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Examining the Starting Dose of Glyburide in Gestational Diabetes

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Abstract

OBJECTIVE—The aim of this study was to determine the impact of initial glyburide dosing on pregnancy outcomes.

STUDY DESIGN—Retrospective cohort of singleton pregnancies complicated by gestational diabetes (GDM) from 2007-2013. Women who received glyburide were compared by initial dose: 2.5mg (n=170) versus 5mg (n=154) total daily dose. The primary maternal outcome was hypoglycemia, defined as a blood glucose <60 mg/dL. The primary neonatal outcome was birth weight. Secondary maternal outcomes included time to blood glucose control, preeclampsia, and cesarean delivery. Secondary neonatal outcomes included macrosomia (>4000g), hypoglycemia (<40 mg/dL), shoulder dystocia, and preterm delivery.

RESULTS—The 5 mg/day glyburide dose did not increase maternal hypoglycemia (26% in the 2.5 mg/day group versus 27% in the 5 mg/day group, AOR 0.67 (CI 0.30-1.49)). An increase in macrosomia in the 5 mg/day group was not significant after adjusting for maternal obesity (AOR 2.16 (CI 0.96-4.88)). Differences in preterm birth and large for gestational age were not significant after adjusting for prior preterm birth and maternal obesity, respectively.

CONCLUSIONS—A higher starting dose of glyburide for the management of GDM was not associated with increased maternal hypoglycemia or decreased adverse neonatal outcomes.

Keywords

gestational diabetes; glyburide; hypoglycemia; macrosomia

Introduction

Gestational diabetes mellitus (GDM), carbohydrate intolerance first recognized during pregnancy, complicates up to 7% of pregnancies in the United States.[1] Previous studies have demonstrated that glycemic control in pregnancies affected by gestational diabetes improves perinatal outcomes.[2, 3] Treatment usually involves dietary changes, blood glucose

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monitoring, and pharmacologic therapy as indicated. When diet modification alone fails to achieve target glucose levels, hypoglycemic agents are routinely started; available pharmacologic options include insulin or oral hypoglycemic agents.

Glyburide is an oral second-generation sulfonylurea commonly used in the management of GDM; it acts primarily by increasing insulin secretion from the pancreatic beta cells. Glyburide has demonstrated similar effectiveness, and greater ease of use, than insulin.[4] Usual doses range from 2.5 to 20 mg daily, dosed either once or twice per day.

Recent reports have noted that, despite a marked increase and widespread use of glyburide, there is a paucity of dosing data in the context of pregnancy.[5, 6] The current dosing regimen is based on studies performed in men and non-pregnant women with type 2 diabetes mellitus;[7, 8] therefore, limited information exists regarding glyburide dosing in pregnant women and its effect on maternal and neonatal outcomes. While prior research suggests an increase in hepatic metabolism in pregnancy, and therefore rapid elimination and decreased bioavailability of glyburide, pregnant women are typically started on glyburide doses appropriate outside of pregnancy due to concerns for maternal and neonatal side effects (e.g. hypoglycemia).[5, 9] Lower initial dosing may, in turn, allow continued hyperglycemia, leading to delayed antenatal glycemic control and poor neonatal outcomes, specifically fetal overgrowth.

Given the lack of evidence evaluating clinical outcomes in relation to glyburide dosage, we aimed to compare pregnancy outcomes in women who received two alternative starting doses of glyburide: 2.5 mg vs. 5mg total daily dose. We hypothesized that higher starting doses of glyburide would be associated with improved neonatal outcomes and shorter time to maternal glycemic control without increasing the risk of maternal hypoglycemia.

Materials and Methods

We performed a retrospective cohort study of all singleton pregnancies complicated by GDM delivered at a single tertiary care center from 2007 through 2013. Institutional review board approval was obtained from the University of Alabama at Birmingham.

Subjects were identified by a diagnosis of gestational diabetes as listed on our obstetric database discharge forms. Standardized chart abstraction forms were used to abstract data from the medical charts by a team specifically trained in chart abstraction. Information was obtained on maternal demographics, medical and obstetrical history, results of GDM screening, antenatal blood sugar logs, initiation and dosing of pharmacologic agents for blood glucose control, intrapartum course, and neonatal outcomes.

