

Metformin versus Insulin in Treatment of Gestational Diabetes

A Thesis

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By

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

لَسْبَحَانَكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

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List of Contents

<i>Subject</i>	<i>Page No.</i>
List of Abbreviations.....	i
List of Tables.....	ii
List of Figures	vii
Introduction	1
Aim of the Work.....	3
Review of Literature	
Gestational Diabetes	4
Insulin.....	21
Metformin	43
Patients and Methods.....	49
Results.....	58
Discussion	69
Summary	75
Conclusion.....	77
Recommendations	78
References	79
Arabic Summary	—

List of Tables

Table No.	Title	Page No.
Table (1):	Factors Affecting Insulin Absorption.....	28
Table (2):	Comparison between group A metformin and group B insulin according to demographic data.	58
Table (3):	Comparison between group A metformin and group B insulin according to average FBS.	61
Table (4):	Comparison between group A metformin and group B insulin according to average 2 hours postprandial(2h pp).....	62
Table (5):	Comparison between group A metformin and group B insulin according to HbA1c before labour.....	63
Table (6):	Comparison between group A metformin and group B insulin according to average AFI.	64
Table (7):	Comparison between group A metformin and group B insulin according to maternal outcome.	65
Table (8):	Comparison between group A metformin and group B insulin according to neonatal outcome.	67

List of Figures

Figure No.	Title	Page No.
Figure (1):	Bar chart between group A metformin and group B insulin according to age.	59
Figure (2):	Bar chart between group A metformin and group B insulin according to parity.	59
Figure (3):	Bar chart between group A metformin and group B insulin according to GA.	60
Figure (4):	Bar chart between group A metformin and group B insulin according to average FBS.	61
Figure (5):	Bar chart between group A metformin and group B insulin according to average 2h PP.	62
Figure (6):	Bar chart between group A metformin and group B insulin according to Hb A1c.	63
Figure (7):	Bar chart between group A metformin and group B insulin according to AFI.	64
Figure (8):	Bar chart between group A metformin and group B insulin according to maternal outcome.	66
Figure (9):	Bar chart between group A metformin and group B insulin according to maternal weight gain.	66
Figure (10):	Bar chart between group A metformin and group B insulin according to neonatal outcome.	67
Figure (11):	Bar chart between group A metformin and group B insulin according to neonatal complications.	68

Abstract

Background: Gestational diabetes mellitus is defined as the form of diabetes that occurs during pregnancy. Women with gestational diabetes mellitus have a great degree of Insulin resistance compared to women without gestational diabetes. **Aim of the Work:** To determine and compare the efficacy and safety of metformin for the treatment of women with gestational diabetes mellitus (GDM). **Patients and Methods:** This prospective randomised controlled clinical open labeled study was conducted on a total of 140 gestational diabetic patients who fulfilled the eligibility criteria. Patients were chosen from those attending the outpatient obstetric clinic of DM or the emergency department in Ain Shams University Maternity Hospital. **Results:** found that metformin is better than Insulin in controlling maternal and neonatal blood glucose levels and HbA1c, reduces maternal weight gain and also reduces the risk of foetal macrosomia. **Conclusion:** use of metformin as an alternative drug to Insulin, is one of the newest trends in treatment protocols of gestational diabetes. It can control effectively the maternal fasting blood glucose level, two hours post prandial blood glucose level and HbA1c. In this study, it was found that it decreases the incidence of foetal macrosomia and limits the maternal weight gain during pregnancy. More studies with larger number of patients are needed to support these results.

Key words: Metformin, Insulin, treatment, gestational Diabetes

Introduction

Gestational Diabetes Mellitus is usually identified in the second trimester of pregnancy. The causes of pancreatic B cell dysfunction which leads to Gestational Diabetes is not fully understood, main factors are: adiposity in pregnancy, autoimmune B cell dysfunction, decrease insulin secretion and increase insulin resistance. Pathophysiology is strongly suggestive of circulating placental and maternal hormones leading to decrease glucose sensitivity by the tissue receptors and subsequently increase in carbohydrate tolerance (*Cerf, 2013*).

