Insulin and glyburide therapy: Dosage, severity level of gestational diabetes, and pregnancy outcome

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Objective: We sought to investigate the association between glyburide dose, degree of severity in gestational diabetes mellitus (GDM), level of glycemic control, and pregnancy outcome in insulin- and glyburide-treated patients.

Study design: In a secondary analysis of our previous randomized study, 404 women were analyzed. The association among glyburide dose, severity of GDM, and selected maternal and neonatal factors was evaluated. Severity levels of GDM were stratified by fasting plasma glucose (FPG) from the oral glucose tolerance test (OGTT). Infants with birth weight at or above the 90th percentile were considered large-for-gestational age (LGA). Macrosomia was defined as birth weight ≥4000 g. Well-controlled was defined as mean blood glucose ≤95 mg/dL. The association between glyburide- and insulin-treated patients by severity of GDM and neonatal outcome was evaluated.

Results: The dose received for the glyburide-treated patients was 2.5 mg–32%; 5 mg–23%; 10 mg–17%; 15 mg–8%; and 20 mg–20%. Patients were grouped into low (≤10 mg) and high (>10 mg) daily dose of glyburide. A comparison between severity of the disease (fasting plasma glucose categories) and highest dose of glyburide revealed a significant difference between the low-95 FPG and the other severity categories (P = .02). Of patients in the well-controlled glycemic group, only 6% required the high dose of glyburide (>10 mg). In patients with poor glycemic control (mean blood glucose >95 mg/dL), 38% received the high dose of glyburide (P = .0001). Comparison between the high glyburide (>10 mg) and the low glyburide dosages (≤10 mg) revealed that the rate of macrosomia was 16% vs 5% and LGA 22% vs 8%, (P = .01), respectively. No significant difference was found in composite outcome, metabolic complications, and Ponderal Index between the 2 dose groups. Stratification by disease severity revealed a significantly lower rate of LGA for both the glyburide- and insulin-treated subjects. No significant difference was found between metabolic, respiratory, and neonatal intensive care unit (NICU) for patients within each fasting plasma glucose severity category.

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We previously demonstrated the efficacy of the use of glyburide in gestational diabetes (GDM) and showed that second generation oral hypoglycemic agents, and especially glyburide, do not significantly cross the placetas of control pregnancies and pregnancies complicated by diabetes. Currently, authorities in the US recommend, in review and editorial articles, the use of glyburide (sulfonylurea) as an alternative pharmacologic therapy to insulin that will result in comparable perinatal outcome in GDM. Recently, Gabbe and Graves stated...“an alternative to insulin therapy is the oral hypoglycemic agent glyburide...In our experience; glyburide has become the first choice of our patients with GDM who require therapy beyond diet.”

Two major questions remain unanswered: will glyburide be as effective as insulin in all severity levels of diabetes? In addition, is there a dose limitation above which the efficacy of glyburide will decrease in comparison to insulin? To date, no studies evaluated the relationship between severity of GDM, dosage requirements, and successful therapy (level of glycemic control and pregnancy outcome). Therefore, we sought to investigate the association between dose of glyburide, degree of GDM severity, level of glycemic control, and pregnancy outcome in insulin- and glyburide-treated patients.

**Material and methods**

**Subjects**

In a secondary analysis of our previous randomized study, 201 glyburide-treated and 203 insulin-treated women were analyzed. Data were obtained from our computerized database and included a demographic profile, social history, and a summary of past obstetric and medical information. All patients were drawn from inner-city maternal health clinics, where they were screened for GDM with a 1-hour, 50-g oral glucose challenge. Subjects with plasma glucose concentrations ≤130 mg/dL at 1 hour underwent a 100-g oral glucose tolerance test (OGTT).

The level of GDM severity, a priori categorized by 10 mg/dL increments, was defined using the fasting plasma glucose (FPG) value on the OGTT. Women with a prepregnancy body mass index (BMI: weight in kilograms divided by the square of the height in meters) of 27.3 or more were considered obese. The definition of obesity was derived from the high prevalence of overweight women in our population.

