INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy, is increasing worldwide and currently complicates up to 10% of the pregnancies. GDM is characterized by insulin resistance or decreased glucose tolerance, which increases throughout pregnancy. GDM is associated with poorer pregnancy outcomes and might have long-term implications for both mother and child. Therefore, it must be recognized precociously and appropriately managed. GDM is the most common cause of diabetes during pregnancy, accounting for up to 90 % of pregnancies complicated by diabetes. Women with GDM have a 40–60 % chance of developing diabetes mellitus over the 5–10 years after pregnancy. Although GDM has been recognized as a disease for time, it remains a controversial entity with conflicting guidelines and treatment protocols ***(Mpondo and Alex Ernest, 2015).***

Gestational diabetes mellitus is generally asymptomatic, usually being detected through systematic screening after the 24th week of pregnancy. Evidence to support screening for gestational diabetes mellitus is indirect and strongly based on the potential adverse effects of hyperglycemia on pregnancy outcomes, and on the effectiveness of gestational diabetes mellitus treatment in preventing these outcomes ***(Dhulkotia et al., 2010).***

Treatment of Gestational Diabetes Mellitus

Treatment of gestational diabetes mellitus using lifestyle advice ± supplementary insulin has shown to be effective and to significantly improve pregnancy outcomes. Lifestyle advice (including dietary advice and exercise) is the primary intervention offered to women diagnosed with gestational diabetes mellitus. However, lifestyle advice alone does not achieve adequate glycaemic control in up to 20% of women, and needs to be supplemented with either oral hypoglycemic or subcutaneous insulin ***(Landon et al., 2009).***

1. Glucose monitoring

Self-monitoring of blood glucose is the cornerstone for achieving the set targets of plasma glucose in order to reduce perinatal mortality. Recommendations from fourth international workshop conference on gestational diabetes mellitus suggest lowering the capillary whole blood glucose concentration to: pre-prandial< or = 95 mg/dl and either 1h postprandial < or = 140 mg/dl or 2h values < or = 120 mg/dl ***(Catherine Allard et al., 2014).***

2. Medical nutrition therapy (MNT) and exercise

Diet is the cornerstone of the management of hyperglycemia in gestational diabetes mellitus irrespective of the pharmacological therapy. The targets to be achieved by medical nutrition therapy are to provide sufficient nutrition to the mother and fetus, provide adequate calories

for maternal weight gain, to achieve normoglycemic state and lastly to prevent ketosis. Addition of 300 kcal /day is usually required in 2nd and 3rd trimester in normal weight women. A minimum of 175g carbohydrate per day should be provided. A moderate exercise program might improve fasting and postprandial glucose level and insulin sensitivity ***(Franz et al., 2002).***

3. Insulin therapy

Insulin therapy is the most validated treatment option when medical nutrition therapy fails to achieve the target glycemic control. Despite emerging evidence supporting the use of glyburide or metformin in the management of GDM, many guidelines continue to recommend insulin as the first-line therapy. This is primarily the result of two factors: pregnancy category B for all insulins except glulisine and glargine, and safety data indicating clinically insignificant amounts of human insulin that cross the placenta. Two RCTs demonstrated that insulin compared with usual prenatal care in the management of GDM resulted in decreased numbers of births associated with shoulder dystocia, macrosomia, and preeclampsia ***(Kristi W Kelley et al., 2015).***

Traditionally, insulin therapy had been considered standard practice for women with gestational diabetes mellitus who could not have been controlled by medical nutrition therapy and physical activity. Insulin therapy can be difficult for pregnant women due to multiple injection

requirements, risk of hypoglycemia, and weight gain ***(Nicholson W and Baptiste-Roberts K, 2011).***

