A STUDY OF METFORMIN VERSUS INSULIN IN THE MANAGEMENT OF DIABETES MELLITUS IN PREGNANCY AT THE KORLE BU TEACHING HOSPITAL

TITUS BEYUO (BSc. MB ChB)

INDEX NUMBER: 10084309

THIS THESIS IS SUBMITTED TO THE UNIVERSITY OF GHANA, LEGON, IN PARTIAL FULFILMENT OF THE REQUIREMENT OF THE AWARD OF M PHIL PHARMACOLOGY

DECEMBER, 2013

DECLARATION BY CANDIDATE

This study is based on my own research, which I carried out under supervision at the Department of Pharmacology, University of Ghana Medical School, College of Health sciences. I declare that, except for references to other people's work, for which I have duly acknowledged, this thesis is original to me. This thesis has not been submitted either completely or in part for the award of any other degree in this or another university.

Signature…… Date……

TITUS BEYUO

(M. Phil Candidate)

DECLARATION BY SUPERVISORS

We declare that the practical work and presentation of this thesis were supervised by us in accordance with the guidelines of thesis in the University of Ghana

Principal Supervisor:

…… Date: ……

Prof. Adjepon-Yamoah

Co-Supervisor:

…….. Date: …….

Prof. Samuel A. Obed

DEDICATION

I dedicate this thesis to the memory of my late parents (Mr. and Mrs. Leo Beyuo), my wife, Vera and our children, Benito Gandaa Beyuo and Titus Pelpuor Beyuo Jnr.

ACKNOWLEDGEMENT

I am eternally grateful to the Almighty God for his grace and mercies that saw me through this work.

My sincere appreciation goes to supervisors: Prof. K. K. Adjepon-Yamoah, Departments of Pharmacology and of Medicine and Therapeutics, University of Ghana Medical School and also to Prof. S. A. Obed, Head of Obstetrics and Gynaecology Department, University of Ghana Medical School. My profound appreciation goes to Dr. K. A. Bugyei, Head Department of Pharmacology for mentoring me throughout this course.

I am very grateful to the staff of the Diabetes Clinic and the National Diabetes Research Laboratory for their vital role in this work. I thank Prof. A. G. B. Amoah and Drs. Gloria Yohuno and Abena Oppong-Anane.

Special appreciation goes to Dr. Samuel Antwi Oppong for thoroughly going through this manuscript and making very useful suggestions. I also acknowledge the support of all consultants in the Department of Obstetrics and Gynaecology for ensuring participation of their patients and following study protocol. I acknowledge Prof. J. D. Seffah for reading through some chapters of this work and making very useful suggestions.

I thank Dr. Kissinger Marfoh and Maxfield Okere of the Public Health Unit, Korle Bu Teaching Hospital for their role in data analysis. I thank the research assistants in the Department of Obstetrics and Gynaecology, Alfred, Emmanuel, and Magdalene Torto for their assistance with this work.

I grateful to the Team B House Officers of the 2013 year group for their role in patient follow-up and data collection, of particular mention are Drs. Bennet Danquah and Kojo Opoku Darko.

I thank all of staff of the Department of Pharmacology for tutorship throughout the M. Phil course. I also appreciate the support of all patient who gave consent and participated in the study.

Finally, I express my profound appreciation to my wife Dr. (Mrs.) Vera Beyuo, for her support and all the sacrifices made during the entire study period and especially for being there for me and our kids, Benito and Titus.

TABLE OF CONTENTS

CHAPTER THREE

CHAPTER FOUR

CHAPTER FIVE

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND ACRONYMS

1HPG…….....One hour post-prandial glucose

2HPP…….....…Two hour post-prandial

ADA……American Diabetic Association

ANC……..…..Antenatal Care

ANOVA…….….Analysis Of Variance

BMI…….Body Mass Index

DNA……....Deoxyribonucleic Acid

FBG…….Fasting blood glucose

GDM……...Gestational Diabetes Mellitus

GLUT4……Glucose Transporter 4

IU……International Units

IUPAC……...….International Union of Pure and Applied Chemistry

KBTH…….…….Korle Bu Teaching Hospital

mg……Milligram

NICU…….…..Neonatal Intensive Care Unit

OCT……..Organic Cation Transporters

OGTT…….……..Oral Glucose Tolerance Test

SD……..Standard Deviation

SHBG……Sex Hormone- Binding Globulin

T2DM……...……Type 2 Diabetes Mellitus

WHO……...…..World Health Organization

PCOS..... Polycystic Ovary Syndrome

ABSTRACT

Background: Diabetes mellitus is an important complication of pregnancy with adverse effects on both mother and fetus. Poor control of pre-gestational diabetes during the period of organogenesis increases the risk of major congenital malformations. While insulin is effective in controlling high blood glucose levels, otherwise resistant to diet and exercise management, several factors hinder its use. Metformin has been found to be a convenient, cheap, effective and safe hypoglycaemic agent in some countries. It is possible that metformin will have similar beneficial effects among Ghanaian pregnant women.

Aim: The main aim of this study was to determine if either metformin monotherapy or metformin in combination with insulin is effective at glycaemic control compared to insulin monotherapy in the management of gestational diabetes mellitus and type 2 pre-gestational diabetes mellitus in Ghanaians.

Methodology: This was a prospective randomized controlled study involving 104 pregnant women with T2DM or GDM at 20-30 weeks gestation. It was an opened labelled trial. Patient randomly assigned to one of the two treatment groups. Participants were followed through their index pregnancy with a 2-weekly glycaemic profile monitoring and maternal weight gain. Babies delivered were followed till the sixth week post-delivery, measuring birth weight, incidence of birth trauma and neonatal intensive care unit (NICU) admission rates. Both laboratory and clinical data were recorded and analyzed.

Results: Ninety percent and 76% of participants in the metformin and insulin groups respectively completed the study. The 2HPG levels were significantly lower in the metformin group than the insulin group with p values of 0.004. The mean FBG and 1HPG levels from enrolment to term was comparable between the two treatment groups. The mean weight gain from randomization to term was significantly higher in the insulin group (4.46 ±2.09kg) than the metformin group (2.21 ±2.42kg) with p <0.0001. Babies whose mothers received insulin when admitted to NICU stayed longer than their counterparts from the insulin treatment group. Other secondary outcome measures did not differ between the treatment groups.

CHAPTER ONE

1.0 INTRODUCTION

1.1 BACKGROUD OF THE STUDY

Diabetes mellitus (DM) is a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbance of carbohydrate, fat and protein metabolism, resulting from defects in insulin secretion, insulin action, or both (WHO, 1999). Diabetes mellitus is broadly grouped into Type I (insulin-dependent diabetes mellitus) and Type II (non- insulin-dependent diabetes mellitus); the latter is the focus of this study. Diabetes mellitus in pregnancy consists of pre-gestational diabetes mellitus and gestational diabetes mellitus. Gestational diabetes mellitus (GDM) is characterized by hyperglycaemia of varying severity diagnosed during pregnancy in patients without previously known diabetes and, usually, but not always, resolving within six weeks of delivery (WHO, 1999). The prevalence of diabetes mellitus world- wide is projected to increase (Ben-Haroush *et al*., 2004).

A study in Nigeria estimated the incidence of diabetes mellitus among pregnant women as 1.7%. Pre-gestational diabetes accounted for 39%, while gestational diabetes was responsible for 61% of cases **(**Ozumba *et al.,* 2004**).**There is no national data on the prevalence of DM among pregnant women in Ghana. Data from Greater Accra estimates the crude prevalence of diabetes mellitus as 6.3% **(**Amoah *et al.,* 2002). It is estimated that 3-10% of pregnancies are complicated by diabetes mellitus (Ferrara *et al*., 2002; Thorpe *et al.,* 2005).

Diabetes mellitus is an important complication of pregnancy with adverse effects on both maternal and foetal outcomes. Treatment options of diabetes complicating pregnancy are limited. Several classes of medicines have been developed based on the pathophysiology of diabetes and

are being used as monotherapy or combination therapies with varying efficacies in the general population of diabetics. In pregnant diabetics, however, exercise and dietary management, followed by insulin therapy where dietary management has failed, has been the general trend. Few countries have added oral hypoglycaemic agents to this management, but lack of adequate data on efficacy and safety in the pregnant population has prevented the use of oral hypoglycaemic agents in several countries**.**

The use of insulin has traditionally been the main stay in the management of DM in pregnancy not adequately controlled on diet and exercise. Though effective, the use of insulin is associated with some disadvantages, such as the inconvenience of repeated injections, high cost, storage problems, hypoglycaemia, and foetal macrosomia, amongst others. In one Indian study, the cost of insulin was found to be ten-fold higher than that of metformin **(**Rai *et al*., 2009).

A number of studies have examined the role of oral antidiabetic medications in managing diabetes in pregnancy. Metformin is one of the promising agents being widely used for this indication in a number of countries. It was first synthesized in the 1920s, but was soon forgotten for the next two decades following the discovery of insulin. Its history has been traced back to the use of a perennial herb, *Galega officinalis* in folklore medicine for the treatment of symptoms now known to be associated with DM **(**Bailey and Day, 2004).

The first clinical trial of metformin was performed by Sterne. He coined the name "Glucophage" (glucose eater) for the drug and published his results in 1957**(**Campbell, 2007).

Recent studies, including randomized controlled studies, suggest that metformin is more convenient, cheaper, effective and safe in pregnancy to mother and baby (Moore *et al.,* 2007; Rowan *et al*., 2008; Rai *et al*., 2009).

1.2 PROBLEM STATEMENT

Diabetes mellitus is a common disease in the adult population in both developed and developing countries. In developing countries in particular, Type 2 diabetes mellitus appears to be on the ascendancy because of life style changes and changing trends in dietary habits. As the disease burden increases in the general population, it is expected that its prevalence in pregnancy will also increase. Pregnancies complicated by diabetes mellitus often require specialized care, because of adverse maternal and foetal outcomes if not properly managed. While several pharmacological options are available to diabetics in the general population for glycaemic control, the pregnant diabetic is often restricted to only insulin, following dietary and exercise management failure. Insulin may not be affordable in low income countries. Frequent power outages or the absence of electricity also hinders its storage and use in rural areas. In addition compliance to the frequent injections may be low.

Metformin which is taken orally is cheaper, more accessible, and more user-friendly, compared to insulin. Metformin is, therefore, a logical option for pregnant diabetics in Ghana. Recent clinical trials support metformin use in pregnancy **(**Rowan *et al*., 2008; Rai *et al.*, 2009), but lack of such data in Ghana still makes metformin use controversial.

Another problem is that the pharmacogenetics of metformin does not support extrapolation of research findings from one population to another, since its excretion is influenced significantly by a variant allele. Treatment failure or toxicity could occur in patients carrying the variant allele (*SLC22A2*) [Wang *et al* 2008].

1.3 JUSTIFICATION

Studies in countries like United States of America (USA), Australia, Canada and India have found metformin as an effective and cheaper alternative to insulin. Genetic variations exist in the pathogenesis of diabetes mellitus, as well as in the metabolism of metformin. Consequently, results from one population may not be applicable to another. It is, therefore, important to do a Ghanaian study. There is no published data on the use of metformin in pregnancy for glycaemic control in Ghanaians. The role of an effective, cheaper and more convenient to use medication in the control of any medical condition in a low – middle income country like Ghana cannot be overemphasized. Poor patient follow-up and monitoring in Ghana makes the use of drugs that do not require frequent monitoring, a preferred option at all times to those requiring frequent monitoring.

Insulin is less affordable and not readily available at all times. The need for refrigeration for effective insulin storage and use in developing countries is associated with difficulties. Unlike insulin, metformin does not require refrigeration for effective storage. Metformin is readily available, and its oral administration is more tolerable to many patients.

1.4 HYPOTHESES

- The glycaemic control will be equally effective with metformin therapy as with insulin therapy in pregnant diabetics in Ghana.
- Weight gain in mother and baby will be lower on metformin therapy compared to insulin.

Rationale: Metformin has been shown to be equally effective and safe as insulin in the management of GDM. Poor compliance to insulin due to high cost, accessibility, storage difficulties and the discomfort of repeated injections is expected to make metformin a more preferred and a better choice.

1.5 AIM

The aim of this study is to determine if metformin monotherapy or metformin in combination with insulin is effective at attaining and maintaining glycaemic targets, compared to insulin monotherapy in the management of gestational diabetes mellitus and Type 2 pre-gestational diabetes mellitus in Ghanaians.

1.6 SPECIFIC OBJECTIVES

- To determine and compare blood glucose profiles between subjects treated with metformin and those treated with insulin.
- To determine the additional insulin requirements and the blood glucose profile in subjects who may require supplemental insulin in the metformin group.
- To measure and compare pregnancy weight gain between the metformin and insulin groups.
- To measure and compare foetal outcomes between the metformin and insulin groups

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 OVERVIEW OF DIABETES MELLITUS (DM)

The World Health Organization (WHO) defines diabetes mellitus as a metabolic disorder of multiple aetiology characterized by, chronic hyperglycaemia with disturbance of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both (WHO, 1999).

