Effect of Metformin on Diabetes Mellitus Prevention in Pregnant Women with Risk Factors

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Abstract

Objective: This study evaluated the efficacy and safety of metformin on prevention of gestational diabetes mellitus in women with high risk of GDM.

Materials and methods: Total number of 189 pregnant women aged between 25 to 35, and 10 to 14 weeks pregnancy, admitted to Mirza Koochakkhan Hospital, Tehran in January 2008 – January 2009 entered to this randomized controlled clinical trial. The women had one of the three risk factors; history of GDM, family history of diabetes, or BMI $\geq 30$ kg/m$^2$, with normal results in the glucose challenge test (GCT) or the glucose tolerance test (GTT). Subjects were randomly split to two groups; 63 women (group A) who received metformin (500 mg, twice a day) and 126 women (group B) did not use metformin. Incidence of gestational diabetes was compared between two groups.

Results: The incidence of gestational diabetes was significantly different between two groups (%1.4 in group A, %15.4 in group B) ($p<0.001$). The study also showed that the insulin requirement was significantly different between two groups after developing GDM (group A %3.6, group B %9.5, $p=0.001$).

Conclusion: Using Metformin can effectively reduce the incidence of GDM in pregnant women at risk.

Keywords: Gestational diabetes mellitus, Metformin, Prevention

Introduction

Gestational diabetes mellitus is defined as carbohydrate intolerance of variable severity with first recognition during pregnancy (1,2). This definition applies whether or not insulin is used for treatment (3). Its incidence differs based on the demographics; in the US for instance it is % 1 to %14 (2). While in Tehran – Iran it is reported to be %4.7 according to the results released by Metabolism Research Center of Tehran University (4).

During normal pregnancy certain hormones cause cellular resistance to insulin so that blood glucose is increased to make proper nutrition source to fetal growth and development (5). This resistance may instigate pancreatic beta cells disorders that manifests itself by GDM (6). Especially if risk factors for GDM are present, pregnancy may tip the balance of glucose–insulin regulation, and abnormally high maternal blood glucose and insulin concentrations may result (7). The etiology of GDM is not known. It may be a combination of genetics and life style (6). There are risk factors to GDM that are either correctable or not (7).

The correctable risk factors include physical inactivity or a sedentary lifestyle, BMI $\geq 25$ kg/m$^2$, history of GDM in previous pregnancies, history of giving
birth with a weight greater than 4000 grams (8).

Uncorrectable risk factors are history of diabetes in first–degree relatives, women aged older than 35 years and ethnicity (from aboriginal, Hispanic, Asian or African descent, south Asian) (7, 9, 10).

More than %60 of women with GDM will develop overt diabetes (type 2) within 4 years past delivery (11). Recurrence of GDM in subsequent pregnancy was documented to be %35–%80 (12). Furthermore GDM is at risk for diabetes later in life (13).

Off springs of women with GDM are prone to develop type 1 or 2 diabetes (1). Large babies are at risk for obesity, which is a risk factor for diabetes (14).

Obese women are %17 at risk of GDM (15). Complications of GDM are fetal macrosomia which may be lead to a difficult labor and delivery, fetal growth which is disproportion resulting in shoulder dystocia, increased rate of cesarean section and neonatal hypoglycemia due to hyperinsulinemia in fetal circulation (1, 8). Metformin is one of the second-generation biguanides. It suppresses hepatic glucose uptake, increases insulin–mediated glucose use; increases splanchnic glucose turnover and decreases intestinal absorption of glucose and use. At the cellular level metformin improves insulin sensitivity. Metformin dose not stimulate insulin secretion, and does not cause hyperglycemia in either diabetic or control subject. Metformin does not stimulate the fetal pancreas to oversecrete insulin.

Half life of metformin is 2 to 5 hours and %90 of it is excreted through kidneys after 12 hours. It is a class B drug, appears to be safe and is not teratogenic during pregnancy (16, 17).

Therapeutic dose of metformin is 500–800 mg per day taken orally up to a maximum of 2000 mg. Administration in the presence of renal disease is contraindicated (18, 19).

From a maternal and fetal diabetic complication point of view, the aim of this study is to evaluate the preventive effect of metformin on GDM high risk women.

**Materials and Methods**

This study is a non placebo double blind clinical trial which was conducted in a period of one year (January 2008 – January 2009) on 189 pregnant women aged between 25–35 and 10–14 weeks of pregnancy who were referred to the women's Hospital, Tehran, Iran. The study proposal was initially approved by the ethics Committee of Tehran University. Selected women had at least one of these risk factors obesity (BMI >30 kg/m²), history of previous GDM and history of diabetes in the first degree relatives.