GDM screening at our institution is standardly performed between 24 and 28 weeks of gestation with a one-hour, 50-gram glucose challenge test. If the glucose challenge test is ≥ 135 mg/dL, women undergo a three-hour, 100-gram oral glucose tolerance test (OGTT). GDM is diagnosed based on the Carpenter-Coustan criteria (at least two out of four plasma glucose values must be elevated: fasting glucose ≥ 95 mg/dL, 1-hour glucose ≥ 180 mg/dL, 2-hour glucose ≥ 155 mg/dL, and 3-hour glucose ≥ 140 mg/dL).[10, 11] If a subject has a fasting blood glucose of ≥ 120 mg/dL, a 100-g glucose load is not administered and a

diagnosis of GDM is made. If a glucose challenge test result is ≥ 200 mg/dL, no further testing is indicated and the subject is treated as GDM. Subjects with a history of pregestational diabetes were excluded from the cohort. All subjects were followed and managed under the supervision of Maternal-Fetal Medicine specialists.

At our institution, all patients diagnosed with gestational diabetes receive individualized dietary counseling and diabetic education. Patients are educated on daily monitoring of fasting and 2-hour post-prandial finger stick blood sugars with the use of a memory-based glucometer, and recording of such values in a daily logbook. These logbooks are then reviewed at each clinic visit by clinical staff. Per protocol, hypoglycemic medications are initiated when ≥ 50% of finger stick blood sugars are elevated from target values of <95 mg/dL fasting and <120 mg/dL at two hours postprandial. If started on glyburide, patients are instructed to take their medication thirty minutes prior to expected mealtime.

Subjects who received glyburide were classified by initial dose: 2.5mg daily versus 5mg daily. The 5 mg/day group included women on 5 mg once daily and women receiving 2.5 mg twice daily, for a total daily dose of 5 mg. Dose escalations are implemented as necessary every 1-2 weeks depending on the finger stick pattern blood sugars, up to a total of 20 mg of glyburide daily, divided in twice-daily 10 mg dosing. Subjects were excluded from the cohort if they had major maternal medical comorbidities other than chronic hypertension (systemic lupus erythematosus, renal disease, cardiac disease, pregestational diabetes, and cystic fibrosis), fetal anomalies, late entry to prenatal care, no ultrasound <26 weeks gestation, no documentation of GDM testing, or did not receive glyburide. Of note, initial dosing of glyburide is at the discretion of the attending physician, depending on the patient's observed blood sugar pattern and clinical history.

The primary maternal outcome was maternal hypoglycemic events, defined by a finger stick blood sugar <60 mg/dL on any of the daily pattern blood sugar values. Secondary maternal outcomes included time to blood glucose control (<50% of blood sugars above fasting and post-prandial goals), final glyburide dose, preeclampsia (as documented in the medical record and defined by new onset of ≥140 mmHg systolic or ≥90 mmHg diastolic blood pressure and new-onset proteinuria of ≥300 mg per 24-hour urine collection or protein/creatinine ratio >0.3), and cesarean delivery.[12] The primary neonatal outcome was birth weight; secondary neonatal outcomes included macrosomia (>4000g), hypoglycemia (≤40 mg/dL in the first 48 hours after birth), preterm birth, shoulder dystocia (as determined by the providers at delivery and recorded in the delivery record), large for gestational age (LGA), and small for gestational age (SGA).

Groups were compared using chi-squared or Fisher's exact tests for categorical variables, and Student's t-test or Mann-Whitney U test for continuous variables, as appropriate. Logistic regression was used to refine point estimates while adjusting for confounding variables. Confounding factors were based on historical confounding factors and results of univariate analyses, and included maternal age, race, prior vaginal delivery, gestational age at diagnosis, gestational weight gain, blood sugar values at the time of the 3 hour glucose tolerance test (GTT), chronic hypertension, prior preterm birth, and maternal obesity (BMI ≥ 30 kg/m^2). Factors were removed in a backward stepwise fashion, based on significant

changes (10%) in the exposure adjusted odds ratio or significant differences between hierarchical models using the likelihood ratio test. All statistical analyses were performed using Stata SE, version 13 (College Station, Texas).

