ASSOCIATION BETWEEN POST PARTUM NON-DIABETIC MATERNAL HbA1C AND FETAL MACROSOMIA AT KENYATTA NATIONAL HOSPITAL

A CASE CONTROL STUDY

INVESTIGATOR:

Dr.Anne Effie Anyango Ouma

H58/83019/2015

MBChB M. MED Student

Registrar, Obstetrics and Gynaecology, University of Nairobi

SUPERVISORS:

Dr. George Gwako

MBChB, M.MED Obs/Gyn,LecturerofObstetrics and Gynaecology, University of Nairobi, Consultant Obstetrician and Gynaecologist Kenyatta National Hospital

Dr. Maureen Owiti

MBChB, M.MED Obs/Gyn, Consultant Obstetrician and Gynaecologist, Kenyatta National Hospital, Honorary Lecturer, Department of Obstetrics and Gynaecology, University of Nairobi.

A research dissertation, submitted to the University of Nairobi, Department of Obstetrics and Gynaecology in partial fulfillment of the requirements for the award of a degree in Masters of Medicine in Obstetrics and Gynaecology.

DECLARATION

This is to declare that this dissertation is my original work, carried out with guidance from my supervisors.It has not been presented for an academic award in any other university and references made to work done by others have been indicated.

CONFLICT OF INTEREST

The machine used, Dirui machine, and the Dirui Industrial Co. Ltd have no interest in the study. Neither did they sponsor nor participate in this project. Funding was done by Kenyatta National Hospital Research and Ethics Programme.

Dr. Anne Effie Anyango Ouma

Signature ...……..…

Date ……..……...…….

APPROVAL

This dissertation has been submitted with our approval as University supervisors:

Signature…….. Date……

Dr. George Gwako

Signature…….. Date……

Dr. Maureen Owiti

ACKNOWLEDGEMENTS

This dissertation becomes a reality with the kind support and help of many individuals. I would like to extend my sincere thanks to all of them.

First of all, I want to offer this endeavor to my Almighty God for the wisdom He bestowed upon me, strength, peace of mind, good health and life, and the kind people He placed in my way to offer guidance in order to finish this research successfully.

I would like to acknowledge Department of Obstetrics and Gynaecology for their kind support throughout this period, and the opportunity to learn and improve my knowledge and skills in this field. Similarly, heartfelt thanks to Kenyatta National Hospital Research and Ethics Program for funding of this proposal, without which this would have been impossible.

My sincere appreciation goes to my supervisors: Dr. George Gwako and Dr. Maureen Owiti for their constant guidance throughout this project which will be going out to continue the work of improving reproductive health. They have been a watchful eye over me during my years in post graduate. I thank them for their tireless efforts, guidance, supervision, encouragement and for sacrificing long hours to ensure that my dissertation goes through.

Appreciation goes to Dr. Alex Bosire, who assisted me in proposal correction and input in production of this document. This also goes to Miss Lydia KemuntoAgwatawho assisted in data collection, patient recruitment, facilitated my interaction with the study participants, sample collection and laboratory data retrieval.

I acknowledge the work done by Dr.WekesaBarasaand Dr.Mark Kola of Westend Institute of Science and Technology who diligently worked on my data and made it look as it does today.

Special thanks to the ethics review board for considerate endorsement and the clients who took time to participate in this study and I hope through them there will be improved antenatal care for mothers in this hospital.

To my lecturers,thank you for your assistance and guidance that lead me to realize my dream.

Special thanks to Mrs. Bertha Ouma and the Late Joel Ouma and the entire Ouma familyfor their constant encouragement throughout this journey.

May God bless you all.

DEDICATION

To my parents, the late Mr. Joel Ouma and Mrs. Bertha Ouma, and family for their support and encouragement through my postgraduate degree. You have made me who I am and gave me morale and support all through my postgraduate training. Most importantly, I dedicate this to Almighty God for constant support and strength throughout my life and through this dissertation.

Thank you.

TABLE OF CONTEXT

LIST OF ABBREVIATIONS

ACOG	American Congress of Obstetricians and Gynaecologists
ADA	American Diabetic Association
AGA	Appropriate for Gestational Age
DM	Diabetes Mellitus
EDTA	EthyleneDiamineTetraacetic Acid
ERC	Ethical Research Committee
FBS	Fasting Blood Sugar
GDM	Gestational Diabetes Mellitus
HDL	High Density Lipoproteins
IQC	Internal Quality Control
ISO	International Organisation for Standardization
KNH	Kenyatta National Hospital
LDL	Low Density Lipoproteins
LGA	Large for Gestational age
MOH	Ministry Of Health
NICE	National Institute for Health and Care Excellence
OGTT	Oral Glucose Tolerance Test
PPH	Post-partum hemorrhage
RBS	Random Blood Sugar
RCOG	Royal College of Obstetricians and Gynaecologists
SEMDA	Society for Endocrinology, Metabolism and Diabetes for South Africa
SOP	Standard Operating Procedure
TG	Triglycerides
UON	University of Nairobi
WHO	World Health Organisation

ABSTRACT

TITLE:ASSOCIATION BETWEEN POST PARTUM NON-DIABETIC MATERNAL HbA1C AND FETAL MACROSOMIA AT KENYATTA NATIONAL HOSPITAL

Introduction: The World Health Organization (WHO) defines macrosomia as an absolute birth weight of 4000 grams and above. Globally, it occurs in 0.5%- 15% of pregnancies and is associated with adverse maternal, fetal and neonatal outcomes and even later on in early childhood regardless of the maternal diabetes Mellitus (DM) status. Although there is a clear association between DM and macrosomia, not much has been studied between macrosomia and their non-diabetic counterparts, yet a majority of the macrosomic infants are born to non-diabetic mothers. HbA1c has been studied and used as a measure of existing high blood sugar levels, mainly for screening and monitoring treatment outcomes. HbA1c levels of 6.5% and abovehave been associated with DM. This study aimed at using non-diabetic maternal HbA1c levels taken in the immediate post-partum period, to identify any possible association between maternal HbA1c and fetal macrosomia. Any association would allow possible use HbA1c as a predictor of fetal macrosomia, warranting aggressive management, thus enabling its use as a screening tool even in non-diabetic patients.

Broad Objective: To determine the association between postpartum non-diabetic maternal HbA1c and fetal macrosomia at Kenyatta National Hospital.

Methodology: Ahospital-based case-control study in which immediatepostpartum non-diabetic maternal HbA1c of 85 women who delivered babies with macrosomia, birth weight of 4000g and above,were compared tothoseof 83 non-diabetic mothers who delivered normal weight babies, birth weight of 2500g-3999g. Daily birth registers andstructured questionnaires were used for screening and data collection. Blood samples were taken and HbA1c determined using latex agglutination method.Statistical analysis was performed using R software. Women were described using sociodemographic and obstetric factors. Characteristics of the cases were compared with the controls using appropriate statistical tests. Maternal age, weight, parity,and HbA1c were summarized into means and compared between the two groups using Student's t-test. Simple logistic regression was used to determine the correlates of elevated HbA1c. Chi-square test of association was used to determine the association. Adjusted Odds Ratio was used to quantify association.

Results: Out of the 83 women delivering normal weight babies, 7(8.4%) mothers had elevated HbA1c, while 7(8.2%) out of the 85 who delivered macrosomic infants had elevated HbA1c.There was no correlation between Age, BMI, Number of ANC visits, history of LGA,

previous family planning use and fetal sex a with elevated HbA1c at a cut off of 6.5%. There was also no significant association between elevated HbA1c and fetal macrosomia.
Conclusion: Age, BMI, Number of ANC visits, history of LGA, previous family planning use and fetal sex are not predictors of HbA1c. HbA1c is not a predictor of fetal macrosomia.
Key words: Macrosomia, Glycated Hemoglobin, Obesity, Non-diabetes, Post-partum.

1.0: INTRODUCTION

1.1 Background

Fetal macrosomia refers to delivery of a baby with an absolute birth weight of 4000grams and above regardless of the gestational age(1). Attempts at prenatal diagnosis have been tried and however accurate they are deemed, the absolute and most accurate weight is the actual weight at birth(2). The global prevalence of macrosomia is between 0.5%-15%, with a prevalence of 7% for >4000g births, 1% for >4500g births, and 0.1% for over 5000g births(2).

Several studies have shown that the prevalence of macrosomia has increased over the years, although with regional differences. With the increasing prevalence of non-communicable diseasesin the third world countries(3,4) even the Sub Saharan region and Kenya, in particular, has carried the weight of some of these conditions like overweight, obesity, hypertension, and Diabetes Mellitus (DM).

1.2 Risk factors of fetal macrosomia

Maternal risk factors associated with the development of fetal macrosomia include diabetes mellitus, obesity, excessive weight gain during pregnancy, sedentary lifestyle, previous large for gestational weight babies(5–7).Increased maternal Body Mass Index has been associated with delivery of macrosomic infants(8).Sedentary lifestyle, poor nutrition and obesity have been associated with diabetes mellitus, which in turn is one of the factors found to increase the rates of macrosomia(9,10).

It's however clear that diabetes mellitus is not the only cause of macrosomia. In fact, despite good glycemic control, congenital malformations and macrosomia were still evident in both diabetic patients and non-diabetic patients (11).

Based on existing literature, macrosomia has left little doubt in as far as the adverse effects on the mother, fetus and infant is concerned. To the mother, it may lead to cervical dystocia, prolonged labor, obstructed labor if neglected and unattended, perineal tears and increased caesarian section rates and postpartum hemorrhage(12). The infant may suffer from hypoglycemia, hyperbilirubinemia, birth injuries such as cephalohematomas among others (8). Macrosomic infants have also been documented to develop metabolic disorders later in life(11,13).

Where levels of HbA1c are elevated in pregnancy, fetal outcomes are likely to be un-favorable; in a study done by Shoba et al (14),the outcomes were more favorable where the maternal HbA1c values corresponded to 4.5%-5%. Where the levels of HbA1c were higher, majority of the new borns were admitted for observation for transient tachypnea (49.5%) and hyperbilirubinemia (16.5%) requiring phototherapy, hypocalcemia requiring calcium supplements (12.6%), hypoglycemia requiring glucose (7.8%) and persistent tachypnea of new-born (5.8%)(14).

1.3 Epidemiology of macrosomia

1.3.1 Global perspective

Many studies have been done globally trying to establish macrosomia and factors associated with it. Fetal growth has been found to take different trajectories in different ethnic groups(15). In a population-based cohort study comparing fetal growth trajectories in pregnancies of European and South Asian mothers, (ethnic groups with dissimilar growth patterns), with and without gestational diabetes mellitus, non-gestational diabetes mellitus pregnancies South Asian fetuses (n = 156) had a slower growth from gestational week 24, compared with Europeans (n = 310)(15).

In the same study, more than two-thirds of the European mothers who were later diagnosed with gestational diabetes mellitus were overweight or obese in early pregnancy, while this was not observed in South Asians. Fetuses of gestational diabetes mellitus mothers tended to be smaller than fetuses of non-gestational diabetes mellitus mothers in week 24 (-0.95 SD (95% CI: -1.53, -0.36), but thereafter grew faster until birth 0.45 SD (0.09, 0.81) (15). This pattern was especially pronounced in fetuses of South Asian mothers with moderate/severe GDM.

1.3.2 Regional perspective

In Morocco, L. Mochhoury, R. Razine, and J. Kasouati et al sought to evaluate the relationship between body mass index, gestational weight gain and relationship between maternal and neonatal morbidity in Moroccan population(8). In this study, the operational definition of macrosomia was birth weight above 4000g. The risk of macrosomia, shoulder dystocia, and moderate hypertension was higher among women whose weight gain was above 16kg, those who were overweight and those with obesity (8). However, there were no

laboratory studies seeking to correlate any abnormalities in glucose regulation with macrosomia and more so in the non-diabetic mothers (8).

In South Africa,J.K Essel et al found that the prevalence of macrosomia was 3.4% of all the singleton deliveries(16). Fetal and maternal outcomes were worse with the macrosomic neonates compared to the controls. Caesarian sections were three times higher than the control groups. Similarly, post-partum hemorrhage and uterine rupture were higher in the cases than the controls(16). The same trend was observed with the neonates whereby shoulder dystocia, brachial plexus palsy, clavicular fractures were only seen in the macrosomic group and interestingly none of these were noted in the normal weight babies. Perinatal deaths were more in the macrosomic group(16).

1.3.4 Kenyan perspective

Studies within Kenyatta National Hospital show that the prevalence of gestational diabetes has been increasing with time. In 1991, a study done by Githaiga revealed the prevalence as 0.15% (17). 10 years later in 2012, a study by B. Nyakundi showed a prevalence of 8.9% which was found to be in line with studies in other African countries of about 7% (18). A study by Omondi Ogutu to determine the prevalence of and associated factors for glucose intolerance among antenatal clients at the Kenyatta National Hospital at 24-36 weeks of gestation, revealed a prevalence of gestational diabetes at 16.7%(19). In this study, glucose intolerance was associated with higher birth weight due to glucose deposition and increased adiposity (19).

Previous findings in Kenyatta National Hospital revealed a prevalence of fetal macrosomia in diabetic mothers as 24.1 %(19). This implies that a majority (75.9%) of the macrosomic babies are born to mothers without diabetes. The study by Bugha to find out factors associated with fetal macrosomia in Kenyatta National Hospital in the year 2016 revealed that apart from diabetes mellitus, maternal age, maternal body mass index, weight gain during pregnancy, previous large babies, high parity and late term pregnancy were associated with macrosomia (20). Despite 68% of the mothers not having a history of diabetes, hyperglycemia, and glycosuria, they still had macrosomic neonates.

2.0: LITERATURE REVIEW

2.1 Background

Macrosomia is an important cause of perinatal morbidity and mortality that equally affects both the mother and the baby(21). Shoulder dystocia, clavicle, and humeral bones fractures, brachial plexus injuries, facial nerve injuries, fetal and infant death are some of the fetal complications that may occur. There is also evidence of a likelihood of the infants developing obesity in their childhood, adolescent and even early adulthood. Consequently, they may be at risk of developing cardiovascular and metabolic complications. On the other hand, maternal complications of fetal macrosomia include prolonged labor, cesarean deliveries, postpartum hemorrhage (PPH), infection and perineal injuries(22).

In as much as macrosomia has been found to be associated with diabetes, it has also been associated with the non-diabetic status as well. In fact, in a six-year retrospective study in Spain on perinatal outcome of macrosomic infants born to diabetic versus non-diabetic mothers, Lloreda Garcia JM et al (23) showed that out of 996 macrosomic babies, only 103 (10.3%) were born to diabetic mothers. This implies that 89.7% of the macrosomic infants were born to non-diabetic mothers.

2.2 Role of HBA1c in diabetes

Glycated hemoglobin(HbA1c) has been used to test glycaemic control for the previous three months in patients with diabetes mellitus without reflecting the daily fluctuations of blood glucose(24). Diabetics rarely achieve such levels, but tight control aims to come close to it. Levels above 9% show poor control, and levels above 12% show very poor control. It is commonly recommended that glycosylated hemoglobinis measured every 3 to 6 months in diabetes.

The Diabetes Control and Complications Trial (DCCT) showed that diabetics who keep their glycosylated hemoglobin levels close to 7% have a much better chance of delaying or preventing diabetes complications that affect the eyes, kidneys, and nerves than people with levels 8% or higher(25). The normal level for glycosylated hemoglobin, therefore, has been set to values less than 7%.

Certain anemias and disorders associated with accelerated red blood cell turnover and shortened red cell span such as hemoglobinopathies (sickle cell disease and glucose -6-

phosphate dehydrogenase deficiency) affect the level of HbA1c (22). Infections such as malaria would also reduce the levels of HbA1c. Other conditions that affect HbA1c levels include after blood loss, surgery, after blood transfusion, alcoholism, chronic renal or liver disease, after administration of, iron, vitamin B12, vitamin C or erythropoietin.

A study by A. Khalafallah, E. Phuah, and A. Al-Barazan et al in a prospective study whose setting was a single tertiary referral center study in Tasmania, Australia tested the utility of HbA1c when used as a screening tool in pregnancy for gestational diabetes. Using a cut-off value for HbA1c at 5.1% for detecting gestational diabetes showed sensitivity of 61% and specificity of 68% with negative predictive value (NPV) of 93%, versus sensitivity of 27% and specificity of 95% with a negative predictive value of 91% when using HbA1c cut-off value of 5.4%. The results suggested that pregnant women with an HbA1c of≥5.4% should proceed with an oral glucose tolerance test (26).

More recently, there has been substantial interest in its utility as a diagnostic test for diabetes and as a screening test for persons at high risk of diabetes. The American Diabetic Association(ADA) recommend the use of HbA1c to diagnose diabetes and this has been found to give equal or almost equal sensitivity and specificity to a fasting or post-load glucose measurements as a predictor of retinopathy(27).

HbA1c is however not used to diagnose gestational diabetes as an oral glucose tolerance test is the current gold standard, and its sensitivity in diagnosis in gestational diabetes is high(25). Although HbA1c is also not routinely used to asses a woman's blood glucose in the second and third trimesters of pregnancy (28), it's important to be aware that the risk of developing gestational diabetes increases with a HbA1c level above 6.5%. HbA1c has been reported in recent studies to have significant importance in monitoring congenital malformation, abortion, perinatal mortality, preeclampsia and postpartum abnormal glucose metabolism(29).