The American Diabetes Association (ADA) grouped diabetes into four clinical classes*:*

- "Type 1 diabetes (results from β-cell destruction, usually leading to absolute insulin deficiency)
- Type 2 diabetes (results from a progressive insulin secretory defect on the background of insulin resistance)
- Other specific types of diabetes due to other causes, e.g., genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of HIV/AIDS or after organ transplantation)
- Gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes**)"** (Diabetes Care, 2012)

Another method for classifying diabetes in pregnancy is the White classification. This classification is widely used to assess maternal and foetal risk. There are two main groups; GDM (class A) and pre-gestational diabetes (classes B-T). There are subdivisions based on associated risks and management (Gabbe *et al*., 2002)

There are 2 sub-classes of gestational diabetes (diabetes which began during pregnancy):

- Class A_1: gestational diabetes; diet-controlled
- Class A_2: gestational diabetes; medication-controlled

The second group of diabetes which existed before pregnancy is sub-classified as follows:

- Class B: onset at age 20 or older or with duration of less than 10 years
- Class C: onset at age 10-19 or duration of 10–19 years
- Class D: onset before age 10 or duration greater than 20 years
- Class E: overt diabetes mellitus with calcified pelvic vessels
- Class F: diabetic nephropathy
- Class R: proliferative retinopathy
- Class RF: retinopathy and nephropathy
- Class H: ischemic heart disease
- Class T: prior kidney transplant

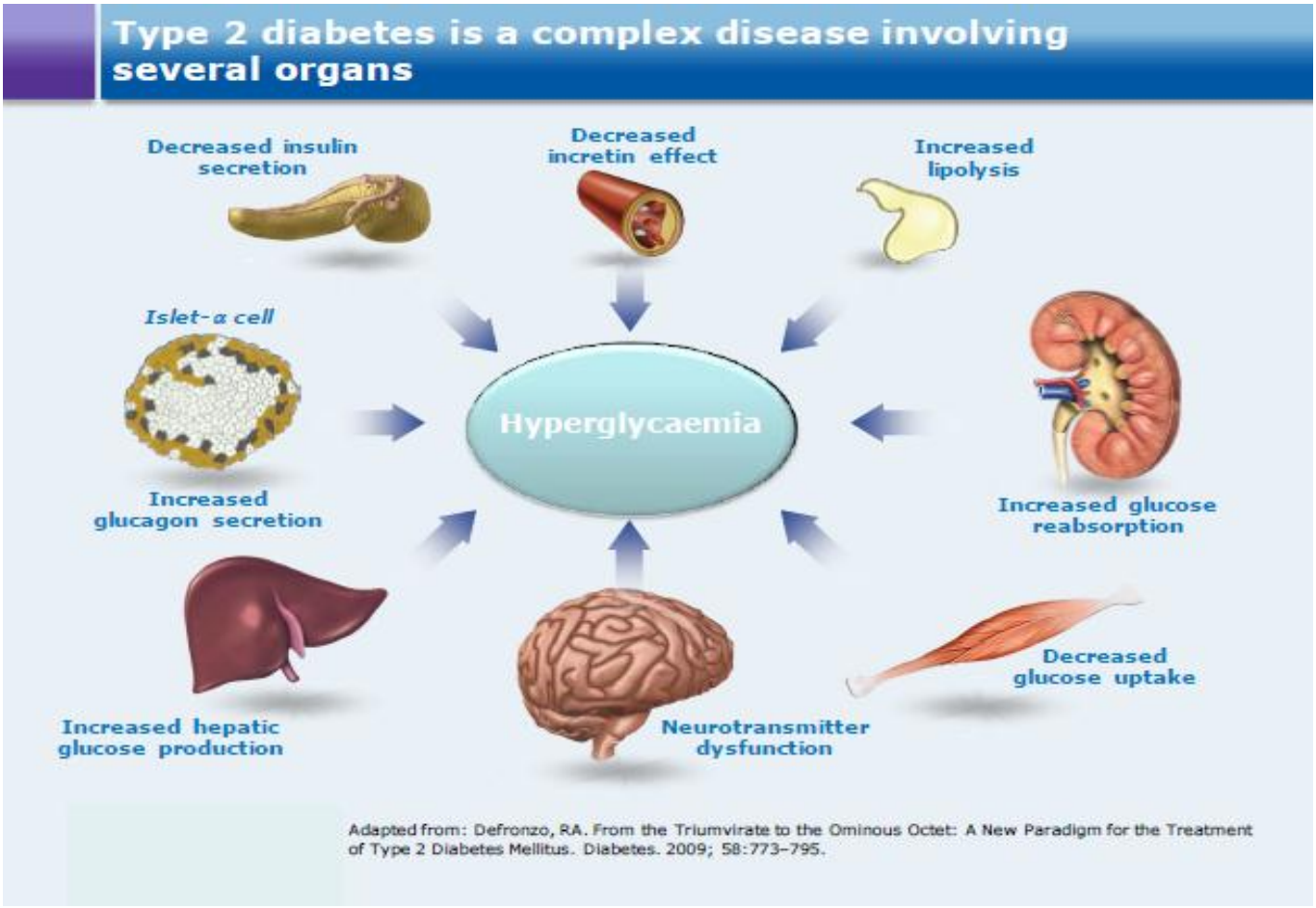
Pregnancy complicated by DM is a high risk pregnancy that often requires frequent monitoring and appropriate care to ensure good outcome to mother and baby. Diabetes mellitus occurring in pregnancy may be pre-gestational or gestational. Majority of cases, however, represent the GDM group.

2.2 TYPE 2 DIABETES MELLITUS (T2DM)

Type 2 diabetes mellitus (T2DM) is a metabolic disorder that is characterized by hyperglycaemia in the context of insulin resistance and relative insulin deficiency (Kumar *et al*., 2005).

The pathophysiology of Type 2 diabetes is characterized by insufficient insulin production from beta-cells in the presence of insulin resistance. Insulin resistance is the inability of cells to respond adequately to normal levels of insulin. It occurs primarily within tissues that require insulin to utilize glucose. These include the liver and fat tissue. The three key pathophysiological mechanisms of T2DM, referred to as the classical triumvirate, were beta-cell failure, insulin resistance in the liver, and insulin resistance in the muscle. (Defronzo, 2009). The paradigm in the pathophysiology has shifted with the discovery of other significant mechanisms in the aetiology of T2DM from the triumvirate to an ominous octet. (Defronzo, 2009).

Figure 2.1: The ominous octet of T2DM



There is evidence to suggest that diabetes in pregnancy may contribute to the increase in prevalence of T2DM (Silverman *et al*., 1995; Dabelea *et al*., 2000). It is hypothesized that an exposure to a diabetic environment *in utero* enhances adolescent and adult obesity (Catalano, 2003; Pettit *et al*., 1983). A study of the offspring of Pima Indian women revealed that, by early adulthood, 45% of the children of women with Type 2 diabetes had developed diabetes compared with 1.4% of the offspring of non-diabetic women (Pettit and Knowler, 1988).

Populations with very high rates of Type 2 diabetes are known to have the highest prevalence of diabetes in women of childbearing age, and many women with gestational diabetes may have had pre-existing, undiagnosed Type 2 diabetes (Feig and Palda, 2002).

2.3 OVERVIEW OF GESTATIONAL DIABETES MELLITUS (GDM)

Gestational diabetes (GDM) is defined as carbohydrate intolerance that begins or is first recognized during pregnancy (WHO, 1999). It is a well-known complication of pregnancy but its prevalence varies greatly due mainly to differences in screening programmes and diagnostic criteria. GDM complicates about 5% of pregnancies with long-term risk of overt DM to mother and fetus (Ben-Haroush *et al*., 2004; Ferrara, 2004; Silverman *et al*., 2004,).

The differences in screening programmes and diagnostic criteria have made comparison of frequencies of GDM difficult among various populations. (Ben-Haroush *et al*., 2004)

GDM constitute a majority of the cases of diabetes seen in pregnancy. It has been estimated in a Nigerian study as 61% of all cases of diabetes in pregnancy. **(**Ozumba *et al*., 2004)

Ethnicity has been identified as an independent risk of GDM, however, in a particular population or ethnic group, the prevalence of GDM is directly proportional to the prevalence of T2DM. In the absence of predisposing factors, the prevalence of GDM is low (Ben-Haroush *et al*., 2004). This has made selective screening a very cost effective tool.

The gestational age at diagnosis is important. Women in whom diagnosis of GDM was made in the first-half of pregnancy, form a high-risk subgroup. They have a higher incidence of obstetric

complications, recurrent GDM in subsequent pregnancies, and future development of Type 2 diabetes. Obesity and need for insulin for glycaemic control also increase the risk of developing T2DM, following GDM. (Ben-Haroush *et al*., 2004).

2.4 PATHOPHYSIOLOGY OF DM IN PREGNANCY

In normal pregnancies, insulin sensitivity falls with advancing gestation (Catalano *et al*., 1999) and this increase in insulin resistance in pregnancy is designed to benefit the fetus because it results in a shift of metabolic fuel supplies from mother to fetus (Buchanan *et al*., 1990). Insulin sensitivity in pregnant non-diabetics is reduced (Buchanan *et al*., 1990).

Resistance to insulin may occur at different levels, such as

a.) pre-receptor (insulin antibodies), as in autoimmune diseases;

b.) receptor (decreased number of receptors on the cell surface), as in obesity, or

c.) post-receptor (defects in the intracellular insulin signaling pathway). [Al-Noaemi and Shalayel, 2011].

Insulin resistance in pregnancy is usually characterized by a post-receptor defect, resulting in the decreased ability of insulin to bring about mobilization of SLC2A4 (GLUT4) from the interior of the cell to the cell surface (Catalano, 2010). This could result from an increase in the plasma levels of one or more of the pregnancy-associated hormones (Kühl, 1991; Hornns, 1985). These hormones- estrogen, progesterone, cortisol, and placental lactogen, are produced mainly from the foeto-placental unit.

Insulin resistance tends to be higher in pregnant women with gestational diabetes than non-diabetic pregnant women. This difference in insulin resistance persists in the post-partum period (Buchanan and Xiang, 2005).

In normal pregnancy, the β-cell normally increases insulin secretion to compensate for the insulin resistance of pregnancy **(**Catalano *et al*., 1991). A defect in pancreatic β-cell function has been proposed as a possible aetiology for GDM. This defect results in an inability of the β-cell to increase insulin secretion to meet the increased demands of insulin posed by pregnancy (Buchanan and Xiang, 2005).

It has been shown that elevated maternal insulin secretion in early pregnancy in women without diabetes leads to gestational weight gain and weight retention post-partum (Scholl and Chen, 2002).

2.5 MANAGEMENT OF DIABETES IN PREGNANCY

The complex aetio-pathogenesis of T2DM and GDM makes management difficult. A multidisciplinary approach is the preferred method for management. The rising trend of diabetes in pregnancy poses a considerable perinatal mortality and morbidity to mother and child. (Clausen *et al*., 2005).

Insulin has traditionally been the mainstay of management of diabetes in pregnancy. However, there has been a number of studies on the use of oral agents in pregnancy. One clinical trial compared the use of glibenclamide and insulin in women with gestational diabetes (Langer *et al*., 2000)

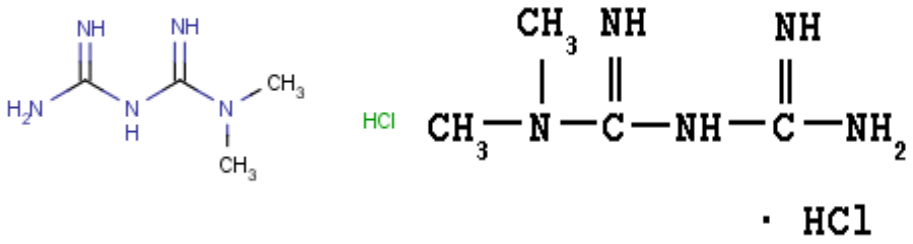
2.6 PHARMACOLOGY OF METFORMIN

Metformin is an oral hypoglycaemic agent which belongs to the biguanide class. Its history has been traced back to the use of a perennial herb, *Galega officinalis.* This herb has white, blue or purple flowers and grows over three feet high and is found in most temperate regions. Its common names include goat's rue, French lilac, Spanish sanfoin and false indigo. In folklore medicine, it is believed that *G. officinalis* was used to treat symptoms now ascribed to Type 2 diabetes (Bailey and Day, 2004). *G. officinalis* continues to be cited for the treatment of diabetes in modern herbal pharmacopoeias (Duke, 2002; Bailey and Day, 2004). French physician, Jean Sterne, is credited with the first clinical trial of metformin (which he called Glucophage) for the treatment of diabetes (Bailey and Day, 2004; Campbell, 2007).

2.6.1 CHEMISTRY/CLASSIFICATION OF METFORMIN

The International Union of Pure and Applied Chemistry (IUPAC)'s systematic name for metformin is ***N,N***-dimethylimidodicarbonimidicdiamide**.** It is also referred to as 1,1-dimethylbiguanide**.** It is a basic compound with molecular mass 129.164 g/mol (free form) and 165.63 g/mol (with HCl).

