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Metformin versus insulin treatment in gestational diabetes in pregnancy in a developing country. A randomized control trial

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ABSTRACT

Aim: To compare treatment with metformin alone, metformin plus insulin and insulin alone in women with gestational diabetes (GDM).

Method: A total of 150 gestational diabetic patients who fulfilled the eligibility criteria were included in this prospective randomized control open labeled study. A risk factor based screening was done followed by a GCT and then local GTT criteria from antenatal clinics. They were initially divided into two groups with odd numbers assigned to metformin treatment and even numbers to insulin treatment. Metformin and/or insulin treatment was given and target blood sugar levels aimed at FBS $\leq$ 100 mg/dl and postprandial levels $\leq$126 mg/dl. Supplemental insulin was added to metformin treatment group to maintain the glycemic targets if required. Patients were followed until delivery and maternal fetal outcomes and pharmacotherapeutic characteristics were recorded on a performa.

Results: Less maternal weight gain was found in the metformin treated groups (9.8 $\pm$ 1.5 kg [metformin alone] vs. 9.8 $\pm$ 1.4 kg [metformin plus insulin] vs. 12.5 $\pm$ 1.1 kg [insulin alone] $P < 0.000$). Preeclampsia was significantly less in metformin treated groups. There were no perinatal deaths in the study. Mean birth weight was significantly less in metformin treated groups (3.4 $\pm$ 0.4 kg vs. 3.3 $\pm$ 0.5 kg vs. 3.7 $\pm$ 0.5 kg $P < 0.01$). Less neonatal morbidity was observed in metformin groups. 42.7% of patients required supplemental insulin (mean dose of 13.6 $\pm$ 2 units) in the metformin group. Mean gestational age at which insulin was added was 31.8 $\pm$ 5.9 weeks.

Conclusion: Metformin is an effective and cheap treatment option for women with gestational diabetes with or without supplemental insulin.

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1. Introducion

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition in pregnancy[1]. Gestational diabetes complicates about 3–6% of pregnancies with prevalence varying widely in different racial groups [2]. The prevalence of diabetes complicating pregnancy is increasing especially in South Asian countries like Pakistan [3], where the prevalence is estimated to be about 3.5% [4]. GDM is a potential cause of maternal morbidity and perinatal morbidity and mortality. These risks can potentially be reduced if glycemic control is maintained during pregnancy. Studies have shown that effective treatment of hyperglycemia in women with GDM can reduce adverse perinatal outcomes [5]. For years insulin therapy remained the mainstay of treatment for gestational diabetes not controlled by dietary modification. Guidance, vigilance and finances are required for safe self administration of insulin therapy to avoid hypoglycemia and maintaining tight glycemic control at the same time. A logical alternative would be a safe and effective oral therapy that should be more acceptable and cheaper for women with GDM. Metformin, an oral bigaunide that lowers glucose levels with a low risk of hypoglycemia, appears to be a good alternative to insulin in women with GDM. Metformin acts by reducing insulin resistance, improving insulin sensitivity probably by activation of AMP kinase and decreasing ATP concentration of hepatocytes [6]. It improves insulin sensitivity and hyperglycemia by reducing hepatic gluconeogenesis and increasing peripheral glucose uptake and utilization. It also reduces markers of endothelial activation which are closely associated with insulin resistance [7,8]. Metformin crosses the placenta and acts as an insulin sensitizer and therefore will not cause neonatal hypoglycemia [9]. Metformin is a FDA class B drug in pregnancy with no reported teratogenic effects in animal models and human studies done in polycystic ovarian pregnancies [10–15].

Pakistan is projected to become the 8th most prevalent country for diabetes mellitus by 2035 [16]. This population has specific challenges in terms of marked insulin resistance, low socioeconomic status, poor compliance, follow up and affordability of insulin.

The current study was designed to assess the effect of metformin treatment in women with GDM with or without supplemental insulin and to compare it with conventional insulin treatment. We hypothesized that in women with GDM in pregnancy metformin treatment compared with insulin will result in better perinatal and maternal outcomes and improved treatment acceptability with low or no additional insulin requirement.

2. Methods

2.1. *Study design and participants*

This trial was a prospective randomized open labeled clinical study with parallel assignment of patients comparing metformin with or without supplemental insulin treatment with insulin alone treatment in GDM. The study was approved by the ethics review board of Dow University of Health Sciences and all participants of the study gave informed written consent. The patients were selected from those attending the antenatal clinics of Lyari General Hospital Karachi and Mamji Hospital Karachi. They belonged to all five major ethnic groups living in urban and rural areas of four provinces in Pakistan. These pregnant women were screened for presence of high risk factors including BMI above 25 kg/m^2, previous history of macrosomic baby with weight 4 kg and above, previous history of GDM, family history of diabetes in first degree relatives, previous history of poor obstetric outcome (abortion, congenital anomalies, intrauterine fetal death, neonatal death), presence of polyhydramnios, pregnancy induced hypertension in present pregnancy and history of polycystic ovarian syndrome and presence of glycosuria in the present pregnancy. A 50 g oral glucose challenge test (GCT) was performed as an initial screening test irrespective of the fasting status and a blood sugar level $\geq$140 mg/dl (7.8 mmol/l) was considered a positive GCT. These women then had a 2 h 75 g oral glucose tolerance test (OGTT) after an overnight fast of 8–10 h. Diagnosis of GDM was made with at least two out of three elevated plasma glucose levels—fasting glucose >95 mg/dl (5.3 mmol/l), 1 h $\geq$180 mg/dl (10 mmol/l) and 2 h $\geq$155 mg/dl (8.6 mmol/l). Women who screened negative at first antenatal visit had repeat screening at 28, 32 and 36 weeks of pregnancy (Fig. 1). Women included in the study were between 20 to 46 years of age and had GDM diagnosed with a singleton pregnancy between 20 and 36 weeks of gestation.

The exclusion criteria were women who have contraindications for metformin intake, a recognized fetal anomaly on ultrasound examination or ruptured membranes at study entry, presence of any other medical disorder (including type 1 and type 2 diabetes), a positive OGTT before 26–28 weeks of pregnancy consistent with diagnosis of overt diabetes in pregnancy and fetal growth restriction (birth weight <10th centile for its gestational age on ultrasound comparing with a 1st dating or early 2nd trimester scan).

3. Allocation and randomisation

Once the diagnosis of GDM was made patients were counseled for dietary and life style modifications including exercise. Dietary advice was made on an individual basis with caloric intake of 25 kcal/kg divided into six times with three meals and three snacks. Caloric content of routine foods was calculated with the help of a dietician and diet charts were given. Women with elevated blood glucose levels and those who did not maintain the desired blood glucose levels on diet and exercise within 1–2 weeks of intervention were included in the study and randomized to treatment with metformin or insulin along with diet and exercise advice. Randomization was done as the eligible patients entered the study with odd number assigned to metformin treatment and even number for insulin treatment irrespective of body weight and GTT values at study entry. Blinding was not possible because of different routes of administration of drugs.

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