Traditionally, Insulin has been known as an effective therapy for GDM as it shows adequate control of raised blood glucose level. It was initially prepared as a lifesaving drug for type 1 DM and the oral antidiabetics were considered to be teratogenic (*Kalra et al., 2015*).

However, Insulin therapy requires multiple daily injections which may reduce patient adherence and it is also not affordable by some patients (*Sorli and Heile, 2014*).

The incidence of diabetes among reproductive -aged women is rising globally. Diabetes in pregnancy is associated with an increased incidence of adverse outcome, for both mother and infant, if the glycemic control during pregnancy is not adequate (*Alfadhli, 2015*).

Nowadays, there have been increasing studies comparing metformin with insulin. But the use of metformin in pregnant women is still controversial. The present study was designed to evaluate and compare the effects of metformin and Insulin on fetomaternal outcomes and glycemic control in GDM patients (*Arashad et al., 2017*).

Metformin is an oral antidiabetic drug being used since 1960 in patients with type 2 DM. Now, it is upgraded to a category B drug as it is not associated with any congenital foetal anomalies. Now, it can be a logical treatment for pregnant females as it produces euglycemic state by improving Insulin sensitivity, reduces hepatic gluconeogenesis, increases glucose peripheral uptake and utilization (*Irons and Minze, 2014*).

Main maternal outcome, (glycemic control): fasting and post prandial glycemic levels were slightly lower in the metformin group as compared with the Insulin group. However, there was no significant difference between the two groups in cesarean delivery rate. There is also less weight gain in the metformin group (*Gui et al., 2013*).

Main neonatal outcomes: average birth weights were slightly lower in the metformin group as compared with the Insulin group. There was no significant difference between the two groups in the incidence of NICU admission; but there is less neonatal hypoglycemia with metformin group (*Li et al., 2015*).

Aim of the Work

To determine and compare the efficacy and safety of metformin for the treatment of women with gestational diabetes mellitus (GDM).

Gestational Diabetes

Gestational diabetes mellitus (sometimes referred to as GDM) is a form of diabetes that occurs during pregnancy (*Alfadhli, 2015*). It is diagnosed when higher than normal blood glucose levels first appear during pregnancy. Women who have risk factors for gestational diabetes should be tested earlier in their pregnancy (*Dirar and Doupis, 2017*).

Causes of gestational diabetes:

Insulin resistance rises as pregnancy progresses and under normal circumstances. This is countered by increasing Insulin production from pancreatic beta cells (*Baeyens et al., 2016*).

Women with gestational diabetes inherently have a great degree of Insulin resistance compared to women without gestational diabetes and thus, coupled with reduced beta cell capacity to produce the required insulin response, leads to maternal hyperglycemia (*Catalano, 2014*).

Normal pregnancy is a state of Insulin resistance:

Pregnancy can be associated with many metabolic, biochemical, physiological, hematological and immunological changes. With no complications at full term, these changes are reversible after delivery. Healthy women pregnancy can be associated with resistance to the action of Insulin on glucose uptake and utilization. Insulin resistance is defined as decreased

ability of target tissues such as liver, adipose tissue and muscle to respond to normal circulating concentrations of Insulin (*Sonagra et al., 2014*).

It is reported that pregnant women require an additional energy of 300 kcal/day over routine energy intake while the average glucose utilized by a growing fetus at the 3rd trimester reaches approximately to 33 $\mu\text{mol/kg/min}$. Maternal Insulin resistance leads to more use of fats than carbohydrates for energy by mother and spares carbohydrates for fetus. Thus, the development of Insulin resistance serves as a physiological adaptation of the mother to ensure adequate carbohydrate supply for the rapidly growing fetus (*Sonagra et al., 2017*).