4. Oral medication

Metformin is a biguanide oral hypoglycemic agent. Metformin decreases hepatic gluconeogenesis, improves peripheral and hepatic sensitivity to insulin and does not induce hypoglycemia or maternal weight gain. However, as Metformin crosses the placenta and the long-term effects in the offspring are unknown. There are more than 10 studies assessing Metformin safety and efficacy. The largest study is known as Metformin in Gestational Diabetes (MiG) study and involved 751 pregnant women with GDM. Some smaller studies have been later performed. Globally, the results have been favorable to Metformin. Compared to women taking insulin, those under Metformin have no difference in maternal glycemic control, congenital abnormalities, macrosomia, rates of neonatal hypoglycemia or other maternal or neonatal adverse outcomes. Moreover, it has been reported less maternal hypoglycemia with the use of Metformin in comparison to insulin regimes ***(Pedro Marques, 2014).***

Metformin is an alternative to insulin and is effective in the treatment of women with gestational diabetes mellitus. A meta-analysis of pregnancy outcomes after first trimester exposure to metformin didn’t show an increased risk of major malformations and other systematic reviews didn’t find substantial maternal or neonatal outcome

differences with use of oral diabetes agents compared with insulin in women with gestational diabetes mellitus. Although it crosses the placenta, metformin appears to be safe in the second and third trimester of pregnancy ***(Pedro Marques, 2014).***

Aim of the Work

This study aims to assess the efficacy of metformin in controlling maternal blood glucose level compared to insulin in women with GDM.

Research Question

In pregnant women with GDM, does metformin control blood glucose level effectively as insulin?

Research Hypothesis

In pregnant women with GDM metformin may control blood glucose level effectively as insulin does.

Gestational Diabetes Mellitus

GDM Definition:

Gestational diabetes mellitus (GDM) is defined as a glucose intolerance that occurs for the first time or it is first identified during pregnancy. The GDM etiology is multifactorial. It has not completely been established yet and several known risk factors may contribute to its onset. To date, there are no shared guidelines on the management and follow up, especially regarding the low income countries. In this paper, we describe the state of art about epidemiology, physiopathology, diagnosis, and management of GDM. Moreover, we focus on the current state in low income countries trying to outline basis for further research ***(Schiavone el al., 2016).***

Diabetes mellitus (DM) is one of the major actual public health issues consisting of chronic hyperglycemia which can damage body organs and systems. Gestational diabetes mellitus (GDM) is a common metabolic complication in pregnancy, denied as a glucose intolerance identifying for the first time during pregnancy ***(Reyes-Lopez R et al., 2014).***

GDM reveals usually between 24 and 28 weeks of gestation, without particular symptoms, but it should be screened as early as possible to avoid severe short and long term complications for mother, fetus or neonate ***(Karamanou et al., 2016).***

GDM Incidence and prevalence:

GDM is becoming an increasing health problem worldwide and one of the most common complications of pregnancy ***(Willer and Hawryluk, 2015)***.

Although the true prevalence of GDM is unknown, GDM is estimated to affect 1% to 14% of pregnancies in the United States annually. GDM prevalence has been steadily increasing with the rise of obesity and type 2 diabetes. Both birth certificates and the Pregnancy Risk Assessment Monitoring System (PRAMS). Approximately 135,000 cases of GDM, representing on average 3-8% of all pregnancies are diagnosed annually in the USA ***(Ben-Harous et al., 2004)***.

The estimated incidence of GDM in Europe is 3% to 5% or 150,000 to 250,000 pregnant women out of the five million who give birth each year ***(Hod, 2003)***.

In Egypt, (Impaired Glucose Tolerance) IGT which occurs during pregnancy affects 7.2% of all pregnancies and is considered a major cause of maternal and fetal morbidity ***(Azmy et al., 2005)***.

Pathophysiology of GDM:

GDM is considered a heterogeneous disease, many biologic and molecular mechanisms of regulating glucose levels are involved ***(Abell et al., 2015).*** It has been demonstrated that:

- Inadequate decrease of the renal threshold for glucose (RTG) that is determined by the nephron's reabsorption capacity, play a role in the development of GDM. Normally, glucose is reabsorbed through sodium glucose transporters in the proximal tubules. However, the renal glucose reabsorption capacity decreases due to reduced glucose transporter expression leading to lower glucose elimination during pregnancy from the molecular point of view, many regulators play a role in the glucose homeostasis and GDM onset.

