Glyburide Versus Metformin and Their Combination for the Treatment of Gestational Diabetes Mellitus: A Randomized Controlled Study

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OBJECTIVE

To compare the efficacy and safety of glyburide versus metformin and their combination for the treatment of gestational diabetes mellitus (GDM).

RESEARCH DESIGN AND METHODS

In this prospective randomized controlled study, we randomly assigned patients with GDM at 13–33 weeks gestation and whose blood glucose was poorly controlled by diet to receive either glyburide or metformin. If optimal glycemic control was not achieved, the other drug was added. If adverse effects occurred, the drug was replaced. If both failed, insulin was given. The primary outcomes were the rate of treatment failure and glycemic control after the first-line medication according to mean daily glucose charts.

RESULTS

Glyburide was started in 53 patients and metformin in 51. In the glyburide group, the drug failed in 18 (34%) patients due to adverse effects (hypoglycemia) in 6 (11%) and lack of glycemic control in 12 (23%). In the metformin group, the drug failed in 15 (29%) patients, due to adverse effects (gastrointestinal) in 1 (2%) and lack of glycemic control in 14 (28%). Treatment success after second-line therapy was higher in the metformin group than in the glyburide group (13 of 15 [87%] vs. 9 of 18 [50%], respectively; $P = 0.03$). In the glyburide group, nine (17%) patients were eventually treated with insulin compared with two (4%) in the metformin group ($P = 0.03$). The combination of the drugs reduced the need for insulin from 33 (32%) to 11 (11%) patients ($P = 0.0002$). Mean daily blood glucose and other obstetrical and neonatal outcomes were comparable between groups, including macrosomia, neonatal hypoglycemia, and electrolyte imbalance.

CONCLUSIONS

Glyburide and metformin are comparable oral treatments for GDM regarding glucose control and adverse effects. Their combination demonstrates a high efficacy rate with a significantly reduced need for insulin, with a possible advantage for metformin over glyburide as first-line therapy.

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Oral hypoglycemic agents for treating gestational diabetes mellitus (GDM) have gained popularity since the studies of Langer et al. (1) and Rowan et al. (2), which demonstrated glyburide (glibenclamide) and metformin to be good alternatives for insulin. Oral hypoglycemic agents are an attractive option to insulin because of their lower cost and ease of administration, which increase patient compliance (3). On the basis of a meta-analysis comparing glyburide and metformin with insulin that found similar efficacy and safety for both mothers and neonates (4), oral hypoglycemic agents are now acceptable medications to treat GDM in official guidelines (5–7); glyburide became the most common first-line medication for GDM in the U.S. (8).

Although treatment with oral hypoglycemic agents seems promising, several concerns still need to be resolved. First, although the success rate in a pioneer study was 96% for patients not requiring insulin (1), later studies have not demonstrated the same efficacy, with 20–25% and 45% of the patients taking glyburide and metformin, respectively, requiring second-line therapy with insulin because of poor glycemic control or adverse effects (2,9). Second, studies comparing the efficacy and safety of glyburide versus metformin have conflicting results regarding the best medication to use as a first-line therapy (10–12). Finally, in studies evaluating oral hypoglycemic medications for GDM, in case of a treatment failure, the second-line treatment was always insulin (1–3,8–14).

To our knowledge, use of additional oral medication in the case of poor glycemic control with a single agent or switching to another oral medication in case of adverse effects with the first-line medication has not been explored. Therefore, the current study aimed to compare the efficacy and safety of glyburide versus metformin in the treatment of GDM and to evaluate the improvement in glycemic control after their replacement as a result of adverse effects or after the addition of the second drug because of failure of the first.

