HBAA pregnant group. However, it may be possible that the persistent cardiac hypertrophy noted in the HBSS women postpartum, though lower than during pregnancy, could eventually result in systolic dysfunction and abnormal ejection fraction during periods of stress which could occur with repeated pregnancies. Hence, there is still need to further stress the importance of limiting family size using safe, effective and long term contraception in these group of women.

A strength of this study was the longitudinal nature of the study that allowed echocardiography to be performed on the same women both during pregnancy and after delivery.

Also, the matching of the study assisted to reasonably eliminate confounding variables.
6.1 CONCLUSION

- This study supports previous findings of enlarged cardiac dimensions during pregnancy, as well as unchanged left ventricular systolic function, and in addition, found an improvement in some of the dimensions post-partum, suggesting that pregnancy does not cause irreversible cardiac compromise.
- These selected pregnant HbSS women in LUTH have optimal systolic cardiac function.
- Successful pregnancy outcome may still be possible in HbSS women with carefully coordinated obstetric and medical management.
- This study also provides baseline data on the physiological changes in the Left Ventricular structure and systolic function in HbSS women and during pregnancy and post-partum.

6.2 LIMITATIONS OF STUDY

1. Cardiovascular changes in pregnancy are completely reversed by 4-6 months postpartum, but this was not used in the study due to convenience and difficulty with follow-up for this length of time.
2. The use of more sensitive forms of left ventricular ejection fraction measurement like speckle tracking and 3D echo were not deployed in this study.
3. The diastolic function was not assessed in this study.

6.3 DISSEMINATION OF FINDINGS

The results of the research is being submitted in part fulfilment of the part II FMCOG Postgraduate Fellowship Examinations. Information charts will be created from the results and displayed in the Antenatal Clinic as part of continuing education for the medical staff and clients.
Abstracts presentation will be made at peer reviewed conferences and manuscript for journal publications will be developed.

6.4 RECOMMENDATIONS

1. Pregnant HbSS women can be reassured that their cardiac systolic function remains optimal during uncomplicated pregnancy.

2. Since there is an increase in cardiac dimensions during pregnancy that is significantly larger than HbAA women, it may be expedient to advise a limitation of family size in order to avoid irreversible damage in future.

LINES OF FUTURE RESEARCH

1. Further long term longitudinal studies to evaluate cardiac changes at 6 months postpartum when cardiovascular changes in pregnancy have fully reversed may further validate this finding.

2. A longitudinal study that would monitor the cardiac structure systolic and diastolic functions of HBSS women before pregnancy, during pregnancy and post-partum may shed more light to the proper preconception and antenatal counselling and management of this group of high risk women may also be necessary.
REFERENCES


**APPENDIX I: PROFORMA**

**COMPARISON OF CARDIAC FUNCTION BETWEEN PREGNANT WOMEN WITH HBSS AND THOSE WITH HBAA USING ECHOCARDIOGRAPHY AT LUTH.**

<table>
<thead>
<tr>
<th>Name &amp; Hospital no</th>
<th>Tel. nos</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Age in years (as at last birthday)</th>
<th>Height (in metres)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight (in kilogrammes)</th>
<th>Pulse rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Body mass index (in kg/m(^2))</th>
<th>Blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Parity</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Haemoglobin genotype:</th>
<th>AA</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Haemoglobin level at Echo (in g/dl, for HbSS patients only)</th>
<th>range in last 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pregnancy status:</th>
<th>pregnant</th>
<th>post-partum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimated gestational age (in weeks) at echo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of time post-partum (in weeks) at echo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Left ventricular dimensions (in cm)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventricular septum (in cm)</th>
<th>Posterior wall thickness (in cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Left atrial dimensions (in cm)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiomegaly:</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ejection fraction (EF)</th>
<th>Fractional shortening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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APPENDIX 2: GENERAL INFORMATION FOR PARTICIPANTS