The National Institute for Health and Care Excellence NICE guidelines issued in 2015 for management of diabetes in the preconception and postnatal period recommend the use of contraception until good glycemic control as assessed by HbA1c level is achieved(28). The guidelines also recommended that preconception HbA1c values should be aimed at a level

below 6.5% if this is achievable without causing problematic hypoglycemia. This gives the reassurance of risk reduction of congenital malformations in the fetus (28).

The National Institute for Health and Care Excellence guidelines however recommend that HbA1c should not be used routinely for assessing glycemic control in the second and third trimesters of pregnancy(28) This recommendation is partly aided by the findings of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study whose findings suggested that glycated hemoglobin measurement is not a useful alternative to an oral glucose tolerance test in pregnant women(30).

The American College of Obstetricians and Gynecologists (ACOG), via the American Diabetes Association (ADA) guidelines 2016 on diabetes management, on the other hand, has more strict values for glycemic targets in pregnancy(31). It recommends the use of values of HbA1c levels of 6.0-6.5% for both pregestational and gestational diabetes and values of <6.0% as pregnancy progresses, as long as it is achieved without hypoglycemia(31).Nonetheless, HbA1c should be maintained as close to normal as is safely possible regardless of maternal Diabetic status (31).

2.3 Changes in HbA1c during pregnancy

During pregnancy, the HbA1c levels have been found to be lower than that of healthy controls(32). None the less, the reference intervals for healthy pregnant women are not clearly defined and there is no consensus on the reference range of HbA1c in pregnant women(29). These studies have however shown that the HbA1c values in non-diabetic individuals are trimester specific(33). In a study done by A R Versantvoort et al to determine the upper reference ranges of HbA1c in non-diabetic pregnant mothers, HbA1c levels were found to be lower in all three trimesters of normal pregnancy compared with the level in non-pregnant women(34).

In the Caucasian population, similar studies have been done to establish reference ranges of HbA1c in none diabetic women. A multicenter study done in Japan on healthy non-diabetic Japanese women by Yuji Hamamatsu, I Shimizu and Y Omori et al to determine the reference ranges of HbA1c in that population found that it ranged between 4.5% and 7%. In this study, HbA1c was found to be higher in pregnant women with proteinuria. The obese group also had a higher HbA1c level. There was a significant reduction of HbA1c levels in the second trimester (35). While this study revealed that strict glycemic control is essential to

reduce perinatal complications, it however excluded mothers in their early postpartum period, which is an area of interest in this study.

A study done in the Netherlands by J K Radder to establish reference ranges of HbA1c among pregnant women revealed that healthy, pregnant women had a low HbA1c, particularly in the first trimester of pregnancy. This might imply that for prevention of congenital malformations and macrosomia in pregnant diabetic women, HbA1C should be below 5% in the first trimester of pregnancy and below 6% in the third trimester(33,34,36).

In yet a different study by O'Conner, Catherine and O' Shea et al done in Ireland was done and it showed that the normal HbA1c reference interval for Caucasian non-diabetic women was 4.8 % – 5.5 % in T1, 4.3 % – 5.4 % in T2 and 4.7 % – 5.7 % in T3. HbA1c was significantly decreased in trimesters 1 and 2 compared to non-pregnant women. In this case, the lower reference range was a bit lower than the Japanese study. This study concluded that HbA1c trimester-specific reference intervals are required to better inform the management of pregnancies complicated by diabetes(33,37).

This therefore implies that in order to prevent macrosomia in pregnant women with diabetes the aim should be to use lower HbA1c levels than in non-pregnant states (34). The same study also revealed a significant correlation between the differences in HbA1c values of the first and the second trimester, in that, most of the women with decreased values from the first to the second trimester had birth weights below the 90^{th} percentile (23.3% of them had birth weight of percentile above 90%)(34).

Yuji Hiramatsu and I. Shimizu et al in a multi-center study to determine the reference ranges in healthy Japanese non diabetic women demonstrated a significant difference in the levels of HbA1c in pregnancy,i.e. between 4.5% to 5.7%. However, obese clients had a higher levels of HbA1c (35).

2.4 HbA1c as a predictor of Macrosomia in pregnancy

Several guidelines have been published to help screen and diagnose diabetes mellitus. Pregnant women without diabetes are screened for possible diabetes between 8-12 weeks and oral glucose tolerance test between 24-28 weeks(18,19,25,38). Few studies have tried to establish association of macrosomia and HbA1c in non-diabetics, and especially so in trying

to establish the reference ranges of HbA1c in normal healthy pregnant populations of multi-ethnic variations.

A multiethnic cohort study in Barcelona showed that there was a 16.7% independent increase of macrosomia in maternal HbA1c levels above 5.9% compared to the counterpart normal weight babies (39). Shobha et al. demonstrated unfavorable outcomes highest in HbA1c of above 5% in non-diabetic mothers in the third trimester(14).

A study done in the Germanyby Bacigalupo G, Langner K and Saling E, which sort to determine glycosylated hemoglobin, glucose tolerance and neonatal outcomes in both gestational diabetes and non-diabetic mothers(40). In this study HbA1c was compared in 69 non-diabetic mothers who were delivered normal weight infants, 33 non-diabetic mothers who delivered macrosomic infants and 51 mothers with gestational diabetes before the onset diabetes (40). The mean HbA1c values were 6.51 (+/- 0.46%), 6.59 (+/- 0.42%) and 7.11 (+/- 0.56%) in Group I, II and III respectively. The HbA1c values of the gestational diabetes group were noted to be significantly higher than those of the non-diabetic groups I and II (p less than 0.001; x2 test). HbA1c values above 7.4% in the non-diabetic mothers were with 95% probability abnormal and indicative of gestational diabetes (40).

Another study done in Asia by Bhavadharini et al to determine the optimal HbA1c in diagnosis of GDM showed that HbA1c levels of >5.0% had a significantly higher prevalence of macrosomia (41).

Mane et al did a multiethnic in Barcelona, Spain study to determine first trimester HbA1c as a predictor of adverse obstetric outcomes(39). In this study, the primary outcome of interest was macrosomia, while the secondary outcomes of interest were preeclampsia, preterm birth and caesarian section rates. After adjusting for other potential confounders, HbA1c of >5.9% was independently associated with a 3 fold increase in macrosomia and preeclampsia. These poor outcomes were independent of a later diagnosis of gestational diabetes (39).

A Chinese study of 2790 non-diabetic women in late pregnancy aimed at determining the effect of the levels of maternal lipids, C-peptide, insulin, and HbA1c on fetal weight at birth revealed that among their newborns. 2236 (80.1%) newborns were found to be appropriate for gestational age (AGA), and 554 (19.9%) newborns were large for gestational age.

Maternal Triglycerides, C-peptide, insulin and HbA1c levels were significantly higher in the large for gestational age group than in the appropriate for gestational age group ($P<0.05$)(11).

Other studies have shown associations of obese non-diabetic pregnancies with high maternal glycated hemoglobin at delivery. R. Ensenauer, l. Brandlhuber and M. Bergmann et al demonstrated this association in obese non-diabetic patients with a cut off of HbA1c of 5.7% and 31.9% of the obese none diabetic clients equaled or exceeded this cutoff. In this study, newborns were more likely to be born large for gestational age(42).

In Tunisia,Sihem Chaouachi, Emira Ben Hamida and Raja Belhaj et al whosort to retrospectively identify gestational diabetes in large babies and determine the HbA1c cutoff value. This study excluded preterm babies, diabetic mothers, and mothers with stillborn infants. Out of the 216 recruited for the study, 100 had large babies (cases) and 113 had normal weight babies.Evaluation of the mean concentration of HbA1c revealed that there was significantly greater levels in the cases than the controls, of (6.17% + 085 vs 5.17 + 0.57 t = 9.78 p <0.001)(43).

This finding by Sihem et al was a bit different from the South African study by Mayet N, Moodley J and Jilal et al (44), who found no difference in the mean HbA1c values between the cases and the controls. In this Tunisian study, the value of HbA1c > 5.85%, was considered as a risk factor for macrosomia in gestational diabetes. 83.5% of mothers with large babies had HbA1c%5.85 vs 7.8%of those with normal sized babies (p <0.0001).It was therefore recommended that HbA1c level can be of value as a postpartum screen for a diagnosis of diabetes and can help to differentiate between a constitutionally large but otherwise normal infant and a large infant of a diabetic mother, and a cut off of 5.85%, should advise maternal and fetal monitoring (43).

Mahesh et al on the other hand sort to determine the use of HbA1c in early post-partum screening of gestational diabetes. This study used HbA1c of above 6.5% to show glucose impairment.HbA1c had reasonable sensitivity and high specificity in comparison to the oral glucose tolerance test in the early post-partum period. In this study, it was however noted that if HbA1c was 6.2% and the fasting blood glucose was normal, oral glucose tolerance test was

not recommended(45). From this, it was recommended that the measurement of HbA1c at delivery could help select women who may need closer postpartum health checks.

Much like other Sub Saharan African countries, Kenya has insufficient local data to validate the course of HbA1c in the Kenyan population, and its association with macrosomia, and more so the course of HbA1c in the non-diabetic pregnant population. HbA1c is not commonly or routinely evaluated antenatally except in the high-risk groups such as the diabetics, and the obese clients. However few studies have been done outside pregnancy in trying to establish the prevalence of undiagnosed pre-gestational diabetes (4).

3.0: STUDY JUSTIFICATION AND UTILITY

Potential utility of HbA1c (glycated hemoglobin) in diabetes mellitus was first mentioned in 1985, and after consideration of available information and data, recommendation was made that i) "HbA1c can be used as a diagnostic test provided that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values and there are no conditions present precluding its accurate measurement" ii) "A HbA1c of 6.5% is recommended as a cut off point for diagnosing diabetes. A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests.

Compared to oral glucose tolerance test, the use of HbA1c is less cumbersome as it does not require any special preparation taken prior to the procedure as compared to the current screening method, oral glucose tolerance test.It also has minimal interlaboratory variability resulting from nausea and vomiting from delayed gastric emptying as occurs while using the oral glucose tolerance test. This makes HbA1c a less cumbersome, more convenient and preferred method in assessment of glycemic control in clients with diabetes (37).

Although there is a definite association between diabetes mellitus and macrosomia, the majority of macrosomic infants are born to non-diabetic mothers. Regardless of maternal diabetic status, these macrosomic infants represent a high-risk group in their perinatal outcomes. There is, therefore, need to determine its association with HbA1c levels in our setting.

Very limited documentation has been done in Kenyatta National Hospital despite the erratic observation of elevated HbA1c in normoglycemic women with macrosomic babies, yet physiologically, HbA1c values are known to fall below normal non-pregnant ranges. Preemptive diagnosis of macrosomia e.g. by symphysial fundal height measurements or sonographic measurements are not as accurate as the actual birth weight upon delivery, hence the choice of early postpartum mothers.

There is equal concern for macrosomic babies, regardless of maternal diabetic status, as they equally tend to develop similar complications. The preferential follow up of diabetic clients compared to the non-diabetic ones increases the threshold of detecting any concerns in the non-diabetic mothers hence placing them at a disadvantage. This creates a need to find a biomarker that is easily available, easy to administer, has less logistical requirement. HbA1c

which is already acceptable in the diabetic population and in the non-pregnant population could be a possible solution.

Recently local data elucidated the factors associated with macrosomia in Kenyatta National Hospital. It was noteworthy that of the participants, caesarian deliveries were 63% among macrosomic babies compared to 40% in the controls. Similarly, the newborn unit admission and stillbirths were more profound on the macrosomic neonates, despite the maternal diabetic status. In fact, 68% had no history of diabetes, hyperglycemia or glycosuria but the neonates were affected all the same.

Other studies in Kiambu Kenya, (outside of pregnancy) have shown that the prevalence of abnormal glucose regulation as 32%, prediabetes as 18% and that of undiagnosed diabetes mellitus as 14%(4). Despite all these, there is still lack of local data of optimum HbA1c values of a healthy pregnant non-diabetic,yet the noted adverse effects of macrosomia, among others, equally affect the diabetic and the non-diabetics.

In 2011 a study of antenatal mothers in Kenyatta National Hospital to determine the presence of glucose intolerance showed that out of 36% of those with glucose intolerance, almost half that number(16.7%) were diabetic which was much higher than the previously reported prevalence of 5%. Other studies especially Asian studies have shown that maternal HbA1c values can predict macrosomia (11,34,35,41,46).

There’s evident knowledge gap as there was no documented evidence on the HbA1c patterns or associations thereof in the study population used(20). Furthermore, the parturients recruited also included diabetic mothers and those with gestational diabetes, which would have been a confounding factor even if the HbA1c levels would have been determined in that study. There were however adverse outcomes of both the mothers and the infant regardless of the diabetes status. In essence, few studies have been conducted to investigate normal reference ranges of HbA1cin pregnant women in their respective trimesters within the Kenyan populace. In any case, more fetal surveillance is done in the diabetic mother than the non-diabetic mother, and this leaves more knowledge to be desired as these fetuses are equally vulnerable to the adverse outcomes.

It is therefore important to find out any associations that would probably provide a parameter for monitoring glycemic control of non-diabetic mothers with Pregestational diabetes in our set up. Any significant association if noted would provide a basis of a parameter that would be useful in informing practice, especially so in increasing surveillance to extend to the non-diabetics in the prediction offetal outcome and hence increase preparedness from the third trimester and subsequent follow up of the infant, even beyond puerperium. This is so since studies have shown that elevated HbA1c at the time of birth has an association with early childhood obesity and metabolic syndrome later in life, it's important to find if there's are any associations within our setup, especially now that our population is prone to increasing levels of noncommunicable diseases.

The fact that previous studies have indicated an association of fetal macrosomia with a mild degree of glucose intolerance, for instance in the case of obesity, the role of early postpartum HbA1c might turn out to be paramount in determining macrosomia as a consequence of possible undiagnosed gestational diabetes, and that in a healthy non-diabetic mother. Furthermore, HbA1c is accessible, less complex to do, require fewer logistics, and it's easily available at Kenyatta National Hospital.

In addition, if indeed any association is found, it can help to differentiate a constitutionally big baby from that resulting from abnormal glucose regulation. It is a single none fasting blood test that has been shown to have greater reliability with less than 6% inter-laboratory variation. Kenyatta National Hospital being the largest referral hospital in Kenya, will give a wider scope of other possible associations that may be beneficial and give an added value to the study due to its multi-ethnic range and capture of mothers from different geographical regions.

4.0: RESEARCH QUESTION

Among immediate postpartum non-diabetic mothers, is glycosylated hemoglobin associated with fetal macrosomia?

5.0: NULL HYPOTHESIS

There is no association between immediate post-partum non-diabetic maternal HbA1c levels and fetal macrosomia in mothers receiving care at Kenyatta National Hospital.

6.0: STUDY OBJECTIVES

6.1 Broad Objective

To determine the association between immediate post-partum non-diabetic HbA1c levels and fetal macrosomia among non-diabetic mothers receiving care at Kenyatta National Hospital.

6.2 Specific Objectives

Among immediate post-partum non-diabetic mothers with fetal macrosomia receiving care in Kenyatta National Hospital:

i. To determine the correlates of elevated maternal HbA1c levels.
ii. To determine the association between immediate postpartum maternal HbA1c levels and fetal macrosomia.

7.0: CONCEPTUAL FRAMEWORK

7.1 *Narrative*

Fetal macrosomia is known to be a cause of fetal and maternal morbidity and mortality, and later childhood obesity and increased risk of metabolic syndrome in childhood. Diabetes mellitus is among other causes such as maternal weight and maternal weight gain during pregnancy, previous history of macrosomic delivery, gestational age, male infant sex, maternal age and ethnicity that have been documented as associated factors and contributors to fetal macrosomia.

It's probably for this reason that high surveillance, and lots of effort such as screening, follow up is done by health care providers in averting this eventuality in the chronic diabetic patient and those with gestational diabetes. However, since macrosomia is not found only in the diabetics, but also the non-diabetics, this subject cannot be wished away especially in a population that has been documented to have increasing numbers of obesity and prevalence of abnormal glucose regulation in the setting of improved nutrition, sedentary lifestyle and improved socio-demographics.

Less attention may be paid to the non-diabetics yet the macrosomia also causes them similar adverse events. In these patients, HbA1c can be a biomarker used to predict adverse fetal outcome and to know which patients to follow up closely even after childbirth if indeed it is found to have a significant association.