RESEARCH DESIGN AND METHODS

Study Design

An open-label parallel-group, randomized controlled trial was conducted at Emek Medical Center, a university-affiliated hospital in Afula, Israel. This study was authorized by the local review board at Emek Medical Center (approval EMC-2-11). Participants provided written informed consent. From 5 January 2012 to 6 June 2014, we recruited women between the ages of 18 and 45 years with GDM diagnosed between 13 and 33 weeks gestation and who required medical therapy because of poor glycemic control with diet alone. GDM diagnosis was established by using Carpenter and Coustan (15) or 1979 National Diabetes Data Group (16) criteria. Poor glycemic control needing pharmacotherapy was defined as preprandial glucose >95 mg/dL, a 1.5-h postprandial glucose of >130 mg/dL, or a daily mean glucose >100 mg/dL after at least 1 week of dietary treatment.

We excluded women without gestational age dating before 24 weeks (according to crown-to-rump length in the first trimester or fetal biometry in the second trimester), with pre-GDM or a first trimester fasting glucose ≥105 mg/dL, with suspected intrauterine growth restriction before 24 weeks, and with major fetal malformations. Assignment to treatment groups was performed by using a computer randomization sequence generation program; the randomization results were sealed in opaque envelopes and kept in the maternal and fetal medicine clinic in a closed study box. The sequence was concealed until intervention was assigned. Patients were enrolled, and interventions were assigned by the physicians listed as investigators in this study.

Interventions

Women with GDM were invited to the GDM clinic at Emek Medical Center. The initial visit included a full medical history by the clinic's attending physician and a BMI recording. In addition, each participant was educated by a dietitian about dietary and lifestyle recommendations for patients with diabetes. All women were instructed on a diet ranging from 25 kcal/kg for overweight and obese women to 35 kcal/kg for women with normal weight and divided into three full meals and four snacks of 50% carbohydrates, 30% fat, and 20% protein. The participants underwent comprehensive guidance on how to measure blood glucose levels by using a memory-based glucometer and on how to complete a daily glucose chart, which was sent to the clinic physician for review by fax or e-mail.

Glycemic control was evaluated by a daily chart of seven measurements: three preprandial, three postprandial, and one taken at 10:00 P.M. The postprandial measurements were taken 90 min after meals because this time interval is when postprandial glucose peaks in a diabetic pregnancy (17). The glucose chart was filled daily for 1 week, after which pharmacotherapy was initiated if repeated preprandial glucose values were >95 mg/dL, repeated postprandial values were >130 mg/dL, or the average daily glucose value was >100 mg/dL. Repeated elevated values occurred when at least 20% of the glucose measurements were elevated beyond the values described above. Glucose values were verified by the glucometer's memory. At that point, patients were asked to participate in the study. Patients were randomly allocated in a 1:1 ratio to two groups receiving either glyburide 2.5–20 mg/day 30 min before a meal and/or at 10:00 P.M. or metformin 850–2,550 mg/day right after meals and/or at 10:00 P.M. according to daily glucose chart values. Treatment failure was defined either as poor glycemic control (repeated preprandial glucose values >95 mg/dL, repeated postprandial values >130 mg/dL, or average daily glucose value >100 mg/dL) or if medication-associated adverse effects led to treatment discontinuation. In those cases, the other oral hypoglycemic medication either was added to the first medication (in the case of poor glycemic control) or replaced it (in the case of an adverse effect of the first medication). If the participant experienced glyburide-induced hypoglycemia (at the minimal dose of 2.5 mg) only during specific times of the day, it was replaced at those times with metformin. If glycemic control was not achieved or the second medication was discontinued because of adverse effects, third-line therapy with insulin was initiated.

Daily glucose charts were sent to the clinic physician for review by fax or e-mail at least once a week. At least once a month, all participants attended the GDM clinic for pregnancy follow-up by a physician, weight measurements, verification of glucose values from the glucometer's memory, the return of empty vials of medications and receipt

of new ones, and sonographic assessment of estimated fetal weight and well-being.

From the 38th week of gestation and each week thereafter until 40 weeks, delivery was considered according to fetal well-being and biometry, glycemic control, and maternal status. After delivery, neonatal metabolic complications were evaluated based on neonatal blood concentrations of bilirubin, calcium, and magnesium and a complete blood count. Need for phototherapy, neonatal birth weight, and head circumference were also recorded.

