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Prescribing patterns and outcomes among patients treated for gestational diabetes mellitus

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ABSTRACT

Insulin is recommended as first-line pharmacologic therapy for gestational diabetes (GDM); however, glyburide and metformin are often used. This study aimed to identify the most commonly prescribed agents for treating GDM, along with the maternal and fetal outcomes associated with their use. Electronic medical records were used to identify the medications prescribed for GDM at a large health system. Data were collected comparing medication failure rate, maternal weight gain, and incidence of fetal macrosomia, neonatal hypoglycemia, and premature delivery between the agents used. Of the 368 patients who met the inclusion criteria, 76.9% were initiated on glyburide, 13.6% were initiated on metformin, 8.2% were initiated on insulin, and 1.4% were initiated on a combination of glyburide and metformin. Glyburide was associated with less medication failure compared to insulin and metformin. There was no significant difference in maternal weight gain, fetal macrosomia, or neonatal hypoglycemia between the three classes of medications. However, recipients of basal and bolus insulin had a higher rate of preterm delivery compared to recipients of glyburide and metformin. Our findings suggest that glyburide and metformin are frequently prescribed over insulin as the initial treatment for GDM and appear to be safe and effective alternatives.

KEYWORDS Diabetes; gestational diabetes; prescribing patterns

Gestational diabetes mellitus (GDM) affects up to 10% of pregnancies in the United States and is associated with maternal and neonatal consequences.[1] The American College of Obstetricians and Gynecologists (ACOG) and American Diabetes Association recommend lifestyle modifications as first-line therapy for all women with GDM. However, if glycemic control is not achieved after incorporating lifestyle modifications, insulin is the medication of choice since it does not cross the placenta.[2,3] According to the ACOG, the recommended starting dose for insulin is 0.7 to 1.0 units/kg daily in divided doses of either long-acting or intermediate-acting insulin in combination with prandial insulin.[2] Alternatives to insulin in GDM include metformin and glyburide. However, both medications cross the placenta, and there is no clear consensus on which agent is preferred.[2,3] While insulin is recommended as first-line pharmacologic therapy for GDM, the convenience of oral agents may preclude its use. The purpose of this study was to identify the most commonly prescribed agents for treating GDM, along with the maternal and fetal outcomes associated with their use.

METHODS

A retrospective chart review was performed on patients requiring medication therapy for GDM at an academic institution in central Texas, and the study was approved by the local institutional review board. Patients were eligible for inclusion if they had a diagnosis of GDM between August 1, 2013, and January 31, 2019. Patients were excluded from the study if they had preexisting type 1 or type 2 diabetes or used any antihyperglycemic medications prior to their diagnosis of GDM. Electronic medical records were used to identify the medications prescribed for GDM. For those initiated on insulin, the starting dose in units/kg was collected. Direct glycemic control could not be assessed since hemoglobin A1c and glucose tests were rarely ordered. Additionally, patient self-monitored blood glucose values were typically used to

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Table 1. Patient characteristics and outcomes stratified by treatment failure

Variable	Total (N = 368)	Treatment failure (N = 59)	No treatment failure (N = 309)	*P* value
Patient characteristics				
Age (years)	31.0 (5.5)	31.0 (6.1)	31.0 (5.4)	0.8
White	190 (52%)	27 (46%)	163 (53%)	0.3
Black	40 (11%)	10 (17%)	30 (10%)	0.1
Hispanic	114 (31%)	19 (32%)	95 (31%)	0.8
Other	24 (6%)			
Patient weight at start of pregnancy (kg)	91.5 (24.6)	98.4 (25.2)	90.2 (24.3)	0.02*
Patient weight at delivery (kg)	100.7 (23.5)	106.4 (23.4)	99.6 (23.5)	0.04*
Weight gain (kg)	9.2 (7.9)	8.0 (8.1)	9.4 (7.9)	0.55
BMI at start of pregnancy (kg/m^2)	34 (8.1)	36.5 (8.2)	33.5 (8.0)	0.01*
BMI at delivery (kg/m^2)	37.4 (7.8)	39.6 (7.7)	37.0 (7.7)	0.01*
Outcome				
Total gestational days	265.3 (12.9)	257.8 (15.5)	266.7 (11.9)	<.0001*
Receiving double therapy	22 (6.0%)			
Treatment failure	59 (16.0%)			
Fetal macrosomia	53 (14.4%)	7 (11.9%)	46 (14.9%)	0.5
Preterm delivery	60 (16.3%)	17 (28.8%)	43 (13.9%)	0.005*
Neonatal hypoglycemia	211 (57.3%)	35 (59.3%)	176 (57.0%)	0.7