**Conclusion:** Glyburide and insulin are equally efficient for treatment of GDM in all levels of disease severity. Achieving the established level of glycemic control, not the mode of pharmacologic therapy, is the key to improving the outcome in GDM.

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**Management approach**

The management protocol included standard nutritional instructions for 3 meals and 4 snacks daily. Patients with fasting plasma glucose on the OGTT ≥95 mg/dL and less than 139 mg/dL, or those who failed to achieve glycemic goals on diet therapy were randomly assigned to insulin or glyburide. If needed, changes in drug dosage occurred after 3 to 7 days of evaluation of glycemic control.

Patients assigned to insulin therapy received an insulin dose based on 0.7 U/kg of actual body weight at admission given subcutaneously 3 times daily and increased weekly as needed. Women assigned to glyburide initially received a morning 2.5 mg oral dose, with an additional 2.5 mg added as needed. When advisable, patients also received 5 mg in the evening. If the targeted level of glycemic control was not achieved, 5 mg was added to the morning and to the evening doses for a total of 20 mg.

All patients were treated to attain the same metabolic goals based on the self-monitoring blood glucose results: overall mean blood glucose levels defined as mean blood glucose from diagnosis to delivery of ≤95 mg/dL, fasting blood glucose levels between 60 and 90 mg/dL, 2-hour postprandial blood glucose levels ≤120 mg/dL, and premeal targets of 80 to 95 mg/dL. Patients with mean blood glucose of ≤95 mg/dL were considered well-controlled, and those with mean blood glucose of >95 mg/dL were considered poorly controlled.

**Fetal and neonatal assessment**

Infants were considered large-for-gestational age (LGA) with birth weights ≥90th percentile based on growth standards developed for our population. Macrosomia was defined as birth weight of 4000 g or more. Infants were evaluated by at least 3 glucose readings during the first hour after birth, and then half hourly for 4 hours. Hypoglycemia was defined as the presence of 2 consecutive blood glucose values of <40 mg/dL. Hyperbilirubinemia was defined as serum bilirubin of at least 12 mg/dL. Bilirubin was measured when there was clinical evidence of jaundice. Polycythemia was defined as hematocrit >60% measured in cord blood of all infants. A composite outcome variable was created for all infants if at least 1 of the following was present: metabolic complications, LGA/macro discomfort, neonatal intensive care unit admission for >24 hours, and the need for respiratory support.
Maternal and neonatal outcome characteristics were stratified for severity of GDM, glyburide dose, and level of glycemic control. We compared the efficacy of insulin and glyburide therapies for each GDM severity level. Analysis was performed using chi-square and Fisher exact test for categoric data. Odds ratio was calculated by Mantel-Haenszel test, and multivariate analysis (logistic regression) was performed to assess the extent to which various risk factors affect or contribute to neonatal outcome. Pearson’s correlation was calculated for continuous data to study the association between treatment modality and explanatory variables.

Results

Of the 404 women enrolled in the study, 201 were assigned to receive glyburide, and 203 to receive insulin. Maternal age, parity, obesity, family history, ethnicity, gestational age at diagnosis, and gestational age at delivery were comparable for the 2 groups. The pre-pregnancy weight was comparable for insulin- and glyburide-treated patients, 76.18 kg vs. 74.19 kg, respectively. Weight gain in pregnancy was 21 ± 15 pounds for the insulin and 21 ± 17 pounds for the glyburide subjects (P = .53).

A positive association between maternal prepregnancy weight and pharmacologic dose was found for both insulin (r = 0.50, P = .0001) and glyburide (r = 0.27, P = .0002). The highest dose of glyburide distribution: 31% of patients were treated with 2.5 mg; 21%, 5 mg; 19%, 10 mg; 9%, 15 mg; and 20% received 20 mg. The mean dose of glyburide was 9.2 ± 6.7 mg, and the mean dose of insulin was 85 ± 48 U.
One hundred and sixty-five women in the glyburide group (82%) and 179 women in the insulin group (88%) achieved the established targets of glycemic control. Patients were further stratified by level of diabetes severity using the fasting plasma results from the OGTT: low-95 mg/dL (n = 196), 96 to 105 mg/dL (n = 94), 106 to 115 mg/dL (n = 67), 116-high (n = 47). With increased severity, there was decreased success in achieving targeted levels of glycemic control. However, at each level of severity, both drugs were equally effective (Figure 1).

