Glyburide for the Treatment of Gestational Diabetes

A critical appraisal

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It has been over 4 years since a randomized controlled trial was published demonstrating clinical equivalency of glyburide and insulin for management of gestational diabetes mellitus (GDM), yet major specialty bodies continue to advocate caution in adopting oral agents as an acceptable modality for management of GDM. To quote recent policy statements by the American Diabetes Association and the American College of Obstetricians and Gynecologists, "Oral glucose-lowering agents have generally not been recommended during pregnancy. . . glyburide is not FDA approved for the treatment of GDM and further studies are needed in a larger patient population to establish its safety" (1).

"At this time, no other oral agent has been shown to be safe and effective in GDM, and this study has not been confirmed. Further study is recommended before the use of newer oral hypoglycemic agents can be supported for use in pregnancy" (2).

The aim of this review is to critically evaluate existing evidence regarding use of glyburide in GDM management accumulating since the publication of the randomized controlled trial by Langer et al. (3).

RANDOMIZED CONTROLLED TRIAL OF GLYBURIDE AND INSULIN

Despite significant concerns regarding teratogenicity (4) and severe neonatal hypoglycemia associated with the use of oral hypoglycemic drugs during pregnancy, especially sulfonylureas (5), Elliott et al. (6) demonstrated that minimal glyburide was detectable crossing the placenta in an in vitro perfusion model, whereas considerable transplacental drug transfer had been documented in earlier sulfonylurea agents (7,8).

Based on these observations, Langer et al. randomized 404 women with GDM to glyburide or insulin treatment. Study eligibility was limited to women with GDM who had fasting plasma glucose concentrations between 95 and 140 mg/dl and were at 11–33 weeks of gestation. Women with fasting plasma glucose concentrations of <95 mg/dl were initially treated with diet but were subsequently enrolled if their glucose concentrations exceeded 95 mg/dl fasting or 120 mg/dl postprandially.

Women assigned to receive insulin were given 0.7 units/kg subcutaneously three times daily, and these doses were modified weekly as necessary. The starting glyburide dose was 2.5 mg orally in the morning and escalated weekly to 5 mg and then 5 mg twice daily. The twice-daily glyburide regimens were escalated to a total of 20 mg to achieve glycemic control. The blood glucose targets for both groups were fasting <90 mg/dl and 2-h postprandial <120 mg/dl. If the blood glucose values of a woman treated with the maximal dose of glyburide did not meet the goals for a 2-week period, her treatment was switched to insulin.

On admission to the trial, there were no significant differences between the two groups in key risk variables including age, BMI, medical history, duration of metabolic treatment, or glucose tolerance test results. At the conclusion of the trial, there were no significant differences in mean maternal glucose concentrations, the percentage of large-for-gestational-age (LGA) infants, macrosomia, neonatal intensive care unit (NICU) admission, or fetal anomalies. Glyburide was not detected in the cord serum of any infant. Only 4% of the glyburide group required insulin therapy. However, only 82% of the glyburide and 88% of the insulin-treated patients achieved the target level of glycemic control, representing a glyburide "failure rate" of 18%. With regard to glyburide dosing during the trial, 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 glyburide dose was 9.2 mg. Of the maternal outcome variables assessed, none were significantly different between groups except the dramatic ($P = 0.03$) reduction in maternal hypoglycemic episodes in the glyburide-treated group (2%) compared with the 20% rate for insulin.

STATISTICAL POWER OF THE GLYBURIDE RANDOMIZED CONTROLLED TRIAL FINDINGS

Despite the demonstration of statistical equivalency of glyburide and insulin for management of GDM, much remains to ponder about the results of this imaginative and groundbreaking trial. How can we be sure that a type 2 statistical error, arising from an undersized study population, did not occur? Unfortunately, a power analysis to gauge study size for key variables of interest is not available for this randomized controlled trial. Considering the nonsignificantly decreased mean fasting plasma glucose in the glyburide group (104 ± 25 mg/dl) compared with that in the insulin group (108 ± 26 mg/dl), this difference would have been statistically significant

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Abbreviations: GDM, gestational diabetes mellitus; LGA, large-for-gestational-age; NICU, neonatal intensive care unit.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Selected neonatal outcome variables*