Study Outcomes

The primary outcomes were *1*) the rate of treatment failure defined as patients needing additional oral hypoglycemic or a second-line therapy either because of poor glycemic control or adverse effects of the first-line medication and *2*) glycemic control according to mean daily glucose charts. Secondary outcomes were the rate of participants requiring second-line therapy as a result of poor glycemic control, the rate of participants requiring second-line therapy because of medication-associated adverse effects, the rate of participants requiring third-line therapy with insulin, preprandial and postprandial glucose values, obstetric outcomes, and neonatal hypoglycemia and metabolic complications. Neonatal hypoglycemia was defined as blood glucose $<$40 mg/dL in the first 24 h postdelivery or blood glucose $<$50 mg/dL from the second day of life.

Statistical Analysis

Sample Size

Assuming 15% treatment failure with glyburide (11) versus 45% with metformin (2), 47 women + 10% dropouts (i.e., 52 women) were needed in each group to detect a 30% difference in treatment failure (two-sided α of 5% and power of 90%). This sample size is sufficient to detect a 10 mg/dL difference in mean daily blood glucose between the two groups with an SD of 15 mg/dL difference (two-sided α of 5% and power of 90%).

Group baseline characteristics and outcomes were compared by using the Student *t* test (or the Wilcoxon two-sample test) for continuous variables and χ^2 test (or Fisher exact test [two-tailed]) for categorical variables. To demonstrate and compare mean daily, preprandial, and postprandial glucose values between study groups, a locally weighted scatterplot smoother (LOESS) nonparametric regression model was used (smooth parameter 0.8) (18). The 95% CIs of the LOESS curves are also presented.

Statistical analyses were carried out with SAS 9.2 software (SAS Institute, Cary, NC). Significance was set at $P <$ 0.05.