- The balance of T-helper cell activity is strongly shifted toward an anti-inflammatory profile, characterized by th-2 cytokines, which have a protective role in the fetal maternal relationship during a normal pregnancy a fine balance occurs between pro- and anti-inflammatory cytokines, needed for the normal development.

- GDM seems to be associated with down-regulation of adiponectin and anti-inflammatory cytokines e.g. (IL-10) and up-regulation of adipokines like leptin and pro-inflammatory cytokines, implicated in insulin resistance e.g (TNF - α, IL-6).

GDM and Insulin Resistance:

Insulin resistance is defined as the inability of a defined concentration to affect a predictable biological

response of nutrient metabolism at the level of the target tissue. Insulin resistance as it relates to glucose metabolism results in decreased glucose uptake in skeletal muscle, white adipose tissue and liver as well as decreased suppression of endogenous (primarily hepatic) glucose production.

Insulin resistance is affected by new biomarker such as Adiponectin, Adipokine, TNF-α and IL-6, Leptin, AFABP, Resistin, Visfatin, Fetuin A, EPC, and Vitamin D ***(Schiavone et al., 2016).***

Complications of GDM

I- Fetal and Neonatal Complications:

1. Macrosomia:

The most common and significant neonatal complication clearly associated with GDM is macrosomia, which has been variously defined as a birth weight greater than 4,000 to 4.500 grams, as well as larger for gestational age, with the birth weight above to 90th percentile for population-specific and set-specific growth curves ***(Amin el al., 2014).***

Macrosomia associated with DM in pregnancy mostly explained due to maternal hyperglycemia results in fetal hyperglycemia and hyper insulinemia this results in increased fetal anabolism and adiposity**.**

For the infant, macrosomia increases the risk of shoulder dystocia, clavicle fractures and brachial plexus injury and increases the need for admission to neonatal intensive care units. For the mother, the risks associated with macrosomia are caesarean delivery, postpartum hemorrhage and vaginal lacerations. There are several recommendations for the management of macrosomia to prevent maternal and fetal birth trauma, including induction of labor and elective caesarean section. Strict regulation of maternal blood glucose levels can limit perinatal adverse outcomes ***(Sheehan el al., 2015)***.

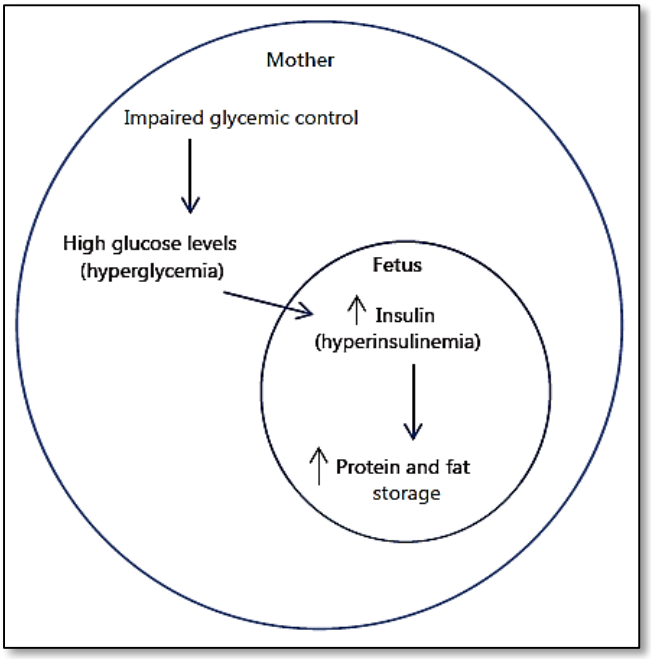

Fig. (1): The modified Pedersen's hypothesis

The modified Pedersen's hypothesis explaining the pathophysiology of macrosomia as shown in figure 1. When maternal glycemic control is impaired and the maternal serum glucose level is high, glucose crosses the placenta but insulin does not. In the second trimester, the fetal pancreas responds to hyperglycemia and secretes insulin in an autonomous manner (hyperinsulinemia). The combination of hyperinsulinemia and hyperglycemia leads to an increase in protein and fat stores in the fetus, resulting in macrosomia. The combination of hyperinsulinemia and hyperglycemia leads to an increase in protein and fat stores in the fetus, resulting in macrosomia ***(Kamana KC, 2015).***