FIGURE 2.2 THE STRUCTURE OF METFORMIN



Source: www.chemistrydaily.com

2.6.2 PHARMACOKINETICS

Metformin is administered orally and absorbed mainly in the small intestine with a bioavailability of 40-60% at doses of 0.5 to 1.0 g. Absorption is complete in 6 hours after oral administration. Its bioavailability tends to decrease with increasing doses. This inverse relationship has led to the proposal of an active, saturable absorption process (Duke, 2012). Its half-life is 2 hours. It is stable and does not bind to plasma proteins (Scheen, 1996; Hardman *et al*., 2001). Metformin decreases absorption of vitamin B12 and folic acid, although reported cases of megaloblastic anemia are rare. Cimetidine decreases the elimination of metformin in healthy subjects (Melchior and Jaber, 1996) Metabolism is insignificant and excretion is primarily renal.

The renal clearance of metformin in men and non-pregnant women has been found to correlate with creatinine clearance, but it exceeded glomerular filtration rate, indicating active net tubular secretion (Scheen, 1996).

A parallel increase in renal clearance of both metformin and creatinine in mid- and late-pregnancy has been demonstrated. While metformin renal clearance increased on average by 49% and 29% in mid- and late-pregnancy, respectively, compared with postpartum, the changes in renal clearance of creatinine were 29% and 21%, respectively. The changes in metformin renal clearance were not dependent on the subjects OCT2 genotype **(**Hebert *et al.,* 2010) though metformin is known to be a substrate for organic cation transporters (OCTs) (Kimura *et al*., 2005; Zhou *et al*., 2007; Wang *et al*., 2008). Renal OCT2 (encoded by *SLC22A2*) has been suggested to play a significant role in the pharmacokinetics of metformin. This is because a 30 to 60% change in metformin secretion clearance and renal clearance and up to a 74% change in its area under the concentration-time curve (AUC) in carriers of the variant *SLC22A2* alleles has been noted (Wang *et al*., 2008; Song *et al* 2008; Chen *et al*., 2009). Metformin has been shown to cross the placenta readily. Umbilical cord concentrations at the time of delivery are at least half of the maternal concentrations and in some cases even exceed them (Hague *et al*., 2003; Vanky *et al*., 2005; Charles *et al*., 2006). A study by Hebert, *et al* (2010) found umbilical cord plasma concentration of metformin to vary from undetectable (<5 ng/ml) to 1263 ng/ml at the time of delivery.

Infant exposure following metformin administration during breast-feeding has been found to be low. The relative infant dose is reported to be between 0.11 to 1.08% of the mother's weight-adjusted dose (Hague *et al*., 2003; Vanky *et al*., 2005; Charles *et al*., 2006).

2.6.3 PHARMACODYNAMICS

Metformin is an effective oral hypoglycemic agent that improves insulin sensitivity **(**Krentz and Bailey, 2005). Metformin has a greater postprandial effect than the sulfonylureas and insulin, and is, therefore, more useful in patients with postprandial hyperglycaemia. The sulfonylureas and insulin, on the other hand, are more effective in managing poorly controlled fasting hyperglycaemia (Melchior and Jaber, 1996).

Metformin reduces free testosterone levels and increased sex hormone-binding globulin (SHBG). It improves menstrual irregularities leading to spontaneous ovulation and improved ovarian response to conventional ovulation induction therapies **(**Krentz and Bailey, 2005).

The introduction of metformin for the treatment of polycystic ovary syndrome (PCOS) provided evidence supporting its use in pregnant women (De Sloover and Ernst, 2001; Awartani and Cheung, 2002; Lord *et al*., 2003). Metformin has been recommended for use during pregnancy for the treatment of gestational as well as pre-existing diabetes mellitus (Guideline Development Group, 2008).

The exact mechanism of action of metformin is not fully understood despite its wide clinical usage. Metformindoes not stimulate insulin secretion. It exerts its hypoglycaemic effect via metabolic activities at several sites of action, including liver, adipocytes, intestine, and muscle cells. The activities in these sites of action (biophases) include:

1) Decreased hepatic glucose output due to decreased hepatic gluconeogenesis and increased glycogenesis and lipogenesis (Christiansen and Hellerstein, 1998);

2) Reduced rate of intestinal glucose absorption **(**Wilcock and Bailey, 1991); and

3) Increased glucose uptake by muscle cells and adipocytes (Bailey, 1996).

The relative contribution of these individual sites of action to the overall glucose-lowering effect is unknown and a subject of continuing research in animal models (Kuhlmann *et al*., 1996). This is because the dose-response relationship of the metabolic effects in individual organs and tissues is obscured by the multifactorial mechanism of metformin and the complex nature of glucose homeostasis in-vivo (Kuhlmann *et al*., 1996).

2.7 CHEMICAL PROPERTIES OF INSULIN

Insulin was discovered in 1921-1922 at the University of Toronto, Canada, by Frederick Grant Banting and colleagues. The name 'insulin' was derived from the Latin word for island "insula", and was actually described before the discovery of insulin. (Shah *et al*., 1997). Insulin is a peptide hormone composed of 51 amino acids with molecular weight of 5808 Da and is secreted by the beta-cells of the pancreas. The precursor of insulin, preproinsulin, is encoded by the INSgene (Bell *et al*., 1980). It plays a central role in regulating carbohydrate and fat metabolism in the body. It is a dimer composed of an A-chain and a B-chain, which are linked together by disulfide bonds. The A-chain contains an intra-chain disulphide bridge linking residue 6 and 11. The monomers aggregate to form dimers and hexamers. A C-chain, which connects A and B chains is released along with insulin after breakdown of proinsulin. (Bell *et al*., 1980). A zinc hexamer is made up of three insulin dimmers. The hexamer is the inactive form of insulin whiles the monomer is the active. The hexamer serves as a way of keeping insulin stable

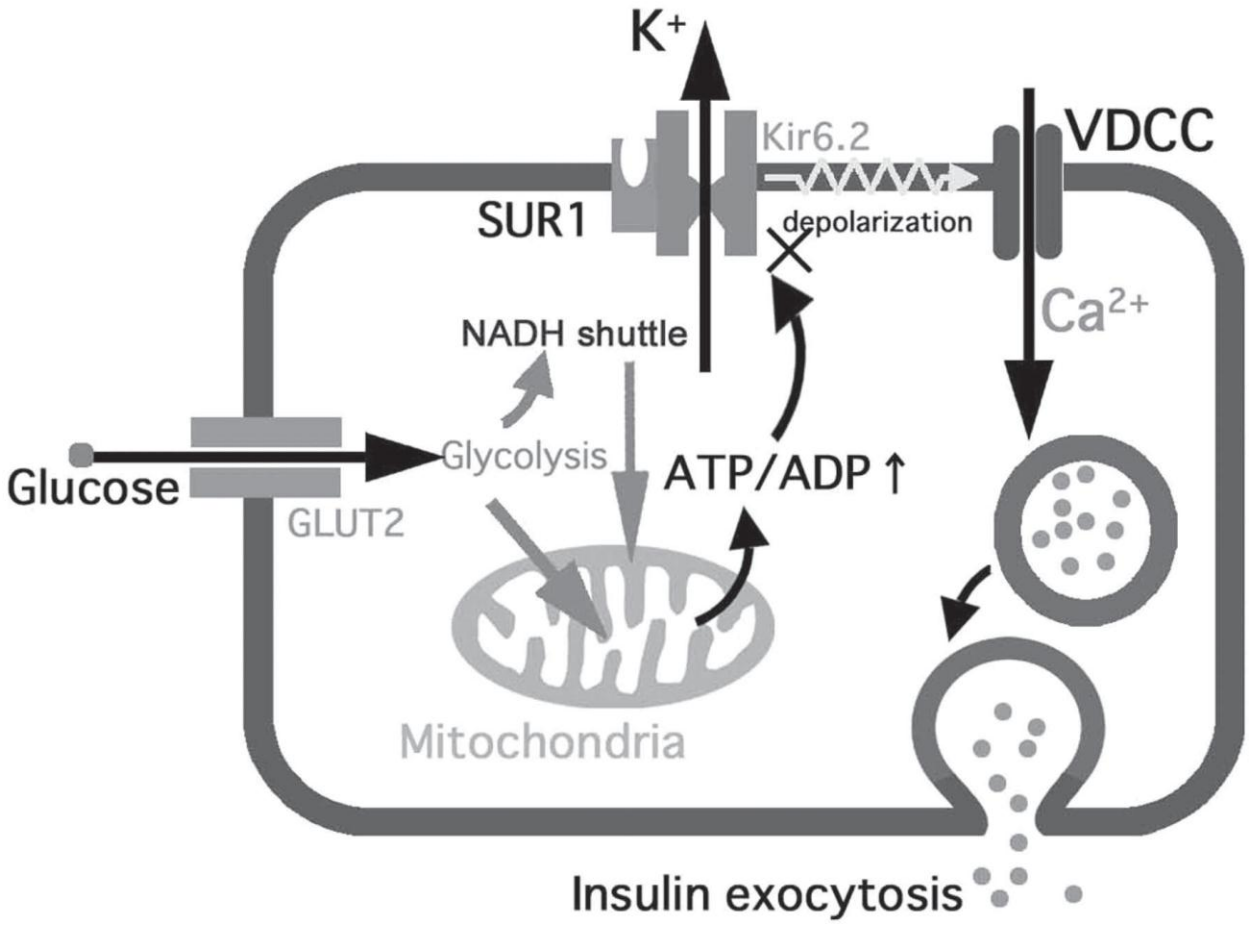
2.7.1 PHYSIOLOGY OF INSULIN SECRETION

The secretion of insulin from the ß-cell occurs in response to various stimuli like glucose, arginine and sulphonylureas, though physiologically glucose is the major determinant. Some neural, endocrine and pharmacological agents can also exert stimulatory effects. (Joshi *et al*., 2007).

The process of insulin secretion begins with uptake of glucose by beta-cells through GLUT-2 receptors. The glucose is subsequently oxidized by glucokinase, which acts as a glucose sensor. Glucose concentrations below 90 mg/dl do not cause any insulin release. Such sub-stimulatory glucose concentrations result in efflux of K^+ through open K_{ATP} channels and this keeps the ß-cell membrane at a negative potential at which voltage-gated Ca^{2+} channels are closed**.** Increasing plasma glucose enhances the uptake and metabolism of glucose by the ß-cell. A rise in ATP concentration result in closure of K_{ATP} channels, leading to beta-cell membrane depolarization, opening of voltage-gated Ca^{2+} channels, Ca^{2+} influx, a rise in intracellular calcium concentration and, ultimately, exocytosis of insulin granules (Joshi *et al*., 2007).

The pancreatic K_{ATP} channel is made of two distinct subunits: a sulfonylurea receptor (the SUR1isoform) and a potassium channel subunit (Kir6.2). (Fig 3). The mature K_{ATP}channel exists as an octamer of Kir6.2 and SUR1 subunits (Fig 2). Sulfonylurea (Gribble and Reimann 2003), and non-sulphonylurea drugs act as insulin secretogogues by closing K_{ATP} channels, bypassing the ß-cell metabolism (Joshi *et al*., 2007).

FIGURE 2.3 SECRETION OF INSULIN



Key:

1. GLUT2- Glucose transport 2
2. GK- Glucokinase
3. VDCC- Voltage-dependent Ca2+-channels
4. Kir6.2- potassium channel subunit
5. SUR1- sulfonylurea receptor

Source: Z. Alex Ma, Ph.D. September 17, 2009

Available online at:
http://sbcny.org/Pdfs/Systems_Biomedicine_Course/diabetes_module/class_4/Diabetes_Class_4_Insulin%20Secretion.pdf

2.7.2 TYPES OF INSULIN

Human insulin is currently produced by recombinant DNA technology. Porcine insulin has been withdrawn from the market and bovine is becoming extinct. The principle of this technology is the introduction of human insulin or proinsulin gene into organisms like *E. coli* or y*east*. The organisms are then incubated to multiply and, in turn, produce insulin or proinsulin which is converted to insulin by enzymatic cleavage. Insulin analogues are produced by modifying amino acid sequence of human insulin (Joshi *et al*., 2007).

Dry human insulin is a microcrystalline powder. It precipitates at a pH of 5.4, and is soluble at a pH of 2-3. One IU of insulin corresponds to 38.5 μg dry substance **(**WHO 1987).

Half-life of injected insulin is about 40 min. Human insulin is available in the short-acting i.e. regular and intermediate-acting i.e. Neutral Protamine Hagedorn (NPH) forms. Insulin analogues include rapid-acting, such as Lispro (Eli Lilly) and Aspart (Novo Nordisk); and long-acting, such as Glargine (Sanofi -Aventis) and Detemir (Novo Nordisk). Ultralente is no longer available on the market, having been withdrawn (Joshi *et al*., 2007).

Premixed insulin and insulin analogues are available, and they come in various ratios of (regular: NPH) such as 30:70; 50:50 and 25:75 proportions of short-acting to intermediate-acting respectively.