Results

Of 1,302 women with a diagnosis of GDM in our obstetric database, 895 were included in the analysis (61 subjects were excluded for late prenatal care, 235 for no documentation of GDM testing, 82 for maternal medical illness, and 29 for congenital malformations). Of these 895 subjects, 339 were started on glyburide. An additional 2 subjects were further excluded for glyburide starting dose not recorded, and 13 were excluded for a glyburide starting dose of 10 mg/day. The remaining 324 subjects were divided between initial dosages: 170 (52.5%) were started on 2.5 mg/day and 154 (47.5%) on 5 mg/day. The baseline characteristics of the cohort are shown in Table 1. Women started on 5 mg/day had a slightly higher pre-pregnancy BMI, and higher fasting glucose level at the time of diagnosis compared to the 2.5 mg/day group; gestational age at delivery and total weight gain in pregnancy were not significantly different between groups. We defined failure of glyburide therapy as requiring insulin initiation at any time during a subject's antepartum course.

The number of women who experienced hypoglycemia antenatally was not significantly different between the groups (27% in the 5 mg/day group vs 26% in the 2.5 mg/day group, AOR 0.67 (0.30-1.49)). Moreover, patients started on 5 mg/day of glyburide who developed hypoglycemia did not have a higher number of hypoglycemic episodes (median 2 versus 1 episode, p=0.84). Women started on higher doses of glyburide did not achieve blood sugar control in a shorter time period (median 14 versus 13 days, p=0.36). Women started on the higher dose of glyburide had a higher ending dose of glyburide (10 vs 5 mg/day, p<0.01). The risk of cesarean delivery and preeclampsia were not significantly different between groups (Table 2).

No statistically significant difference was found in birth weight (p=0.37). A nominal increase in macrosomia in the 5 mg/day group was not statistically significant after adjusting for maternal obesity (AOR 2.17, 95% CI 0.96-4.88). An increase in preterm birth in the 5 mg/day group was also not statistically significant after adjusting for prior preterm delivery. The incidence of large for gestational age infants was not significant after adjusting for maternal obesity and fasting glucose on GTT. Other secondary neonatal outcomes, including shoulder dystocia and neonatal hypoglycemia, were not significantly different between groups (Table 3).

Comment

Evidence-based guidelines for selecting a starting dose of glyburide in the management of women with GDM are limited. We hypothesized that maternal and neonatal outcomes of interest correlate with the degree of antenatal glucose control; this, in turn, is dependent on adequate pharmacologic management of GDM once diet therapy alone fails. Starting at a lower medication dose may decrease the incidence of maternal hypoglycemia, while

increasing the time to blood glucose control, possibly leading to worse pregnancy outcomes. In this cohort of selected patients, we found no significant differences in maternal or neonatal outcomes between the 2.5 mg/day and 5 mg/day starting dose, a finding which may be at least partially due to baseline differences in groups, such as an increased prevalence of higher body mass index and higher fasting glucose on GTT in women started at higher doses of glyburide. Of note, both groups required dose increases and had a time to glucose control of 2 weeks, suggesting that perhaps neither group was initiated on a sufficient glyburide dose.

Langer et all have previously compared outcomes of glyburide (2.5 mg/day starting dose) versus insulin for the management of gestational diabetes.[13] Based on their findings, glycemic control and neonatal adverse events, including macrosomia, respiratory distress syndrome, transient tachypnea of the newborn, and neonatal hypoglycemia, were similar between groups. The majority of their patients were controlled with 10 mg/day of glyburide or less, with higher doses of glyburide being associated with poor glycemic control. However, this study did not provide information about the optimal starting dose of glyburide, as their starting dose was standardized across patients. We are not aware of any report that compares starting doses.