7.2 Diagrammatic

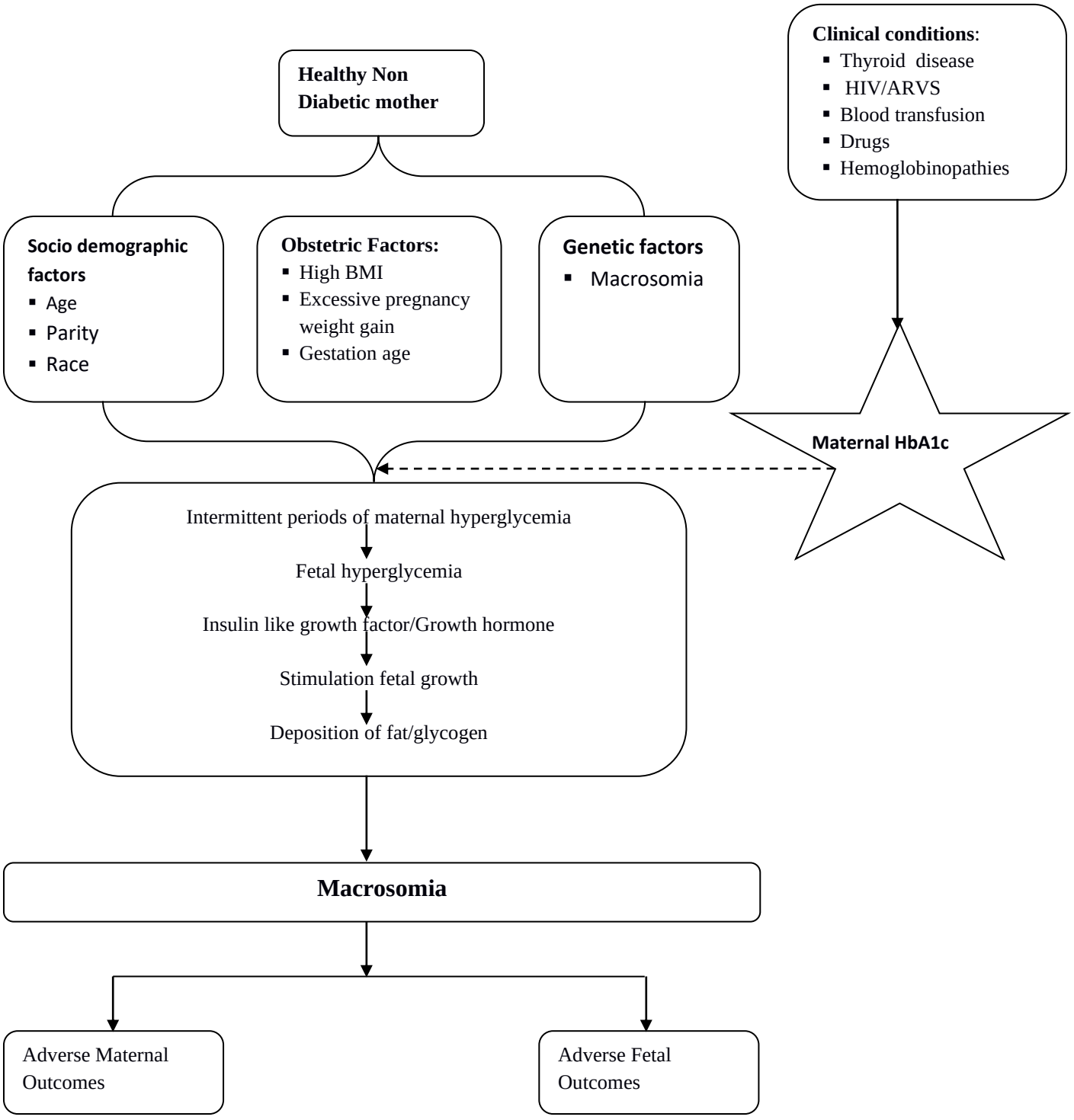


Figure 1: *Conceptual Framework*

8.0: STUDY METHODOLOGY

8.1 Study Design

This was a hospital-based Case-Control study whereby mothers who delivered babies with birth weights of 4000g and above were enrolled as cases while mothers who delivered children with birth weights of between 2500g and 3999g were enrolled as controls.

8.2 Study Setting

The study was conducted at the Kenyatta National Hospital labor ward and postnatal wards. The Kenyatta National Hospital, founded in 1901 and is situated in Nairobi county in Kenya, is a public national tertiary referral and teaching hospital for the University of Nairobi's College of Health Sciences and Kenya Medical Training College and other medical colleges in Kenya. It has an average bed capacity of 1800. It has a heterogeneous population that caters for patients of all walks of life, from Nairobi County, its environs, referrals from other hospitals in the country and the greater East African Region. Several medical specialist departments are hosted here including the department of obstetrics and gynecology, which conducts approximately 10,000 deliveries per year, which encompasses both vaginal and caesarian deliveries, as it is linked to two operating theatres and a blood transfusion unit that operates 24 hours daily. This means that it is able to adequately and efficiently handle any possible emergencies and provide comprehensive care to patients. The labor ward and postnatal wards are part of the obstetric arm of this department, hence it was well suited to carry out this research. It also has a biochemistry laboratory within its vicinity that does immediate HbA1c analysis, hence enabling immediate specimen analysis upon collection. This study was therefore carried out in the hospital's labor ward and postnatal rooms in the three antenatal/postnatal wards GFA, GFB, and 1A. In addition, the hospital also draws its clientele countrywide, serving a population with diverse cultural and socioeconomic backgrounds. Moreover, with the institution increasingly attending to an increased number of clients especially after the introduction of free maternity services by the Ministry of Health, added to its suitability for the study.

8.3 Study Population

The Study population was non-diabetic women in their immediate postpartum period who delivered at term (>37 weeks gestation) at the Kenyatta National Hospital and met the eligibility criteria, their neonates.

8.4 Eligibility Criteria

8.4.1 Inclusion criteria

Mothers in the immediate postpartum period who were able and willing to give consent and meeting the following criteria:

A. CASES

a) Had not been diagnosed with diabetes at the time of delivery

b) Gestational age of more than 37 weeks

c) Given birth to singleton babies

d) Given birth to neonates with birth weight above 4000g for cases

B. CONTROLS

a) Had not been diagnosed with diabetes at the time of delivery

b) Gestational age of more than 37 weeks

c) Given birth to singleton babies

d) Given birth to neonates with birth weight between 2500g to 3999g

* Immediate post-partum period was defined as the first 24 hours post-delivery.

8.4.2 Exclusion criteria

A) CASES

a) Mothers with confirmed Diabetes mellitus or RBS≥11.1mmols/l

b) Women had not delivered at Kenyatta National Hospital

c) Mothers with known Thyroid disease or any thyroid medications

d) Mothers on Iodine supplementation

e) Mothers with documented anemia 10.0g/dl, known hemoglobinopathies including sickle cell disease/trait

f) Mothers who had undergone blood transfusion in the last 3 months

g) Very sick patients

h) HIV patients and patients on Antiretroviral drugs (ARVs)

i) None consenting mothers

B) CONTROLS

a) Mothers with confirmed Diabetes mellitus or RBS≥11.1mmols/l

b) Women who had not delivered at Kenyatta National Hospital

c) Mothers with known Thyroid disease or any thyroid medications

d) Mothers on Iodine supplementation

e) Mothers with documented anemia 10.0g/dl, known hemoglobinopathies including sickle cell disease/trait

f) Mothers who would have undergone blood transfusion in the last 3 months

g) Very sick patients

h) HIV patients and patients on Antiretroviral drugs (ARVs)

i) None consenting mothers

8.5 Sample Size Determination

The sample size was calculated using the difference in proportions - Fleiss JL formula (Statcalc epi-info™) as outlined below. The following assumptions were considered during the calculation:

$$n = (\frac{r+1}{r}) \frac{(\bar{p})(1-\bar{p})(Z_{\beta} + Z_{\alpha/2})^2}{(p_1 - p_2)^2}$$

n = sample size per arm

r = ratio of controls to cases, 1:1 in this case

P_1= proportion of mothers with elevated HbA1c among mothers with macrosomia, in this case, 7.8% (Sihem et al)

P_2=proportion of mothers with elevated HbA1c among mothers with normal weight neonates, in this case, 22.8%

Ṕ =measure of variability, taken as 22.8+2.8/2

Z_{β}=Value corresponding to the power of the study, in this case, 80% = 0.84

Zα = Value corresponding to the normal standard deviate at 95% C.I, in this case, = 1.96, with 0.05 level of significance

P_1- P_2 = effect size (difference in proportions)

Odds ratio to be detected of 3.0

Applying this in the Statcalc epi info software gives a value of 85 as shown below:

Unmatched Case-Control Study (Comparison of ILL and NOT ILL)

Two-sided confidence level:	95%
Power:	80 %
Ratio of controls to cases:	1
Percent of controls exposed:	7.8 %
Odds ratio:	3.8
Percent of cases with exposure:	24.3 %

	Kelsey	Fleiss	Fleiss w/ CC
Cases	78	77	88
Controls	78	77	88
Total	156	154	176

With the above assumptions and using a similar study done in South Africa, where the proportion of mothers with elevated Hb1C levels was 7.8%, the calculated sample size per arm was 77: with10% non-response rate, this came to 85 per arm.

8.6 Definition of variables

To achieve the objective a case-control study design was employed whereby;

1. Cases were 85 women in their immediate postpartum period receiving care at KNH during the recruitment period who delivered infants with a birth weight above 4000g.
2. Controls were 85 women in their immediate postpartum period receiving care at KNH during the recruitment period who delivered infants of normal birth weight i.e. between 2500g to 3999g.
3. Non-diabetic mothers in this study were mothers who had not been diagnosed with diabetes by the time they delivered and with RBS of <11.1mmol /l.
4. The correlates of elevated HbA1c in this study included;
    i. Sociodemographic factors
        - Age and Parity.
    ii. Obstetric factors
        - High body mass index, excessive pregnancy weight gain, gestational age, history of large for gestational age and fetal sex.

8.7 Data Collection Procedure

8.7.1 Sampling procedure

The study participants were identified from the delivery register, where the patient's delivery information including the birth weight is usually recorded. All women who had delivered neonates with birth weight of 4000 grams and above were approached to participate in the study as the cases. Sequential enrolment was done until the sample size of 85 was reached.

For every case recruited, there was concurrent recruitment and enrollment of one participant as a control. This was done using simple random sampling from participants who delivered neonates with birth weight between 2500g and 3999g.

Once the participants have been identified, they were individually interviewed in a private area, by either the principal investigator or any of the trained research assistants. They were given information on the purpose of the study, possible risks and benefits of the study, rights as a volunteer and anything else to their point of clarity. They werealso given sufficient time to read, understand and ask any questions to their satisfaction. Once clear both verbal and written consent (Annex 2: Consent form) were administered to participants in both arms of the study before enrolment to those who chose to participate.

8.7.2 Data collection instruments

These included:

- *Tools*

Daily birth register: This was used to identify the cases and the controls.

A standard checklist: This was a standardized recruiting checklist to assist principal investigator and the two qualified research assistants (a registered clinical officer or a registered nurse) screen for inclusion/exclusion criteria in the process of recruitment of participants.

A structured questionnaire: This questionnaire was administered by the Principal Investigator or either of the two qualified and trained research assistants to the recruited participants. The two research assistants were a registered clinical officer and a registered nurse. These questionnaires were used to assess the bio-data and the sociodemographic characteristics of the mothers, the antenatal records, the information on the index pregnancy and the previous obstetric history. For each questionnaire, a unique identifier was assigned which matched the

participants' laboratory request form. Phlebotomy was done thereafter, and the standard operating procedures were duly followed during this process.

Data collection form/ laboratory request form: This was used to collect the data from the laboratory.

- Equipment

Electronic Digital Blood Glucose Testing Kit (Blue): this was used to check the RBS of the clients that were being screened (for exclusion of overt diabetes) for the purposes of recruitment.

Dirui machine; this was the machine used at the laboratory in the analysis of HbA1c.

8.7.3 Filling of the questionnaire

Once recruitment and consent had been obtained, a unique study number was allocated to the participant. The principal investigator and the trained research assistants administered structured questionnaires to the participants who filled the appropriate responses with regards to the participant's age, marital status, parity, last menstrual period, history of previous macrosomic deliveries. Ante-partum and intrapartum records were used as a source of corroborative reference to obtain information on height, weight at the time of delivery, antenatal visits, mode of delivery, gestational age at onset of labor, maternal and fetal complications during and after labor.

Once the questionnaires were filled, two milliliters of venous blood was immediately collected by the principal investigator and the research assistants which were used to obtain the RBS levels, by use of the Electronic Digital Blood Glucose Testing Kit (Blue), for exclusion of overt diabetes, and thereafter transported immediately in an EDTA bottle (purple topped vacutainer) at room temperature, to the laboratory for analysis.

Analysis was done at the Kenyatta National Hospital, Department of Laboratory Medicine biochemistry laboratory 16 which is two hundred meters from the obstetrics and gynecology department, by a registered medical laboratory technologist, within two hours of registration of the samples at the Biochemistry Laboratory reception. No storage was required. The standard technical operating procedure that was employed was Glycated Hemoglobin Enzymatic Assay Method (KNH/LAB MED-BIOCHEM/SYP/017F7 VERSION 1) (Annex 4).

The principal researcher and the research assistants were responsible for retrieving the results from the laboratory, after which they were kept under lock and key by the principal researcher.

A summary of data collection was as depicted in the following flow chart.

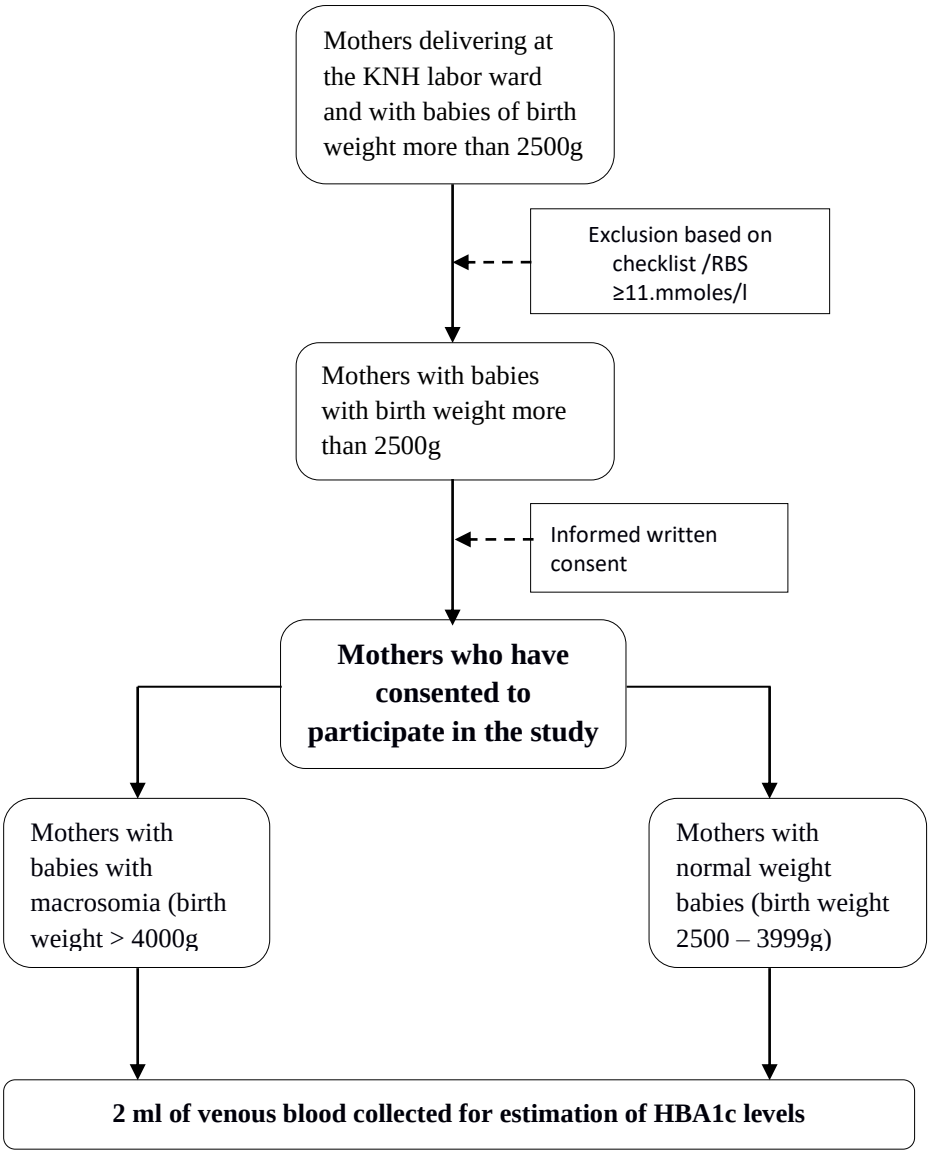


Figure 2: *Flow chart of Data Collection Procedure*

8.7.4 Data Quality Assurance

Pre-test of the study instrument was carried out in order to structure and modify the grammar used so as to avoid bias, misinterpretations, ambiguity and improve content validity. The research assistants were trained on the study methodology, how to conduct the interview and information retrieval.

The quality control measures in the analysis of the HbA1c was done as per the laid down protocols in the scheduled ICQ of the Technical Operating Procedures. (Annex 4)

8.7.5 Data Management and analysis

Data was received in paper form. The questionnaire and clinical data collection form were linked to the unique identifier lab forms. Data verification was done by the principal investigator on a daily basis. The verified data was then entered into the excel software, by two data clerks through the double data entry technique.

A biostatistician was consulted for the process of data entry and analysis. The verified data was thereafter imported to R software for data cleaning, categorization of variables and subsequent analysis. Missing data, duplicity of data and data inaccuracies were checked and corrections were done. The final master copy of received data was archived and backed up for future reference. A copy of this was now be used for analysis.

Data analysis was done using R software. Comparison of sociodemographic, obstetric and medical characteristics of women with macrosomic neonates disaggregated into elevated and normal HbA1c was done using students T-test for continuous variables and chi-square for categorical data as appropriate. The outcomes were presented in form of graphs, charts, and tables. Measures of dispersion such as the mean, median and mode will be used to describe continuous data variables such as age, BMI and birth weights for the neonates.

The risk factors associated with the development of macrosomia such as the BMI, parity, age were further analyzed and associations of variance determined. Multivariate analysis of the factors was done and tests of ANOVA conducted as appropriate. The association between elevated HbA1C levels and macrosomia was calculated and chi-square test used to establish the level of significance; HbA1c of 6.5% and above was considered elevated. Adjusted Odds ratio was be used to quantify any association as shown in the dummy tables (Annex 7).