1. The research is undertaken to find out the change in how your heart works and its size when you are pregnant and if it returns to normal after you have delivered.
2. A scan of the heart called echocardiogram will be performed on you in addition to your routine investigations.
3. Your participation in this research will be at no additional cost to you.
4. You and your baby are at no risk at all from participation in this study.
5. Information generated from this study is for purpose of research.
6. Information received from you will be treated as confidential.
7. You have the right to ask questions on any aspect of this study that is not clear to you before you participate.
8. You are guaranteed the right to withdraw from the study at any time without any reason.
9. Special return cards will be provided for you for easy contact during your six weeks postnatal visit for the follow-up echocardiogram.
APPENDIX 3: CONSENT FORM FOR PARTICIPANTS
COMPARISON OF CARDIAC FUNCTION BETWEEN PREGNANT WOMEN WITH HBSS AND THOSE WITH HBAA USING ECHOCARDIOGRAPHY AT LUTH.

I have read and understood the information sheet and this consent form. I have had an opportunity to ask questions about my participation.

I understand that I am under no obligation to take part in this study.

I understand that I have the right to withdraw from this study at any stage without giving any reason.

I agree to participate in this study.

Name of participant: _____________________________________

Signature of participant: _________________________________

Signature of researcher: _________________________________

Date: _________________

For illiterate ones, the above has been interpreted to me…………………..
By……………………in…………….language, and I understand clearly…………………..

Contact details of the researcher

Name of researcher: DR Zubaida Aliyu

Address: Department of Obstetrics and Gynaecology, Lagos University Teaching Hospital.

Email / Telephone: zubaidualyu@yahoo.com 08034930699
APPENDIX 4

SPECIAL RETURN CARD

Name & hospital nos.............................................. Age (in years at last birthday)................
Address............................................................... Phone nos..................................................
Date of echocardiogram.............................. Gestational age at echocardiogram.................
Genotype....................... LMP.......................... EDD.............................
Actual date of delivery........................................
Date of six weeks postnatal visit.................................
Date of follow-up echocardiogram............................
Doctor’s phone nos............................................
LAGOS UNIVERSITY TEACHING HOSPITAL
HEALTH RESEARCH AND ETHICS COMMITTEE
PRIVATE MAIL BAG 12003, LAGOS, NIGERIA
e-mail address: luthethics@yahoo.com

Chairsman
ASSOC. PROF. N. U. OKUBADEJO
MB ChB, FMCP

Chief Medical Director:
PROF. AKIN. OSIBOGUN
MBBS (Lagos), MPH (Columbia), FMCPH FWACP

Administrative Secretary
MR. D. J. AKPAN
B.SC. BUS. ADMIN, MIHSAN

Chairman, Medical Advisory Committee
DR. M. O. OGUNLEWE
BDS, FWACS.

UTH HREC REGISTRATION NUMBER: NHREC: 19/12/2008a
Office Address: Room 107, 1st floor, UTH Administrative Block
Telephono: 234-1-5852717, 5852187, 5852209, 5852158, 5852111

7th September, 2015

NOTICE OF EXPEDITED REVIEW AND APPROVAL

PROJECT TITLE: “MATERNAL CARDIAC FUNCTION IN PREGNANCY: A COMPARATIVE STUDY OF HAEMOGLOBIN SS VERSUS AA WOMEN IN LAGOS UNIVERSITY TEACHING HOSPITAL (LUTH)”.

HEALTH RESEARCH COMMITTEE ASSIGNED NO.: ADM/DCST/HREC/APP/428
NAME OF PRINCIPAL INVESTIGATOR: DR. ZUBAIDA ALIU
ADDRESS OF PRINCIPAL INVESTIGATOR: DEPT. OF OBSTETRICS AND GYNAECOLOGY, LUTH.

DATE OF RECEIPT OF VALID APPLICATION: 31-07-15

This is to inform you that the research described in the submitted protocol, the consent forms, and all other related materials where relevant have been reviewed and given full approval by the Lagos University Teaching Hospital Health Research Ethics Committee (LUTHHREC).

This approval dates from 07-09-2015 to 07-09-2016. If there is delay in starting the research, please inform the HREC so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of this dates. All informed consent forms used in this study must carry the HREC assigned number and duration of HREC approval of the study. In multiyear research, endeavor to submit your annual report to the HREC early in order to obtain renewal of your approval and avoid disruption of your research.