CHAPTER THREE

3.0 METHODOLOGY

3.1 STUDY DESIGN

The study design was a prospective, randomized controlled study. It was an open-labelled trial designed with the intention to treat. Patients were randomly assigned into the two treatment groups – insulin and metformin groups. A block size of four was used for patient enrolment. This is because, information from the Diabetes Centre of Korle-Bu Teaching Hospital reveals that, on the average, four (4) women with GDM are seen on a clinic day, and a similar number is also seen at the Antenatal Clinic in the Obstetrics and Gynaecology Department of the same hospital . For a block of four (4) patients seen at the clinic for the first time, they were made to pick randomly one paper each from an envelope. The sequence of picking was in the order in which they reported to the clinic;" first to report, first to pick". These envelopes contain inscriptions that assigned participants to a particular group; two for each group. This was repeated till the desired sample size was attained**.**

Glycaemic profile measurement did not include glycosylated haemoglobin (HbA1c) levels for logistic reasons and also because available literature gives conflicting relationships between HbA1c levels and pregnancy outcome in GDM. The National Collaborating Centre for Women's and Children's Health commissioned by National Institute for Health and Clinical Excellence (NICE) guideline on diabetes in pregnancy and the International Diabetes Federation global guideline on pregnancy and diabetes recommend that HbA1c should not be used routinely to assess glycaemic control in the second and third trimesters (IDF2009; National Collaborating Centre for Women's and Children's health, 2008).

Treatment was administered to each according to the study treatment protocols. Subjects in both groups were followed through their routine antenatal schedule and their blood glucose levels were checked and recorded during these visits, according to existing protocols. A similar protocol was used when patients were admitted as in-patients.

3.2 STUDY AREA AND DURATION

The study was conducted at the Maternity Unit and the Diabetes Centre of the Korle-Bu Teaching Hospital from 1st January, 2013 to 31st October, 2013. It involved both in- patients and out-patients in these units.

3.3 STUDY SUBJECTS

3.3.1 Eligibility criteria

Women aged 18 to 45 years, who were pregnant with single fetus at gestational age of 20 to 30 weeks and have been diagnosed with Type 2 DM or Gestational Diabetes and met the Hospital's criteria for starting insulin therapy, were considered eligible subjects.

The criteria for the diagnosis of pre-gestational diabetes mellitus was a plasma glucose concentration of ≥ 7 mmol/L after an overnight fast or plasma glucose concentration of ≥ 11.1 mmol/L 2 hours after a 75g glucose drink (WHO,1999).

The criteria for diagnosing GDM in this study was the ADA2012 recommendation (Diabetes care, 2012):

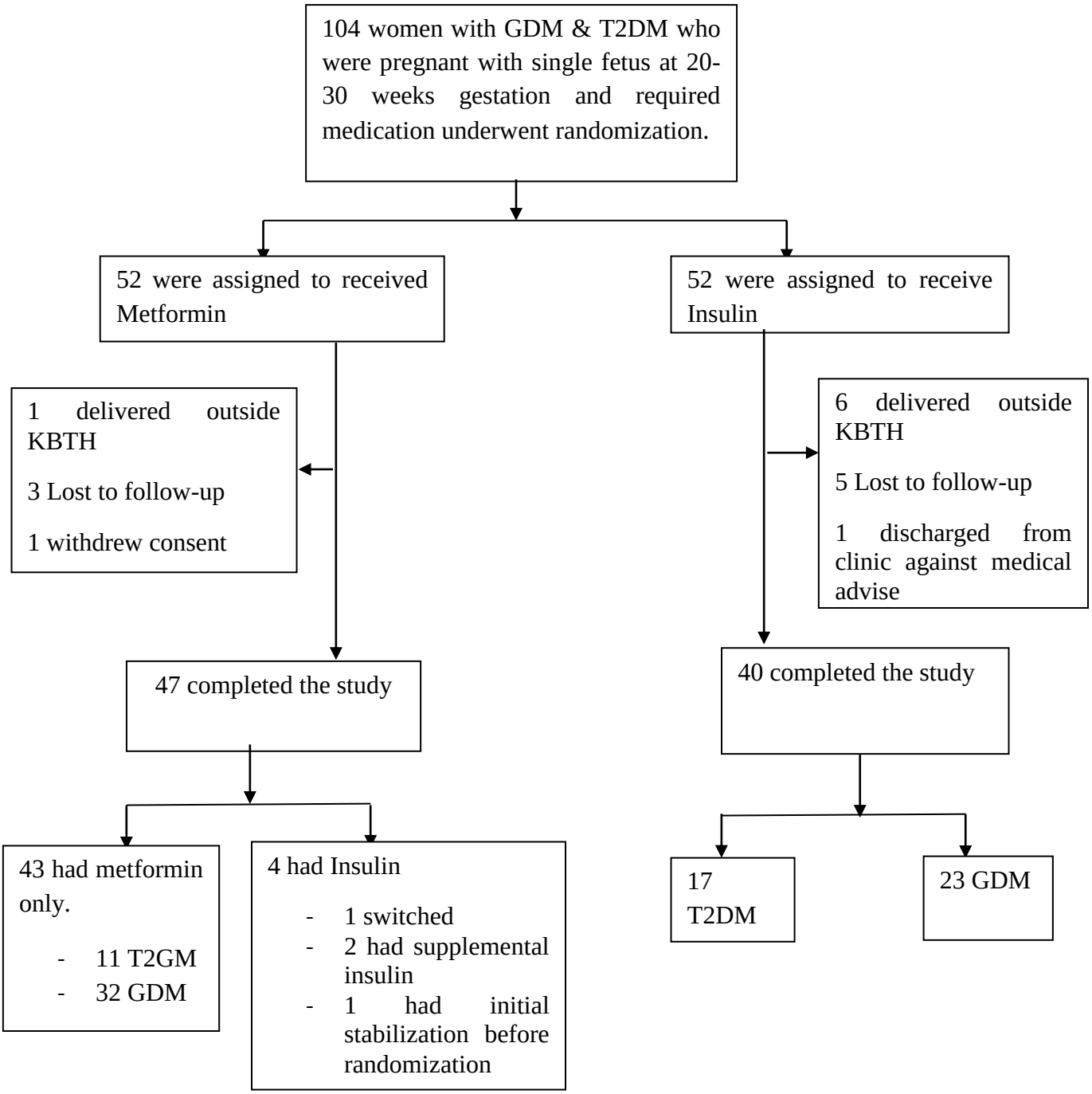
- FBS > 5.1 mmol/l
- 1HPG>10.0 mmol/L or
- 2HPG>8.5 mmol/L.

Subjects diagnosed according to the above criteria that were unable to achieve the above targets following management on diet and exercises were eligible for the study.

3.3.2 Exclusion criteria

Exclusion criteria included patients with pre-gestational diabetes mellitus who require insulin to achieve glycaemic control and patients with contra-indications to metformin therapy.

Figure 3.1 Subject enrolment



3.4 SAMPLE SIZE DETERMINATION

Sample of this study was calculated using the two sampled mean formula below (Chow *et al*., 2002)

$$N = \frac{2S_p^2(Z_\alpha + Z_\beta)}{m_1 - m_2}$$

Where;

N = Sample size, S_p^2= pooled variance, Z_α= level of significance, Z_β = power of the study, $m_{1=}$ mean value of metformin group and $m_{2=}$ mean value insulin group.

Using the formula above, the estimated sample size was 47 per group.

To allow for a non-respondent rate of about 10%, the number of subject recruited in each group was 52.

The following assumptions were made:

- From a previous study (Rowan *et al*., 2008), a minimum difference of 4mg/dl (0. 22 mmol/l) was estimated in the mean 2HPG between the two groups, a power of 80% and α of 0.05.
- This difference was also assumed to be clinically significant.

3.5 TREATMENT PROTOCOL

Metformin Group

In the metformin group, the starting dose of metformin was 500mg once a day and increased gradually over two (2) weeks, to meet glycaemic targets of FBS < 5.1 mmol/L, 1HPG < 10.0mmol/L and 2HPG < 8.5 mmol/L.

The maximum dose allowed per study protocol was 2500mg per day. Insulin was added if targets could not be reached on metformin alone at maximum doses. Subjects that received supplemental insulin were excluded from the metformin group and analysed as treatment failures.

Insulin group

In the Insulin group, both soluble insulin and premixed insulin were prescribed, according to hospital protocols, when necessary. There was no brand restriction. Common brands patients received included Lispro®(Eli Lilly), Aspart®(Novo Nordisk) Humulin®(Eli Lilly), lantus®(Sanofi-aventis) and mixtard®(Novo Nordisk).Both premixed insulin and soluble insulin were administered subcutaneously in the deltoid region. Total daily dose of premixed insulin at initiation was calculated for most patients as 0.3 IU/kg body weight. However for patients admitted with high blood glucose levels and managed on sliding scale with soluble insulin their starting dose was based on total daily requirement. The total daily dose was then divided into two: two-thirds of the dose is given in the morning 30 minutes before breakfast and one-third of the daily dose given in the evening 30 minutes before supper. The total dose of insulin was

titrated for each patient to achieve the above glycaemic targets. In a few patients, a combination of both soluble insulin and premixed insulin was administered three times a day before meals on regular basis to achieve glycaemic control targets

Patients who did not achieve glycaemic targets on their out-patient doses after attempts at titrations were admitted to the ward and treated with soluble insulin to determine their new optimum insulin requirements. All patients were educated by both nurses and doctors while on admission on the disease and self-administration of the correct doses of insulin before discharge.

Treatment failures

Supplemental insulin for treatment failures in the metformin group was prescribed according to the same protocols as the insulin arm of the study. Samples from participants in the insulin group who required oral hypoglycemic agent supplementation for effective control were also analysed as treatment failures. Four patients fell in this group, thus comparative analysis could not be done

3.6 DATA COLLECTION

Basic demographic data was recorded. Subjects were followed through their index pregnancy, with 2-weekly blood glucose checks and occasionally blood glucose profile monitoring in hospital. Blood glucose monitoring included patient self-monitoring, ward nurses monitoring and laboratory monitoring. The most commonly used glucometer by patients and nurses was the one touch brand; select® and ultra® (LifeScan, Inc. USA). The values used in the analysis were that of the laboratory results from the diabetes research laboratory. All laboratory samples were taken

and analysed at the diabetes research laboratory by staff of the same laboratory. While capillary blood was used in the patients self-monitoring and monitoring by ward nurses via finger prick sample, venous blood was used for laboratory blood glucose profile analysis. Analysis of Fasting Blood Glucose (FBG), one- hour post-prandial glucose (1HPG), two- hour post-prandial glucose (2HPG) were carried out, using the Mindray BS-400®(Mindray Medical Int. Ltd, China) chemistry analyzer. The method for glucose determination was enzymatic photometric testing.

Weight records from the antenatal records were analysed. Patients are weighed using Seca®(gmbh&Co. Kg Germany). The dose of metformin required for optimal glycaemic control for each patient and peri-partum events like gestational age at delivery, type of delivery, foetal birth weight, and NICU admissions were retrieved from patient notes and analysed.

3.7 STATISTICAL ANALYSIS

Prior to statistical analyses, the data were examined through statistical package for social science **(**SPSS) Version 16.0 for accuracy of data entry and completeness. Summary statistics including appropriate tables and charts were used in analyzing the data. Line graph was used to show trends in glycaemic profile. Data was also examined for assumptions of normality (i.e. Shiparo-Wilk) and homogeneity of variance (i.e. Levene's test). Differences in variables were determined by mixed repeated measure anova with 3 within subject factors and one between group factors. All the assumptions were met except the sphericity. Thus, the Greenhouse-Guisser correction was used in the analysis. If difference was detected a post-hoc analysis was done using the t tests to examine intragroup difference and intergroup comparisons. Chi-square test for categorical

data and z-score for differences in proportions were used where applicable. A of p - value <0.05 was considered significant.

CHAPTER FOUR

4.0 RESULTS

4.1 GENERAL SAMPLE CHARACTERISTICS

A total of 104 participants with GDM & T2DM who were pregnant with single fetus at 20-30 weeks gestation and required medication were enrolled in the study and underwent randomization. Ninety percent and 76% of participants in the metformin and insulin group respectively completed the study. Four persons who completed the study, were assigned to receive metformin but received both treatment drugs.

The two treatment groups were comparable in several demographic and pre-enrolment characteristics from tables 4.1 and 4.2 respectively. There were no significant differences observed in age, parity, marital status, BMI and the two pre- treatment weight categories. There was however significant difference in the gestational age at enrolment with the metformin group being recruited at a higher gestational age, $p = 0.017$.

No significant difference was observed in the classification of diabetes between the two treatment groups. Again, no significant difference was observed in the prevalence of co-morbid conditions in the index pregnancy. The obstetric history was similar in both treatment groups.