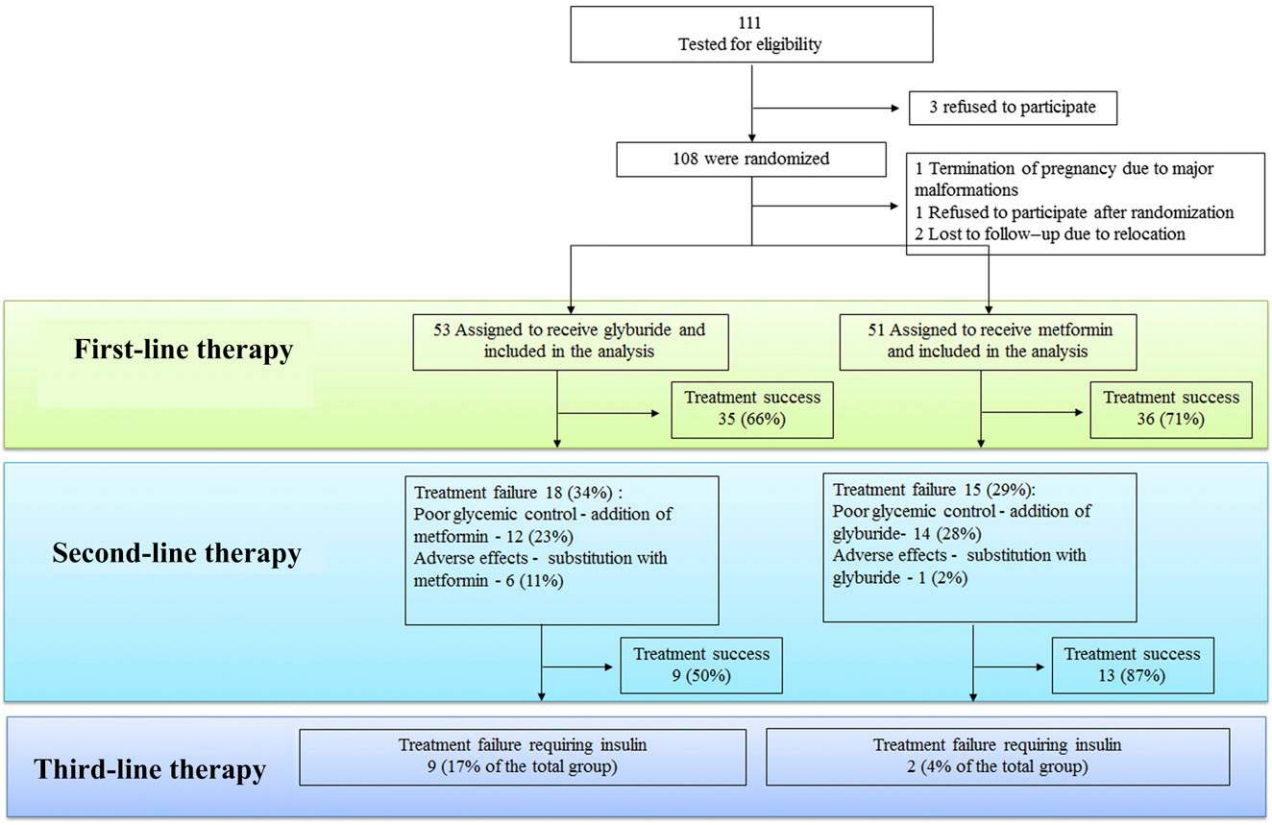

Figure 1—Patient flowchart of recruitment and treatment failure and success with glyburide vs. metformin. Treatment failure was defined as either poor glycemic control, in which case an additional oral hypoglycemic drug was added, or adverse effects leading to drug discontinuation, in which case the treatment was switched to the second-line treatment. If addition/switching to the second-line treatment resulted in poor glycemic control or adverse effects leading to drug discontinuation, the treatment was switched to insulin (third-line therapy). No statistical difference was found between the rate of poor glycemic control ($P = 0.6$) and adverse effects ($P = 0.11$) of glyburide vs. metformin after the first-line therapy. No statistical difference was found for second-line therapy between the groups ($P = 0.6$). The need for third-line therapy with insulin was lower in the metformin group than in the glyburide group ($P = 0.03$).

RESULTS

The patient flowchart is described in Fig. 1. The analysis included 53 and 51 patients who started treatment with glyburide and metformin, respectively. The study period lasted from recruitment until delivery. Baseline characteristics at recruitment were comparable between the groups (Table 1). Maternal and neonatal outcomes are presented in Table 2. Treatment failure after first-line treatment because of poor glycemic control or adverse effects were comparable between the groups (glyburide 18 [34%], metformin 15 [29%]; $P = 0.6$). The adverse effect requiring medication discontinuation was hypoglycemia in the glyburide group and gastrointestinal discomfort in the metformin group. The rate of adverse effects did not differ significantly between the treatments ($P = 0.11$). Treatment success after second-line therapy was higher in the metformin group than in the glyburide group (13 of 15 patients [87%] vs. 9 of 18 patients [50%], respectively; $P = 0.03$). In the glyburide group, nine (17%) patients eventually were treated with insulin compared with two (4%) in the metformin group ($P = 0.03$). The indications for insulin treatment were adverse effects in four patients and poor glycemic control in seven. The combination of the drugs reduced the need for insulin from 33 (32%) to 11 (11%) patients ($P = 0.0002$), indicating that a protocol comprising two oral hypoglycemic agents as first- and second-line therapy is effective for glycemic control in 89% of patients. Similar results were obtained after excluding the 27 women with a GDM diagnosis before 24 weeks gestation. In the glyburide group, 15 of 40 patients (38%) experienced treatment failure compared with 9 of 37 (24%) in the metformin group ($P = 0.2$). Mean daily, preprandial, and postprandial glucose values throughout the study period were comparable between the groups (Fig. 2). Other maternal, obstetrical, and neonatal outcomes were comparable between the groups (Table 2).