	Glyburide	Insulin	Difference	Percent difference	Required number per group
LGA	24 (12%)	26 (13%)	−1%	−8%	17,277
Birth weight	3,256 ± 543	3,194 ± 598	62	−2%	1,281
Ponderal index >2.85	18 (9%)	24 (12%)	−3%	−25%	1,646
Birth weight >4 kg	14 (7%)	9 (4%)	3%	75%	909
Intravenous glucose	28 (14%)	22 (11%)	3%	27%	1,916
Hypoglycemia	18 (9%)	12 (6%)	3%	50%	1,214
Hyperbilirubinemia	12 (6%)	8 (4%)	2%	50%	1,317

Adapted from Langer et al. (3).

with an approximate doubling in study size to 450 subjects per group.

Table 1 summarizes certain other neonatal outcomes observed in this trial, all of which were statistically nonsignificant. When the relatively small differences for these outcomes are expressed as a percent change, potentially important findings emerge. For example, the increases among glyburide-treated subjects in neonatal hypoglycemia, the need for intravenous glucose infusion, and neonatal hyperbilirubinemia range from 27 to 50% above the rates observed in insulin-treated women. There was a relatively small reduction in mean birth weight (2%) in the glyburide arm, but the 8% reduction in LGA infants and a 25% reduction in obese newborns (ponderal index >2.85) with glyburide could represent opportunity for impressive clinical improvement. All of these differences would have been statistically significant had 1,500–2,000 subjects, rather than ~200, been enrolled in each study arm during the trial.

In a reanalysis of the 2000 randomized controlled trial, Langer et al. (9) subsequently addressed the issues of glyburide dose, GDM severity, and pregnancy outcome. Patients were grouped into low (≤10 mg) and high (>10 mg) daily glyburide dose groups and low (≤95 mg/dl) or high (>95 mg/dl) GDM severity groups based on fasting glucose tolerance test values. The rate of macrosomia was 16 vs. 5% and LGA 22 vs. 8% ($P = 0.01$), respectively, in the high and low glyburide dose groups. Stratification by disease severity (using the level of fasting glucose on glucose tolerance test) revealed equally lower rates of LGA for both the glyburide- and insulin-treated subjects in the low-severity group. In the higher-severity group, the rates of macrosomia and LGA were also similar in the glyburide and insulin arms, but the rates of neonatal obesity (ponderal index >2.85) and neonatal metabolic complications were almost 50% higher in the glyburide group (NS). If the study size had been expanded to 400 per treatment arm, these differences might have been significant.

Based on these findings, the authors suggested that achieving an excellent level of glycemic control, rather than the mode of pharmacological therapy, is the key to improving the outcome in GDM. However, if statistically significant differences in neonatal morbidities had been reported from a larger randomized controlled trial, would glyburide be considered a viable treatment for GDM or a hazardous alternative?

MORE RECENT CASE-CONTROL AND COHORT STUDIES USING GLYBURIDE

— At present, there is a growing acceptance of glyburide use as a primary therapy for GDM (10). Although no new randomized trials have subsequently been completed since the randomized controlled trial of Langer et al. (3) in 2000, five retrospective reports of glyburide treatment for GDM have been published comprising 504 glyburide-treated patients.

Jacobson et al. (11) performed a retrospective cohort comparison of glyburide and insulin treatment of GDM. Patients with fasting plasma glucose >140 mg/dl on glucose tolerance testing were excluded. The insulin group ($n = 268$) consisted of those diagnosed in 1999 through 2000, and the glyburide group ($n = 236$) was diagnosed in 2001 through 2002. Glyburide dosing began with 2.5 mg in the morning and increased by 2.5–5.0 mg weekly. If the dose exceeded 10 mg daily, twice-daily dosing was considered. If glycemic goals were not met on a maximum daily dose of 20 mg, patients were changed to insulin.

Because of the retrospective nature of the study, there were small differences in a few of the pretreatment variables in the insulin group, including a 4% higher mean BMI (31.9 vs. 30.6 kg/m^2, $P = 0.04$) and a 4% higher fasting glucose on glucose tolerance test (105.4 ± 12.9 vs. 102.4 ± 14.2 mg/dl), but the remaining maternal demographics were comparable. The insulin group consisted of 268 subjects, and 236 were in the glyburide group.