2. Congenital Malformations

Another controversial association is that between GDM and congenital malformations. The anomalies commonly associated with diabetic pregnancies include cardiovascular, central nervous system, genitourinary, gastrointestinal and skeletal disorders ***(Celebrezze and Catalano, 2000)***.

Recommendations of the Fifth International Workshop Conference on GDM (**2005**) stated that GDM with onset in mid-pregnancy or later pregnancy, not associated with an increased prevalence of congenital malformations. However, GDM diagnosed with elevated fasting plasma glucose (>120 mg/dl, >6.7mmol/L) or HbA1c ≥7.0% especially when detected early in pregnancy, possibly represents preexisting type II DM and is associated with a rate of anomalies which is higher than that found in the general obstetric population ***(Metzger et al., 2007)***.

3. Neonatal Hypoglycemia

Neonatal hypoglycemia is defined by a serum glucose value less than 35 mg/dl for full term and less than 25 mg/dl for premature infants. The diagnosis should be based on two consecutive low values taken 30 minutes apart.

Neonatal hypoglycemia occurs when plasma insulin levels in the newborn remain high after cord clamping and transplacental source of glucose has been blocked ***(Metzgar et al., 2008)***.

Infants of women with GDM have an incidence of neonatal hypoglycemia that approaches 30-50% ***(Celebrezze and Catalano, 2000)***.

4. Polycythemia

Thirty percent of infants born to women with GDM have polycythemia, compared with 6% of infants born to normal glucose tolerance, defined as a venous hematocrit >65% at delivery.

Fetal hyperglycemia and hyperinsulinemia result in relative chronic intrauterine hypoxemia, and thus to an increase in erythropoietin levels and in red cell production

The significant levels of polycythemia sometimes seen in infants of women with GDM my lead to hyperviscosity syndrome and renal vein thrombosis ***(Contreras et al., 2011)***.

5. Hyperbilirubinemia

Hyperbilirubinemia is another morbidity common to the infants of the women with GDM, complicating up to 20% of these births as compared with 10% of the general population. Hyperbilirubinemia is defined as neonatal serum bilirubin levels >13 mg/dl. The exact cause is still unknown.

Theories include an associated complication of polycythemia and the result of an immature bilirubin

conjugation system in the neonate. Treatment includes recognition of the problem with initiation of phototherapy or exchange transfusion, depending on severity ***(Celebrezze and Catalano, 2000)***.

6. Hypocalcemia and hypomagnesaemia

Neonatal hypocalcemia defined as a total serum calcium level below 7 mg/dl or an ionized calcium level of less than 3 mg/dl, affects 50% of infants born to women with GDM. Pregnancy is marked by reduced level of magnesium (this is thought to occur because of urinary magnesium loss associated with maternal hyperglycemia and resultant polyuria) and parathyroid hormone in women with GDM, whereas maternal level of total calcium are unchanged, which may result in fetal hypomagnesaemia ***(Celebrezze and Catalano, 2000).***

This then leads to reduced concentrations of fetal parathyroid hormone and finally, to neonatal hypocalcemia ***(Harmel and Mathur, 2004)***.

7. Respiratory Distress Syndrome (RDS)

The infants of the women with GDM have a relative risk rate of 5.6% for developing RDS until the gestational age of 38.5 weeks, when the incidence of RDS becomes that of the general population ***(Celebnezze and Catalano, 2000)***.

RDS is more common in infants of women whose pregnancies were associated with poor glycemic control, in