8.8 Ethical considerations

Permission to conduct the research was sought from the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee. Verbal and written Informed consent was obtained from the study participants prior to recruitment, and they were accorded anonymity with the information treated with confidentiality.

Random Blood Sugar (RBS) was used instead of Oral Glucose tolerance test (OGTT) and fasting Blood Sugar (FBS) to exclude overt diabetes, in order to avoid keeping new parturients in a fasting state just for the sake of the study. The amount of blood taken (2 ml) is a very small amount that a one time off specimen would not affect the physiological functions of the participant. The collection of blood samples was done at the ward instead of the laboratory, to avoid newly delivered mothers from walking all the way to the biochemistry laboratory 200m away. Very sick patients or patients with other selected comorbidities are excluded from the study as by the exclusion criteria.

Data collected was kept under lock and key only accessible to the principal investigator. Participants had a right to withdraw from the study and the standard of care was not compromised on refusal to participate in the study.

Any obstetric or neonatal complications were managed according to existing protocols. Participants found with elevated HbA1c levels were contacted either in person or by phone and advised on follow up.

The result of the study was disseminated via presentation to the department of obstetrics and gynecology, University of Nairobi.

8.9 Study limitations

The anticipated study limitations included deliberate giving of incorrect information by the study participants and recall difficulties during the filling in of the questionnaires. To mitigate this, the standard checklists and the questionnaireswere very extensive. In addition, the use of collaborative history from the patient's files and antenatal clinic cards was done.

Selection bias when selecting the control group, but this was mitigated by use of random sampling of the controls.

The use of random blood sugar to exclude overt diabetes instead of Oral Glucose Tolerance Test. This is due to the fact that Kenyatta National Hospital does not have a protocol for follow up for gestational diabetes and chronic diabetes mellitus in pregnancy, and oral glucose tolerance test is not routinely done to all mothers at the antenatal clinic, hence no prior oral glucose tolerance test results. The risk factor screening that is done has been found to have low sensitivity and specificity(18).In addition, not all mothers who attend antenatal clinic at Kenyatta National Hospital deliver at the hospital, similarly, not all mothers delivering at Kenyatta National Hospital received antenatal care there or had an oral glucose tolerance test done and documented at the point of they received their focused antenatal care.

The quality of recording clinical findings during the antenatal period as clinicians do not fill all sections of the antenatal booklet, and some of the clients did not have their antenatal records as they attended different facilities.

9.0: RESULTS.

The study period was from1st August 2018 to 28th September 2018. A total of 255 mothers were screened. 170 participants, 85 in each arm, met the inclusion criteria and were recruited to the study. However, 2 mothers from the control group withdrew their consent during the study and therefore were not included in the analysis.

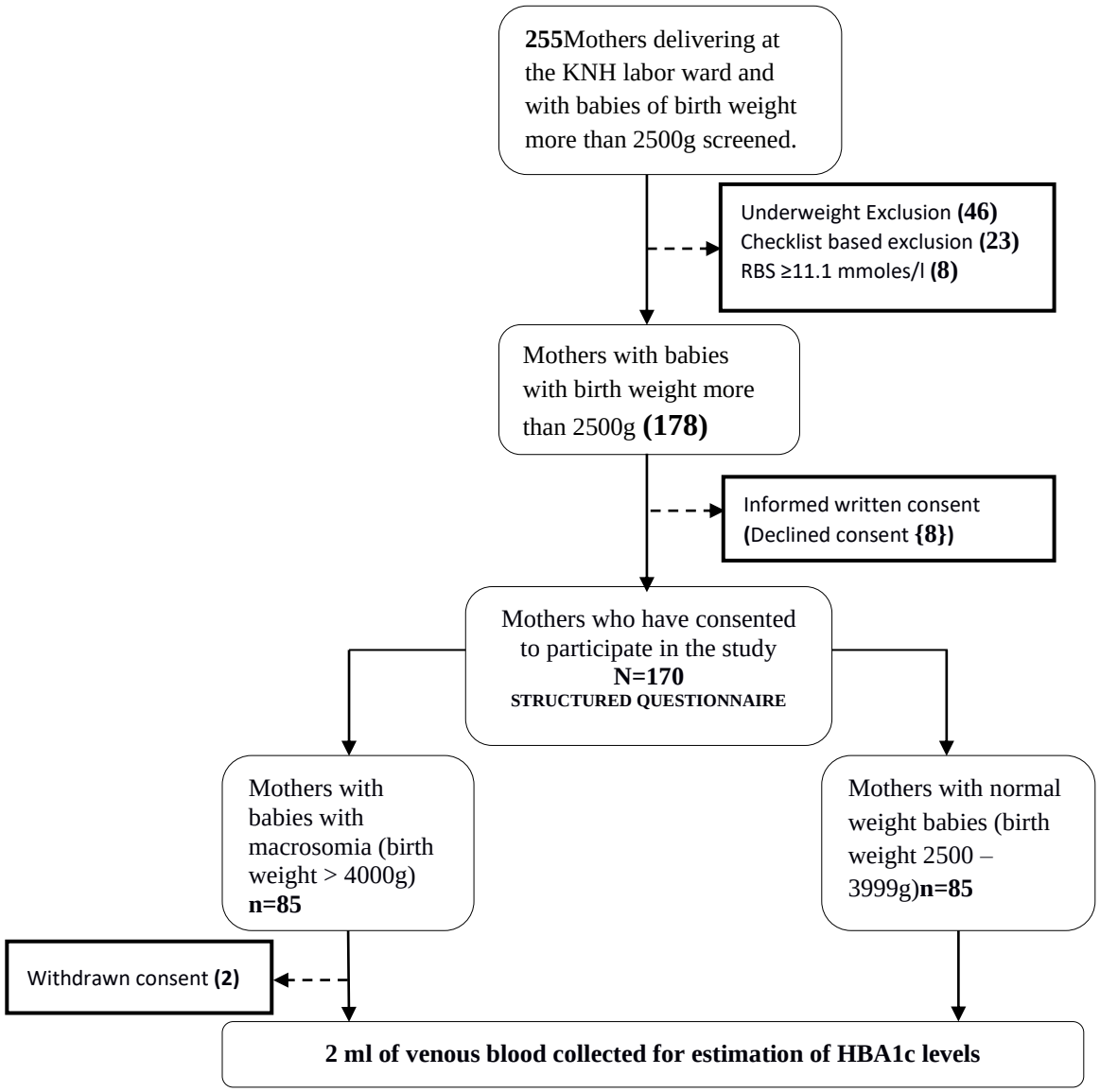


Figure 3: Flow chart for recruitment of study participants.

Table 1: Baseline descriptive analysis of immediate postpartum non-diabetic mothers delivering macrosomic babies at Kenyatta National Hospital.

Variable	Category	Normal (N = 83)	Macrosomia (N = 85)
Age(Years)		25.75(SD 5.23)	29.11 (SD 5.27)
Height(m)		1.68(SD 0.10)	1.74(SD 0.09)
Marital Status	Married	65(78.31 %)	82(96.47 %)
BMI	Overweight	2 (2.40%)	10 (11.76%)
Parity	PrimiGravida	39 (46.98%)	69 (81.28%)
FamilyPlanning history	Hormonal	38 (45.78%)	54 (63.53%)
History of DMScreening	Yes	53 (63.85%)	65 (76.47%)
No of ANC Visits	Less than 4Visits	26 (31.32%)	11 (12.94%)
History of LGA babies	Yes	6(7.22 %)	16(18.82 %)
Fetal Weight(kg)		3.23(SD 0.382)	4.27 (SD 0.25)
FetalSex	Female	44 (53.01%)	36 (42.35%)
HbA1c (%)		5.62(SD 0.60)	5.85 (SD 0.84)

Table 1: A total of 85 participants per arm were recruitedinto this study, two in the control group withdrew their consent. The mean age in the normal weight was 26 years vs 29 years in the macrosomic group, most participants were married(96% cases vs 78%control group). 2.4% vs 12%were overweight in the control vs the case group respectively. Most of the macrosomic group were primis (81%) and most participants in both groups had attended more than 4 ANC visits. The mean HbA1c value in the case group was 5.85% (SD 0.60) while that of the control group was 5.62% (SD0.84).

Figure 4: Individual HbA1c values of postpartum Non-Diabetic mothers delivering macrosomic babies at Kenyatta National Hospital.

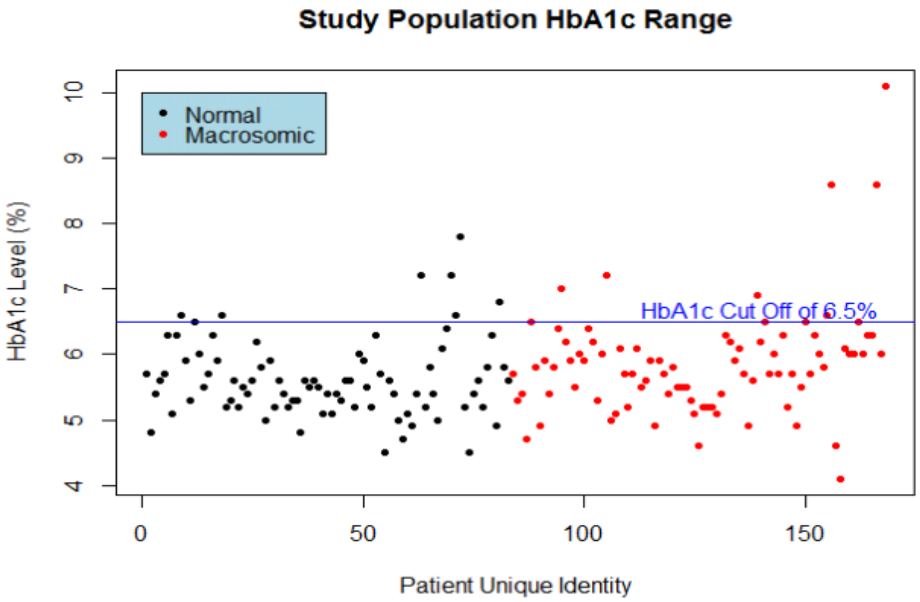


Figure 4: Scatter plot diagram of Individual HbA1c values in the two study subject groups. HbA1c range from 4.1%-10.1% in the case group vs 4.5%-7.8% in the control group.

Table 2:Frequency distribution and analysis of sociodemographic correlates of Elevated HbA1c inimmediate postpartum non-diabetic mothers delivering macrosomic babies at Kenyatta National Hospital.

		Normal weight (n=83)		Macrosomia (n=85)		OR	95% C.I	P value
	HbA1c(%)	<6.5 (%)	≥6.5 (%)	<6.5 (%)	≥6.5 (%)			
Age	< 35	70(84)	6(7)	67(79)	6(7)	1.34	(0.20,5.50)	0.714
	≥35	6(7)	1(1)	11(13)	1(1)			
Parity	Primi	38(46)	6(7)	14(16)	2(2)	0.38	(0.12,1.16)	0.089
	Multip	38(46)	1(1)	64(75)	5(6)			
Marital Status	Single	16(19)	2(2)	3(4)	0(0)			
	Married	60(72)	5(6)	75(88)	7(8)			

Table 2: There was no significant association found between elevated immediate postpartum HbA1c with age and parity.

Table 3: Frequency distribution and analysis of obstetric correlates of elevated HbA1c in immediate postpartum non-diabetic mothers delivering macrosomic babies at Kenyatta National Hospital.

		Normal weight (n=83)		Macrosomia (n=85)		OR	95% C.I	P value
	HbA1c(%)	<6.5 (%)	≥6.5 (%)	<6.5 (%)	≥6.5 (%)			
Hx LGA	Yes	6 (7)	0(0)	14(16)	2(2)	1.01	(0.15,4.1)	0.991
	No	47(57)	6(7)	64(75)	5(6)			
Prior FP Used	Hormonal	35(42)	3(4)	51(60)	3(4)	0.85	(0.65,1.11)	0.354
	Non hormonal	41(49)	4(5)	27(32)	4(5)			
Weight gain(Kgs)	≥16	3(4)	0(0)	3(4)	1(1)	1.32	(0.28,6.86)	0.724
	<16	73(88)	7(8)	75(88)	6(7)			
BMI	Obese>30	41(49)	3(4)	45(53)	3(4)	1.93	(0.26,9.88)	0.457
	Overweight 25-30	1(1)	1(1)	9(11)	1(1)	0.67	(0.20,2.25)	0.513
	Normal 18.5-24.9	34(41)	3(4)	24(28)	3(4)			
Fetal Sex	Male	37(45)	2(2)	45(53)	4(5)	0.66	(0.21,1.98)	0.459
	Female	39(47)	5(6)	33(39)	3(4)			
Gestation	Early term	67(81)	6(7)	77(91)	7(8)	0.09	(0.00,2.21)	0.021
	Term	9(11)	1(1)	1(1)	0(0)			
ANC Visits	< 4	24(29)	2(2)	11(13)	0(0)	0.57	(0.09,2.21)	0.471
	≥4	52(63)	5(6)	67(79)	7(8)			

Table 3: There was statistically significant association between Term gestation and elevated HbA1c. The odds of developing macrosomia with exposure to elevated HbA1c was 0.086 times less in the term group (p 0.021). No association was found between history of LGA, prior FP use, pregnancy weight gain, BMI, Fetal sex, Gestation and number of ANC visits with elevated HbA1c.

Table 4: Association between postpartum non-diabetic maternal HbA1c and Fetal Macrosomia at KNH.

		Normal weight (n=83)	Macrosomia (n=85)	OR	95% C.I	P value
HbA1c	≥ 6.5%	7(8.4%)	7(8.2%)	0.974	(0.32, 2.97)	0.714
	< 6.5%	76(91.6%)	78(91.8%)			

Table 4: There was no significant association found between elevated HbA1c and Fetal macrosomia.

Table 5: Multivariate Analysis of postpartum non-diabetic maternal HbA1c and Fetal Macrosomia at Kenyatta National Hospital.

		Normal weight (n=83)		Macrosomia (n=85)		AOR	(95% C.I)	P value
	HbA1c (%)	<6.5 (%)	≥6.5 (%)	<6.5 (%)	≥6.5 (%)			
Age	<35	6(7)	1(1)	11(13)	1(1)	1.91	(0.25, 10.57)	0.477
	≥35	70(84)	6(7)	67(79)	6(7)			
Parity	Multip	38(46)	1(1)	64(75)	5(6)	0.21	(0.34, 1.04)	0.064
	Primi	38(46)	6(7)	14(16)	2(2)			
Hx LGA	Yes	6 (7)	0(0)	14(16)	2(2)	1.93	(0.24, 11.36)	0.479
	No	47(57)	6(7)	64(75)	5(6)			
Prior FP Used	Hormonal	35(42)	3(4)	51(60)	3(4)	0.95	(0.22, 4.20)	0.938
	Non hormonal	41(49)	4(5)	27(32)	4(5)			
Weight gain(Kgs)	≥16	3(4)	0(0)	3(4)	1(1)	1.32	(0.28, 6.86)	0.383
	<16	73(88)	7(8)	75(88)	6(7)			
BMI	Obese>30	41(49)	3(4)	45(53)	3(4)	2.74	(0.31, 19.32)	0.318
	Overweight 25-30	1(1)	1(1)	9(11)	1(1)	0.84	(0.22, 3.37)	0.798
	Normal 18.5-24.9	34(41)	3(4)	24(28)	3(4)			
Fetal Sex	Male	37(45)	2(2)	45(53)	4(5)	0.56	(0.15, 1.96)	0.363
	Female	39(47)	5(6)	33(39)	3(4)			
Gestation	Early Term	67(81)	6(7)	77(91)	7(8)	1.30	(0.06, 11.94)	0.835
	Term	9(11)	1(1)	1(1)	0(0)			
ANC Visits	< 4	24(29)	2(2)	11(13)	0(0)	0.34	(0.02,2.36)	0.352
	≥4	52(63)	5(6)	67(79)	7(8)			

Table 5: Multivariate analysis reveals no significant association between immediate postpartum non-diabetic maternal HbA1c and Fetal macrosomia.

10.0: DISCUSSION

Establishing a biomarker for glucose regulation and macrosomia in the non-diabetic mother in a large obstetric unit like Kenyatta National Hospital would be of great value. Such a marker would increase surveillance and preparedness from the third trimester and subsequent follow up of the infant. HbA1c is a convenient, single non-fasting, easily available and easy to administer. It has less logistical requirement, and exhibits a less inter and intra laboratory variability.

In the present study,the HbA1c reference ranges were 4.1%-10% in the case group while 4.5%-7.8% the control group. The mean HbA1c was found to have no statistical difference in the two groups;5.85% (SD 0.84) in cases vs 5.62% (SD 0.60) in the controls. This is similar to most studies such as by Mayet and Jilal et al, Bacigalupo et al and Ronald Coen et al who also found no appreciable differences between the mean values of the two groups, i.e. 7.68% (SD 1.51) vs 7.65% (SD 1.15); 6.59% (SD 0.42) vs 6.51% (SD 0.46); 6.7%(SD 1.5) vs 6.5%(SD 0.2) respectively(40,44,47). However, our study showed a lower mean HbA1c value compared to the other two. This could be attributable to the difference in the determination of the HbA1c levels. The present study used the Latex agglutination method whereas the others used the Cation exchange chromatography.However, Sihem et al found the mean concentration of HbA1c to be significantly greater in the macrosomic group, (6.17% SD 0.85 vs 5.17% SD 0.57 $p < 0.001$)(43),attributable to the HbA1c cut off of 5.85% in that study.