Table 4.1 Demographic characteristics of participants

Variable	Metformin N = 43	Insulin N = 40	p-value
Age-yr (mean ±SD)	33.51 ±4.67	33.10±4.56	0.686
Parity {no. (%)}			
Nulliparous	7 (16.3)	8 (20.0)	0.660
P1 – P4	33 (76.7)	29 (72.5)	0.657
≥P5	3 (7.0)	3 (7.5)	0.927
Marital status {no. (%)}			
Married	43(100.0)	39(97.5)	0.482
Single/Divorced	0 (0.0)	1(2.5)	
BMI-kg/m^2	33.47± 6.95	32.61±6.21	0.56
Weight at enrolment {no.(%)}			
<90kg	24 (57.1)	28 (70.0)	0.227
≥90kg	18 (42.9)	12 (30.0)	

Table 4.2 Maternal pre- enrolment clinical characteristics

Variable	Metformin N = 43	Insulin N = 40	p-value
Gestational Age (weeks) {median , inter-quartile range(25-75)}	28, (26 - 29)	26, (23 - 28)	**0.017**
Classification of diabetes {no. (%)}			
GDM	32(74.4)	23(57.5)	0.103
T2DM	11(25.6)	17(42.5)	
Co-morbid condition in pregnancy {no. (%)}			
Essential Hypertension	6(14.0)	5(12.5)	1.000
Sickle cell disease	1 (2.3)	0 (0.0)	1.000
Others*	3 (7.0)	3 (7.5)	1.000
Obstetrics history {no. (%)}			
Miscarriages	12 (27.9)	15 (37.5)	0.351
Stillbirths	3 (7.0)	2 (5.0)	1.000
Early neonatal deaths	1 (2.3)	2 (5.0)	0.607
Big baby (>4.0kg)	5 (11.6)	2 (5.0)	0.095
Caesarian section	14 (32.6)	14 (35.0)	0.820
Others**	3 (7.0)	3 (7.5)	1.000

*One patient each in the metformin group had malaria, multiple uterine fibroid, anaemia as a co-morbid condition whiles one each for insulin had hepatitis B, G6PD and goiter.
**One patient each in the metformin group had IUFD, gestational diabetes, PIH in their obstetric history whiles insulin group had one patient each with gestational diabetes, post-partum haemorrhage and IUFD.

The mean weight gain from enrolment to term was significantly higher in the insulin group (4.46 ±2.09 kg) than the metformin group (2.21 ±2.42 kg) with p <0.0001 as shown in Table 4.3 below. The mean FBG and 1HPG level from enrolment to term was similar in both treatment groups with p values of 0.928 and 0.078 respectively. The 2HPG levels were significantly lower in the metformin group than the insulin group with p value of 0.004.

Table 4.3 Mean weight gain and glycaemic profile from enrolment till term

	Metformin	**Insulin**	**P-value**
Weight gain(kg)	2.21 ±2.42	4.46 ±2.09	<0.0001
FBG (mmol/L)	6.42 ±0.98	6.62 ±1.57	0.928
1HPG (mmol/L)	8.95 ±1.27	9.62 ±1.44	0.078
2HPG(mmol/L)	7.84 ±1.43	9.05 ±1.89	0.004

4.2 PRIMARY OUTCOME

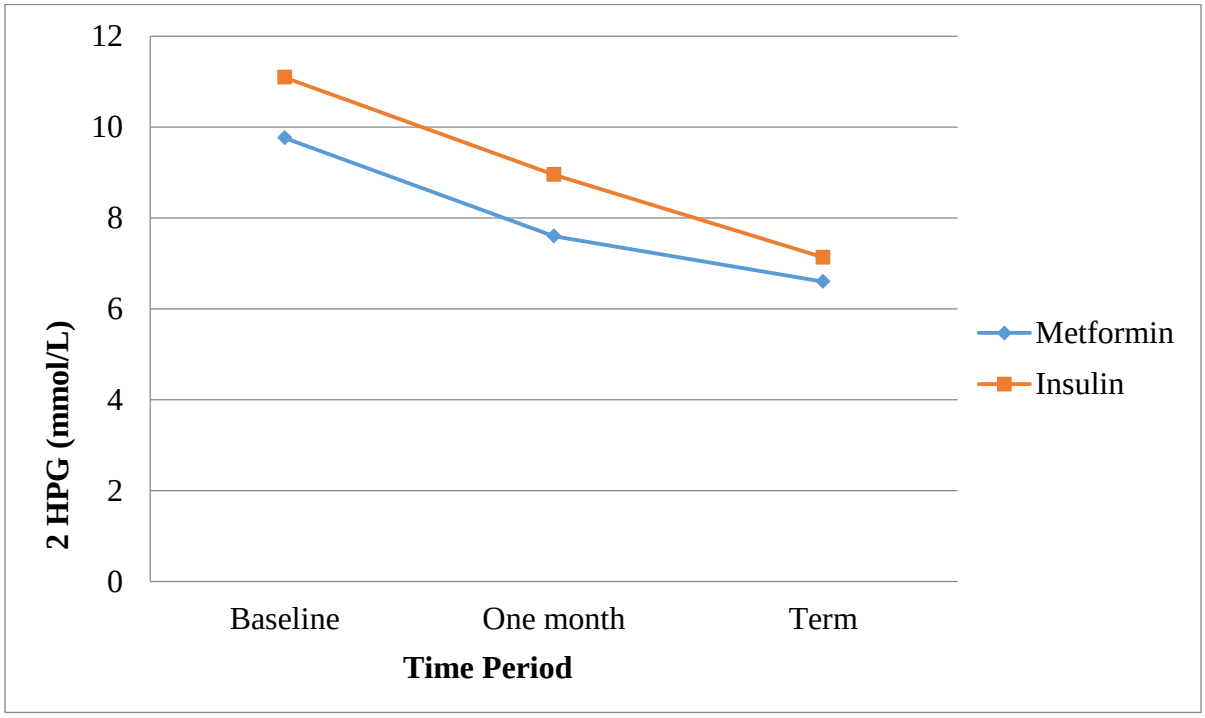
Table 4.4 2HPG for the metformin and insulin groups across the three time periods

	Metformin			Insulin			
Time period	N	Mean#	SD	N	Mean#	SD	P-value
Baseline	41	9.76	2.12	40	11.09	3.07	0.024
One month	41	7.60	1.55	40	8.95	2.41	0.003
Term	41	6.60	1.22	40	7.13	2.08	0.163

Mean values were measured in mmol/L

2HPG= Two hour post prandial glucose

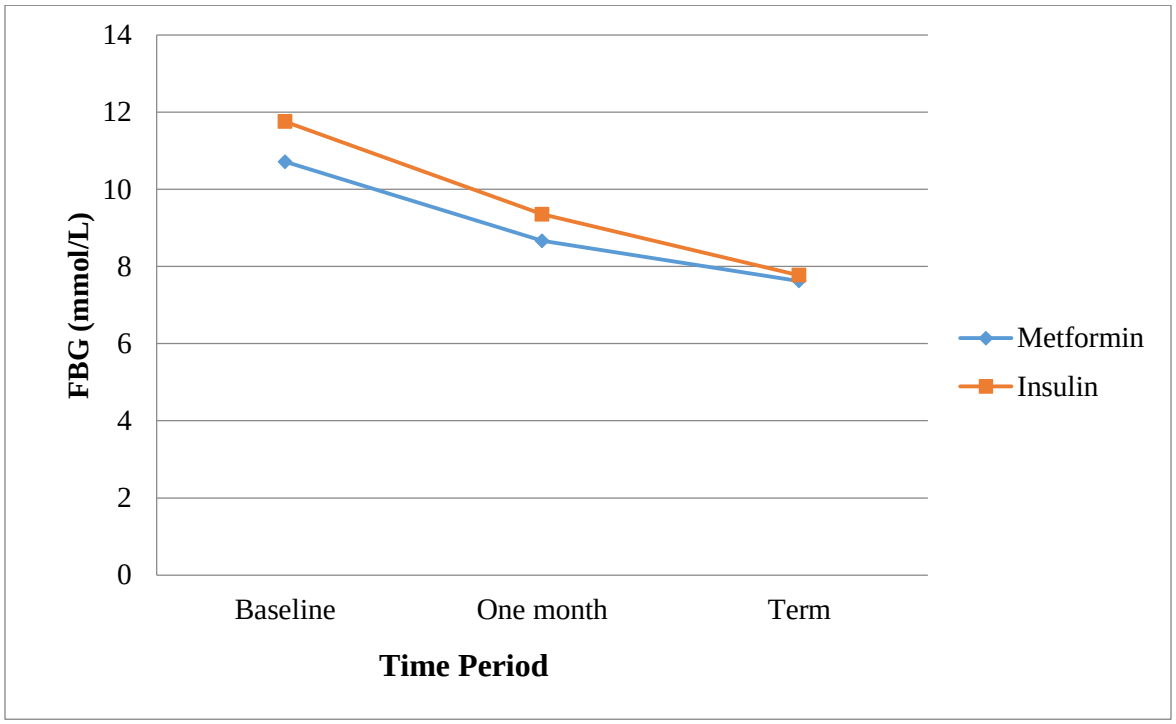
Figure 4.1 Line graph showing the mean 2HPG levels against time for the two treatment groups.



The 2HPG level decreased from baseline to term for treatment groups. A repeated measure analysis of variance, using the Greenhouser-Guisser correction, showed that there was a significant difference in the 2HPG values between the different times of measurement (F (2, 78) = 64.26, p < .0001). No significant difference in 2HPG was found between the insulin and metformin group with respect to time, (F (2, 78) = 3.031, p = 0 .054). However, the metformin group had a significant 1.21mol/L drop in 2HPG compared to insulin (F (1, 79) = 9.169, p = 0.003).

4.3 SECONDARY OUTCOMES

Figure 4.2 Pattern of mean FBG levels against time for the two treatment groups.



This graph represents the trend in the mean FBG values measured at enrolment (baseline), at one month and at term for both treatment groups. The FBG level decreased from enrolment to term in both groups. The FBG for the insulin group at baseline was 7.80 ± 2.30 mmol/L and this was slightly higher than the 7.73± 1.51mmol/L for metformin. This difference was however not significant. The mean FBG for metformin remained lower than that of insulin throughout the course of the pregnancy, but no significant difference was observed.

Figure 4.3 Pattern of mean 1HPG levels against time for the two treatment groups.

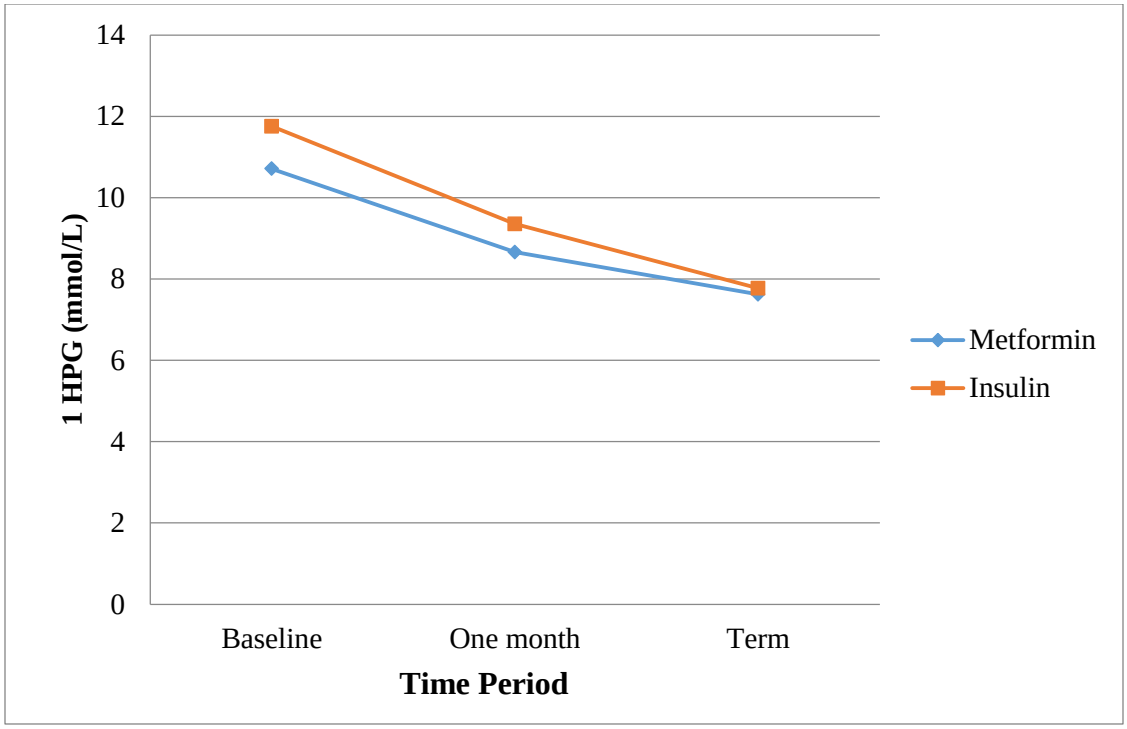


Table 4.5 Pregnancy outcome

VARIABLES	METFORMIN	INSULIN	P-VALUE
Mode of delivery no. (%)			
SVD	18 (41.9)	14 (35.9)	0.653
C/S	25 (58.1)	25 (64.1)	
Indication for C/S no. (%)			
Severe pre-eclampsia/eclampsia + unfavourable cervix	4 (16.0)	7 (28.0)	0.306
Diabetes+ failed induction	3 (12.0)	6 (24.0)	0.269
Previous uterine surgeries	7 (28.0)	3 (12.0)	0.157
Macrosomia (big baby)	3 (12.0)	3 (12.0)	1.000
Foetal jeopardy	3 (12.0)	3 (12.0)	1.000
Advanced maternal age + Patient's request	2 (8.0)	1 (4.0)	0.551
Primip breech presentation	1 (4.0)	1 (4.0)	1.000
Grandmultiparity + failed induction	1 (4.0)	0 (0.0)	1.000
Secondary arrest of labour	0 (0.0)	1 (4.0)	1.000
Type 2 placenta praevia	0 (0.0)	1 (4.0)	1.000
CPD	1 (4.0)	0 (0.0)	1.000