One of the most commonly cited side effects of glyburide is its association with maternal hypoglycemic events. The American Diabetes Association defined hypoglycemia in 2005 as a blood glucose <70 mg/dL; this definition is based on studies of glycemia in non-pregnant diabetic patients and does not consider physiologic changes of pregnancy.[14] Hernandez et al have previously reported that our current targets of normoglycemia may warrant significant reassessment in the context of pregnancy.[15] Indeed, overall lower blood sugars may be the norm in pregnancy, and values as low as 50-60 mg/dL may not be clinically significant. In our study, up to 27% of our cohort had at least one episode of hypoglycemia at some point in their antenatal finger stick blood glucose monitoring, as defined at our institution by any daily finger stick blood glucose <60 mg/dL; however, the number of hypoglycemic episodes in those having an event was low and not significantly different between the two groups (1 event in the 2.5 mg/day group versus 2 events in the 5 mg/day group, p=0.84). These findings are similar to previous literature reported by Brustman et al that demonstrated a 33% incidence of at least one episode of hypoglycemia in glyburide-treated patients.[16] In that study, incremental increases in glyburide dosing did not raise the incidence of maternal hypoglycemic episodes in pregnancy. Our study goes further by showing no statistically significant difference in maternal hypoglycemic events between the 2.5 mg/day and 5 mg/day starting dose of glyburide.

The main strength of our study is in the detailed clinical information obtained regarding maternal and neonatal outcomes, including weekly maternal finger stick blood glucose logs. All diagnoses of GDM were confirmed, based on our institution's diagnostic protocol. In our analysis, we evaluated starting dose of glyburide, gestational age at initiation of glyburide, maximum dose of glyburide, and reported pattern blood glucose values by week. This allowed for calculation of time to blood glucose control, one of the main factors assessed by our data. Additionally, we had over 300 subjects receiving glyburide in our cohort, enabling

us to examine less frequent neonatal outcomes and their associations with initial glyburide dose.

No study is without limitations. The two exposure groups in our cohort were significantly different with regards to fasting GTT test results and obesity. These undoubtedly influenced the providers' clinical judgment regarding starting dose of glyburide. Although we attempted to adjust for these confounding factors using logistic regression, unmeasured differences in the cohort may remain. Moreover, due to the nature of our study design, we were unable to obtain information on whether reported episodes of maternal hypoglycemia caused symptoms and were therefore clinically significant, limiting our assessment of the primary outcome.

We also acknowledge that power may be limited to fully delineate the relationship between starting dose of glyburide and outcomes. We feel, however, that we had the power to detect clinically significant differences in the majority of our outcomes. A post-hoc power analysis assuming a Type 1 error of 0.05 demonstrated >90% power to detect a two-fold increase in cesarean delivery rates, preeclampsia, and LGA infants; it also demonstrated >85% power to detect a two-fold increase in maternal hypoglycemic events and macrosomia. There was limited power to detect a difference in outcomes with <10% incidence.

While a higher starting dose of glyburide in selected patients is not associated with increased maternal hypoglycemia, it was also not associated with improved neonatal outcomes; this may be due to the maternal characteristics associated with a higher starting dose regimen. As patients started on higher regimens of glyburide tended to have higher fasting glucose values, more chronic hypertension, and higher BMI, we would have expected worsened outcomes in this group. These findings suggest that, until more dosage data on glyburide use during pregnancy is available, starting doses of 2.5-5 mg/day are similarly acceptable alternatives for clinical use. More studies, including randomized controlled trials on starting dosage, pharmacokinetics, and pharmacodynamics of glyburide, are essential to assess adequate start doses of glyburide, incidence of side effects, and pregnancy outcomes.