With regard to outcomes, this study size was insufficient to detect less than a doubling of the rate of macrosomia/LGA and a 44% increase in neonatal hypoglycemia. Given the cases available in this study, there were no statistically significant differences in gestational age at delivery, mode of delivery, birth weight, LGA, or percent macrosomia. No significant differences were noted in neonatal hypoglycemia and phototherapy, although the differences in these variables were consistently higher in the glyburide group, ranging from 4 to 15%. These dif-

Table 2—*Selected neonatal outcome variables*

	Insulin (%)	Glyburide (%)	*P*
Birth weight (g)	3,599 ± 650	3,661 ± 629	0.28
LGA number (%)	63 (24)	60 (25)	0.62
Macrosomic number (%)	64 (24)	60 (25)	0.69

Adapted from Jacobson et al. (11).

Table 3—*Selected maternal outcome variables*

	Insulin	Glyburide	*P*
Fasting glucose (mg/dl)	97 ± 12	90 ± 12	0.001
1-h postprandial glucose (mg/dl)	137 ± 23	131 ± 23	0.001
2-h postprandial glucose (mg/dl)	118 ± 19	117 ± 23	0.05
Maternal hypoglycemia <60 mg/dl (%)	0.08%	0.20%	0.001
Percent glucose within goal	63%	86%	0.001

Adapted from Jacobson et al. (11).

ferences were too small to be statistically significant given the numbers of subjects in this study (Table 2). The rate of preeclampsia doubled in the glyburide group (12 vs. 6%, $P = 0.02$). Women in the glyburide group also had significantly lower post-treatment fasting and postprandial blood glucose levels (Table 3). The glyburide group was also superior in achieving target glycemic levels (86 vs. 63%, $P < 0.001$). The failure rate (transfer to insulin) was 12%. It should be noted that there was a nonsignificant trend to increased rates of hypoglycemia and hyperbilirubinemia in newborns of glyburide-treated subjects. In summary, this study was too small to convincingly demonstrate clinical equivalency between glyburide and insulin in terms of neonatal outcome but provided significant evidence that glyburide can be used to improve maternal glycemic control when compared with insulin.

Conway et al. (12) reported a retrospective cohort of 75 glyburide-treated GDM patients. Target glucose values were ≤95 mg/dl for fasting and 2-h postprandial values ≤115 mg/dl. Patients were initially started at a dose of 2.5 mg/day, given in the morning and escalated according to the protocol used in the randomized controlled trial of Langer et al. Good glycemic control was achieved by 84% of the subjects with glyburide, and 16% were switched to insulin. The gestational age at start of therapy was lower (23.3 ± 7.0 vs. 28.7 ± 5.4 weeks; $P = 0.03$), and the overall mean glucose level was higher (113.9 ± 10.0 vs. 108.0 ± 5.7 mg/dl; $P = 0.01$) in the women who were switched to insulin. The rate of fetal macrosomia was similar between women successfully treated with glyburide and those who converted to insulin (11.1 vs. 8.3%; $P = 1.0$), and mean birth weight was also similar (3,327 ± 634 vs. 3,267 ± 815 g; $P = 0.78$). A higher proportion of infants born to women in whom glyburide had failed required intravenous glucose infusions in the nursery, owing to hypoglycemia (25.0 vs. 12.7%; $P = 0.37$).

Kremer and Duff (13) reported the outcomes of a cohort of 73 women with GDM treated with glyburide. Of these, 81% had acceptable glucose control on medical therapy and 19% were transferred to insulin. Approximately one-third required a dose of 2.5 mg daily, and half were successfully managed at ≤5 mg. The rates of NICU admission and neonatal morbidities were not reported.

Chmait et al. (14) managed a cohort of 69 women with GDM with glyburide. Patients were transferred to insulin therapy if they reached a maximum dose of 20 mg/day and were not yet in adequate control. The glyburide failure rate was 19%. Gestational age at glyburide initiation ($P < 0.01$), pretreatment fasting blood glucose levels ($P < 0.001$), and 1-h postprandial values ($P < 0.001$) were significant factors predicting glyburide failure (sensitivity 98%, specificity 65%). Neonatal morbidity was not reported.