Patients were grouped into low (<10 mg) and high (≥10 mg) doses of glyburide. For the first 2 GDM severity groups (low-95 and 96 to 105 mg/dL), the majority of patients were on the low glyburide dose (P = .001). In contrast, for the 2 higher severity levels (106 to 115 and 116-high mg/dL), the rates of patients using high and low doses were similar. We further compared the mean dose of pharmacologic therapy in each severity level of GDM. In patients using the glyburide therapy, no significant difference was found between the low-95 and the 96 to 105 mg/dL levels of severity. A significant difference was found between the former 2 groups and the 106 to 115 and 116-high levels of severity (P = .0001). A significantly lower dose of insulin was used in the low severity level in comparison to the other 3 levels (P = .0004) (Figure 2). In addition, there was a linear relationship between glyburide dose and failure to achieve targeted levels of glycemic control (Figure 3).

Perinatal outcome was analyzed by disease severity and mode of pharmacologic therapy. Although no significant difference was found in each severity category between the insulin- and glyburide-treated subjects, a significantly lower LGA rate was found in the mild (low-95 mg/dL) in comparison to the other 3 categories (P = .01) (Figure 4). Further stratification by fasting plasma glucose into low-95 mg/dL and 96-high mg/dL revealed a significantly lower rate of LGA in both insulin- and glyburide-treated subjects in the low severity category. No significant difference was found in other adverse outcome measures between insulin and glyburide in the 96-high mg/dL severity level (Table I).

Finally, a logistic regression analysis was performed in which the dependent variable was LGA to evaluate the net effect of several independent variables on pregnancy outcome (Table II). Only severity levels of GDM, mean blood glucose, weight gain in pregnancy, and previous macrosomia were significant. Treatment modality, obesity, parity, race/ethnicity, and maternal age were not significant contributors.

**Table I**  Perinatal outcome by severity of gestational diabetes (fasting plasma glucose from the OGTT)

<table>
<thead>
<tr>
<th>Fasting plasma glucose in the oral GTT</th>
<th>≤95 mg/dL</th>
<th>Glyburide</th>
<th>&gt;95 mg/dL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at delivery</td>
<td>Insulin</td>
<td>38.5 ± 1.9</td>
<td>38.8 ± 1.5</td>
</tr>
<tr>
<td>Large for gestational age (LGA)†</td>
<td>Glyburide</td>
<td>7.7%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Macrosomia</td>
<td></td>
<td>2.0%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Ponderal index &gt;2.85</td>
<td></td>
<td>11.7%</td>
<td>10.2%</td>
</tr>
<tr>
<td>Metabolic complications</td>
<td></td>
<td>18.8%</td>
<td>20.9%</td>
</tr>
<tr>
<td>Composite outcome</td>
<td></td>
<td>25.3%</td>
<td>27.5%</td>
</tr>
<tr>
<td>Cord-serum insulin μU/mL</td>
<td></td>
<td>16 ± 15</td>
<td>14 ± 9</td>
</tr>
</tbody>
</table>

* Overall, no significant difference in adverse pregnancy outcome between the low-95 mg/dL category and 96-high mg/dL category in both insulin- and glyburide-treated groups.
† Significant difference in the rate of LGA between the low-95 mg/dL and the 96-high mg/dL categories by chi-square analysis (P = .01).