BMI indicates body mass index. Data presented as mean (SD) or n (%).
*$P < 0.05$.

make medication adjustments, and these values were not routinely documented in the medical record. Thus, if additional therapy was required after the initial medication, the patient was considered to have a treatment failure. Data were collected comparing maternal weight gain, along with the incidence of fetal macrosomia, neonatal hypoglycemia, and premature delivery between the medications used. Fetal macrosomia was defined as a fetal birth weight of >4 kg. Neonatal hypoglycemia was defined as a blood glucose value < 45 mg/dL in the first 24 hours of life. Premature delivery was defined as delivery before 37 weeks' gestation.

Baseline characteristics were described using descriptive statistics. Frequencies and percentages were used to describe categorical variables. Means and standard deviations (or medians and ranges where appropriate) were used to describe continuous variables. Baseline characteristics and outcome measures were compared using Student's *t* test or the nonparametric equivalent for continuous variables. A chi-square test (or Fisher's exact test when appropriate) was used to test for associations in bivariate comparisons. An analysis of variance model (or Kruskal-Wallis test when appropriate) was used to test for differences in continuous variables between the 3+ groups. The post hoc Tukey's test was used for pairwise comparisons when analysis of variance showed a statistically significant result. All analyses were performed using SAS, Version 9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 368 patients met the inclusion criteria during the study period. The mean age of patients was 31 years, and 52% were white. The average weight and body mass index at the start of pregnancy were 91.5 kg and 34.0 kg/m^2, respectively *(Table 1)*.

Glyburide was the most common medication initiated by providers (76.9%), followed by metformin (13.6%) and insulin (8.2%). Five patients were started on a combination of glyburide and metformin, and due to the small number, they were excluded from the comparison analysis. One patient was started on metformin along with insulin and was included in the insulin initiation group. Of 30 patients placed on insulin as initial therapy, 17 were initiated on basal/bolus therapy. This included 10 patients on NPH and aspart, five patients on NPH and regular, one patient on 70/30 NPH/regular, and one patient on NPH and lispro. Eleven patients were initiated on basal-only therapy, and all of these were NPH. Two patients were initiated on bolus-only therapy, with one placed

Table 2. Clinical outcomes by initial medication

Outcome	Glyburide (N = 283)	Dual insulin (basal and bolus) (N = 17)	Single insulin (basal or bolus) (N = 13)	Metformin (N = 50)	*P* value
Treatment failure	31.0 (11.0%)	10 (33.3%)		15 (30.0%)	<.0001*
Fetal macrosomia	43 (15.2%)	4 (13.3%)		4 (8.0%)	0.4
Preterm delivery[a]	40 (14.1%)	7 (41.2%)		8 (16.0%)	0.01*
Preterm delivery[b]	40 (14.1%)		3 (23.1%)	8 (16.0%)	0.6
Neonatal hypoglycemia[c]	160 (56.5%)	7 (41.2%)	10 (76.9%)	31 (62.0%)	0.2
Weight gain (kg)	9.1 (7.6)	10.9 (11.0)	9.9 (10.6)	8.6 (8.3)	0.7
Weight-based insulin dose		0.74 (0.18)	0.13 (0.09)		<.0001*

[a]Basal and bolus insulin therapy vs. glyburide vs. metformin.
[b]Single insulin therapy vs. glyburide vs. metformin.
[c]Basal/bolus insulin therapy vs. single insulin therapy ($P = 0.05$).
*$P < 0.05$.
Data presented as mean (SD) or n (%).

on aspart and one placed on lispro. A total of 61 patients were initiated on insulin at some point during treatment, with the majority placed on basal/bolus compared to single insulin therapy (63% vs 37%). The average weight-based insulin dose was 0.8 units/kg for basal/bolus therapy and 0.14 units/kg for single insulin therapy.