Gestational age at delivery [M+IQR]	38.20 (37.40 – 39.20)	38.20 (37.80 -39.3)	0.523
<37 weeks	6 (41.0)	4 (10.0)	0.740
<=37 weeks	37 (86.0)	36 (90.0)	
Birth weight (kg)	3.37 ±0.65	3.45 ±0.87	0.632
1 minute APGAR [Median + IQR]	7.0 (7.0 – 8.0)	7.0 (7.0 – 8.0)	0.522
5 minute APGAR [Median + IQR]	9.0 (8.0 – 9.0)	9.0 (8.0 – 9.0)	0.488

Table 4.6 Maternal and feto-neonatal complication

VARIABLE	**METFORMIN**	**INSULIN**	**P VALUE**
Maternal complications no. (%)			
Gestational hypertension	15 (34.9)	7 (17.5)	0.086
Polyhydramnios	4 (9.3)	2 (5.0)	0.677
Antenatal Admission. No.(%)	33 (47.1)	37 (52.9)	0.048
No. of admissions [median + interquartile range]	1 (1 – 2)	1 (1 – 2)	0.507
Reasons; no (%)			
Glycaemic control	25 (58.1)	31 (77.5)	0.060
BP control	15 (34.9)	10 (25.0)	0.327
Others***	9 (20.9)	5 (12.5)	0.305

Foetal complications			
IUGR			
Foetal distress	0 (0.0)	1 (2.5)	0.482
	1 (2.3)	2 (5.0)	0.607
Neonatal complications no. (%)			
Birth Trauma	0 (0.0)	1 (2.5)	0.482
Baby Resuscitated[#]	5 (11.9)	4 (10.0)	1.000
NICU referral	43 (100.0)	39 (97.5)	0.482
Reasons for NICU referral no. (%)			
Pre-maturity	4 (9.3)	3 (7.5)	1.000
Birth asphyxia	2 (4.7)	3 (7.5)	0.668
Macrosomia (big baby)	5 (11.6)	7 (17.5)	0.447
Respiratory distress syndrome	1 (2.3)	1 (2.5)	1.000
Meconium aspiration	0 (0.0)	1 (2.5)	0.482
Low birth weight	0 (0.0)	1 (2.5)	0.488
Routine (diabetic mother)	26 (61.9)	22 (57.9)	0.715
NICU admissions no. (%)	15 (34.9)	19 (48.7)	0.204
Duration of admission (mean±SD)	2.20 ±1.27	3.59 ±1.87	0.022

Diagnosis at NICU no. (%)[##]			
Pre-maturity	2 (4.8)	3 (7.5)	0.672
Birth asphyxia	2 (4.8)	2 (5.0)	1.000
Macrosomia (big baby)	2 (4.8)	5 (12.5)	0.259
Hypoglycaemia (<2.6mmol/L)	3 (7.1)	7 (17.5)	0.189
Respiratory distress syndrome	3 (7.1)	6 (15.0)	0.307
Neonatal jaundice	1 (2.4)	1 (2.5)	1.000
Meconium aspiration	0 (0.0)	1 (2.5)	0.488
Sepsis/at risk of sepsis	0 (0.0)	1 (2.5)	0.488
Small for date	0 (0.0)	4 (10.0)	0.052
Stable	11 (25.0)	8 (20.0)	0.545
Hernia	1 (2.0)	0 (0.0)	0.332
Polycythaemia	1 (2.0)	0 (0.0)	0.332
Outcome of NICU admission no. (%)			
Discharged	16 (100.0)	18 (95.7)	1.000
Died	0 (0.0)	1 (100.0)	

***other reasons why patients had antenatal admissions include: glucose profile (6) and one each for polyhydramnios, UTI, right leg cellulitis for the metformin group whiles the insulin group had 4 for glucose profile and one for UTI.

[#] For the purpose of this study a baby is deemed to have been resuscitated if an anaesthetist or neonatologist was called in to resuscitate the baby.

[##] All babies born to diabetic mothers are routinely sent to the neonatologist for examination. Babies found to be stable are discharged. The diagnosis listed are additional reasons for referral.

No association was observed between treatment type and pregnancy complications like gestational hypertension and polyhydramnios. Antenatal admission was higher in the insulin group.

At delivery (Table 4.5 above), women from both groups had the same median gestational age (38 weeks 2 days), with babies from women in the Insulin group registering slightly higher mean birth weight of 3.45 kg than that of metformin 3.37 kg. However, this difference was not significant. (P = 0.632).

One baby in the Insulin group had birth trauma, whiles the metformin group did not register any (Table 4.6 above). Out of the total babies referred to NICU on account of Macrosomia, 12.5% were from the Insulin group, whiles the remaining 4.8% belonged to metformin group which was consistent with the Insulin group having a slightly greater weight than metformin.

An independent samples T-test was conducted to assess the difference in length of stay per NICU admission. The results showed that the babies from the Insulin group were staying significantly longer than the metformin group (3.59 days and 2.20 days, respectively, P = 0.022)

Table 4.7 Total daily dose of metformin and insulin per subject during the course of treatment

	Metformin (mg)			**Insulin (IU)**		
Time period	Median	Minimum	Maximum	Median	Minimum	Maximum
First month	1000	500	2000	30	12	78
Second month	1500	500	2000	38	16	86
Last month	2000	500	2000	43	16	98

The median dose of medication in both groups increased from enrolment to term. In the metformin group, the median dose increased from 1000mg daily in the first month of enrolment to 2000mg at term. Patients used different brands of metformin. In the insulin treatment group, the median daily insulin requirement increased from 30 IU to 43 IU. The maximum daily dose of insulin used was 98 IU. This involved both soluble and pre-mixed insulin.

Only two subjects, who were randomized to receive metformin, had supplemental insulin, because of difficulty in achieving glycaemic targets at maximum doses. This number was considered too small for comparative analysis with either treatment groups. Two subjects also switched from metformin to insulin inadvertently.

CHAPTER FIVE

5.1 DISCUSSION

The rising trend of diabetes in pregnancy poses a considerable maternal and perinatal morbidity and mortality (Clausen *et al*., 2005).The management of DM in pregnancy depends on the classification and severity. The complex aetio-pathogenesis of T2DM and GDM makes management difficult. A multidisciplinary approach is the preferred method for management. The practice for patients with GDM has been to manage with diet and exercise initially. Pharmacotherapy is then started only after failure of glycaemic control on diet and exercise.

Insulin has traditionally been the mainstay of management of diabetes in pregnancy. There have been a number of studies on the use of oral agents such as metformin and glyburide in pregnancy (Rowan *et al*., 2008; Rai*et al*., 2009; Nicholson *et al*., 2009; Dhulkotia *et al*., 2010).

The aim of this study was to determine if metformin monotherapy or metformin in combination with insulin is effective at attaining and maintaining glycaemic targets compared to insulin monotherapy in the management of gestational diabetes mellitus and Type 2 pre-gestational diabetes mellitus in Ghanaians. The results are discussed below.

5.2 AGE AND DIABETES IN PREGNANCY

The mean age was not significantly different between treatment groups (p =0.686) and this suggests that in this study there is probably no confounding effect of age on the control of diabetes in pregnancy. The proportion of pre-gestational diabetes mellitus (T2DM) among pregnant women with diabetes who were enrolled in the study was 33.73%. The findings of this study is consistent with that of Ozumba and colleagues who reported a 39% proportion of pre-gestational diabetes in a Nigerian population with the rest being gestational diabetes (Ozumba *et al*., 2004). It is also consistent with the assertion that prevalence of Type 2 diabetes mellitus is increasing in the young and reproductive age group (Rosenbloom *et al*., 1999)

5.3 OBESITY AND THE CONTROL OF DIABETES IN PREGNANCY

The pre-pregnancy BMI, which would have been more appropriate in controlling for obesity as a confounding factor in the management of diabetes in this study, could not be assessed. However, the BMI at enrolment was comparable (p= 0.56), as was maternal weight categories of less than 90 kg and 90 kg and above (p= 0.227). The metformin treatment group had a slightly higher proportion of the higher weight category. This was, however, not significant. Obesity has been identified as a risk factor for the future development of T2DM in women diagnosed with GDM (Ben-Haroush *et al*., 2004).

The mean weight gain from enrolment to term was significantly higher in the insulin group than the metformin group with p <0.0001. This is consistent with a study conducted by Janet A. Rowan and colleagues who found a 0.4 kg gain in mean weight from enrolment to term among pregnant women treated with metformin, compared to 2.0 kg in those treated with insulin

($p<0.0001$) [Rowan *et al*., 2008]. The reason for this reduction in weight gain is not clear, but decreased in appetite of the women treated with metformin could be a possible cause.

5.4 GESTATIONAL AGE AT ENROLMENT

The median gestational age of participants in the metformin group at enrolment was significantly higher in the metformin group (28weeks) than that of participants in the insulin group (26weeks) with *p* of 0.017. This could be partly explained by the distribution of T2DM and GDM within the study groups. For participants with pre-gestational diabetes, the gestational age at enrolment will reflect, to a large extent, their gestational age at booking. The insulin treatment group had forty-two percent of participants being T2DM, hence their lower median gestational age at enrolment. The median gestational ages in both groups at enrolment were lower than the 30 weeks reported by Janet Rowan and her colleagues in the metformin versus insulin for the treatment of gestational diabetes (Rowan *et al*., 2008). This difference may be explained in part by the addition of T2DM patients to this study, while they focused only on GDM.

In the case of GDM patients, the gestational age at diagnosis is very important. This is because women in whom diagnosis of diabetes mellitus is made for the first time in the first half of pregnancy, invariably become diabetic after the pregnancy. This group of women form a high-risk subgroup. They have a higher incidence of obstetric complications, recurrent GDM in subsequent pregnancies, and future development of Type 2 diabetes (Ben-Haroush *et al*., 2004).

For this study, however, the gestational age at enrolment may not exactly represent the gestational age at diagnosis in most cases. This is because, most participants with GDM following diagnosis are first managed on diet and exercise before medication treatment is

considered if glycaemic profile is not satisfactory. There could also be delays in presentation, diagnosis and referral from peripheral health facilities to the study sites. When gestational age was controlled for in the analysis, the primary and secondary outcomes remained the same.

5.5 COMORBID CONDITIONS IN INDEX PREGNANCY

Comorbid conditions that have adverse influence on maternal and foetal outcomes were examined to minimize any confounding effect. The prevalence of hypertensive disorders (pre-gestational) was not significantly different between the treatment groups. Gestational hypertension complicated 34.9% of all pregnancies in the metformin group, compared to 17.5% in the insulin group, and this difference was statistically significant, p= 0.086.

5.6 MATERNAL WEIGHT AND DIABETES IN PREGNANCY

The weight at enrolment was not significantly different between the two treatment groups. Since the pre-pregnancy or early pregnancy BMI was not assessed, the enrolment weight was categorized into high (≥90 kg) and low (<90 kg). No significant difference was found in either weight category between metformin and insulin treatment groups. Maternal obesity has been shown to correlate with adverse pregnancy outcomes, such as pre-eclampsia, gestational diabetes, foetal macrosomia and caesarean deliveries (Cnattingius *et al*., 1998; Sebire *et al*., 2002). Some perinatal problems, including increased risk of birth asphyxia, birth trauma, and neonatal hypoglycaemia are associated with maternal obesity (Edwards *et al*., 1996). A

comparable baseline maternal weight, therefore, eliminates the confounding effect of obesity on the outcome of this study.

Maternal weight gain during pregnancy can serve as a means of assessing the well-being of the pregnant mother (Varma, 1984), as well as predicting foetal outcomes, whereas inadequate weight gain serves as a risk factor for intra-uterine growth restriction, pre-term delivery and low birth weight in infants (Lawoyin, 1991; Marsoosi *et al*., 2004), excessive weight gain can lead to adverse maternal and foetal outcomes (Kumari , 2001).

Independent of the pre-pregnancy weight, excessive weight gain during pregnancy increases the risk of cesarean section, unsuccessful trial of labor after cesarean section, developing pre-eclampsia, retaining excessive weight after delivery, and becoming overweight or obese in later life (Stuebe *et al*., 2009).

In pregnant diabetics, however, the problem is excessive weight gain than inadequate weight gain. One may hypothesize that decreasing weight gain during pregnancy may result in improved outcome to both mother and baby. Therefore, one of the objectives of the study was to compare the mean weight gain in pregnancy between the two treatment groups. The mean weight gain from randomization to term was significantly higher in the insulin group than the metformin group with $p < 0.0001$. This is consistent with findings by Janet Rowan and her colleagues in the metformin versus insulin for the treatment of gestational diabetes (Rowan *et al*., 2008). This reduction in weight gain is expected to improve insulin sensitivity, decrease the risk of becoming obese later in life (Stuebe *et al*., 2009), and for patient with GDM it may reduce the risk of developing T2DM (Ben-Haroush *et al*., 2004).