**Table II**  Logistic regression for LGA as dependent variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDM severity</td>
<td>2.13</td>
<td>1.09-4.18</td>
</tr>
<tr>
<td>Mean blood glucose</td>
<td>1.99</td>
<td>1.04-3.83</td>
</tr>
<tr>
<td>Weight gain in pregnancy</td>
<td>3.81</td>
<td>1.81-8.05</td>
</tr>
<tr>
<td>Previous delivery of infant with macrosomia</td>
<td>3.73</td>
<td>1.70-8.18</td>
</tr>
<tr>
<td>Parity</td>
<td>1.81</td>
<td>0.85-3.83</td>
</tr>
<tr>
<td>Treatment modality</td>
<td>1.27</td>
<td>0.68-2.38</td>
</tr>
<tr>
<td>Maternal prepregnancy weight</td>
<td>1.87</td>
<td>0.94-3.71</td>
</tr>
</tbody>
</table>

**Comment**

We found that glyburide and insulin are equally efficacious for GDM treatment in all severity levels of diabetes when FPG on a GTT was between 95 and 139 mg/dL. Over 80% of GDM patients requiring pharmacologic intervention will achieve the established levels of glycemic control with glyburide. The majority of patients (71%) will require, on average, up to 10 mg daily dose of glyburide to achieve established levels of glycemic control. Reaching established levels of glycemic control and not the mode of therapy is the key to improving pregnancy outcome in GDM women.
The primary effect of sulfonylurea drugs is to enhance insulin secretion.\textsuperscript{21,22} Studies have demonstrated that these drugs can also enhance peripheral tissue sensitivity to insulin.\textsuperscript{23,24} Because beta cell exhaustion plays an important role in the development of overt diabetes and insulin secretion and resistance are characteristics of GDM, it follows that the use of a sulfonylurea agent is beneficial in the prevention of GDM complications in high-risk populations.

Several retrospective and 2 randomized studies evaluated the use of sulfonylurea drugs (1st and 2nd generations) and metformin during pregnancy.\textsuperscript{25,29} In 1971, Notelowitz et al\textsuperscript{28} studied the efficacy of sulfonylureas, diet, and insulin in a randomized study design. He defined good control as mean blood glucose <150 mg/dL. Although the study had a small sample size, 80% of the sulfonylurea or diet patients achieved the targeted level of control. In contrast, only 36% of the insulin-treated patients achieved the targeted category.

In the primary analysis of our study,\textsuperscript{1} we found that 82% of the glyburide and 88% of the insulin-treated patients achieved the established levels of glycemic control. In the current study, heretofore not described, we showed that in all severity levels of GDM, the success rate for achieving established levels of glycemic control is similar in insulin- and glyburide-treated patients. As the level of disease severity increases, the success rate for achieving established levels of glycemic control decreases. Since the recommended threshold for initiation of pharmacological therapy is fasting plasma glucose >95 mg/dL and/or 2-hour postprandial value >120 mg/dL, it follows that for the majority of patients, glyburide therapy can be the drug of choice when diet treatment fails. Moreover, the majority of patients can be successfully treated with a 2.5 to 10 mg/daily dose of glyburide. Indeed, in our previous study,\textsuperscript{1} only 8 patients out of 203 were transferred from glyburide to insulin therapy.

When patients were stratified by severity level of GDM, no significant difference was found in neonatal size, metabolic complications, and composite outcome variable between the 2 treatment modalities. Finally, the logistic regression analysis was performed to determine the relative contribution of each independent variable historically known to contribute to LGA. Overall, mean blood glucose determination, severity of GDM (categorized by the fasting plasma from the OGTT), previous macrosomia, and weight gain in pregnancy were the only significant contributors associated with increased risk for adverse outcome in pregnancy. Treatment modality was not a contributing risk for adverse outcome.

In summary, in our experience, glyburide has become the drug of choice for use in GDM when pharmacologic intervention is required, regardless of severity level of GDM. The noninvasive, cost-effective\textsuperscript{30} patient-friendly regimen lends itself more readily to potential patient compliance. Although both treatment modalities show comparable perinatal outcome, it appears from our, and other investigators’ experience that oral therapy is more readily accepted than insulin injections. However, failure to achieve established levels of glycemic control, regardless of the choice of treatment modality, will result in adverse perinatal outcome.

References