Of the 368 patients, 53 experienced fetal macrosomia and 60 had preterm labor. Neonatal hypoglycemia was observed in 211 newborns. Fifty-nine patients had treatment failure with their initial medication and required additional therapy. Fewer patients on glyburide had treatment failure compared to insulin and metformin (11.0% vs 33.3% vs 30%, $P < 0.0001$) *(Table 1)*. There were no significant differences in age or race among patients who had treatment failure with their initial medication. However, patients who had treatment failure with their initial medication had a higher initial weight and body mass index at the start of pregnancy and at delivery in comparison to the patients who did not. Additionally, treatment failure with the initial medication was associated with a higher preterm delivery rate (28.8% vs 13.9%, $P = 0.005$) *(Table 1)*. Recipients of basal/bolus insulin had higher rates of preterm delivery relative to recipients of glyburide and metformin (41.2% vs 14.1% vs 16.0%, $P = 0.01$). Basal/bolus insulin therapy was associated with less neonatal hypoglycemia compared to single insulin therapy (41.2% vs 76.9%, $P = 0.05$) *(Table 2)*.

DISCUSSION

While the ACOG recommends insulin for the initial management of GDM, this study found that glyburide was most commonly initiated, followed by metformin and insulin. NPH was the only basal insulin used in this population, and insulin aspart was the most commonly prescribed bolus agent. Most insulin users were prescribed a basal/bolus regimen at an average weight-based dose of 0.8 units/kg, which aligns with the ACOG recommendation of 0.7 to 1.0 units/kg. Most patients initiated on single insulin therapy were prescribed NPH at an average dose of 0.14 units/kg. While there is no specific weight-based recommendation for single-insulin therapy in GDM, this is consistent with the recommended starting dose of basal therapy in the general diabetes population of 0.1 to 0.2 units/kg.

Several studies have sought to assess the comparative safety and efficacy of glyburide, metformin, and insulin in GDM with inconsistent results. A meta-analysis by Guo et al found no significant difference in glycemic control between glyburide and insulin or metformin and insulin.[4] However, the MeDiGes study published in 2021 found that metformin was associated with better postprandial glycemic control compared to insulin.[5] Studies directly comparing the efficacy of metformin and glyburide in GDM are conflicting. Nachum et al showed comparable glycemic control and failure rates between metformin and glyburide; however, a study by Moore et al demonstrated a significantly higher failure rate with metformin.[6,7] In the current study, glycemic values were not assessed, but glyburide had a significantly lower failure rate than metformin or insulin.

Regarding safety outcomes, the meta-analysis by Guo et al concluded that insulin was associated with a higher risk of preeclampsia, neonatal intensive care unit admission, neonatal hypoglycemia, maternal hypoglycemia, maternal weight gain, and macrosomia compared to metformin. Additionally, glyburide was associated with a higher rate of neonatal hypoglycemia compared to insulin and more maternal weight gain compared to metformin.[4] In the MeDiGes study, insulin was also associated with more maternal weight gain and maternal hypoglycemia compared to metformin.[5] The current study found no significant differences in maternal weight gain, neonatal hypoglycemia, and fetal macrosomia between glyburide, metformin, and insulin. However, the

incidence of preterm delivery was significantly higher in those treated with insulin compared to oral agents. Preterm delivery was also more likely to occur in patients who had treatment failure with the initial medication. This could be attributed to those requiring insulin and those who had treatment failure having worse glycemic control overall; however, this cannot be confirmed as it was not analyzed in the current study.

This study has several limitations. Due to the retrospective chart review, the rationale for the initial medication choice by providers was not identified. Additionally, due to limitations in documentation, parts of the data may have been missing or incomplete. While treatment failure was defined by the addition of new therapy, hemoglobin A1c and glucose values were not recorded; therefore, glycemic control could not be assessed. Glycemic control can significantly impact clinical outcomes, so the findings in this study could be attributed to differences in glycemic control rather than differences in medications.

In conclusion, glyburide and metformin are commonly chosen over insulin as initial medication therapy for GDM and appear to be safe and effective alternatives.

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