Similarly, just like most other studies, this study revealed no statistical significance in correlation between elevated non-diabetic maternal HbA1c and age, BMI, parity, type of family planning previously used, history of previous macrosomic baby and number of ANC visits made, when the variables were subjected to logistic regression with a HbA1c cut off of 6.5% as per the WHO and ACOG guidelines(40,44). ACOG via the ADA guidelines Diabetes in pregnancy, however recommends stricter values for glycemic targets in pregnancy: 6.0%-6.5% for pregestational and gestational DM and ≤6.0% as the pregnancy progresses(31). However,there was statistically significant association between early term gestation and elevated HbA1c. The odds of developing macrosomia with exposure to

elevated HbA1c was 0.086 times less in the term group (p 0.021). None the less, its clinical significance remains unclear, and may need to be further evaluated and established.

Other studies however showed a contrary result to the present study, with different cut offs.R. Ensenauer et al in the PEACHES study demonstrated association between obese non-diabetic and high maternal HbA1c at delivery[adjusted odds ratio 3.56 (95% CI 1.64-8.02) p< 0.001] (42). This cohort study used a cut off of ≥5.7%, hencean increased HbA1c value of this value reflected a state of maternal dysglycemia in pregnancy with consequences to fetal growth. Coen et al showed a correlation between macrosomic infant withpre pregnancy obesity and greater pregnancy weight gain, withHbA1c cut off of 6.78%. This could also be attributable to the fact that macrosomia was considered to be >3.5kg, much lower than the WHO definition and a higherHbA1c cut off of 6.78% (47).

Controversies equally arise in the correlation between HbA1c and fetal macrosomia. Using a cut off 6.5%, the findings of the present study were similar to other studies, in that, no significant correlation was demonstrable between HbA1c and birth weight. The studies done by Mayet et al, Bacigalupo et al, Coen et al and Fadel et al showed no significant correlation(40,44,47). Contrary to these, Widness et al, Steel et al and Sihem et al's findings showed HbA1c to be a good predictor of fetal weight(p <0.01, and 5.85%, p <0.0001 respectively)(43,48,49).This series however noted that with a cut off of 5.5% there was marginal significant association between HbA1c and occurrence of fetal macrosomia (p=0.046). This case would suggest that the odds of a mother giving birth to a macrosomic baby is 0.63 times. Sihem et al also had similar results, in that, with a cut off of 5.85% (p <0.0001) HbA1c was considered as a risk factor for macrosomia(43). Other studies(29) have also suggested the use of a lower HbA1c cut off of 5.5% combined with fasting plasma glucose to diagnose glucose intolerance in the postpartum period.

The findings on this study were based on additional corroborative data ascertained from the patients' files and actual laboratory analysis served to avoid recall bias. Another strength is that it was the first of its kind in our set up therefore forming a baseline for other prospective studies. Most importantly, the study used an enzymatic assay method, which is an additional strength as enzymatic HbA1c assays have the highest specificity among all HbA1c assay methods. Our limitation was the lack of documented data, particularly OGTT as it is not routinely done in our set up during pregnancy to rule out DM, which is a potential

confounding, necessitating the use of exclusion RBS of ≥11.1mmoles/L for overt diabetes. This study however assumed that due to randomization during recruitment of study participants, any potential confoundingof DM would randomly fall on both arms of the study in an equal measure, and would therefore minimally affect our analysis.

From our findings, the present study concluded that;among non-diabetic mothers delivering macrosomic babies at Kenyatta national hospital,maternal age, parity, BMI, Number of ANC visits, previous family planning use and history of macrosomia do not correlate to elevated maternalHbA1c. Similarly, there was no significant association between immediate postpartum non-diabetic maternal HbA1c and fetal macrosomia.

We therefore do not recommend the use of HbA1c as a predictor of fetal macrosomia. Nonetheless, lower HbA1c cutoffs should be considered in subsequent studies. In addition, larger multicenter studies would be beneficial as there is no documented consensus for the reference ranges of HbA1c in healthy non-diabetics.

11.0: REFERENCES

1. Campbell S. Fetal macrosomia: a problem in need of a policy. Ultrasound Obstet Gynecol [Internet]. 2014 Jan 1 [cited 2017 Jun 15];43(1):3–10. Available from: http://doi.wiley.com/10.1002/uog.13268
2. Macrosomia: Background, Pathophysiology, Epidemiology [Internet]. [cited 2017 Jun 17]. Available from: http://emedicine.medscape.com/article/262679-overview?pa=HqVJjRZzSXnQas67b1ZedslPFoMlT6soGvxekRtJ554CCYNlDvCYvACN6pyvrf7G0Dn6bXqb5MIVz9mhzqdAxoWfkdv4Rj2QCl5B1YazCpo%3D
3. Swaminathan K, Veerasekar G, Kuppusamy S, Sundaresan M, Velmurugan G, Palaniswami N. Noncommunicable disease in rural India: Are we seriously underestimating the risk? The Nallampatti noncommunicable disease study. Indian J Endocrinol Metab [Internet]. 2017 [cited 2017 Sep 1];21(1):90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28217505
4. Meme N, Amwayi S, Nganga Z, Buregyeya E. Prevalence of undiagnosed diabetes and pre-diabetes among hypertensive patients attending Kiambu district Hospital, Kenya: a cross-sectional study. Pan Afr Med J [Internet]. 2015;22:1–12. Available from: http://www.panafrican-med-journal.com/content/article/22/286/full/
5. Legardeur H, Girard G, Journy N, Ressencourt V, Durand-Zaleski I, Mandelbrot L. Factors predictive of macrosomia in pregnancies with a positive oral glucose challenge test: Importance of fasting plasma glucose. Diabetes Metab [Internet]. 2014 Feb [cited 2017 Jun 14];40(1):43–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24051249
6. Sommer C, Sletner L, Mørkrid K, Jenum AK, Birkeland KI. Effects of early pregnancy BMI, mid-gestational weight gain, glucose and lipid levels in pregnancy on offspring's birth weight and subcutaneous fat: a population-based cohort study. BMC Pregnancy Childbirth [Internet]. 2015 Dec 3 [cited 2017 Jun 14];15(1):84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25879215
7. Li G, Kong L, Li Z, Zhang L, Fan L, Zou L, et al. Prevalence of macrosomia and its risk factors in China: A multicentre survey based on birth data involving 101 723 singleton term infants. Paediatr Perinat Epidemiol. 2014;28(4).
8. Mochhoury L, Razine R, Kasouati J, Kabiri M, Barkat A. Body mass index, gestational weight gain, and obstetric complications in Moroccan population. J

Pregnancy [Internet]. 2013 [cited 2017 Jun 15];2013:379461. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23936654

9. Fazzi C, Saunders DH, Linton K, Norman JE, Reynolds RM. Sedentary behaviours during pregnancy: a systematic review. Int J Behav Nutr Phys Act [Internet]. 2017 Mar 16 [cited 2017 Jun 14];14(1):32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28298219

10. Gaudet L, Ferraro ZM, Wen SW, Walker M. Maternal obesity and occurrence of fetal macrosomia: a systematic review and meta-analysis. Biomed Res Int [Internet]. 2014 [cited 2017 Jun 14];2014:640291. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25544943

11. Hou R-L, Zhou H-H, Chen X-Y, Wang X-M, Shao J, Zhao Z-Y. Effect of maternal lipid profile, C-peptide, insulin, and HBA1c levels during late pregnancy on large-for-gestational age newborns. World J Pediatr [Internet]. 2014 May 7 [cited 2017 Jun 14];10(2):175–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24801236

12. Alsammani MA, Ahmed SR. Fetal and maternal outcomes in pregnancies complicated with fetal macrosomia. N Am J Med Sci [Internet]. 2012 Jun [cited 2017 Jun 14];4(6):283–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22754881

13. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic Syndrome in Childhood: Association With Birth Weight, Maternal Obesity, and Gestational Diabetes Mellitus. Pediatrics [Internet]. 2005 Mar 1 [cited 2017 Jul 20];115(3):e290–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15741354

14. Shobha P, Mathen S, Abraham J. Glycosylated hemoglobin values in nondiabetic pregnant women in the third trimester and adverse fetal outcomes: An observational study. J Fam Med Prim Care [Internet]. 2016 [cited 2017 Jun 15];5(3):646. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28217599

15. Sletner L, Jenum AK, Yajnik CS, Mørkrid K, Nakstad B, Rognerud-Jensen OH, et al. Fetal growth trajectories in pregnancies of European and South Asian mothers with and without gestational diabetes, a population-based cohort study. PLoS One [Internet]. 2017 [cited 2017 Jun 14];12(3):e0172946. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28253366

16. Essel JK, Opai-Tetteh ET. Macrosomia - maternal and fetal risk factors. South African Med J [Internet]. [cited 2017 Oct 9];85(1):43–6. Available from: https://www.ajol.info/index.php/samj/article/view/149624/139127

17. Githaiga M. Outcomes of Pregnancy in DM at the Kenyatta National Hospital. University Of Nairobi; 1991.
18. Alex Nyakundi B, Qureshi MBChB Z, Obs M, Lecturer S. department of Obstetrics and Gynaecology in partial fulfilment of the requirements, for the award of a degree in Masters of Medicine in Obstetrics and Gynaecology. [cited 2017 Jul 19]; Available from: http://obsgyn.uonbi.ac.ke/sites/default/files/chs/medschool/obsgyn/Dr Alex Bosire.pdf
19. Omondi-Ogutu. East african MEdical Journal. East Afr Med J. 2011;88(9).
20. ARNOLD BUGAH BUNYOLI. Factors associated with fetal macrosomia at kenyatta national hospital. university of nairobi; 2016.
21. Koyanagi A, Zhang J, Dagvadorj A, Hirayama F, Shibuya K, Souza JP, et al. Macrosomia in 23 developing countries: An analysis of a multicountry, facility-based, cross-sectional survey. Lancet. 2013;381(9865).
22. Cunningham F, Leveno K, Bloom S, Spong CY, Dashe J. Williams Obstetrics 24/E. 2014 [cited 2017 Jul 28]; Available from: https://www.mheducation.com.au/media/wysiwyg/AUS/Professional/bookseller/2014/may/Medical_May.pdf
23. Lloreda-García JM, Sevilla-Denia S, Rodríguez-Sánchez A, Muñoz-Martínez P, Díaz-Ruiz M. Perinatal outcome of macrosomic infants born to diabetic versus non-diabetic mothers. Endocrinol y Nutr (English Ed [Internet]. 2016 Oct 1 [cited 2018 Mar 27];63(8):409–13. Available from: https://www.sciencedirect.com/science/article/pii/S2173509316300885
24. Ganongs Review Of Medical Physiology 25th Edition : Free Download & Streaming : Internet Archive [Internet]. [cited 2017 Jun 29]. Available from: https://archive.org/details/GanongsReviewOfMedicalPhysiology25thEdition
25. Amod A, Bh A-E. The 2012 SEMDSA Guideline for the Management of Type 2 Diabetes (Revised) Special Guideline Edition. JEMDSA J Endocrinol JEMDSA [Internet]. 2012 [cited 2017 Jul 19];17(2):1–95. Available from: www.jemdsa.co.za
26. Khalafallah A, Phuah E, Al-Barazan AM, Nikakis I, Radford A, Clarkson W, et al. Glycosylated haemoglobin for screening and diagnosis of gestational diabetes mellitus. BMJ Open [Internet]. 2016 Apr 4 [cited 2017 Jun 30];6(4):e011059. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27044587
27. Renz PB, Cavagnolli G, Weinert LS, Silveiro SP, Camargo JL. HbA1c Test as a Tool

in the Diagnosis of Gestational Diabetes Mellitus. Wagner B, editor. PLoS One [Internet]. 2015 Aug 20 [cited 2017 Sep 1];10(8):e0135989. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26292213

28. Diabetes in pregnancy: management from preconception to the postnatal period | Guidance and guidelines | NICE. [cited 2017 Jul 19]; Available from: https://www.nice.org.uk/guidance/ng3/chapter/1-recommendations#preconception-planning-and-care-2

29. Yu H, Qi X, Wang X. Application of glycated hemoglobin in the perinatal period. Int J Clin Exp Med [Internet]. 2014 [cited 2017 Aug 29];7(12):4653–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25663962

30. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study [Internet]. [cited 2017 Jul 28]. Available from: http://www.medscape.com/viewarticle/759187

31. ADA Guidelines Diabetes in Pregnancy GDM | NDEI [Internet]. [cited 2017 Jul 19]. Available from: http://www.ndei.org/ADA-diabetes-management-guidelines-diabetes-in-pregnancy-GDM.aspx.html

32. Herranz L, Saez-de-Ibarra L, Grande C, Pallardo LF. Non-glycemic Dependent Reduction of Late Pregnancy HbA1c Levels in Women With Type 1 Diabetes. 2007 [cited 2017 Sep 5]; Available from: http://care.diabetesjournals.org/content/diacare/early/2007/03/15/dc06-2568.full.pdf

33. O ’connor C, O ’shea PM, Owens LA, Carmody L, Avalos G, Nestor L, et al. Trimester-specifi c reference intervals for haemoglobin A 1c (HbA 1c) in pregnancy. Clin Chem Lab Med. 2012;50(5):905–9.

34. Versantvoort ARE, van Roosmalen J, Radder JK. Course of HbA1c in non-diabetic pregnancy related to birth weight. Neth J Med [Internet]. 2013 Jan [cited 2017 Jun 16];71(1):22–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23412819

35. Hiramatsu Y, Shimizu I, Omori Y, Nakabayashi M. Determination of reference intervals of glycated albumin and hemoglobin A1c in healthy pregnant Japanese women and analysis of their time courses and influencing factors during pregnancy. Endocr J [Internet]. 2012 [cited 2017 Jun 16];59(2):145–51. Available from: https://www.jstage.jst.go.jp/article/endocrj/59/2/59_K10E-410/_pdf

36. Radder JK, Roosmalen J Van. HbA1c in healthy, pregnant women. Neth J Med 63: 256-259. 2017;(April):256–9.

37. Khalafallah A, Phuah E, Al-Barazan AM, Nikakis I, Radford A, Clarkson W, et al.

Glycosylated haemoglobin for screening and diagnosis of gestational diabetes mellitus. BMJ Open [Internet]. 2016 Apr 4 [cited 2017 Jun 16];6(4):e011059. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27044587

38. Trusler J, Meyer M, Fedler C, Du Plessis M. Screening and diagnosing Diabetes Mellitus during pregnancy: Revised Criteria Why revise the Gestational Diabetes Mellitus criteria ? [cited 2017 Jun 30]; Available from: https://www.ampath.co.za/wp-content/newupload/2014/11/pathchat_15-FINAL.pdf

39. Mañé L, Antonia Flores-Le Roux J, Benaiges D, Rodríguez M, Marcelo I, José Chillarón J, et al. Role of first trimester HbA1c as a predictor of adverse obstetric outcomes in a multi-ethnic cohort. [cited 2017 Sep 5]; Available from: http://public-files.prbb.org/publicacions/85d19110-993a-0134-724a-00155df14f0e.pdf

40. Bacigalupo G, Langner K, Saling E. Glycosylated hemoglobin (HbA1), glucose tolerance and neonatal outcome in gestational diabetic and non-diabetic mothers. J Perinat Med [Internet]. 1984 [cited 2018 Jan 16];12(3):137–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6502440

41. Bhavadharini B, Mahalakshmi M, Deepa M, Harish R, Ranjit U, Anjana R, et al. Elevated glycated hemoglobin predicts macrosomia among Asian Indian pregnant women (WINGS-9). Indian J Endocrinol Metab [Internet]. 2017 [cited 2017 Sep 1];21(1):184. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28217520

42. Ensenauer R, Brandlhuber L, Burgmann M, Sobotzki C, Zwafink C, Anzill S, et al. Obese nondiabetic pregnancies and high maternal glycated hemoglobin at delivery as an indicator of offspring and maternal postpartum risks: The prospective PEACHES mother-child cohort. Clin Chem. 2015;61(11).