5.7 TREATMENT OPTIONS AND GLYCAEMIC CONTROL

There is evidence that metformin is an effective oral hypoglycemic agent that improves insulin sensitivity (Krentz and Bailey, 2005). Metformin has been shown not to be inferior to insulin for glycaemic control in GDM (Rowan *et al*., 2008). In a case series from South Africa involving T2DM in pregnancy, Coetzee and Jackson found that, if the objective of strict blood glucose control was achieved, the perinatal mortality rate compared favourably with that of Type 1 diabetes. Their regimen included a rapid recourse to insulin if metformin did not produce good glycaemic control (Coetzee and Jackson, 1986). There is insufficient data on randomized controlled trials of metformin in the management of T2DM in Africa.

A key objective of this study was to determine blood glucose profile in pregnant women with both GDM and T2DM who were treated with metformin and compare the profile with those treated with insulin. In this study, the mean FBG and 1HPG level from enrolment to term was similar in both treatment groups with p values of 0.928 and 0.078, respectively. This is consistent with results from a large randomized controlled trial involving only GDM patients (Rowan *et al*., 2008). The 2HPG levels were significantly lower in the metformin group than the insulin group with p value of 0.004. The metformin group had a significant 1.21 mol/L drop in 2HPG over the study period compared to insulin.

This agrees in part with the long-standing knowledge that metformin has a greater postprandial effect than insulin, while insulin, on the other hand, is more effective in managing poorly controlled fasting hyperglycaemia (Melchior and Jaber, 1996).

Further analysis of the pattern of glycaemic control with repeated measure analysis of variance, using the Greenhouser-Guisser correction, showed that there was a significant difference in the 2HPG values between the different times of measurement (baseline, one month, term).

No significant difference in 2HPG was found between the insulin and metformin group with respect to time, as both groups had a reduction from baseline to term. However, the metformin group had a significant 1.21mmol/L drop in 2HPG compared to insulin after a month of treatment.

The FBG level decreased from enrolment to term in both groups. The FBG for the two treatment groups was comparable at baseline. The mean FBG for metformin was lower than that of insulin throughout the course of pregnancy, but no significant difference was observed. This agrees in part with the long-standing knowledge that metformin has a greater postprandial effect than insulin, while insulin, on the other hand, is more effective in managing poorly controlled fasting hyperglycaemia (Melchior and Jaber, 1996).

The mean 1HPG values showed a decreasing trend in both treatment groups. No significant difference was observed at all times of measurements between the two groups. Metformin treatment group, however, had lower values compared to insulin from randomization (baseline), through to term. From this study, metformin exhibits a more pronounced blood glucose lowering effect during the 2-hour post-prandial period than the 1-hour post-prandial period. This is consistent with the assertion that metformin has a greater postprandial effect than insulin (Melchior and Jaber, 1996).This effect appears to be related to duration from the last meal or glucose load.

Glycosylated haemoglobin was not assessed in this study and the reason for its exclusion has been explained in the methodology section.

5.8 PREGNANCY OUTCOMES AND TYPE OF TREATMENT

In this study, the median gestational age at delivery (38 weeks 2 days) was comparable between the two treatment groups, suggesting the type of treatment may not have an effect on the duration of pregnancy. This is consistent with result of Rowan and her colleagues in the metformin versus insulin for the treatment of gestational diabetes (Rowan *et al.*, 2008).Maternal complications such as gestational hypertension and polyhydramnios did not differ between the treatment groups in this study.

Babies born to women in the Insulin group registered a higher mean birth weight, this difference was, however, not significant. (P = 0.632). This may be explained by the better post-prandial glucose profile in the metformin group.

No significant difference was observed in the perinatal morbidity and mortality measures such as APGAR scores, birth trauma, need for resuscitation, and NICU admission rate. An independent samples T-test was conducted to assess the difference in length of stay per NICU admission. The results showed that the Insulin group stayed significantly longer than the metformin group (3.59 days and 2.20 days, respectively, P = 0.022). This was a surprise finding, because no significant difference was observed in the various diagnoses made at NICU to explain this. It may, however, be explained by the higher numbers of neonates in the insulin group who were diagnosed with respiratory distress syndrome (RDS) and hypoglycaemia. This has financial implications to the family, as well as the healthcare system.

One baby in the insulin group who was admitted to NICU with respiratory distress syndrome died, but the exact cause of death was not established. Autopsy was not done. The significance of this was unclear, since the total numbers in each treatment group was small.

5.9 DAILY DOSAGE REQUIREMENT

The median dose of medication in both groups increased from enrolment to term. This may be a reflection of the falling insulin sensitivity with advancing gestational age. (Catalano *et al*., 1999) In the metformin group, the median dose increased from 1000mg daily in the first month of enrolment to 2000mg at term. Patients used different brands of metformin. In the insulin treatment group, the median daily insulin requirement increased from 30 IU to 43 IU. The maximum daily dose of insulin used was 98 IU. This involved both soluble and premixed insulin.

Only two subjects who were randomized to receive metformin had supplemental insulin because of difficulty in achieving glycaemic targets at maximum doses. This number was considered too small for comparative analysis with either treatment groups. It has, however, been shown that patient on metformin requiring supplemental insulin use smaller doses compared to those managed on insulin only (Rowan *et al*., 2008). Two subjects switched from metformin to insulin inadvertently. They were also excluded from the analysis. The small number of participants that required supplemental insulin maybe due to the study design. In this study, all patients admitted and stabilized on insulin through a sliding scale or modified Alberti's regimen were excluded.

5.8 LIMITATIONS OF THE STUDY

1. Two major industrial actions/ withdrawal of services by hospital pharmacists and doctors, each lasting a little over 2 months during the study period, hampered the study. It resulted in difficulties in drug supplies, as well as discontinuation of antenatal care in study site and subsequent delivery outside of the study site.

2. Supplemental insulin requirements could not be determined, because of the small number of subjects in this group.

3. It was an open-labelled trial. The ideal could have been a double blind study involving larger samples. This would have required more time and, perhaps, involvement of other centres. The physical properties of the study drugs make double-blinding difficult.

5.9 SUMMARY

1. Metformin was found to be effective in achieving and maintaining glycaemic control. Metformin showed a significant 2HPG lowering effect than insulin
2. There was a significant reduction in weight gain during the pregnancy in the metformin treatment group compared to the insulin group
3. Babies of mothers treated on insulin stayed longer at NICU compared to their counterparts in the metformin treatment group, though the admission rates did not differ.
4. Babies in the metformin treatment group had an insignificantly lower birth weight.
5. Pregnancy outcomes (both mother and baby) were comparable, with no significant adverse outcome recorded.

5.10 CONCLUSION

The findings of this study suggest that metformin monotherapy is equally effective in achieving glycaemic targets in the management of diabetes in pregnancy. It is more effective than insulin in lowering the 2HPG level. Metformin significantly reduces weight gain in pregnancy complicated by diabetes compared to insulin.

5.11 RECOMMENDATIONS

1. Large sample sized randomized controlled studies will be required to fully evaluate the long-term effects of metformin therapy on both offspring and mother. These studies could, for instance, look at the development of T2DM in offspring as well as women with GDM.

2. A larger study to evaluate the compliance and cost benefit of the two treatment modalities.

REFERENCES

Al-Noaemi MC and Shalayel MHF (2011). Pathophysiology of Gestational Diabetes Mellitus: The Past, the Present and the Future. In: *Gestational Diabetes*. pp 91-114

Amoah AGB, Owusu SK and Adjei S (2002). Diabetes in Ghana: a community based prevalence study in Greater Accra Diabetes. *Research and Clinical Practice*, **56(3)**:197-205

Awartani KA and Cheung AP (2002). Metformin and polycystic ovary syndrome: a literature review. *J ObstetGynaecol*; **24 (5)**: 393-401

Bailey C, Path M and Turner M (1996). Metformin. *N Engl J Med*, **334**:574–579.

Bailey CJ, and Day C (2004). Metformin: its botanical background. *Practical Diabetes International*, **21(3)**:115–7.

Bell GI, Picket RL, Rutter WJ, Cordell B, Tischer E and Goodman HM (1980). Sequence of the human insulin gene. *Nature*,**284**: 26-32

Ben-Haroush A, Yogev Y, and Hod M (2004). Epidemiology of gestational diabetes mellitus and its association with Type 2 diabetes. *Diabet Med*, **21**:103-113

Buchanan TA, Metzger BE, Freinkel N and Bergman RN (1990). Insulin sensitivity and B cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. *Am J ObstetGynecol*.**162**: 1008–1014

Campbell IW (2007). Metformin—life begins at 50: A symposium held on the occasion of the 43rd Annual Meeting of the European Association for the Study of Diabetes, Amsterdam, The Netherlands, September 2007. *British Journal of Diabetes & Vascular Disease*.**7**:247–252.

Catalano PM (2003). Obesity and pregnancy—the propagation of a vicious cycle. *J Clin Endo*, **88**: 3505–3506.

Catalano PM, Huston L, Amini SB and Kalhan SC. (1999). Longitudinal changes in glucosemetabolism during pregnancy in obese women with normal glucose tolerance and gestational diabetes mellitus. *Am J Obstet Gynecol*, **180**:903–916.

Charles B, Norris R, Xiao X, and Hague W (2006). Population pharmacokinetics of metformin in late pregnancy. *Ther Drug Monit*, **28**:67–72.

Chen Y, Li S, Brown C, Cheatham S, Castro RA, Leabman MK, *et al* (2009). Effect of genetic variation in the organic cation transporter 2 on the renal elimination of metformin. .*Pharmacogenet Genomics*, **19**:497–504.

Chow SC, Shao J and Wang H (2002). A note on sample size calculation for mean comparisons based on non-central T-Statistics. *J. Biopharm. Stat*,**12 (4)**: 441–456.

Christiansen MP and Hellerstein MK (1998). Effects of metformin on hepatic glucose metabolism. *CurrOpinEndocrinol Diabetes*, **5**:252–255.

Clausen TD, Mathiesen E, Ekbom P, Hellmuth E, Mandrup-Poulsen T andDamm P (2005). Poor pregnancy outcome in women with Type 2 diabetes. *Diabetes Care*,**28**: 323–328.

Coetzee EJ and Jackson WPU (1986). The management of non-insulin-dependent diabetes during pregnancy. *Diabetes Res ClinPrac*, **1**: 281–287.

Dabelea D, Hanson RL, Lindsay RS, Pettit DJ, Imperatore G, Gabir MM *et al* (2000). Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant siblings. *Diabetes*, **49**: 2208–2211.

De Sloover KY and Ernst ME. Use of metformin in polycystic ovary syndrome. *Ann Pharmacother*, **35 (12):** 1644-1647

Defronzo, RA (2009). From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. *Diabetes*, **58**:773–795.

Dhulkotia JS, Ola B, Fraser R and Farrell T (2010). Oral hypoglycaemic agents vs insulin in management of gestational diabetes: a systematic review and metaanalysis. *Am J Obstet Gynecol.***203**: 457 e451-459

Diabetes Care (2012) vol. 35 no. Supplement 1 S11-S63

Duke JA (2002). In: *Handbook of medicinal herbs*, 2nd edn. Boca Raton, Florida: *CRC Press;* 337.

Feig DS and Palda VA (2002). Type 2 diabetes in pregnancy: a growing concern. *Lancet*, **359**: 1690–1693.

Ferrara A, Hedderson MM and Selby JV (2002). Prevalence of gestational diabetes mellitus detected by the National Diabetes Data group or the Carpenter and Coustan plasma glucose thresholds. *Diabetes Care.* **25(9):**1625–1630.

Gabbe SG, Niebyl JR and Simpson JL (2002). *Obstetrics: Normal and Problem Pregnancies*.5th ed. Churchill Livingstone, New York, ISBN 0-443-06572

Gribble, FM and Reimann, F (2003). Sulphonylurea action revisited: the post-cloning era. *Diabetologia*. **46**:875-891.

Guideline Development Group (2008). Management of diabetes from preconception to the postnatal period: summary of NICE guidance. *BMJ*, 336:714–717.

Hague WM, Davoren PM, McIntyre D, Norris R, Xiaonian X and Charles B (2003). Metformin crosses the placenta: a modular for foetal insulin resistance (Letter). *Br Med J*, **327**:880–881.

Hardman JG, Limbird LE, and Gilman AG (2001). In:*The Pharmacological Basis of Therapeutics.* 10th ed. New York, NY: McGraw-Hill, p. 1705

Hebert MF, Eyal S, Easterling TR, Carr D, Umans JG, Miodovnik M, *et al* (2010). Pharmacokinetics of Metformin during Pregnancy. *DMD* **38(5)**: 833-840

Hornns PJ. (1985). On the decrease of glucose tolerance in pregnancy. A review. *Diabet Metab*., **11(5):** 310-315.

International Diabetes Federation (2009).*Global guideline on pregnancy and diabetes*.

Joshi SR, Parikh RM and Das AK (2007). Insulin _ History, Biochemistry, Physiology and Pharmacology. *J Assoc Physicians Ind* **55(Suppl 19)** Available online at:http://www.japi.org/july2007/suppliment/19.pdf. Sourced on: 5th June, 2013.

Kimura N, Okuda M and Inui K (2005) Metformin transport by renal basolateral organic cation transporter hOCT2. *Pharm Res,* **22**:255–259

Krentz AJ and Bailey CJ (2005) Oral antidiabetic agents: current role in type 2 diabetes mellitus. *Drugs,* **65**:385–411.

