Can Metformin Reduce Recurrence of Gestational Diabetes in Obese Women?

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Abstract

Objective: To evaluate the efficacy of using metformin in pregnancy on prevention of recurrence of gestational diabetes in obese women.

Methods: This is a multicentric randomized non placebo clinical trial including 91 obese women with past history of GDM women in 2 groups. 44 women in intervention group used metformin therapy during the second trimester of pregnancy compared to 47 women in control group. Screening test for GDM were performed to all women at 12-14 week and at 24-28 week gestation to detect cases with recurrent GDM.

Results: Women in the intervention group showed a significant lower rate of recurrence of GDM in the second pregnancy compared to women in the control group (18.1% vs 53.1%, OR=0.19, 95% CI=0.07–0.5, p<0.001).

Conclusion: Using metformin in the second trimester of pregnancy can effectively reduce the recurrence of GDM in obese women.

Key Words: Metformin – Gestational diabetes – Obese women.

Introduction

GESTATIONAL diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity with first onset or recognition in pregnancy [1]. Obesity is defined as body mass index (BMI) ≥30kg/m². Obesity is an established significant risk factor for GDM and being obese or severely obese increases the risk of GDM by a factor 3.6 and 8.6, respectively [2]. The prevalence of GDM in the USA is 2-10% with about 10-95% increases in prevalence reported over the last two decades [1]. Similarly, the prevalence of obesity in pregnancy has risen dramatically in recent years in both developing and developed countries [3]. Approximately 60% of women of reproductive age are overweight or obese in the USA and other developed countries [4]. GDM is associated with adverse pregnancy outcomes which are of a greater impact and frequency in obese compared to non obese women [5]. GDM increases rates of preterm labour, induced labour, cesarean deliveries, hypertension, pre-eclampsia, dysfunctional labour, postpartum haemorrhage, infections; increased perinatal morbidity (e.g., macrosomia, shoulder dystocia, birth injuries, neonatal hypoglycemia, infections and jaundice) and perinatal mortality as well as increased risk of developing type 2 diabetes, metabolic syndrome and cardiovascular disease in women and their offsprings [6].

GDM in an index pregnancy increases the risk of recurrent GDM in subsequent pregnancies. The reported frequency of recurrent GDM varies widely, from 30 to 84%, depending on some factors such as ethnicity, body weight, BMI, maternal age and the diagnostic criteria used [7]. Getahun et al., [8] reported that compared to women who were free of GDM in their first pregnancy, those with past history of GDM in their first pregnancy had a 13 fold increased risk of GDM in a second pregnancy, those who were free of GDM in the first pregnancy but experienced the disease in their second pregnancy, had a 15 fold increased risk of GDM in the third pregnancy and those with GDM in their first two pregnancies had a 26 fold increased risk of GDM in the third pregnancy. Lup and Stys [9] reported that increased body weight is a major risk factor of GDM recurrence and the risk of GDM recurring in obese women in subsequent pregnancies may range from as high as 60% to 90%. Therefore, obese women with past history of GDM have had at least two major risk factors for recurrence of GDM in their next pregnancies and seeking an effective preventive measure is an obstetric merit.
Pregnancy increases requirements for insulin secretion, increases insulin resistance and demands on pancreatic β-cells promoting development of GDM particularly in women with pre-existing insulin resistance such as our target population. Therefore, interventions that reduce insulin resistance and reduce requirements for endogenous insulin secretion, preserve β-cell function, and are proposed to prevention of GDM as well as type 2 DM [10]. Metformin is one of the second generation biguanides. It suppresses hepatic glucose production, enhances peripheral glucose uptake, increases insulin sensitivity and decreases intestinal absorption of glucose. Metformin does not stimulate insulin secretion, and does not cause hypoglycemia in either diabetic or control subjects [11]. The US Diabetes Prevention Program (DPP) demonstrated that, in women with past history of GDM, metformin is associated with 50% risk reduction in progression to type 2 diabetes and this beneficial effect of metformin was mainly observed in subjects with BMI >35kg/m² [11]. Many advantages including cost effectiveness, easy administration, safety, weight neutrality, low risk of hypoglycemia and cardiovascular protection moved metformin to be the first line therapy [11] and a first line agent for the prevention of type 2 diabetes as recommended by the American Diabetes Association (ADA) [12]. From an obstetric view, metformin is a class B drug, appears to be safe, not teratogenic and does not stimulate the fetal pancreas to over-secrete insulin [13]. Metformin use during pregnancy provides adequate glucose control, less weight gain and lower rates of neonatal hypoglycemia [14]. Evidence from observational studies suggests that babies exposed to metformin in utero exhibited no adverse sequelaes [15].

