Egyptian Pediatric Association Gazette 66 (2018) 15–21

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Contents lists available at ScienceDirect

Egyptian Pediatric Association Gazette

journal homepage: www.elsevier.com/locate/epag

Is metformin a viable alternative to insulin in the treatment of gestational diabetes mellitus (GDM)? Comparison of maternal and neonatal outcomes

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Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance that occurred or is diagnosed for the first time during pregnancy.[1] It reflects a failure of the pancreas to respond to the progressive insulin resistance of latter stages of gestation by appropriately increasing cell mass and insulin secretion.[2]

GDM affects approximately 3–6% of all pregnancies.[1] It is growing in prevalence and, if left untreated, is associated with poor maternal and fetal outcomes. Congenital anomalies, macrosomia, hypoglycemia, respiratory distress syndrome, hypocalcemia, and hyperbilirubinemia are the neonatal consequences of this complication.[3,4] The risk of fetal malformations and mortality is 2–5 times higher than normal pregnancy.[5]

Intrauterine hyperglycemia is not only associated with increased perinatal morbidity and mortality, but also with increased life-long risks of the exposed offspring for obesity, metabolic, cardiovascular, and malignant diseases.[6,7]

The investigators found a linear correlation between higher levels of maternal glucose and adverse outcomes.[8] Based on these findings, it has been suggested that screening for undiagnosed type 2 diabetes should occur at the first prenatal visit in women with risk factors for GDM. Women not previously known to have diabetes and who have no risk factors should be screened for GDM at 24–28 weeks of gestation.[9] Timely treatment of pregnant women with hyperglycemia is important. Initial treatments consist of glucose monitoring, medical nutrition therapy, and lifestyle interventions, including moderate exercise. When these treatment options fail, insulin therapy is the next step and remains the mainstay of pharmacotherapy.[10] The use of insulin is a standard treatment for gestational diabetes because of its high effectiveness; also, it is believed that insulin does not cross the placental barrier because of its large molecular size.[11] However, Results from previous studies showed that anti insulin antibody is produced in response to insulin transcription in pregnant women with GDM and insulin can cross the placenta as a part of the insulin antibody complexes.[11,12] This autoimmune response to exogenous insulin can affect fetal development.[11] Furthermore, insulin injection has disadvantages such as fear, anxiety, repeated injections, the need for education, skills in dose adjustment and injection, the risk of hypoglycemia, more weight gain in pregnant women, requiring refrigeration and high costs.[13,14]

Although the standard therapy for women with gestational diabetes requiring drug treatment is insulin, 2 oral agents have been increasingly viewed as potential alternatives. Several observational and randomized controlled trials have addressed the use of oral agents in gestational diabetes, mainly glibenclamide and metformin.[3,11] Both glibenclamide and metformin are considered in National Institute for Health and Care Excellence (NICE) guidance,[15] and American College of Obstetricians and Gynecologists (ACOG) practice bulletin.[12]

Metformin, a biguanide derivative, works primarily by reducing hepatic glucose output, improving peripheral glucose uptake, reducing endogenous insulin levels and reducing insulin resistance probably by mechanisms of the drug that include mitochondrial actions have been known for many years and are still believed to be the primary site of drug action.[16]

Although insulin remains a popular, reliable treatment option, the use of oral agents is an attractive alternative to

Abbreviations: FBS, Fasting Blood Glucose; 2hrsPPBS, 2Hours Post Prandial Blood Sugar; GA, Large for Gestational age; NICU, Neonatal Intensive Care Unit; RCT, Randomized Controlled Trial; RDS, Respiratory Distress Syndrome; SGA, Small for Gestational Age.

Peer review under responsibility of Egyptian Pediatric Association Gazette.

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https://doi.org/10.1016/j.epag.2018.01.002
1110-6638/

insulin for their easier administration, lower cost, and better acceptance.[13]

The aim of the present study was to compare risks and benefits of insulin and metformin in terms of short-term outcomes when used for women with gestational diabetes requiring drug treatment.

Subjects and methods

This prospective randomized study was carried out from March 2016 to June 2017. In this clinical trial, 250 women whose pregnancies had been complicated by GDM were enrolled in the study. The population was recruited from the antenatal clinics of Alglaa Teaching Hospital.

The ethical committee approval was obtained. The research course was completely explained to all participants before the trial began. The aim of the study, the benefits, effectiveness, and possible side effects of two treatment methods were explained to all patients and written informed consents were obtained.

The criteria for selecting patients included the following: women aged from18 to 42 years old, 22–30 weeks of gestation, singleton pregnancy with no recognized fetal congenital anomaly, the absence of known kidney, hepatic, haematological, malabsorption or some other significant gastrointestinal disease and/or Hypoxic cardio-respiratory disease. Women who experienced premature rupture of membranes, severe bleeding or one of the above mentioned diseases during the study were excluded from the study. Exclusion criteria also include; Cases with Pre-existing type 1 or type 2diabetes or currently taking metformin for some other indication. Only Women who were followed-up regularly at the outpatient clinic, and who were delivered at the hospital were included.