Table 1—Patient characteristics

	Glyburide ($n = 53$)	Metformin ($n = 51$)
Age (years)	32.8 ± 5.0	33.6 ± 5.3
Age >35 years	19 (36)	20 (41)
Parity	2.7 ± 1.6	2.8 ± 1.8
Primiparous	17 (32)	12 (27)
Weight (kg)	75.0 ± 14.4	75.2 ± 15.5
Height (m)	1.62 ± 0.07	1.62 ± 0.06
Prepregnancy BMI (kg/m^2)	28.6 ± 4.7	28.6 ± 5.5
GDM diagnosis by the National Diabetes Data Group criteria	21 (39)	24 (47)
GDM diagnosis <24 weeks	13 (25)	14 (27)
Treatment initiation (weeks)	29.4 ± 4.0	29.6 ± 4.1
Mean daily glucose value at recruitment (mg/dL)	109.8 ± 11.4	110.2 ± 7.8
Mean preprandial glucose value at recruitment (mg/dL)	95.9 ± 10.4	96.8 ± 10.5
Mean postprandial glucose value at recruitment (mg/dL)	127.6 ± 19.1	125.4 ± 12.8

Data are mean ± SD or *n* (%).

CONCLUSIONS

This study compared the efficacy and safety of glyburide and metformin for the treatment of GDM. In this randomized controlled trial, both treatments were similar in their efficacy and safety. Oral hypoglycemic drugs to treat GDM were suggested previously by studies that compared either glyburide or metformin to insulin, demonstrating comparable results (4). The information regarding which drug is superior is much more scarce because only two randomized controlled trials compared glycemic control by glyburide and

Table 2—Maternal and neonatal outcomes

	Glyburide ($n = 53$)	Metformin ($n = 51$)	*P* value
Gestational age at delivery (weeks)	38.1 ± 1.5	37.6 ± 1.2	0.3
Preterm delivery	4 (8)	6 (12)	0.5
Induction/augmentation	25 (47)	16 (31)	0.1
Caesarean section	17 (32)	18 (35)	0.7
Mean daily glucose value under treatment (mg/dL)	100.9 ± 10.4	101.3 ± 9.4	0.9
Mean preprandial glucose value under treatment (mg/dL)	88.7 ± 10.2	91.3 ± 8.8	0.2
Mean postprandial glucose value under treatment (mg/dL)	115.3 ± 13.8	112.6 ± 12.3	0.3
Maternal weight gain (kg)	8.7 ± 6.6	8.4 ± 7.0	0.8
Birth weight (g)	3,199 ± 493	3,249 ± 491	0.6
Birth weight percentile	62 ± 28	65 ± 27	0.7
Macrosomia >4,000 g	1 (2)	2 (4)	0.6
Large-for-gestational-age neonate	7 (13)	10 (20)	0.4
Shoulder dystocia	1 (2)	0	1
Gestational hypertension/preeclampsia	5 (9)	2 (4)	0.4
Apgar score at 1 min <7	2 (4)	2 (4)	1
Apgar score at 5 min <7	1 (2)	0	1
Cord pH*	7.27 ± 0.08	7.27 ± 0.07	0.8
Head circumference (cm)	33.9 ± 1.5	34.3 ± 1.2	0.3
Neonatal hypoglycemia	1 (2)	5 (12)**	0.09
Neonatal hyperbilirubinemia	19 (36)	14 (27)	0.4
Phototherapy	10 (19)	9 (18)	0.9
Neonatal polycythemia	3 (6)	2 (4)	1
Neonatal hypocalcemia	2 (4)	0	0.5
Neonatal hypomagnesemia	1 (2)	0	1

Data are mean ± SD or *n* (%). *Cord pH was available for 51 and 41 neonates in the glyburide and metformin groups, respectively. **Three women were switched to glyburide. Consequently, two of six newborns with hypoglycemia were exposed at birth to metformin and four to glyburide.