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Table 1

Characteristics of the study cohort

Characteristic	2.5mg Qday Starting Dose (n=170)	5mg Qday Starting Dose (n=154)	p
Age (yrs)	28.9 ± 6.1	29.3 ± 5.9	0.52
Race or ethnic group			0.22
White	18 (11.1)	27 (18.9)	
Black	93 (57.4)	81 (56.6)	
Hispanic	49 (30.3)	35 (24.5)	
Other	2 (1.3)	0 (0.0)	
Nulliparous	47 (27.7)	44 (28.6)	0.85
Public Insurance	139 (86.3)	117 (81.8)	0.28
Smoking	28 (16.5)	33 (21.4)	0.25
Chronic hypertension	23 (13.5)	27 (17.5)	0.40
GDM in prior pregnancy	31 (18.2)	27 (17.5)	0.87
Neonatal macrosomia in prior pregnancy	23 (13.5)	21 (13.6)	0.98
Pre-pregnancy BMI (kg/m^2)	34.5 ± 8.1	36.5 ± 9.3	0.04
Obese (≥30.0)	116 (69.9)	120 (79.5)	0.05
Gestational age at diagnosis of GDM	25.8 ± 4.1	25.7 ± 4.7	0.87
50-g Glucose Challenge Test (screening test), 1 hr value (mg/dL)	187 ± 32	194 ± 38	0.08
3 hr oral GTT (diagnostic test) (mg/dL)			
Fasting	107 ± 15	116 ± 24	<0.01
1 hour	203 ± 29	205 ± 32	0.76
2 hour	177 ± 28	185 ± 29	0.07
3 hour	138 ± 33	131 ± 31	0.24
Gestational age at glyburide initiation	31.3 ± 7.5	30.8 ± 6.0	0.51
Highest fasting blood sugar upon starting glyburide	121 ± 21	126 ± 25	0.24
Failed glyburide	4 (3.1)	5 (4.0)	0.67
Gestational age at delivery	38.2 ± 2.0	37.8 ± 2.8	0.08
Total gestational weight gain (kg)	13.3 ± 10.3	13.4 ± 10.3	0.87
Gestational Weight Gain Less than IOM Recommendations	31 (18.7%)	31 (20.5%)	0.12
Within IOL Recommendations	38 (22.9%)	21 (13.9%)	
More than IOL Recommendations	97 (58.4%)	99 (65.6%)	

BMI, body mass index; GTT, glucose tolerance test; GDM, gestational diabetes mellitus Data are mean +/− standard deviation or n (%), unless otherwise specified

Table 2
Maternal Outcomes by Starting Dose of Glyburide

	2.5mg/Day (n=170)	5mg/Day (n=154)	p	Adjusted Odds Ratio (AOR)
Hypoglycemic events (yes/no)	26 (15.3)	27 (17.5)	0.59	0.67 (0.30-1.49) *
Number of hypoglycemic episodes in those having an event	1 (1-3)	2 (1-3)	0.84	-
Time to blood glucose control (days)	13 (7-21)	14 (7-22)	0.36	-
Maximum glyburide dose (mg)	5 (2.5-10)	10 (5-12.5)	<0.01	-
Preeclampsia	34 (20.0)	40 (26.0)	0.20	1.24 (0.59-2.61) *
Cesarean delivery	81 (47.7)	69 (44.8)	0.26	0.85 (0.45-1.63) †
Primary Cesarean	33 (27.1)	35 (29.2)	0.71	1.07 (0.48-2.36) †
Required insulin	6 (3.6)	10 (7.2)	0.16	-
Percentage of prenatal visits with glycemic control	71.4 (37.5-100)	61.5 (28.6-90.0)	0.16	-

Data are median (interquartile range), or n (%), unless otherwise specified

* Adjusted for maternal obesity, hypertension, and fasting blood sugar >95 mg/dL on GTT

† Adjusted for maternal obesity, fasting blood sugar>95, and prior vaginal delivery

Table 3
Neonatal Outcomes and Starting Dose of Glyburide

	2.5mg/Day Glyburide Starting Dose (n=170)	5mg Glyburide/day Starting Dose (n=154)	p	Adjusted Odds Ratio (AOR)*
Birth weight (g)	3423 ±701	3499 ± 803	0.37	-
Macrosomia (>4000 g)	26 (15.3)	40 (26.0)	0.02	2.16 (0.96-4.88)†
Preterm birth (<37 weeks)	23 (13.5)	34 (22.1)	0.04	1.75 (0.96-3.16)*
Shoulder dystocia	7 (4.1)	3 (2.0)	0.26	-
Neonatal hypoglycemia	31 (18.9)	41 (27.7)	0.07	1.33 (0.66-2.70)‡
LGA	34 (20.0)	45 (29.2)	0.05	1.76 (0.85-3.64)†
SGA	10 (5.9)	4 (2.6)	0.15	0.66 (0.16-2.82)†

Data are mean +/− standard deviation or n (%), unless otherwise specified

*Adjusted for prior preterm delivery

†Adjusted for maternal obesity, fasting on GTT >95

‡Adjusted for maternal obesity, fasting on GTT>95, last blood sugar prior to delivery, and gestational age at delivery