The National code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the code including ensuring that all adverse events are reported promptly to the HREC. No changes are permitted in the research without prior approval by the HREC except in circumstances outlined in the code. The HREC reserves the right to conduct compliance visits to your research site without previous notification.

CHAIRMAN
ASSOC. PROF. N. U. OKUBADEJO
CHAIRMAN, LUTH HEALTH RESEARCH ETHICS COMMITTEE
APPENDIX 6: EXTENSION OF ETHICAL APPROVAL

LAGOS UNIVERSITY TEACHING HOSPITAL
HEALTH RESEARCH ETHICS COMMITTEE

PRIVATE MAIL BAG 12003, LAGOS, NIGERIA
e-mail address: luthethics@yahoo.com

Chairman
PROF. N. U. OKUBADEJO
MB, ChB, FMCP

Administrative Secretary
D.J. AKPAN
B.Sc. (Hons) BUS. ADMIN,
MIHMSAN

Chief Medical Director:
PROF. CHRIS BODE
FMCS (NIG) FWACS

Chairman, Medical Advisory Committee
PROF. O. A. FASANMADE
MBBS, FWACP, FACP, FNSEM

LUTH HREC REGISTRATION NUMBER: NHREC: 19/12/2008a
Office Address: Room 107, 1st Floor, LUTH Administrative Block
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7th September, 2016

NOTICE OF EXTENSION/AMENDMENT OF RESEARCH APPROVAL DATE/TOPIC

PROJECT TITLE: "COMPARISON OF CARDIAC FUNCTION BETWEEN PREGNANT WOMEN WITH HBSS AND THOSE WITH HAA USING ECHOCARDIOGRAPHY AT THE LAGOS UNIVERSITY TEACHING HOSPITAL, LAGOS, NIGERIA".

HEALTH RESEARCH COMMITTEE ASSIGNED NO.: ADM/DST/HREC/APP/428

NAME OF PRINCIPAL INVESTIGATOR: DR. ZUBAIDA ALIYU

ADDRESS OF PRINCIPAL INVESTIGATOR: DEPT. OF OBSTETRICS AND GYNAECOLOGY, LUTH.

DATE OF RECEIPT OF VALID APPLICATION: 31-07-15

DATE OF RE-APPLICATION FOR EXTENSION/AMENDMENT OF RESEARCH APPROVAL DATE/TOPIC: 06-09-16

This is to inform you that the research described in the submitted protocol, the consent forms, and all other related materials where relevant have been reviewed and given full approval by the Lagos University Teaching Hospital Health Research Ethics Committee (LUTHHREC).

This approval dates from 07-09-2016 to 07-09-2017. If there is delay in starting the research, please inform the HREC so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of this dates. All informed consent forms used in this study must carry the HREC assigned number and duration of HREC approval of the study. In multiyear research, endeavor to submit your annual report to the HREC early in order to obtain renewal of your approval and avoid disruption of your research.

The National code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the code including ensuring that all adverse events are reported promptly to the HREC. No changes are permitted in the research without prior approval by the HREC except in circumstances outlined in the code. The HREC reserves the right to conduct compliance visits to your research site without previous notification.

PROF. N. U. OKUBADEJO
CHAIRMAN, LUTH HEALTH RESEARCH ETHICS COMMITTEE
3rd August, 2017.

The College Registrar,
National Post Graduate Medical College,
Km 26, Lagos–Badagry Express way,
PMB 2003, Ijanikin, Lagos
Lagos state.

Dear Sir,

EVIDENCE OF PRESENTATION OF DISSERTATION AT DEPARTMENT SEMINAR

This dissertation “comparison of cardiac function between pregnant women with HBS and those with HBAA using echocardiography in LUTH was presented at the weekly Departmental seminar on 2/8/2017 by the candidate DR ZUBAIDA AYIYU. She is presently a Senior Registrar preparing for the Part II Fellowship Examination in Obstetrics and Gynaecology of the National Post Graduate Medical College.

The Head of Department, the supervisors of the dissertation, the coordinator of Residency Training in the department, consultants and residents were in attendance. The comments, corrections and contributions made were noted, and changes effected in dissertation.

Dr K.S. Okunade
Chairman Residency Training Committee,
Department of Obstetrics and Gynaecology
LUTH