43. Sihem Chaouachi, Emira Ben Hamida, Raja Belhaj, Ahlem Bezzine, bashir Zouari, semia BelHaj Ahmed, et al. Postpartum levels of glycosylated hemoglobin in mothers of large babies: A Prospective Study. Tunis Med J [Internet]. 2009 [cited 2018 Jan 17];87(09):589–95. Available from: https://translate.google.com/translate?hl=en&sl=fr&u=http://www.latunisiemedicale.com/article-medicale-tunisie_1160_en&prev=search

44. Mayet N, Jialal I, Naicker RS, Moodley J, van Middelkoop A. Maternal glycosylated haemoglobin values after delivery of large infants and unexplained stillbirths. S Afr Med J [Internet]. 1983 Oct 29 [cited 2017 Jun 16];64(19):739–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6623284

45. Katreddy M V, Pappachan JM, Taylor SE, Nevill AM, Indusekhar R, Nayak AU. Hemoglobin A1c in early postpartum screening of women with gestational diabetes. World J Diabetes [Internet]. 2013 Jun 15 [cited 2017 Sep 1];4(3):76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23772276

46. Shi P, Yang W, Yu Q, Zhao Q, Li C, Ma X, et al. Overweight, Gestational Weight Gain and Elevated Fasting Plasma Glucose and Their Association with Macrosomia in Chinese Pregnant Women. Matern Child Health J [Internet]. 2014 Jan 20 [cited 2017 Jun 14];18(1):10–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23784612

47. Coen RW, Porreco R, Cousins L, Sandler JA. Postpartum glycosylated hemoglobin levels in mothers of large-for-gestational age infants. Am J Obstet Gynecol [Internet]. 1980 Feb 1 [cited 2018 Jan 16];136(3):380–2. Available from: http://linkinghub.elsevier.com/retrieve/pii/0002937880908650

48. Pollak A, Brehm R, Havelec L, Lubec G, Malamitsi-Puchner A, Simbrunner G, et al. Total glycosylated hemoglobin in mothers of large-for-gestational-age infants: a postpartum test for undetected maternal diabetes? Biol Neonate [Internet]. 1981 [cited 2018 Jan 16];40(3–4):129–35. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7284498

49. Steel JM, Thomson P, Johnstone F, Smith AF. Glycosylated Haemoglobin Concentrations In Mothers Of Large Babies [Internet]. Vol. 282, British Medical Journal (Clinical Research Edition). BMJ; [cited 2018 Jan 17]. p. 1357–8. Available from: https://www.jstor.org/stable/29501692

12.0: ANNEXES

Annex 1: Study Questionnaire

Date: _____Case: [ ] Control: [ ] U.A No._____

Section A: Bio data and Socio - demographic characteristics

1. Age in complete years……Y.O.B…….
2. Marital Status: Single [ ], Married [ ], Separated [ ], Divorced [ ], Widowed [ ].
3. Religion: Christian [ ], Muslim [ ], others (specify)…….
4. Nationality……..
5. Ethnic tribe…….
6. Usual residence…….……..……
7. Weight (in kilograms):
    a. Last weight recorded after 37 weeks of gestation or before delivery……
    b. Weight in the 1st trimester or preconception period……..…….……
    c. Weight Change…….……..……..…
8. Height (in meters) ……
9. Body mass index:

$$\frac{\text{Weight (7a)}}{(\text{Height (8)})^{2.}\,\text{K}}$$

BMI_____

Section B: Antenatal Records

1. Antenatal clinic attendance: Yes [ ] No [ ]
2. Number of visits…….…….
3. Antenatal profile

    a) Antenatal profile done: Yes [ ] No [ ]

    b) If 3a is yes, Hemoglobin levels……...g/dl

    Blood Group (ABO)…… (Rhesus)……

    VDRL…..…….

    HIV……....
4. Diabetes screening

a) Screening of diabetes in latest pregnancy, Yes [ ], No [ ] if yes method of screening…….……...

b) History of Diabetes, Yes [ ] , No [ ]

c) If 4a is yes on medication [ ] Diet Control [ ]

Section C: Latest Pregnancy

1. Parity…….…….……....
2. Post natal day number (1, 2, 3, 4 or 5)……...
3. Gestation at time of delivery……..…. (Weeks)…....……. (Days).
4. Mode of Delivery:
   a) Spontaneous vaginal delivery. [ ]
   b) Assisted Vaginal delivery [ ]
   c) Caesarean section [ ]
5. Fetal Outcome
   a) Gender: Male [ ] Female [ ]
   b) Live Infant [ ]
   c) Still Birth [ ]
   d) NBU admission, [ ]

Section D: Previous Obstetric history

1. Previous history of big baby Yes [ ] No [ ]
2. a) History of family planning Yes [ ] No [ ]
   b) If 3a is yes, method of family planning……..…….

Section F: Blood Sample

1. Blood sample taken Yes [ ] No [ ]
2. RBS (mmoles/l)…….……..
3. If no, document the exclusion criteria used……...……..…..…….
4. Color of vacutainer code ……..……

Annex 2: Consent form

Part 1: Information Sheet

Title of the study: Association between non-diabetic maternal HbA1c and fetal macrosomia at Kenyatta National Hospital.

Principal Investigator: Dr. Anne Effie A. Ouma MBChB, Mmed Obs/Gyn (Student)

Introduction

Dr. Anne Effie A. Ouma is a post graduate student in the department of Obstetrics and Gynecology, University of Nairobi, currently carrying out a study: Association between HbA1c with fetal Macrosomia at Kenyatta National Hospital. The purpose of this consent form is to give you the information that you will need to decide whether or not to be a participant in the study. Feel free to ask any questions about the purpose of the research, what happens if you participate in the study, possible risks and benefits, your rights as a volunteer and anything else in this form that is not clear. When we have answered all your questions, you may decide to be in the study or not. This process is called the "informed consent". You are invited to participate in this study and can take all the time you need to make the decision. Kindly take time to read through the information provided. If there are any questions, comments or clarifications, please feel free to ask the principal investigator or the research assistants.

May I continue? YES/NO

This study has been approved by the Kenyatta National Hospital-University of Nairobi Ethics and Research committee protocol No._____

PURPOSE OF THE STUDY / WHAT IS THIS STUDY ABOUT?

The aim of this study is to collect information and find out the association between HbA1c a substance that is associated with increased glucose level in the blood, with the delivery of a large baby (equal to or more than 4000 grams) at Kenyatta National Hospital, this is in order as to better manage our patients and reduce the adverse outcomes for both the mother and the baby, and allow for adequate follow up if need be. Participants in this study will be asked questions about their age, weight, attendance to antenatal clinic, previous deliveries if any, and any medications they take. Thereafter, participants will have a choice to undergo a blood test to determine the level of HbA1c. There will be approximately one hundred and seventy

participants in this study, randomly chosen. We are asking for your consent, to consider participating in this study.

PROCEDURE / WHAT WILL HAPPEN IF YOU DECIDE TO BE IN THIS STUDY?

If you agree and decide to participate in this study, the following will happen:

You will have to sign and also date the consent form. A copy of the completed form will be made and given to you to keep. You will be interviewed in a private area, where topics such as medical history and medications taken will be covered. Afterwards you will then complete a questionnaire that will be provided to you. The interviewer will be present for any questions or clarifications you may have. Once you have filled, a small sample of blood (about 2 milliliters) will be taken from your forearm in order to test for the HbA1c. This blood sample will be taken to the Kenyatta National Hospital laboratory.

We will ask for a telephone number where we can contact you if necessary. If you agree to provide your contact details, it will only be used by people in this study and never be shared with others. The reason we may need to contact you is if we found any concerns such as elevations of the HbA1c that would require you to be followed up closely thereafter.

POTENTIAL RISKS AND DISCOMFORT

There are no anticipated risks associated with this study besides the minimal physical pain of the injection during drawing of blood.

POTENTIAL BENEFITS

You will benefit by receiving free testing, and free health information. We will refer you to specialized care and support where necessary. The information given to the research team by you is aimed to better understand and manage patients who deliver large infants. You will also be able to better understand your condition, so as to be better prepared in future pregnancies. In case the test is higher than expected, you will be called personally and informed on what follow up you will need.

CONFIDENTIALITY

The information that you give will be very confidential. No names will be used and instead, we will assign you a unique identification number in a password protected computer

software. Only the research team will have access to the information provided. We will keep all your paper record which under lock and key. Upon completion of the study, results will be shared only to the relevant parties. However, no system of protecting your confidentiality can be absolutely secure, so there is still a small possibility that someone could find out that you were in this study and find out information about you.

WILL BEING IN THIS STUDY COST YOU ANYTHING?

No. the test will be done free of charge.

RIGHT TO REFUSE/CAN YOU WITHDRAW FROM THE STUDY?

Participation in the study is solely voluntary, therefore, you do not have to take part if you do not desire to. You may decide to withdraw from the study at any time you wish. Declining from participating or withdrawing will not in any way influence your current or future treatments/interventions and all your rights will be respected.

PART 11: CONSENT FORM (STATEMENT OF CONSENT)

Participant's statement

I have read and understood the information provided above. I have been fully explained to about the study and have had the opportunity to ask questions which have been answered to my satisfaction in a language I understand. The risks and the benefits have been explained to me. I freely agree to participate in this study voluntarily and have not been coerced/manipulated or bribed in any way, and that I may choose to withdraw at any time.

I understand that all efforts will be made to keep information regarding my personal identity confidential.

I agree to participate in the study	YES	NO
I agree to have a sample of my blood taken for the study	YES	NO
I agree to provide contact information for follow up	YES	NO

Participant's Name: ---------- OR Thumb Print of Participant

Participant's Signature: ---------- Date: ----------

Witness's Signature: -- ---------- Date: ----------

Statement by Researcher

I the undersigned have explained to the participant about the study. I have given the participant an opportunity to ask questions relevant to the study, and I have answered correctly to the best of my abilities. I have confirmed the participant has given consent voluntarily.

Name of Researcher: ----------

Signature: ----------

Date: ----------

Who to contact

If you have any further questions, concerns or clarifications about the study, please feel free to contact:

Dr. Anne Effie A. Ouma (Principal Investigator)
P.O Box 298-00502 NAIROBI
Nairobi
Tel: 0723989641, Email: effanne@gmail.com

Dr. George Gwako (MBChB, Mmed Obs / Gyn.)-Supervisor
Lecturer, Department of Obstetrics and Gynecology,
University of Nairobi,
Consultant obstetrician/Gynecologist
Kenyatta national hospital
Tel:0722992268, Email: gngwako@gmail.com

Dr. Maureen Owiti (MBChB, Mmed Obs /Gyn,)-Supervisor
Consultant obstetrician/ Gynecologist
Kenyatta National Hospital,
Honorary Lecturer, Department of Obstetrics and Gynecology,
University of Nairobi Tel: 0722274488 Email: drmaureenowiti@gmail.com

Prof Mark L. Chindia,
Secretary, KNH-UoN ERC
P.O Box 19679-00202 Nairobi.

Tel: (254-020) 2726300-9, Email: uonknherc@uonbi.ac.ke

FomuyaIdhiniyaUtafiti

Sehemuya kwanza: Maelezo

MadayaUtafiti: Uhusianokatiyakujifunguamwanaaliyenauzitomkubwana "HbAckatikahospitalikuuya Kenyatta.

MtafitiiMkuu: Daktari Anne Effie A. Ouma., Mwanafunzikatikaidarayauzazinamagonjwanawanawake

Utangulizi

Daktari Anne Effie Ouma nimwanafunziwa Chuo Kikuu cha Nairobi anaangaziamaswalayauzazinaafyayawanawakekwajumla. Ninafanyauchunguzikuhusu: Uhusianokatiyakujifunguamwanaaliyenauzitomkubwana 'HbA1c' (ambayohutusaidiakuelewajinsisukarihudhibitiwamwilini). Maudhuiyaridhaahiini kukupa maelezoutakayohitajikutumiakatikauamuziyakushiriki au kutoshirikikatikauchunguzihuu. Uwe hurukuulizamaswaliyoyotekuhusulengo la utafitihuu, ninikinachotokeaukishirikikatikautafiti, faidanahasarayakushiriki,nahakizakokamaaliyejitoleakushiriki, nachochotekileambachohakielewekivyema.

Tutakapokuwatumejibumaswaliyakoyote,utaamuwakushirikikatikauchunguzi au la. Mchakatohuuunaitwaridhaayamaelezo, maanake "informed consent." Unakaribishwakushirikikatikauchunguzihuunawawezachukuamudawowoteunayoitajikufanya uamuziuamuziwakushirikinikwahiariyako. Kama kunamaswaliyoyote au ufafanuziutakaohitajika, kuwahurukuwasilianamdadisimkuu au manaibu wake.

Je, nawezakuendelea? NDIO/ LA

Utafitihuuumekubaliwanakamatiyamaadiliyautafitiyahospitalikuuya Kenyatta nachuokikuu cha Nairobi, itifakinambariP86/02/2018.

LENGO LA UTAFITI/ UTAFITI WAHUSU NINI?

Uchunguzihuuunaniayakukusanyataarifailikutambuakamakunauwezekanowauhusianowowet eulekatiya HbA1c, kituambachokwawingihuusiananakuongezekakwakiwango cha sukarimwilini, nakujifunguamtotowauzitowajuu(gramunneelfu/4000g) hasaakwa wale

ambaohawanaugonjwawakisukari.
Kugunduauhusianohuuunawezakutusaidiakuboreshamatibabu, kupunguzamadhara,nahatakutuwezeshakutambuawatuwanaohitajikufuatiliwa Zaidi. Ukikubalikushiriki, utaulizwamaswalakuhusuumri, uzani, kuhudhuriaklinikiyaakina mama wajawazito, uzaziuliotanguliaikiwaipo, namadawayoyote. Baadayeutakuwanachaguo la kufanyiwauchunguziwadamukupatakiwango cha HbA1c. Takribanwatumiamojanasabiniwatashiriki. Tunaombaridhaayako, kukubalikushiriki.

NAMNA / NINI KITAKACHOTOKEA UKISHURIKI?

Ukikubalikushirikikwautafiti, zifuatazozitafanyika:

Utahitajikakutiasahihinatarehekwafomuyaidhini/makubaliano.
Nakalayafomuhiiitatengenezwanautapewamojakuwekanakubakinayo.
Utafanyiwamahojianomahaliyakibinafsi,kuhusumadatofautikama vile magonjwayoyote, au madawayoyoteambayohuendaikawahutumia.baadayeutapewafomuiliyonamaswaliambayoutahitajikakujibu.
Mdadisiatakuwepokujibumaswaliyoyoteambayohuendaukawanayoiwapomaelezo Zaidi yatahitajika.
Baadayakujazafomu,
damukidogoitachukuliwamkononiambayoitapelekwakwamaabarayahospitalikuuya Kenyatta kupimakiwango cha HbA1c.
Tutaombanambariyakoyasimuambayotutawasilianananaweweijapoitahitajika.Ukikubalikutupa maelezoyamawasiliano,
itatumikatuunawahusikawautafitihuupekeenahaitashirikishawenginekamwe.
Tunawezawasilianananaweikiwakiwango cha HbA1c itakuwajuu, kiwango cha kuhitajikufuatiliwa.

UWEZEKANO WA HATARI NA USUMBUFU

Hakunahasarainayotarajiwakatikauchunguzihuuisipokuwauchungukidogowasindanoyakutoakiasikidogo cha damu.

FAIDA INAYOTARAJIWA

Utafaidikakwakupatakipimo cha bure, namafunzoyahabarizaafya. Matokeoyauchunguzihuuyanalengo la kutoamatibabu bora

kwawaadhiriwawanaojifunguawatotowaliona kilo kupitailiyoyakawaidanakuboreshaafyakwavizazivijavyo. Ikijaikawakwambakiasi cha HbA1c imepitakiasi, mtafitimkuuatakupigiasimukukuelezeamaelezoyajisnsiutahitajikufuatiliwa Zaidi.

USIRI

Habariutakayopeanaitakuwayasiri. Matokeoyauchunguzihuuyatawekwasiri. Hakunamajinayatatumika.
Utapewanambarihalisiitakayowekwakwakompyutailiyotunzwananenosiri.Wadadisituundiowatawezakupatahabarihii. Rekodizakaratasizitafungiwachiniyakifulinaufunguo. Matokeoyauchunguziyatakabidhiwakwawanaohusika. Hatahivyo, hakunamfumoambaounausalamahalisi,
kwahiyokunauwezekanoingawamdogomtukupatahabarikuwaukokwenyeutafitinakupatahabariyako.

JE, KUSHIRIKI KWENYE UTAFITI UTAKUGARIMU CHOCHOTE?

Hapana/la. Kipimokitakuwa cha bure.

HAKI YA KUKATAA/ WAWEZA KUJIONDOA KWENYE UTAFITI?

Kushirikikatikauchunguzihuu, nikwakujitoleakwahiariyako. Unahakiyakujitoakwauchunguziwakatiwowotebilayamadharayoyote,
namatibabuyakobadoyataendeleakwanjiamwafakabilamatatizoyoyote.
Kutoshirikinihakiyako, nahakihiiitaheshimiwa.

SEHEMU YA PILI: MAKUBALIANO (TAARIFA YA IDHINI)

Taarifayamshirika.

Nimesomananikaelewaujumbeuliokohapajuu.

Nimeelezewakikamilifukuhusuutafitihuunanilipatanafasiyakuulizamaswaliyaliyojibiwakwau kamilifukutumialughaninayoielewa. Nimeelezewakuhusufaidanahasarayautafiti. Nimekubalikushirikikatikautafitihuubilakulazimishwaamakupewahongo,nanawezakuchaguak utoshirikiwakatiwowote.

Naelewakwambajuhidizotezitafanywakuwekausirikuhusuhabariyanguyakibinafsi.

Nimekubalikushirikikwenyeutafiti	NDIO	HAPANA/LA
Nimekubalikutolewasampuliyadamu cha utafiti	NDIO	HAPANA/LA
Nimekubalikutoahabariyamawasilianoyakufuatiliwa	NDIO	HAPANA/LA

Jina la Muhusika: …… AU AlamayaKidole…….

Saini yaMuhusika: ……

Tarehe: ……..

Saini yaShahidi: …… Tarehe: …….

TaarifayaMdadisi

Nimewaelezeawahusikakuhusuutafitinanikawapatianafasiyakuulizamaswali.

Nimeyajibumaswaliyoteniwezavyo.

Nimehakikishakuwawanaohusikawamekubalikwahiariyao.

Jina la mdadisi: ……..……

Saini: ……..