Fines et al. (15) reported a case-control study of glyburide and insulin treatment with 51 patients in the glyburide group and 32 in the insulin (control) group. There was no difference in maternal age, gravidity, parity, gestational age at delivery, birth weight, or NICU admissions between the two groups. Five neonates in the glyburide group had a birth weight >4,000 g, compared with nine (9) in the insulin group ($P = 0.2$). However, ponderal index, a measure of infant adiposity, was found to be significantly lower in the glyburide group (2.5 ± 0.29 vs. 2.8 ± 0.33; $P = 0.003$). Tighter glycemic control was achieved in the glyburide group when compared with the insulin group (mean daily average plasma glucose levels were 115.4 ± 10.1 and 128.0 ± 18.6 in the glyburide and insulin group, respectively; $P = 0.008$). Indeed, all glucose values obtained (fasting morning; postprandial breakfast, lunch, and dinner) were ~12 mg/dl lower in the glyburide versus the insulin patients ($P < 0.05$). The rates of NICU admission were similar (16% in both groups), and the rates of neonatal hypoglycemia were not reported.

SUMMARY OF COHORT STUDIES

— Three themes emerge from the five cohort studies published since 2000: *1*) the rate of glyburide failure is ~20% in most clinical populations, and failure is significantly more likely in patients with fasting glucose levels >115 mg/dl; *2*) the rate of neonatal hypoglycemia/hyperbilirubinemia is possibly increased with the use of glyburide compared with insulin; and *3*) mean maternal fasting and postprandial glucose values appear to be lower with glyburide treatment.

Going forward, several issues regarding use of glyburide in management of GDM remain to be considered: *1*) the need for larger randomized controlled trials with adequate power to evaluate the possible reduction in neonatal obesity that would be expected to be associated with improved glycemic control observed with glyburide treatment in three studies; *2*) an adequately powered randomized controlled trial to clarify the possibility of increased neonatal metabolic abnormalities with glyburide treatment; and *3*) clinical studies to determine the optimum dosing regimen for glyburide.

GLYBURIDE PHARMACOKINETICS

— Glyburide dosing dogma, evolved over the past 40 years, is to use the agent once daily, with twice-daily doses reserved for refractory cases. These recommendations, as captioned in the *Physicians' Desk Reference*, are based largely on animal and a few human studies of nonpregnant subjects. More recent studies of glyburide pharmacodynamics, albeit also performed in nonpregnant subjects, suggest that the Food and Drug Administration–recommended dosing protocols may not necessarily be optimal in pregnancy. During development of the drug in the late 1960s, single-dose studies in nondiabetic subjects demonstrated glyburide absorption within 1 h, peak levels at ~4 h, and low but detectable levels at 24 h. The decrease of glyburide in the serum yielded a terminal half-life of ~10 h, so the glucose-lowering effect could be expected to persist for 24 h after a single morning dose.

However, more recent data have shown that glyburide peaks earlier in the serum and has a significantly shorter half-life than previously believed. This is partly because glyburide has two major hydroxyl metabolites, both of which are

biologically active and excreted equally in the bile and urine. Although advice in the *Physicians' Desk Reference* indicates that the glyburide metabolites provide no significant contribution to glyburide's hypoglycemic action (1/400th and 1/40th, respectively, of glyburide potency), it should be remembered that these data were obtained in rabbits.

Yin et al. (16) studied the glucose and insulin responses to glyburide in a group of nonpregnant nondiabetic subjects with three cytochrome p450 gene variants. Patients with p450 gene polymorphisms might have potentially differing rates of glyburide metabolism. After a 5-mg oral dose, serum glyburide levels peaked at 2.75 h in all three groups. However, peak glyburide concentrations were 72% higher in the *CYP2C9*1/*3* subjects compared with *CYP2C9*1/*1* subjects, with a corresponding near doubling of glyburide elimination half-life from 2.09 to 3.58 h. Similarly, the mean reductions in blood glucose after glyburide dosing were 17.9% ($P < 0.012$) greater in the *CYP2C9*1/*3* subjects compared with the *CYP2C9*1/*1* subjects. Levels of active glyburide metabolites were not investigated. However, this study demonstrates that an oral glyburide dose peaks at 2.75 h and lowers serum glucose in a dose-dependent manner. And the half-life of glyburide in the circulation, which ranges from 2 to 4 h, is considerably less than the quoted drug half-life of 10 h.