Exclusion criteria were history of renal diseases, type 1 or 2 diabetes, megaloblastic anemia, B12 deficiency, allergy to metformin, alcohol consumption and abnormal GCT (glucose challenge test with 50 gram glucose after one hour >130 mg/dl).

Women were divided to two groups; A and B. For group A metformin was started 500 mg twice daily throughout the pregnancy until delivery or up to development of the GDM. In contrast, no anti–diabetic drug was given to group B.

Both groups underwent prenatal care and were tested with GCT 50 gr between 24 to 28 weeks of gestation. If their glucose was greater than 130 mg/dl after one hour the subject was suspected to GDM; then GTT with 100 gr would be given after 8–10 hours overnight fast. The GDM diagnosis would be confirmed if two variables of standard GTT 100 gr were abnormal (fasting blood sugar greater than 95 mg/dl, after 1 hour >180 mg/dl, after 2 hours >155 mg/dl, after 3 hours >140 mg/dl).

Women with abnormal GTT were instructed to take a diet of 2 weeks. If their blood sugar was not normal, for group A metformin was discontinued and insulin was given to both groups. Statistical analysis of the data was performed with SPSS version 18.

Categorical variables were compared using the X² test (Fisher's exact test) and continuous variable were analyzed using the Student's t test. Multi variable logistic regression was used for statistical analysis. The p–value less than 0.05 was considered statistically significant.

**Results**

A total of 189 cases were studied in two groups; 58 in group A, and 126 in group B. Five women were excluded from the study, four did not contest to the tests and one woman had therapeutic abortion (down syndrome).

According to the demographic and clinical characteristics, mean age was 30.3 (± 2.90) for group A and 30.29 (± 30.281) for group B, BMI >30 kg/m² in group A was 55.%1 and in group B was %51.5, positive familial history of type 2 diabetes in group A was %57 and in group B was %55.3, positive history of previous GDM in group A was %10.7 and in group B was %7.1. Differences were not statistically significant between two groups.

The rate of GDM in group A was %1.6, whereas it was %15.4 for group B (p=0.001).
The study also showed requirement to insulin was significantly different between two groups after GDM was developed (Group A %3.6, Group B %9.5, \( p = 0.001 \)).

According to logistic regression analyses, the history of previous GDM was a strong predictor of present GDM (\( p<0.001, OR= 81.1 \)). Family history of type 2 diabetes increased risk of GDM up to three times and BMI >30 kg/m\(^2\) up to 5.5 times which were not strong predictors of present GDM.

**Discussion**

Similar studies are scarce, however, there are studies showing that metformin in pregnant PCO’s cases reduce cellular need and resistance to insulin and decrease insulin secretion by pancreatic beta cells. Gilbert & Codon reported that the rate of congenital malformation in metformin users during pregnancy not only was not increased but also had protective effect (%1.7 Vs %7.2) (20).

Gloeck and colleagues demonstrated the use of metformin in pregnant PCO's cases were safe and efficiently decreased GDM (%3 Vs %23) (21, 22).

Jackubwicz and colleagues showed preventive effect of metformin to decrease early pregnancy loss on non diabetic PCO's pregnant women (%11 Vs %58) and no increase in fetal malformation or neonatal hypoglycemia was observed (23).

There are studies that showed that taking metformin does not decrease pregnancy complications such as GDM, preterm labour, neonate weight (24).

Comparing maternal and neonatal outcomes in women with GDM treated with either metformin or insulin showed that women treated with metformin had less weight gain and improved neonatal outcome for premuturity, neonatal jaundice,and NICU admission, compared with those treated with insulin. There was no difference between the metformin and insulin group comparing pre–eclampsia, gestational hypertension, induction of labour, and cesarean section (25).

A systematic review on four studies from 2007 years that compared benefits and risks of oral hypoglycemic agents with insulin in women with GDM showed that there is no substantial maternal or neonatal outcome differences with the use of glyburide or metformin in comparison to insulin (26).

**Conclusion**

This study was conducted in order to establish preventive effect of metformin in women who had risk factors for GDM. The rate of GDM in group A was %1.6, whereas it was %15.4 for group B (9.5 times). Also if GDM develops, the need to insulin is comparably lower. History of GDM is an important factor in further GDM (\( p=0.001 \)).

Studies with larger sample sizes in different setting are necessary to confirm gestational safety and efficacy of metformin.

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**References**