Many studies had proved metformin to be effective in preventing type 2 diabetes in population at risk [16-18] and preventing GDM in pregnant women with polycystic ovarian syndrome (PCOS) [19-21]. However, evidence on its effective role in preventing GDM recurrence in obese women is lacking. We hypothesized that metformin due to its metabolic and obstetric properties may perform this task.

**Subjects and Methods**

We conducted a multicentric prospective randomized non placebo clinical trial (Al-Azhar Teaching Hospital Egypt and Safa El-Madina Hospital K.S.A). Between August 2011 and October 2013 in 3 centers. The study included total 96 obese women with past history of GDM with current singleton pregnancy at 12-14 weeks gestation. Cases having pregestational diabetes, major chronic illnesses, corticosteroid therapy, megaloblastic anemia, B12 deficiency and allergy to metformin were excluded. Detailed history and complete physical examination were performed and informed consent was obtained from all women. After taking the consent, random allocation to either the intervention or control group was conducted by an individual who is independent to the study by drawing opaque numbered envelopes. Women were divided into two groups; intervention group that included 47 women to them, metformin was administered after allocation and control group that included 49 women to them, no antidiabetic drug was given. Women in intervention group were instructed to take one tablet metformin 500mg once daily during the first week then twice daily for the next week then 750mg twice daily for the rest of the study period. Both groups underwent regular prenatal care and compliance was assessed during the prenatal car visits.

GDM documentations in the index pregnancies were obtained from the medical records in the participating centers. Body weights were measured on a digital scale with height rod (6439, Detecto, USA). Weight was measured to the nearest kilogram and height to the nearest centimeter. BMI was calculated as weight in kg/height in squared meters (kg/m²). Women with BMI >35 were included in the study.

50-g, 1-hr GCT screening test for GDM was performed twice for all women, first, prior to study at 12-14 weeks gestation to exclude cases with pregestational or type 2 diabetes and second time at 24-28 week gestation after one week cessation of metformin to avoid the possible masking effect of metformin for GDM. Women with plasma glucose values ≥140 mg/dl on the screening test went on to receive a diagnostic 100-g, 3-hr GTT. GDM was defined according to ADA with plasma glucose thresholds for the diagnostic test, two or more values meeting or exceeding the following cut points: fasting 95mg/dl; 1-hour 180mg/dl; 2-hour 155mg/dl; 3-hour 140mg/dl [1]. All plasma glucose measurements were performed using the hexokinase method. The primary outcome was the proportion of women diagnosed with GDM between 24-28 weeks. Secondary outcome was the adverse effects of metformin therapy.

Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0. Continuous variables are presented as mean±SD, and categorical variables are presented as absolute numbers and percentage. The comparison of continuous variables between the groups was performed using Student’s t-test. Categorical
data between the groups were compared using Chi-squared test or Fisher’s exact test as appropriate. We used logistic regression models to generate adjusted odds ratios and their 95% confidence intervals. Statistical significance was considered achieved when \( p \) was less than 0.05.

**Results**

96 women were enrolled in this study but 5 women were excluded from the study including two women for fetal loss (one in each group) and 3 women were dropped out (two in intervention group and one in control group). So that, 91 women completing the study included 44 women in intervention group and 47 women in the control group. Table (1) shows that there were no significant differences between both groups regarding basic characteristics such as maternal age, BMI, family history of diabetes and parity.

There were no significant differences between both groups regarding to gastrointestinal complaints (diarrhea, nausea, vomiting, abdominal discomfort or cramps). No incidence of maternal hypoglycemia or lactic acidosis were observed in both groups.