As the pregnancy advances to third trimester, Insulin sensitivity may gradually decline to 50% of the normal expected value. This decline is reported to be mediated by a number of factors such as increase in the levels of estrogen, progesterone, human placental lactogen (hPL), among other factors. Progesterone suppresses the phosphoinositol 3-kinase-mediated pathway by reducing the Expression of IRS-1 (Insulin receptor substrate1) (*Wei et al., 2014*). Gradually increasing progesterone concentration with advancement of normal pregnancy is associated with increased inhibition Insulin-induced glucose transporter type 4 (GLUT 4) translocation and glucose uptake. Estrogen concentration is also

high in pregnancy. 17β -estradiol diminishes Insulin sensitivity at high concentrations (*Soma-Pillay et al., 2016*).

Human placental lactogen(HPL) has both Insulin-like and anti-Insulin effects. In vitro, it has been shown to increase lipolysis and free fatty acids (FFAs) in adipocytes. Increased hPL level in pregnancy is found to increase glucose uptake, oxidation, and incorporation of glucose into glycogen, which may favor glycogen storage in the mother (*Sonagra et al., 2014*).

Other factors such as increased levels of serum cortisol, Tumor necrosis factor α (TNF α , ILs etc., can interrupt the Insulin signaling pathway and can lead to Insulin resistance during normal pregnancy (*Zhang et al., 2017*).

Insulin resistance is the condition in which there is a decreased in the action of Insulin on body tissue at normal concentration of plasma Insulin. This can be as a result of a number of factors such as defective molecular structure of Insulin, defective receptor functioning or defective signal transduction pathway. In the acquired condition, the defect is either in receptor affinity for Insulin or as a result of some interruption in signalling pathway of Insulin down the receptor (*Boucher et al., 2014*). To compensate this Insulin resistance, there is increased production of Insulin from beta cells of Islet of Langerhans leading to hyperinsulinemia.

Insulin producing capacity of pancreatic beta cells is not infinite (*Jones et al., 2010*). Gradually beta cell functioning also declines leading to a reduction in Insulin production and the condition progresses to glucose intolerance and subsequently, to diabetes mellitus (*Cerf, 2013*).

Many researchers have noted that age is one factor affecting Insulin sensitivity and that with an increase in age, there is a progressive increase in Insulin resistance (*Hoscheidt et al., 2016*).

Serum Insulin levels were significantly higher in 3rd trimester when compared with 2nd trimester and those of the 2nd trimester were significantly higher when compared with 1st trimester ($p < 0.05$). These findings therefore suggest that there is progressive rise in Insulin secretion as the pregnancy advances, indirectly signifying an increase in Insulin resistance as the pregnancy advances (*Lacroix et al., 2013*).

Women with increased Insulin resistance are more prone to develop preeclampsia & gestational diabetes. Preeclampsia is associated with increased expression of TNF α and other inflammatory marker which causes Insulin resistance. Increased Insulin resistance leads to dyslipidemia that can worsen the placental ischemia leading to vicious cycle of ischemia-inflammation-IR-dyslipidemia-ischemia (*Barden et al., 2004*). In prospective studies it is proven that most women,

who develop gestational diabetes, have increased Insulin resistance caused by alteration in Insulin signaling pathway, abnormal subcellular localization of GLUT4 transporters, increased expression of the membrane glycoprotein PC-1 or reduced insulin-mediated glucose transport (*Lee et al., 2017*).

Increased Insulin resistance is also associated with occurrence of premature labour, antepartum or postpartum hemorrhage and fetal complications like intrauterine growth restriction or fetal overgrowth and prematurity. Presence of Insulin resistance also increases risk of development of metabolic syndrome, diabetes mellitus, hypertension, hyperlipidemia, and cardiovascular disorders later in life (*Sonagra et al., 2014*).

Screening for Insulin resistance can be advised to all pregnant women. Insulin sensitivity can be improved in these women by modifying diet, lifestyle, amount and type of physical activity. Balanced diet providing required quantity of macro and micro nutrients with good amount of dietary fibers can be prescribed. Avoidance of sedentary lifestyle and increasing amount of activity should be advised before, during and after pregnancy. Mild exercises such as walking and climbing stairs, can be advised for women with increased Insulin resistance during pregnancy. Such intervention should