Kühl C. (1991). Aetiology of gestational diabetes. *Baillieres Clin Obstet Gynaecol*., **5**: 279–92.

Kuhlmann J, Puls W and Wiernsperger N (1996). Preclinical pharmacology of biguanides. In: *Oral Antidiabetics, edsKuhlmann J, Puls W (Springer Verlag, Berlin).*

Kumar V, Fausto N, Abbas AK, Cotran RS and Robbins SL (2005). In:*Robbins and Cotran Pathologic Basis of Disease* (7th ed.). Philadelphia, Pa.: Saunders. pp. 1194–1195. ISBN 0-7216-0187-1

Kumari AS (2001). Pregnancy outcome in women with morbid obesity. *Int J Gynaecol Obstet* **73(2):**101-107.

Langer O, Con Way DL, Berkus MD, Elly M-J, Xenakis MD and Gonzales O (2000). A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med*, **343**: 1134–1138.

Lawoyin TO (1991). Maternal weight and weight gain in Africans. Its relationship to birth weight. *J Trop Pediatr***37(4)**:166-171.

Lord JM, Flight IH and Norman RJ (2003). Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ,* **327**:951–953.

Marsoosi V, Jamal A and Eslamian L (2004). Pre-pregnancy weight, low pregnancy weight gain, and preterm delivery. *Int J Gynaecol Obstet,* **87(1):**36-37.

Melchior WR and Jaber LA (1996). Metformin: an antihyperglycemic agent for treatment of type II diabetes.*AnnPharmacother*, **30 (2)**: 158-164.

Moore LE, Briery CM, Clokey D, Martin RW, Williford NJ, Bofill JA, et al (2007). Metformin and insulin in the management of gestational diabetes mellitus: preliminary results of a comparison. *J Reprod Med,* **52(11):**1011-5.

National Collaborating Centre for Women's and Children's health (2008). Commissioned by the National Institute for Health and Clinical Excellence. *Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period.* London: RCOG Press,

Nicholson W, Bolen S, Wiktop CT, Neale D, Wilson L, and Bass E (2009). Benefits and risks of oral diabetes agents compared with insulin in women with gestational diabetes: a systematic review. *Obstet Gynecol* **113**:193-205

Ozumba BC, Obi SN and Oli JM (2004). Diabetes mellitus in pregnancy in an African population. *Int J Gynaecol Obstet.* **84(2):**114–119.

Pettit DJ and Knowler WC (1998). Long-term effects of the intrauterine environment, birth weight and breast feeding on Pima Indians. *Diabetes Care***11**: B138–141.

Pettit DJ, Baird HR, Aleck KA, Bennett PH and Knowler WC (1983). Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. *N Engl J Med* **308**: 242–245.

Rai L, Meenakshi D and Kamath A (2009). Metformin--a convenient alternative to insulin for Indian women with diabetes in pregnancy. *J Med Sci*, **63(11):**491-7.

Rowan JA, Hague WM, Gao W, Battin MR and Moore MP (2008). Metformin versus Insulin for the Treatment of Gestational Diabetes. *N Engl J Med*,**358**:2003-15.

Scheen AJ (1996). Clinical pharmacokinetics of metformin. *ClinPharmacokinet*; **30**:359–371.

Shah SN, Joshi SR and Parmar DV (1997). History of Insulin. *J Assoc Physicians Ind*, **45 (Suppl 1)**:4-9.

Silverman BL, Metzger BE, Cho NH and Loeb CA(1995). Impaired glucose tolerance in adolescent offspring of diabetic mothers. Relationship to foetal hyperinsulinaemia. *Diabetes Care***18**: 611–617

Song IS, Shin HJ, Shim EJ, Jung IS, Kim WY, Shon JH, et al (2008). Genetic variants of the organic cation transporter 2 influence the disposition of metformin. *Clin Pharmacol Ther* **84***:*559–562.

Stuebe AM, Oken E and Gillman MW (2009). Associations of diet and physical activity during pregnancy with risk for excessive gestational weight gain. *Am J Obstet Gynecol*, **201(1):**58-61.

Thorpe LE, Berger D, Ellis JA, Bettegowda VR, Brown G, Matte T, et al (2005). Trends and racial/ethnic disparities in gestational diabetes among pregnant women in New York city, 1990–2001. *Am J Pub Hlth.* **95(5):**1536–1539.

Vanky E, Zahlsen K, Spigset O and Carlsen SM (2005). Placental passage of metformin in women with polycystic ovary syndrome. *Fertil Steril,* **83**:1575–1578.

Varma TR (1984). Maternal weight and weight gain in pregnancy and obstetric outcome. *Int J Gynaecol Obstet,* **22(2):**161-166.

Wang ZJ, Yin OQ, Tomlinson B and Chow MS (2008). OCT2 polymorphisms and in-vivo renal functional consequence: studies with metformin and cimetidine. *Pharmacogenet Genomics 18:637–645.*

WHO (1987). Expert Committee on Biological Standardisation. *Thirtyseventh report*: 25-6.

WHO (1999). Department of Noncommunicable Disease Surveillance. *Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus*. Geneva.

Wilcock C and Bailey CJ (1991). Reconsideration of inhibitory effect of metformin on intestinal glucose absorption. *J Pharm Pharmacol,***43**:120–121.

Zhou M, Xia L and Wang J (2007). Metformin transport by a newly cloned proton-stimulated organic cation transporter (plasma membrane monoamine transporter) expressed in human intestine. *Drug MetabDispos***35**:1956–1962.

APPENDIX

CASE RECORD

A study of metformin versus insulin in the management of gestational diabetes mellitus and type 2 pre-gestational diabetes mellitus at Korle-Bu Teaching Hospital.

Date enrolled: __ __/__ __/20__ __ Time:__ __/__ __ hrs Folder No:_____

Randomization group: _____

Telephone No._____

Name: _____ Gravidity [__] Parity [__]

Date of birth…….. __ __/__ __/__ __ __ __

Age (last half year)……....years [__] mths [__]

Marital status (1=married, 2= single/divorced/separated/widowed)…… [__]

Weight at enrollment (kg) …….. [__] [__] [__].[__]

Height (meters) ……..…….. [__ __].[__]

LMP……..__ __/__ __/20__ __

EDD (by LMP)……..…__ __/__ __/20__ __

EDD (by early/first ultrasound scan)……...…__ __/__ __/20 __ __

Gestational age (by LMP estimate)…….weeks [__ __]days[__ __]

Gestational age (by ultrasound scan estimate) ……...…weeks [__ __] days[__ __]

Classification of diabetes mellitus (1=GDM, 2=T2DM)…… [__]

Co-morbid conditions in this (index) pregnancy (please tick all that apply)

1. Gestational hypertension .....…..……...…… [__]
2. Essential hypertension …… [__]
3. Sickle cell disease ……..……... [__]
4. Asthma ……..…….. [__]
5. Others (specify) _____

Obstetric history [previous pregnancies/deliveries] (please tick all that apply)

1. Miscarriage(s)……... [__]
2. Stillbirth(s) ……..……. [__]
3. Early neonatal death(s) ……...……. [__]
4. Big (Macrosomic) baby (birth weight greater 4.0kg) ……..……...… [__]
5. Congenital anomaly ……..…… [__]
   - ❖ Specify _____
6. Caesarean section…… [__]
7. Other(s) specify _____

Baseline measurements

1. FBG (mmol/L) ……...……. [__] [__]. [__]
2. 1HPG (mmol/L)……...…… [__] [__]. [__]

3. 2HPG (mmol/L) ……...……... [__] [__]. [__]
4. Maternal weight (kg) …..……..……..… [__] [__] [__].[__]

Measurements at one month

1. FBG (mmol/l) ……...……. [__] [__]. [__]
2. 1HPG (mmol/L)……...…… [__] [__]. [__]
3. 2HPG (mmol/L) ……...……... [__] [__]. [__]
4. Maternal weight (kg) …..……..……..… [__] [__] [__].[__]

Measurements at 36/37 weeks gestation

1. FBG (mmol/L) ……...……. [__] [__]. [__]
2. 1HPG (mmol/L)……...…… [__] [__]. [__]
3. 2HPG (mmol/L) ……...……... [__] [__]. [__]
4. Maternal weight (kg) …..……..……..… [__] [__] [__].[__]

Maternal peri-partum events

Mode of delivery (1=SVD, 2=Assisted vaginal delivery, 3= C/S)……..… [**__]**

If Caesarean section what is the indication:

1._____

2._____

3._____

Neonatal peri-partum events

Gestational age at delivery ……...…. weeks [__ __] days [__]

Outcome of delivery (1 =live birth,2 =fresh stillbirth, 3= macerated stillbirth) …….[__]

Birth weight (kg)…….…….. [__] [__] [__].[__]

APGAR score ……...…….. 1 min [__]5min [__]

Birth trauma * (1=none, 2=mild, 3=moderate/severe)……..… [__]

Was baby resuscitated? (1= yes, 2= no) …….……..……. [__]

NICU referral (1= yes, 2 = no) ….……...……...…… [__]

If yes, reason for referral (please tick all that apply)

1. Pre-maturity ……...…… [__]
2. Birth asphysia ……..…….. [__]
3. Macrosomia (big baby)…….…. [__]
4. Respiratory distress syndrome……... [__]
5. Birth trauma……...… [__]
6. Congenital anomalies……..… [__]
7. Neonatal jaundice……..… [__]
8. Meconium aspiration…….…… [__]
9. Sepsis /at risk of sepsis…….……..…… [__]
10. Small for gestational age (SGA) (BW less than 2.5kg)……. [__]
11. Others (specify) _____

Complete this portion for babies seen at NICU only.

NICU Admission (1= yes, 2= no) ……... [__]

Duration of admission (days) ……..… [__ __ __]

Diagnosis at NICU (tick all that apply)

1. Pre-maturity ……...…… [__]
2. Birth asphysia ……..…….. [__]
3. Macrosomia (big baby)…….…. [__]
4. Hypoglycaemia (less than 2.6mmol/l) ……...….. [__]
5. Respiratory distress syndrome……... [__]
6. Birth trauma……...… [__]
7. Congenital anomalies……..… [__]
8. Neonatal jaundice……..…. [__]
9. Meconium aspiration…….…… [__]
10. Sepsis /at risk of sepsis…….……..…… [__]
11. Small for gestational age (BW less than 2.5kg)……. [__]
12. Others (specify) _____

Outcome of admission (1=discharged; 2= died) ……. [__]

ADVERSE EVENTS

Maternal (tick all that apply)

1. Antenatal admissions ……... [__]

   Number of admissions ……. [__]

   If admitted, reasons for admission;

   Glycaemic control ……..…….. [__]

   BP control …… [__]

   Premature rupture of membranes ……..…..…. [__]

   Bleeding per vagina (specify cause) _____

   Others (specify)_____

2. Gastrointestinal events requiring dose reduction……..…..…. [__]
3. Gastrointestinal events requiring treatment cessation……...….. [__]
4. Renal impairment (mild/moderate) ……..…….……. [__]
5. Renal impairment (severe requiring dialysis) ……..…. [__]
6. Surgery other than C/S (specify with indication) ……

   ……..…

7. Maternal death …… [__]

Foetal/neonatal

1. Intrauterine growth restriction (confirmed by ultrasound) …….…….….. [__]
2. Foetal distress ……..……..….. [__]
3. Intrauterine foetal death ……..... ……..…… [__]

   State gestational age at which diagnosis was made..… weeks [__ __]days [__]

4. Other events (specify) _____

2 WEEKLY MONITORING

DATE/DOSE	GESTATION (WEEKS)	WEIGHT (kg)	FBG (mmol/L)	1HPG (mmol/L)	2HPG (mmol/L)

TREATMENT PROTOCOLS

Treatment targets

1. FBS < 5.4 mmol/l
2. 1HPG < 10.0mmol/L
3. 2HPG < 8.5 mmol/L.

Metformin Group

1. Starting dose of Metformin will be 500mg once a day
2. Increased by 500mg every two (2) weeks, to meet glycaemic targets.
3. Maximum dose should not exceed 2500mg per day.
4. Please add Insulin on reaching maximum dose according to insulin protocol below. Please note that maximum tolerable dose of each patient may differ from the stated maximum dose..

Insulin group

1. Starting dose is 0.3 international units per kilogramme body weight.
2. Divide thetotal dose calculated above into two.
3. Give 2/3 of the dose in the morning 30 minutes before breakfast and 1/3 of the daily dose in the evening 30 minutes before supper.
4. Administer subcutaneously in the deltoid region.
5. Adjust daily dose for each patient to achieve the above glycaemic targets.
6. The maximum dose of Mixtard for out-patient care for the purpose of this study is 0.5 international units per kilogramme body weight

7. Please refer patients who are unable to achieve targets after titrating to maximum doses for admission to the maternity ward.
8. Treat the above patients (in point 7) with soluble insulin to determine their optimum insulin requirements. When their glycaemic targets are met, premixed insulin dose equivalent to the total soluble insulin requirements per day while on admission can be started before discharge.

Treatment failures

1. Supplemental insulin for treatment failures in the Metformin group should be prescribed according to the same protocols in the insulin group.