Tarehe: ……**…**

Kuwasiliana

Kwa maswaliyoyote au ufafanuziwowotewasilianana:

Daktari Anne Effie A. Ouma
Mtafitimkuu
Sanduku la Posta: 298-00502
Nairobi
Nambariyasimu: 0723989641
Baruapepe: effanne@gmail.com

Daktari George Gwako (MBChB, Mmed Obs / Gyn.)-Msimamizimkuu
Mhadhiri, Idarayauzazinamagonjwayawanawake,
Chuo Kikuu Cha Nairobi,
Mshaurimkuuwauzazinamagonjwayawanawake,
HospitaliyaKitaifaya Kenyatta
NambariyaSimu: 0722992268
Baruapepe: ggwako@gmail.com

Daktari Maureen Owiti (MBChB, Mmed Obs /Gyn,)-Msimamizi
Mshaurimkuuwauzazinamagonjwayawanawake,
HospitaliyaKitaifaya Kenyatta,
Mhadhiriwaheshima, IdarayaUzazinamagonjwayawanawake,
Chuo Kikuu cha Nairobi NambariyaSimuTel: 0722274488
BaruaPepe: drmaureenowiti@gmail.com

Profesa Mark L. Chindia,
Katibu, KNH-UoN ERC
Sanduku la Posta: 19676-00202,
Nairobi.
Nambariyasimu: (254-020)2726300-9
BaruaPepe: uonknh_erc@uonbi.ac.ke

Annex 3a: Standardized Recruitment Check List

Medical History Screen	**YES**	**NO**
Do you have a history of Diabetes Mellitus?		
Have you ever been screened/ tested for diabetes? Comment on the method used…….		
Have you ever had glycosuria?		
If have been tested for diabetes, were you told you have DM or not?		
Have you ever been treated for diabetes mellitus?		
Have you ever been treated for any thyroid disease?		
Do you have sickle cell disease? Have you ever been investigated for it?		
Have you ever been treated for chronic kidney disease/kidney problems?		
Have you ever been treated for anemia in the last three months?		
Have you been transfused in the last three months?		
Have you been transfused after current labor process?		
Have you ever been treated for any bleeding disorder?		
Has your doctor ever prescribed for you any form of specific diet?		
Have you ever been treated for hypertension?		
Have you ever had thyroid any surgeries?		
If yes to surgeries, please specify.		
Do you attend any medical clinic?		
If yes to medical clinic please specify		

Annex 3b: Standardized Recruitment Check List

Drug history: Have you ever used any of the following medication?	YES	NO
Insulin		
Metformin(Glucophage,glucomet,glyf,merforal, forminal,ranophage,tabrophageglumetza, baymet,bigomet,conformin, riomet//glucovance)		
Chlorpropamide(diabecon,diabemide,diabenese,diabetex,dibonis,westcopramide)		
Glibenclamide(nogluc,Euglucon, betanase, daonil,glibenil,glibesyn, glibetics,gliborol,glicon,melix,)		
Gliclazide (diacron,diamicron,diapro,glidiet,glizid, reclide,ziclin)		
Glipizide (bimode, diactin, glipistin, glucosid,glynase)		
Gluquidone (glulenor)		
Pioglitazone(glitas,glustin,pioday,pioglit,piogluc,pioz)		
Rosiglitazone (avindia, avandamet)		
Any antidiabetic/combination medication(novonorm, novonodisk, premil)		
Thyroxin(eltroxin, tiroy)		
Propiolthyuracil		
Carbimazole (cabrel, antithroxin, neomercazole)		
Vitamin C (ascorbic acid,flavorola,redoxon,limcee)		
Hydroxyurea		
Erythropoietin		
Are you currently on any medication? If yes, which medication? ARVs?		

Annex 4a: Analysis Technique Insert

2. Blank absorbance: A≤0.700
3. The minimum test limit: test normal saline 20 times repeatedly, and the minimum test limit is determined as 2% by average +2 times SD.

♦Standardization Traceability

The constant value of calibrator can be traced to international reference BCR-405.

♦Matters Need Attention

1. Cautions for Operation

1.1 The product is only for in vitro diagnosis.

1.2 Do not add reagent during the test.

1.3 Avoid the contact between the reagent and skin mucous membrane. If it is accidentally splashed on skin or eyes, wash damage parts immediately with plenty of water, in serious cases, medical care treatment should be seek immediately.

2. Cautions for safety

2.1 Consider the product as dangerous materials that may cause HIV, HBV, HCV and other infections. To avoid the risk, use single-use gloves.

2.2 Avoid contact with skin, clothes, and eyes. Once in contact with skin or clothes, rinse the contact part with plenty of water, and go to see a doctor.

2.3 The samples and waste liquid have potential infectious risk, and the user should manage them according to the laboratory safety operation rule, local laws and regulations.

♦Reference

1. Bunn,H. F. et al. Diabetes 1981；30：613.
2. Trivelli L. A. et al. N Engl J MED 1971; 284: 353.
3. NCCLS.Interference Testing in Clinical Chemistry;Approved Guideline,2005.

♦Date of Approval and Revision: 07/2017

♦Packaging Specification

No.	Specifications			Type
232021202002	R1: 2×15mL	R2-A: 1×0.5mL R2-B: 1×9.5mL	Calibration sample: 5×1mL	DIRUI CS-400/600/800/1200/1300/1600/6400 Package
232021202001	R1: 2×15mL	R2-A: 1×0.5mL R2-B: 1×9.5mL	Calibration sample: 5×1mL	DIRUI CS-240/300 Package
232021202010	R1: 2×15mL	R2-A: 1×0.5mL R2-B: 1×9.5mL	Calibration sample: 5×1mL	DIRUI CS-T Package

♦P.S.: CS Series Auto-Chemistry analyzer parameters

Model	CS-240	CS-300	CS-400	CS-600	CS-800	T200	T240	T300	CS-1600	CS-6400	CS-1300
Name	HbA1C	HbA1C	HbA1C	HbA1C	HbA1C	HbA1C	HbA1C	HbA1C	HbA1C	HbA1C	HbA1C
Unit	%	%	%	%	%	%	%	%	%	%	%
Method	2 point end	2 point end	2 point end	2 point end	2 point end	2 point end	2 point end	2 point end	2 point end	2 point end	2 point end
Time	20	20	10	10	10	15	13	10	9	12	9
Photometric point	20-31	20-31	20-31	22-41	21-31	27-40	28-43	28-47	19-31	19-31	21-33
Main wavelength	660	660	660	660	660	660	660	660	660	660	660
Sub wavelength	0	0	0	0	0	0	0	0	0	0	0
Reagent R1/T1	300	300	300	300	300	300	300	300	300	300	300
R2/T2	100	100	0	100	0	100	100	100	100	100	0
R3/T3	—	—	100	—	100	—	—	—	—	—	100
R4/T4	—	—	0	—	0	—	—	—	—	—	0
Normal volume of serum sample	8	8	8	8	8	8	8	8	8	8	8
Absorbance limit	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3
Reaction type	Positive reaction	Positive reaction	Positive reaction	Positive reaction	Positive reaction	Positive reaction	Positive reaction	Positive reaction	Positive reaction	Positive reaction	Positive reaction
Prozone check	-3.3 Lower limit	-3.3 Lower limit	-3.3 Lower limit	-3.3 Lower limit	-3.3 Lower limit	-3.3 Lower limit	-3.3 Lower limit	-3.3 Lower limit	-3.3 Lower limit	-3.3 Lower limit	-3.3 Lower limit
Calibration method	Sample stripe	Sample stripe	Sample stripe	Sample stripe	Sample stripe	Sample stripe	Sample stripe	Sample stripe	Sample stripe	Sample stripe	Sample stripe
Deflection check	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Discreteness check	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Sensitivity check	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14
Blank horizontal check	-0.1~0.7	-0.1~0.7	-0.1~0.7	-0.1~0.7	-0.1~0.7	-0.1~0.7	-0.1~0.7	-0.1~0.7	-0.1~0.7	-0.1~0.7	-0.1~0.7
Linearity range	2~14	2~14	2~14	2~14	2~14	2~14	2~14	2~14	2~14	2~14	2~14

Notes on symbols and marks

LOT	Batch code		Expiry date
	Manufactured by	IVD	In Vitro Diagnostic Use
	Please read package insert		Store at
EC REP	Authorised Representative	CE	European In Vitro Diagnostic Medical Device Directive 98/79/EC(IVDD)

DIRUI®

DIRUI Industrial Co.,Ltd.
95 Yunhe Street, New & High Tech. Development Zone
Changchun, Jilin 130012 P.R. China
Tel :+86(431)85100409
Fax:+86(431)85172581

E-mail:dirui@dirui.com.cn
Http://www.dirui.com.cn

EC REP
EMERGO EUROPE Prinsessegracht 20
2514 AP The Hague The Netherlands

DIRUI®

HbA1C

GLYCOHEMOGLOBIN A 1C REAGENT KIT (LATEX AGGLUTINATION METHOD)

♦Product Name

GLYCOHEMOGLOBIN A 1C REAGENT KIT (LATEX AGGLUTINATION METHOD)

♦Intended Use

The reagent is used for the in vitro quantitative measurement of glycohemoglobin content in human blood.

Glycohemoglobin is some special parts of glucose molecules and hemoglobin A molecular component in the blood. It will conduct slow and irreversible non-enzymatic reaction in the red blood cell, resulting in HbA1c (Ketone and amine compound) eventually. This solid compound's combination process is slow. This combination is not prone to change. It will not pour out of the cell. Therefore, glycohemoglobin will be more stable than blood sugar. That is short-term increase of blood sugar, HbA1c level would not rise, A short period of blood sugar decrease will not lead to the decrease of HbA1c level. Therefore, the clinical detection of HbA1c is with high clinical value. The test of glycohemoglobin level reflects average blood sugar of 1-3 months before test. It contributes to the early diagnosis of diabetes; contributes to normal control blood sugar for diabetes patients; contributes to an overall assessment of the occurrence of diabetic complication. It is also a good indicator of the crowd diabetes screening and the long term blood sugar control level of diabetes patients.

♦Principle

This method applies the way of testing the percentage of HbA1c in total Hb directly through the antigen-antibody reaction. Total Hb and HbA1c with the latex have the same non-specific adsorption of the solid-phase technology, while adding the specificity monoclonal antibody of HbA1c form the latex-HbA1c-mouse anti-human HbA1c monoclonal antibody complex. This complex form agglutination because of the goat anti-mouse IgG antibodies, agglutination volume vary due to the surface of solid-phase volume HbA1c. By measuring the absorbance, and compare with the standard curve of concentration percentage of HbA1c, the percentage content of HbA1c in the sample on total Hb can be derived.

♦Reagent Composition

Reagent 1	Latex	0.10%
Reagent 2-A	Goat anti-mouse IgG antibody glycine buffer	0.08mg/mL (Goat anti-mouse IgG antibody)
		60mmol/L (Glycine Buffer)
Reagent 2-B	Mouse anti-human HbA1c monoclonal antibody glycine buffer	0.05mg/mL (Mouse anti-human HbA1c monoclonal antibody)
		60mmol/L (Glycine Buffer)
Hemolysate	H_2O	/

Component of kits with different lot numbers are not interchangeable.

♦Storage Conditions and Shelf Life

1. The reagent should be kept at temperature of 2℃~8℃ and sealed in dry place without sunlight. The shelf life is 12 months.
2. Under condition of 2℃~8℃, the open vial stability of R1 is 30 days, R2 is 14 days. The reagent should not be frozen.

♦Suitable Device

This reagent is suitable for all kinds of semi-auto and full automatic chemistry analyzers. All kinds of application parameter of automatic chemistry analyzers are prepared for reference.

♦Sample Requirements

Use anti-coagulation, put it aside for more than 3 hours, after 2-minute centrifugation, collect a sample volume of 10μL from the blood cell layer, or 2000rpm, add 1mL dissolve blood hemolysis, hemolytic samples should be protected from light at 4℃, it can be stored for 10 days.

♦Method

1. Reagent preparation:

Reagent R1:R1 can be used directly after opened.

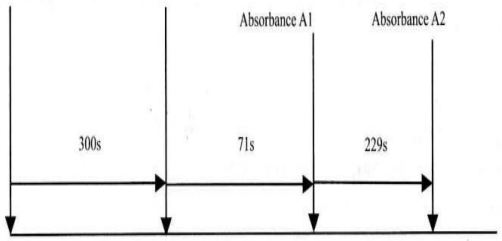
Reagent R2: Mix a bottle of R2-A with a bottle of R2-B into working reagent R2. R2 can be used. When open R2-A, be careful about rendering the R2-A adheres to the cap. Aspirate R2-A to join R2-B, wash the bottle of R2-A with R2-B repeatedly, make R2-A fully integrate into R2-B. Hold it upside down so that the reagent can be fully mixed.

2. Test condition (parameters)

Temperature	37℃	Reagent 1 Volume	300 μL
Main Wavelength	660 nm	Reagent 2 Volume	100 μL
Sub Wavelength	800 nm（not necessary）	Sample Volume	8 μL
Optical Path	1.0cm	Reaction Time	300s
Absorbance Range	0 ~ 3.2 A	Test Mode	2 point end assay

3. Testing procedure

Sample volume : 8μL
Reagent 1 volume: 300μL
Reagent 2 volume: 100μL
Temperature: 37℃
Main wavelength: 660nm



4. Calibration

It is suggested to use supplementary calibrator as instructed. When lot number is changed or QC is invalid, calibration shall be conducted again.

5. QC

It is suggested to use QC products produced by Dirui. The laboratory shall establish its own QC area and limit. If QC value is out of control, correction measures shall be taken.

6. Calculation

Enter the corresponding values, using non-linear calculation model. Make dose/response curve according to the value of absorbance and calibration serum. Content of the sample can be calculated according to the absorbance value on dose/response curve.

♦Reference Range

3.8~5.8%

The reference range applied is the expected value for this method, which is only for reference. It is recommended for all laboratories to do relevant tests to validate such range or establish their own reference ranges.

♦Explanation of Results

1. If the reaction temperature is 25℃ or 30℃, the hatch time should be prolonged to 8 minutes or 6 minutes.
2. HbA1c content measurement is only one of the indicators of clinical diagnosis for patients, and clinicians also conduct a comprehensive diagnosis including body, history diagnosis, as well as other items and diagnostic methods.

♦Limit

1. The accuracy of results relies on the control of calibration, testing temperature and time.
2. When bilirubin is ＞684μmol/L (40mg/dL) , ascorbic acid is ＞50mg/dL, carbamylation Hb is ＞7.5 mmol/L, acetylationHb is ＞5.0 mmol/L, chylomicron is ＞2000, the test result will be affected.

♦Specifications

1. Linearity: up to 14%

Annex 4b: KNH Biochemistry Laboratory Technical Operating Procedure

Kenyatta National Hospital
Department Of Laboratory Medicine
Biochemistry Laboratory

Hospital Road off Ngong Road
P.O. Box 20723
Nairobi, TEL: 020 272 6300

TECHNICAL OPERATING PROCEDURE

PROCEDURE	GLYCATED HAEMOGLOBIN ENZYMATIC ASSAY METHOD
SOP	KNH/LAB MED – BIOCHEM /SYP/017F7
COPY NO.	

	NAME	TITLE	SIGNATURE	REVIEW DATE
AUTHORED BY		Safety Officer		31/12/2017
REVIEWED BY		Quality Officer		31/12/2017
AUTHORIZED BY		In-Charge		31/12/2017

1.0 Purpose/Applicability

This document establishes the procedure for testing , reporting ,transmission and dispatch of test results for HbA1c.

2.0 Scope

This SOP applies to all the specimens which have been appropriately received and logged in by the Biochemistry Laboratory , Kenyatta National Hospital for the purpose of determining glycated or glycosylated haemoglobin in the reportable units of percentage(HbA1 C %).

3.0 Terms and definitions

Client -The Patient or any other person who delivers a specimen to the Laboratory.

Specimen -The material obtained from the human body and brought to the laboratory for the purpose of establishing the cause of disease.

Sample - The material that has been processed and is ready for analysis.

Op.NO - Out Patient Number. Used to see patients in clinics and Accident and Emergency Department when not admitted.

IP.NO. -In patient Number. Used when a patient is admitted in the Wards.

Processing - all the sequence of activities involved in turning a specimen into a sample ready for analysis using any equipment or methodology.

Specimen quality –established acceptance and rejection criteria for each type of specimen regarding the requested investigations.

QMS - Management System to direct and control an organization with regard to quality.

QO - Quality Officer

SOP -Standard Operating Procedures (written by each Laboratory and approved by The Head of Department or the Laboratory In-Charge)

Health Information Personnel –The personnel deployed by the Department of Health Records Information services to the Department of Laboratory Medicine for the purposes of capturing and documentation of patient data.

TAT -Result Log out time minus Specimen Log in time.

Conc HCL - Concentrated Hydrochloric Acid.

Log in - Record the specimen in the Laboratory register (KNH 240) indicating the exact time received and all the other accompanying patient details as well as assigning a Laboratory identification number.

Log out - Record in the Laboratory register (KNH 240) the exact time the result is ready for collection by the client.

Analysis - Any technical process or activity that leads to the production of results

Verify - Confirm that the specimen/sample/result details match those on the request or report form (KNH 211) as ordered by the Clinician.

Validation - Counterchecking the quality of results including units and then signing them.

Clinician - A person charged with the clinical management of a patient in the ward or clinic.

Technical Personnel – A Medical Laboratory Technician/Technologist as defined by the Medical Laboratory Technician/Technologist Act No.10 of 1999.

Pathologist - A Medical specialist working in the Laboratory as defined by the Medical Practitioners and Dentists Act.