All Gestational diabetic women were diagnosed for the first time in the study, based on Oral Glucose Tolerance Test (OGTT) according to The American Diabetes Association (ADA) criteria for the diagnosis of GDM; depending on 75-gm glucose load then checking the fasting,1-h, 2-h and 3-h serum glucose concentration. The glucose threshold values are 95 mg/dL (5.3 mmol/L), 180 mg/dL (10.0 mmol/L), 155 mg/dL (8.6 mmol/L), and 140 mg/dL (7.8 mmol/L) respectively. Two or more abnormal values are required for diagnosis.[17]

All the pregnant women included had attempted regular healthy lifestyle intervention (healthy diet and performing exercise) for at least one week without satisfactory blood glucose level. All women are encouraged to Try a 10 min. walk a few days a week and gradually add 5–10 min. of exercise each day. For most people, a healthy goal is 30 min. of walking most days of the week. Also they were encouraged to add more time to their activity like doing their housework or playing with their kids. They were informed that by becoming more active, they can lower their blood sugar and keep diabetes under control. Also, women were instructed that they don't have to overdo it and only to do moderate exercise (walking or other activities), that makes heart beat a little faster and breathe a little harder.

Sample collection and laboratory analysis

Ten ml of venous blood were withdrawn from each woman after 6–8 h fasting. First two ml of collected blood was taken on EDTA tubes for complete blood picture (CBC) by automated cell counter. Second two ml collected in EDTA vacutainer, this sample was freshly used for measurement of HbA1c level by using HPLC ion exchange chromatography according to manufacturer's instructions. The last four ml were left to clot; centrifugated at 3000 rpm for 5 min. After centrifugation serum was separated for the routine chemistry investigations (fasting blood glucose (FBS), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Albumin, Total protein, urea, and serum creatinine) by using BT 3500, Clinical Chemistry, Turbidimetric and ISE analyzer (Rome-Italy) supplied by Alfa Diagnostic Biotecnica Instruments. A random urine sample was collected in sterile cup for physical, chemical and microscopical examinations.

Baseline characteristics were recorded for all randomised women. Fasting blood sugar (FBS) was estimated in eligible women. For all women with FBS higher than 95, glucose tolerance test, FBS, and BS at 1, 2, and 3 h after drinking 75 g of glucose solution were requested. If two of these criteria (BS >95, 1 h >180, 2 h >155, and 3 h >140) were high, GDM was diagnosed.[18]

Usual obstetric care was offered at the antenatal clinics. In enrolled patients, routine antenatal laboratory investigation was done (CBC, Liver function tests, Kidney function tests, urine analysis, and coagulation profile.). Serum HbAIc was done at the entrance of study and at around 37 weeks of pregnancy. Detailed ultrasound study was done.

Out of the 250 eligible women, 125 women were randomised to receive metformin group[1] and 125 to receive insulin group.[2] Women who were recruited to receive metformin (Group 1) were started on 500 mg, once a day (1 pill orally) after lunch and this was increased in a weekly stepwise manner as tolerated by the patient to a maximum of 2500 mg a day allowing a total of 2–3 weeks to achieve target blood glucose values. If BS was not controlled within 2 weeks of taking the maximum dose of metformin, Insulin therapy was started and these patients were excluded from the study. Once the target values were achieved, women had antenatal care once every 2 weeks.

Women in Group:[2] Insulin was given subcutaneously in 2 divided doses calculated according to body weight (½ unit per kilogram of body weight) as follows: Morning; NPH 2/3 + Regular insulin 1/3 and Evening; NPH 1/2 + Reg 1/2. Women were taught home capillary blood glucose monitoring using a glucometer (Patients who were not cooperative or were unable to learn the techniques were admitted to the hospital). Monitoring At home, fasting (FBS) and 2-hour postprandial blood sugar (2hr.PPBS) had been measured after the three main meals. Glycemic profile (FBS & 2hr.PPBS) were done weekly in the hospital Lab. (venous samples) for all cases and the dose of drugs was modified accordingly at each antenatal visit till delivery.

The purpose of treatment was to reduce fasting plasma glucose levels to <90 mg/dl as well as decrease 2 h postprandial glucose to <120 mg/dl.

Maternal outcomes including; gestational age, maternal glycaemic control, pre-pregnancy weight and height, body mass index (BMI), pregnancy-induced hypertension, preterm birth before 34 weeks, mode of delivery and complications of delivery such perineal tears and postpartum hemorrhage.

Mode and time of delivery were decided around 38 weeks of pregnancy. After delivery, all neonates were shifted to a special care unit under the supervision of a neonatologist who was masked to the fact that the mother was part of an ongoing clinical trial. The details of the pregnancy, delivery and neonatal outcomes were then recorded.

Neonates were given hourly feeds. The first feed was usually given within 30 min of birth, and blood glucose levels were checked every 30 min during the first 3 hr. after birth then every 3hr. with a glucometer.

Neonatal outcomes included; Apgar scores at the first and fifth minutes, birthweight (macrosomia; birth weight >4000 g), IUGR, hypoglycemia (blood glucose <40 mg/dl), hypocalcemia (calcium <7 mg/dl in the first 3 days after birth), hyperbilirubinemia (bilirubin >12 mg/dl in the first 7 days after birth) need for phototherapy [19], fetal anomalies, Stillbirth or neonatal death, respiratory distress