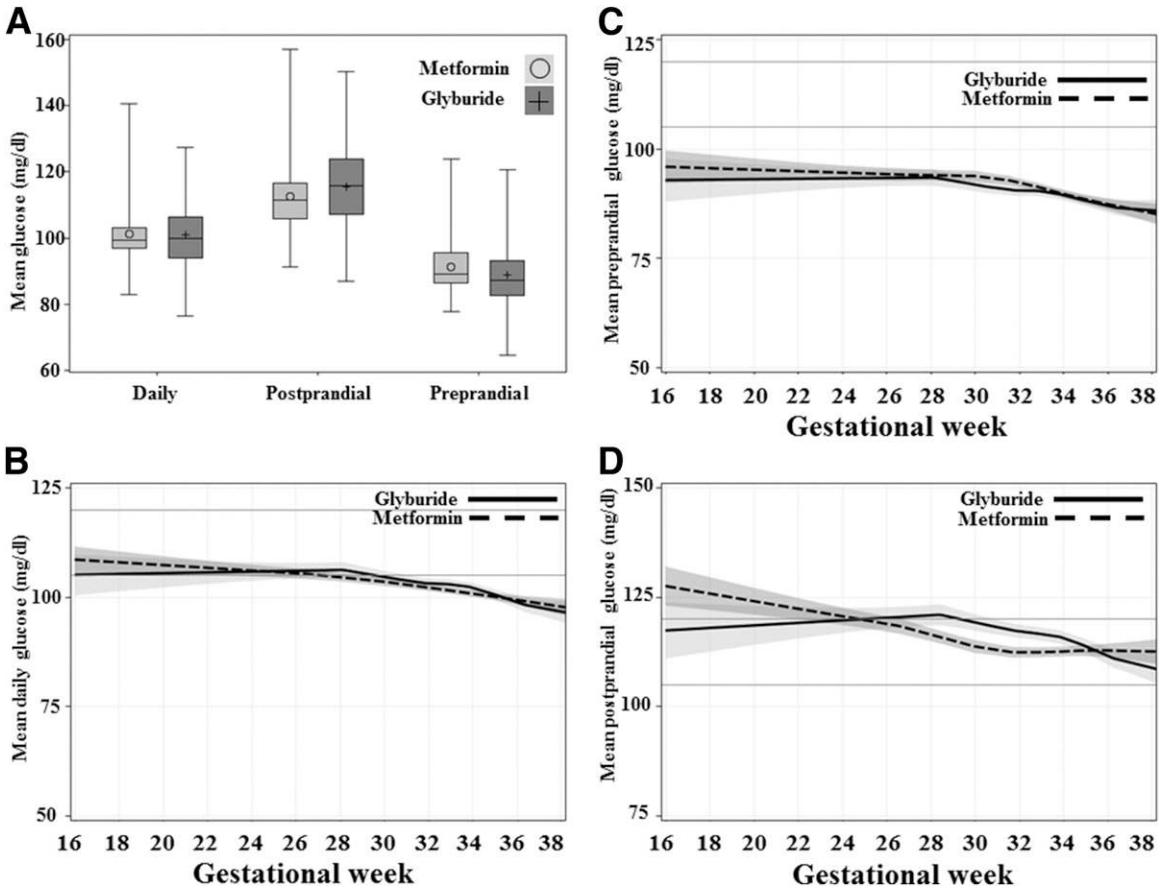

Figure 2—Glycemic control under treatment according to daily glucose charts of glyburide vs. metformin throughout the study period. *A*: Box plot representing the mean daily, preprandial, and postprandial glucose values throughout the study period. *B–D*: LOESS curves (smoothing parameter 0.8) representing the mean daily, preprandial, and postprandial glucose values at each week of gestation. The difference between the postprandial glucose values (*D*) during 26–36 weeks gestation was not statistically significant (Wilcoxon two-sample test $P = 0.18$).

metformin in the treatment of GDM (10,11). In both these studies, no difference was found in the primary outcome of glycemic control. However, treatment failure leading to insulin use was ~25% and comparable in one study (10) but higher for metformin than for glyburide (35% vs. 16%, respectively) in the other (11).