Women in the intervention group showed a significant lower rate of recurrence of GDM at time of second screening test compared to women in the control group (18.1% vs 53.1%, Odds ratio (OR) = 0.19, 95% Confidence Interval (CI) = 0.07–0.5, \( p < 0.001 \); Table 2).

**Table (2): Recurrence of GDM in both groups.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention group n=44</th>
<th>Control group n=47</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence of GDM (n, %)</td>
<td>8 (18.1%)</td>
<td>25 (53.1%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Discussion**

Results of this study indicate that metformin use during the second trimester of pregnancy among obese women with past history of GDM, significantly reduces recurrence of GDM. Pregnancy increases insulin resistance which is a normal phenomenon emerging in the second trimester, increasing demands on pancreatic \( f_1 \)-cells. Thus the hallmark of GDM is an increased insulin resistance. Women with GDM cannot compensate for this resistance by increased insulin secretion of the \( f_1 \)-cells such as in normal pregnancy. Placental hormones, and to a lesser extent increased fat deposits during pregnancy, seem to mediate insulin resistance during pregnancy [22]. Obese pregnant women are more resistant to the actions of insulin and more frequently associated with \( f_1 \)-cell dysfunction than lean women particularly if past history of GDM is coexisting. This suggests a potential role of metformin in these women via reducing both insulin resistance and requirements for endogenous insulin secretion in order to preserve \( f_1 \)-cell function and prevent the development of GDM [10].

Similar studies are scarce, however, there are studies showing that metformin in pregnant women with PCOS, reduces cellular need and resistance to insulin. Glueck and colleagues [19] demonstrated the use of metformin in these women were safe and efficiently reduced incidence of GDM. Ratner et al., [17] reported that metformin therapy reduced the incidence of type2 diabetes by approximately 50% compared with the placebo group and metformin, on the other hand, may be as much as 3 times more effective in reducing the incidence of diabetes in those with a history of GDM compared with those without. Mangahas et al., [18] reported that at a median follow-up of 10 years after initial enrollment in the DPP trial, metformin reduced the incidence of overt diabetes for adults with one or more risk factors that is consistent with our results.

Randomized controlled trial of metformin versus insulin showed that women preferred metformin in tablets to insulin injections, and that metformin is safe and equally effective as insulin [23]. Studies 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 prematurity, 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 [24]. A systematic review of 4 studies from 2007 that compared benefits and risks of metformin with insulin in women with GDM showed that there is no substantial maternal or neonatal outcome differences with the use of metformin in comparison to insulin [13].

Contrary to our results, Vanky et al., [25] reported that metformin treatment from first trimester to delivery did not reduce GDM in women with PCOS. However, in addition to difference in methodology between our study and Vinky’s study, no limitations were set on BMI or PCOS phenotype on inclusion of the latter. 95% of the participants were Caucasians which was an obvious limitation of Vinky’s study. Another explanation could be that all participants had diet and lifestyle intervention, which has been reported to be beneficial and could theoretically mask the effect of metformin.

There were several limitations to this study. First, this study was missing blinding and placebo controlling that would give more power to the study but it was technically difficult. Second, administration of metformin was only limited to the second trimester of pregnancy. The pathogenesis of GDM is timed to the second trimester [25] and administration of the drug in first trimester might mask the gastrointestinal upsets which are not uncommon adverse effects of both metformin and early pregnancy. Also possible worrying feel of teratogenic effect of any drug by some women, even theoretically, might negatively affects their compliance. Absence of drug administration during third trimester raises supposition that effects of metformin on insulin sensitivity may disappear after stopping the drug. The available data does not provide direct measures of insulin sensitivity; it also remains uncertain whether the glucose levels are stabilized or still rise after discontinuing metformin. With the current understanding of the effects of metformin on carbohydrate metabolism, it is possible that a part of the effects of metformin are due to beta-cell protection and preservation [24]. Another studies may be necessary to decide if metformin acts via masking diagnosis rather than true prevention of GDM. Third limitation was the relatively small sample size of the study. Studies with larger sample sizes in different settings are necessary to confirm gestational safety and efficacy of metformin in obese women or women with other risk factors of GDM.

Conclusions:
Using metformin in the second trimester of pregnancy can effectively reduce the recurrence of GDM in obese women.

References
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