Rydberg et al. (17) studied the relationship between serum concentrations of glyburide and its two main metabolites in a placebo-controlled randomized single-blind crossover study in eight nonpregnant subjects. Glyburide and its active metabolites, 4-*trans*-hydroxyglyburide (M1) and 3-*cis*-hydroxyglyburide (M2), were given intravenously and orally (3.5 mg dose). A 20% reduction in glucose level was achieved when oral glyburide reached a serum concentration of 87 ng/ml, whereas metabolite 4-*trans*-hydroxy-glyburide required only 19 ng/ml and 3-*cis*-hydroxy-glyburide required 42 ng/ml to achieve the same effect. There was also a high degree of variability among subjects. Thus, considering glyburide's active metabolites, these appear to have significant hypoglycemic function in humans, resulting in a prolongation of glyburide's hypoglycemic effect.

To clarify the potential difference in drug action when given as a single dose, or chronically over weeks, Jaber et al. (18) studied glyburide pharmacodynamics during multiple-dose administration. A significant prolongation in the elimination half-life ($t_{1/2}$: week 0, 4.0 ± 1.9 h; week 6, 13.7 ± 10.5 h; and week 12, 12.1 ± 8.2 h) was observed during chronic dosing. These results suggest possible drug accumulation or tissue sensitization by glyburide. This study further demonstrates that significant differences in glyburide pharmacokinetics exist between single-dose and steady-state conditions.

Glyburide and other sulfonylurea hypoglycemic drugs have been associated with severe hypoglycemia in nonpregnant subjects. Yogev et al. (19) examined the prevalence of undiagnosed asymptomatic hypoglycemic events in diabetic patients using a continuous glucose monitoring system for 72 consecutive hours. The device recorded 288 measurements per day, and hypoglycemic episodes were defined as >30 consecutive minutes of glucose value below 50 mg/dl. Asymptomatic hypoglycemic events were recorded in 63% of insulin-treated patients, in 28% of glyburide-treated patients, and none of the nondiabetic subjects. The mean hypoglycemic episodes per day was significantly higher in insulin-treated patients (4.2 ± 2.1) than in glyburide-treated patients (2.1 ± 1.1) ($P = 0.03$). In insulin-treated patients, the majority of the hypoglycemic events were nocturnal (84%), whereas in glyburide-treated patients, episodes were equally by day and night.

GLYBURIDE AND OTHER ORAL AGENTS: FUTURE DIRECTIONS

What do these studies suggest about glyburide dosing during pregnancy to optimize fetal outcome? First, pharmacodynamic studies with glyburide should be performed in pregnant women, especially after chronic administration to clarify the differences in drug action during pregnancy. Second, until these pharmacodynamic studies are performed, modification of glyburide dosing protocols can reasonably be made to accommodate more recent evidence. For example, since peak action of glyburide is between 2 and 4 h after dosing, and given that the peak in glucose after feeding in GDM occurs at 90 min (20), glyburide should be administered at least 1 h before a meal to optimally control postprandial glucose excursions. Third, since more recent studies of glyburide clearance indicate that the half-life in nonpregnant subjects is 2–4 h, not 10 h, glyburide can be given more frequently than twice daily. Also, since these studies indicate that active metabolites have a major role in sustaining glyburide's hypoglycemic action, administration of glyburide at bedtime can be effective in controlling fasting glucose values.

SUMMARY

The clinical experience with glyburide treatment of GDM has moved ahead of the science. A single randomized controlled trial of glyburide versus insulin indicates that glyburide treatment can provide a relatively safe alternative to insulin therapy. Subsequent retrospective trials have shown that up to 20% of GDM patients, especially those with substantial pretreatment hyperglycemia, are likely to require adjunctive or alternative therapy with insulin. These follow-on trials have also demonstrated that glyburide treatment, compared with insulin, actually results in lower mean glucose values and a higher percentage of "excellent glycemic control" with fewer hypoglycemic episodes. With the emerging view that glyburide treatment compared with insulin improves glycemic profiles, it should be expected to reduce the frequency of newborn obesity. Larger randomized controlled trials are necessary to clarify this question and the concerns regarding neonatal metabolic morbidity in glyburide-treated offspring.

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