The current study is original in two respects. First, it was designed to answer two primary outcomes: glycemic control and treatment failure as a result of either poor glycemic control or adverse effects. We chose to add treatment failure as a primary outcome, as opposed to previous studies, because we believed that this outcome better answers which drug is superior, which particularly holds true in the case of glycemic control eventually being achieved in both groups with insulin (with which treatment failure is rare). Analysis of only the patients with good glycemic control after oral treatment is also problematic because of selection bias of the successful group of each treatment, in which smaller differences between glucose levels are expected, leading to the study being underpowered. Second, this study examined the usefulness of the second oral hypoglycemic agent as second-line therapy and insulin only as a third-line therapy. To our knowledge, this study is the first to examine this objective. We hypothesized that because the two medications act with different mechanisms (1,2), one would succeed where the other failed to achieve glycemic control and particularly if the medication was discontinued because of adverse effects. This strategy raised treatment success from 69% to 89%, leading to only 11% of the patients needing insulin. These results support the benefit of using an additional oral hypoglycemic agent in the case of a treatment failure before switching to insulin.

The patients who started with metformin had a lower probability of requiring insulin. We speculate that this finding is a result of the rate of treatment failure due to adverse effects (although it did not reach statistical significance) being lower in the metformin group than in the glyburide group; therefore, more patients used both medications simultaneously for poor glycemic control. In addition, because metformin increases insulin sensitivity (2), it might have potentiated the effect of glyburide when the later was added.

The superiority of metformin was suggested in previous studies as well. In the meta-analyses of Balsells et al. (3) and Poolsup et al. (19), metformin compared with insulin was associated with less maternal weight gain, a lower rate of gestational hypertension, and lower postprandial blood glucose. The efficacy of glyburide as an oral agent in GDM was questioned because glyburide was inferior to both insulin and metformin. Glyburide was inferior to insulin because of an elevated risk for neonatal intensive care unit admission, respiratory

distress, neonatal hypoglycemia, birth injury, increased birth weight, large-for-gestational-age neonate, and macrosomia (3,13,14,19). Compared with metformin, glyburide was associated with a lower fasting blood glucose during treatment but a higher maternal weight gain, birth weight, macrosomia, large-for-gestational-age newborn, and neonatal hypoglycemia (3,12). A possible explanation is that in contradiction to earlier studies reporting that glyburide does not cross the placenta considerably (1,20), more-recent studies that used more sensitive methods to detect plasma concentrations of glyburide found that glyburide readily crosses the placenta, reaching 50–70% of total maternal plasma concentration with similar average concentrations of maternal and umbilical cord plasma of the unbound fraction and greater than the maternal plasma concentration in 20–37% of the samples (21,22). Thus, glyburide might lead to fetal overgrowth and neonatal hypoglycemia through excessive fetal insulin secretion, whereas metformin increases insulin sensitivity in the target organs without causing hyperinsulinism (2). The favorable effects of metformin should be balanced with a possible increase of preterm births after metformin treatment compared with insulin (2,3,14) but not glyburide (3).

The strengths of this study are its prospective randomized control trial design; the high recruitment rate, which decreased the selection bias; the use of multiple aspects for evaluating treatment results, including both glycemic control and adverse effects; and the addressing of neonatal complications. Besides being conducted at a single site, the limitations of this study are that patients and providers were not blinded to treatment allocation and that treatment failure after second-line oral hypoglycemic agents and differences in neonatal outcomes were secondary outcomes. These limitations should be addressed in future studies, preferably of multicenter design.

In conclusion, glyburide and metformin are comparable oral treatments for GDM regarding glucose control and treatment failure. Their combination allows a higher efficacy rate with a significant reduced need for insulin that should be reserved for patients who failed to respond to both oral treatments or who experienced adverse effects as a result of both.

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