4.0 Responsibilities

4.1 Roles of personnel

4.1.1 The Health information personnel receive the client request and confirm the required details.

4.1.2 A qualified technical personnel perform the test.

4.2 Safety;

4.2.1 The Safety Officer takes care of the safety issues in the Laboratory.

4.2.2 All the staff to observe safety as outlined in the safety manual.

5.0 Equipment and Reagent

5.1 Equipment

5.1.1 EDTA vacutainers or Heparinised Vacutainers for specimen collection or Eppendorf tubes.

5.1.2 Adjustable pipette capable of measuring 100 - 1000 µl (1.0 ml) for haemolysin aliquoting.

5.1.3 Adjustable pipette capable of measuring 10 - 100 µl (1.0 ml) for erythrocyte aliquoting

5.1.4 The Automated analyser in use for the test.

5.1.5 Centrifuge for specimen preparation.

5.2 Reagents

R1	Tris buffer	2.7 mol/l
R2	Peroxidase	1500U/L
	Fructosyl peptide Oxidase	1500 U/L
Pre-treatment Solution	Haemolysin	5 g / L
Calibrator	Concentration is specific to the lot number and is on the container label.	
Quality Control	Concentration is specific to the lot number and is on the container label.	

6.0 METHODOLOGY

6.1.1 Background

Haemoglobin (Hb) consists of four protein chainswith four haem portions , and is the red pigment located in the red blood cells (Erythrocytes).Its main function is to transport oxygen and Carbon dioxide in blood .Each Hb molecule is able to bind four oxygen molecules.Hb consists of a variety of subfractions and derivatives.Among this heterogeneous group of haemoglobins , HbA1C is one of the glycated haemoglobins , a subfraction formed by the attachment of various sugars to the Hb molecule.HbA1C is formed in two steps by the non-enzymatic reaction of glucose with the N- terminal amino groups of the Beta –chain of normal adult haemoglobin(HbA) .The first step is reversible and yields labileHbA1c.This slowly rearranges in the second reaction step to yield stable HbA1c.In the erythrocytes , the relative amount of stable HbA converted to stable HbA1c increases with the average concentration of glucose in the blood.The conversion of stable HbA1c is limited by the erythrocytes's lifespan of approximately 100 to 120 days.As a result , HbA1c reflects the average blood glucose level during the preceding 2 to 3 months.HbA1c is thus suitable for monitoring long term blood glucose control in individuals with diabetes mellitus.More recent glucose levels have a greater influence on the HbA1c level.The approximate relationship between HbA1c and mean blood glucose value during the preceding 2 to 3 months has been analysed by several studies.

6.1.2 TEST OR ASSAY PRINCIPLE

In the first reaction , the concentration of haemoglobin is measured at an absorbance of fixed wavelength , and simultaneously the fructosyl dipeptides are generated from the N – terminal amino groups of the beta-chain of HbA1c by the reaction of protease.In the second reaction , the reaction of Fructosyl peptide oxidase (FPOX) with fructosyl dipeptides , the generated hydrogen peroxide allows 10-carboxymethylaminocarbonyl)-3,7-bis(dimethylamino) phenothiazine sodium salt to develop a colour in the presence of peroxidase.The change in absorbance is measured for HbA1c determination.The combined assay results for haemoglobin and HbA1c are used to calculate and express HbA1c (%).

6.2 Test procedure
Refer to appendix 1

6.3 Results dispatch and archiving.
6.3.1 For results outcome and interpretation **(Refer to appendix 1)**
6.3.2 The Health information personnel dispatches the validated results directly to the patient who shall sign for the collection.

6.4 Quality Control
6.4.1 Commercial controls are available for scheduled IQC.

6.5 Possible interferences
6.5.1 Use of expired reagents
6.5.2 Use of specimen haemolysed during phlebotomy

6.6 Calculation of the results
Refer to appendix 1

6.7 Biological reference intervals
Refer to appendix 1

6.8 Reportable intervals
Refer to appendix 1

6.9 Critical values
It is used as a monitoring test so critical values are not significant.

6.10 Potential source of variation
Failure to observe the expiry dates of reagents or sample integrity.

7.0 References

7.1 ISO 15189: 2012(E) Standard.

7.2 Junge w , Wilke B , et al.Determination of reference intervals in adults for Haemoglobin A1C (HbA1c).Poster presentation 18th International Diabetes Federation Congress , Paris , 2003.

7.3 CLSI.Evaluation Of Precision Performance Of Quantitative Measurement Methods;Approved Guideline – Second Edition.CLSI document EPs – A2[ISBN 1-56238 -542-9.CLSI,940 West ValleyRoad,SSuite1400,Wayne,Pa19087 USA ,2008.

8.0 Appendices

8.1 Appendix 1: Test procedure
8.2 Appendix 2: Staff training record

Appendix 1

1.1Specimen Receiving and Registration

Responsible staff : Health Information personnel at the reception.Verify the integrity of each specimen in terms of packaging , right container ,volumes and whether the test is done in Biochemistry Laboratory .Refer to the specimen rejection and acceptance criteria (Refer to : KNH / LAB MED – BIOCHEM /SYP /017F4 Separate urgent or emergency specimens from routine ones and mark them with a colour as'P' to denote priority. Priority samples shall be run within one hour from the time of registration in the Laboratory. Unmarked or routine samples shall be run within two hours from the time of registration at the Biochemistry Laboratory reception.

1.1.1 Immediately hand over the priority specimens to the testing personnel for processing, testing and reporting.

1.2 Specimen Preparation and assaying

1.2.1 Centrifuge or spin the whole blood at 2000 revolutions per minute **(2,000 RPM)** for **5 minutes.**

3.2.2 Aliquot **25µl** of the deposited red blood cells into a sample cup or Eppendorf microfuge tube ,using the calibrated pipette in use.

3.2.3 Add **500µ** l of the haemolysin / denaturant or pretreatment solution to the **25 µl** of the aliquoted erythrocytes.

3.2.4 Shake the mixture vigorously in a closed ependorf microfuge tube or vacutainer till lysis is achieved.

3.2.5 Homogeneously mix the resultant haemolysate gently and then run the assay after

5 minutes using the appropriate automated analyzer.

3.2.6 Whole blood is stable for 3 days at 15 - 25 ^{0}c or 7 days at 2 - 7^{0}c.(Haemolysate is stable for 8 hours and 24 hours respectively) at the same temperatures quoted.

3.3 Result Validation, Interpretation and Indication for Repeat Testing

Responsible Staff: Laboratory In - charge, Testing Personnel

3.3.1 Refer to reporting of results SOP (KNH / LAB MED - BIOCHEM /SYP/ 017F5)

3.4 Transcription and release of ready results

Responsible Staff: Laboratory In – charge, Testing Personnel

3.4.1 Validate / verify test results and in appropriate reporting units.

3.4.2 Sign or initial the relevant column of the request/printed report form.

3.4.3 Result entry or matching with request forms can be done by trainees or competent staff whilst authorization is only done by competent technical staff

3.4.4 Immediately take the completed request/ result form to reception for dispatch either to specific patients or into pigeon holes.

3.4.5 Misplaced Results

3.4.5.1 Ask the client at the reception , for the attendance card and date when test was performed or the receipt.

3.4.5.2 search in the Laboratory register for the log in number previously.

3.4.5.3 Search results in the History mode using the Laboratory number and reprint once confirmed as correct.

3.4.5.4 A competent technical staff verifies the results and signs or initials the reprint copy.

3.4.5.5 Write a remark to the effect that results were initially lost on the comment column of the request form and dispatch.

3.5Reference Ranges

SAMPLE TYPE		SI UNITS (%)
Whole Blood	According to IFCC	2.9 ----- 4.2
	According to NGSP / DCCT	4.8 ---- 5.9
	According to JCCLS	4.3 ------ 5.8

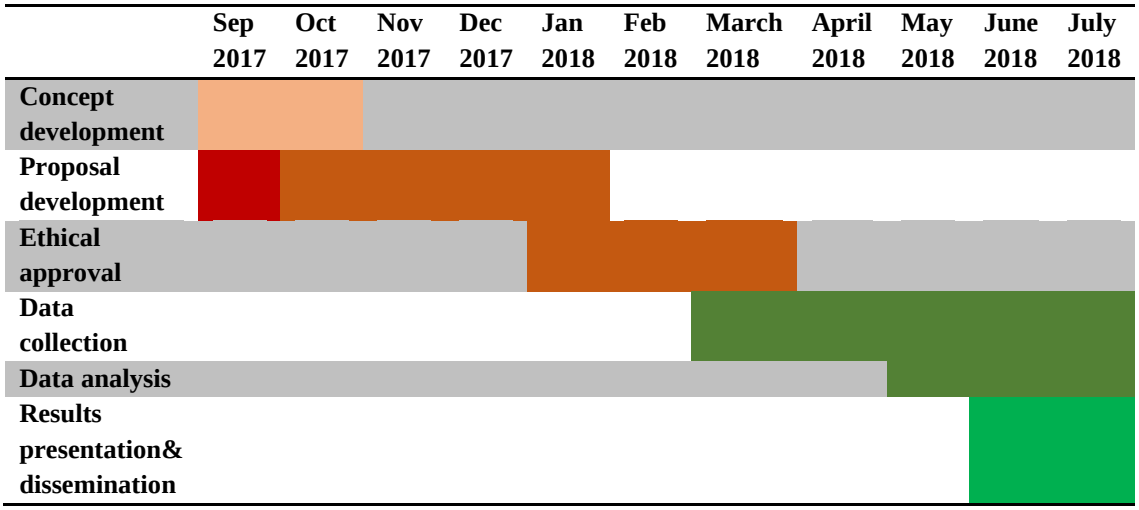
Kenyatta National Hospital
Department Of Laboratory Medicine
Biochemistry Laboratory

Hospital Road off Ngong Road
P.O. Box 20723
Nairobi, TEL: 020 272 6300

5.2 Reagents

R1	Tris buffer	2.7 mol/l
	Peroxidase	1500U/l

Annex 5: Study Timelines



Annex 6: Study Budget

Component	Duration/Number	Cost (kshs)	Total (kshs)
Research assistant	2	20000	40,000/=
Statistician	1	30000	30,000/=
Lab charges HbA1c	170	1000	170,000/=
RBS/FBS charges	170	150	25,500/=
Printing			
Consent form	200	20	4,000/=
Questionnaires	200	20	4,000/=
Final report	124	10	1,240/=
Miscellaneous	5000		5,000/=
TOTAL			**279,000/=**

Annex 7: Dummy Tables/Charts

Objective 1: Correlates of elevated immediate postpartum maternal HbA1C among non-diabetic mothers with fetal macrosomia.

Table 1: Frequency distribution of Socio demographic factors

		LGA n =85		**AGA n =85**		**OR (95% C.I)**	**P Value**
		< 6.5%	≥ 6.5%	< 6.5%	≥ 6.5%		
Age	< 35						
	≥35						
Parity	Primigravida						
	More than One child						
Marital status	Single						
	Married						
	Other						
Religion	Christian						
	Muslim						
	Other						
Usual residence	Urban						
	Sub Urban						
	Rural						
Ethnicity							

Table 2: Frequency distribution of obstetric factors

		LGA n =85		AGA n =85		OR (95% C.I)	P Value
		< 6.5%	≥ 6.5%	< 6.5%	≥ 6.5%		
History of LGA	Yes						
	No						
History of FP use	Hormonal						
	Non hormonal						
	Combined						
Pregnancy weight gain	≥16 kilograms						
	8-15 kilograms						
BMI	25-29.99						
	≥30						
Fetal Sex	Male						
	Female						
Gestation	Early term						
	Term						
	Late term						
	Post dates						

5.6.2 Objective 2: To determine the association between maternal HbA1c and Macrosomia

Table 3: Association between maternal HBA1C and Macrosomia

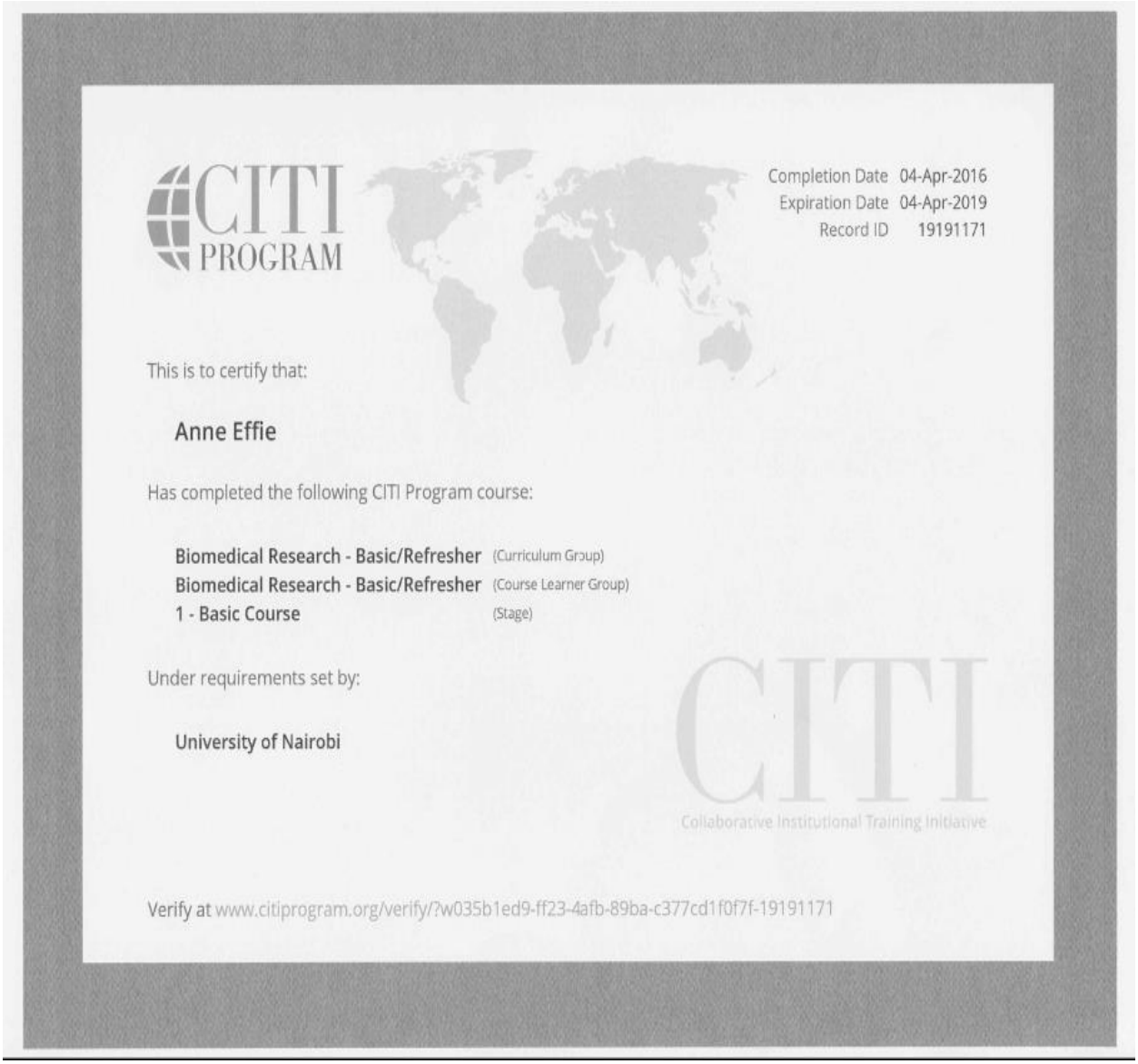
	LGA	AGA
HbA1c ≥6.5%	a	b
HbA1c <6.5%	c	d

OR = ad/bc

Table 4: Multivariate Analysis of association between maternal HbA1c and Macrosomia

		LGA n =85		**AGA n =85**		**OR (95%C.I)**	**AOR**	**P Value**
		< 6.5%	≥ 6.5%	< 6.5%	≥ 6.5%			
Age	< 35							
	≥35							
Usual Residence	Urban							
	Rural							
Pregnancy Weight gain	≥16 kg							
	<16 kg							
BMI	25-29.99							
	≥30							
Fetal sex	Male							
	Female							
Gestation	Early term & term							
	Late term Post dates							

Annex 8: CITI certificate of Good Clinical Practice



CITI PROGRAM

Completion Date 04-Apr-2016
Expiration Date 04-Apr-2019
Record ID 19191171

This is to certify that:

Anne Effie

Has completed the following CITI Program course:

Biomedical Research - Basic/Refresher (Curriculum Group)
Biomedical Research - Basic/Refresher (Course Learner Group)
1 - Basic Course (Stage)

Under requirements set by:

University of Nairobi

CITI
Collaborative Institutional Training Initiative

Verify at www.citiprogram.org/verify/?w035b1ed9-ff23-4afb-89ba-c377cd1f0f7f-19191171

Annex 9: KNH-UON ERC Approval

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KENYATTA NATIONAL HOSPITAL APPROVED 09 MAY 2018 KNH/UoN-ERC P.O Box 20723-00202 NRB.

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/159

May 9, 2018

Dr. Anne Effie Anyango Ouma
Reg. No.H58/83019/ 2015
Dept.of Obs/Gynae
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Ouma

RESEARCH PROPOSAL – ASSOCIATION BETWEEN POST PARTUM NON-DIABETIC MATERNAL HbAIC AND FETAL MACROSOMIA AT KENYATTA NATIONAL HOSPITAL (P86/02/2018)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is from 9th May 2018 – 8th May 2019.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director, CS, KNH
The Chairperson, KNH-UON ERC
The Assistant Director, Health Information, KNH
The Dean, School of Medicine, UoN
The Chairman, Dept.of Obs/Gynae, UoN
Supervisors: Dr. George Gwako, Dr. Maureen Owiti