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Treatment of gestational diabetes mellitus: glyburide compared to subcutaneous insulin therapy and associated perinatal outcomes

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Abstract

Objective—To examine perinatal outcomes in women with gestational diabetes mellitus treated with glyburide compared to insulin injections.

Study design—This is a retrospective cohort study of women diagnosed with gestational diabetes mellitus (GDM) who required pharmaceutical therapy and were enrolled in the Sweet Success California Diabetes and Pregnancy Program between 2001 and 2004, a California state-wide program. Women managed with glyburide were compared to women treated with insulin injections. Perinatal outcomes were compared using chi-square test and multivariable logistic regression models; statistical significance was indicated by $p < 0.05$ and 95% confidence intervals (CI).

Results—Among the 10,682 women with GDM who required medical therapy and met study criteria, 2073 (19.4%) received glyburide and 8609 (80.6%) received subcutaneous insulin injections. Compared to insulin therapy and controlling for confounders, oral hypoglycemic treatment was associated with increased risk of birthweight >4000 g (aOR = 1.29; 95% CI [1.03–1.64]), and admission to the intensive care nursery (aOR = 1.46 [1.07–2.00]).

Conclusion—Neonates born to women with gestational diabetes managed on glyburide, and were more likely to be macrosomic and to be admitted to the intensive care unit compared to those treated with insulin injections. These findings should be examined in a large, prospective trial.

Keywords

Gestational diabetes mellitus; treatment; perinatal outcomes

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Introduction

Gestational diabetes mellitus (GDM) complicates approximately 3–9% of pregnancies and is associated with increased maternal and neonatal morbidity [1–3]. The diagnosis and treatment of GDM can improve perinatal outcome [4]. Management of GDM initially begins with dietary modification, exercise, and self glucose monitoring, with the addition of medical therapy if euglycemia cannot be achieved by diet and exercise alone [1,5,6]. Until recently, subcutaneous insulin, which does not cross the placenta, has been the first-line treatment of GDM due to concerns that oral hypoglycemic agents, particularly sulfonylurea drugs, may potentially cause fetal anomalies and neonatal hypoglycemia [7,8]. Recent studies have shown that the newer sulfonylureas, e.g. glyburide and glipizide, cross the placenta in trace amounts and may be safe during pregnancy [9,10].

The use of glyburide as an alternative treatment of GDM has been a more common practice since the publication of a randomized-controlled trial in which 404 women with GDM were assigned to receive either subcutaneous insulin or oral glyburide [11]. Since the study's primary outcome was the achievement of 'desired level of glycemic control,' it was not statistically powered to examine the less common neonatal complications that can be associated with hyperglycemia [11]. Although the authors did not observe a statistically significant difference in perinatal outcome between the comparison groups, there was a trend toward higher frequency of neonates with birthweight >4000 g and hyperbilirubinemia in the glyburide group [11].

Following this study, many clinicians embraced glyburide as an alternative to insulin in the treatment of GDM. In a study which compared women with GDM who received glyburide to historical controls treated with insulin, the authors report no difference in birthweight, macrosomia, or cesarean delivery but did observe a statistically significantly higher incidence of preeclampsia, neonatal hyperbilirubinemia, and longer stay in the intensive care nursery with glyburide treatment compared to insulin [12]. Furthermore, another study that examined the efficacy of insulin, glyburide, and acarbose for the treatment of GDM found glyburide to be more effective than acarbose in achieving glycemic control but showed a higher rate of macrosomia and neonatal hypoglycemia compared to insulin [13].

The effect of glyburide as an alternative to insulin for the treatment of GDM deserves further investigation. We examined a large cohort of women diagnosed with GDM in California and enrolled in the Sweet Success program, a multidisciplinary, out-patient program that provides comprehensive education, nutrition, psychosocial, and medical services [14]. Perinatal outcome in women with GDM treated with glyburide were compared to those managed with subcutaneous insulin.

Material and methods

We conducted a retrospective cohort study of women with singleton pregnancies diagnosed with GDM who were enrolled in the Sweet Success California Diabetes and Pregnancy Program (CDAPP) and delivered between January 1, 2001 and December 31, 2004. The CDAPP is as part of the Regional Perinatal Programs of California established by the Maternal, Child, and Adolescent Health Branch of the California Department of Health Services. Information regarding maternal characteristics, prenatal care (including treatment modality of GDM at the initial and the last Sweet Success visits), delivery, neonatal outcomes, and postpartum care were collected by trained personnel using standardized, validated data collection forms. Exclusion criteria were multifetal gestations, pregestational diabetes (Type 1 or Type 2), GDM diagnosed prior to 10 weeks gestation, diet-controlled gestational diabetes, gestational age (GA) at delivery <20 weeks, and women with unknown

treatment status. The goals of glycemic control were fasting plasma blood glucose <95 mg/dL and 1-h postprandial plasma blood glucose <130 mg/dL. Institutional Review Board (IRB) approval was obtained from the Committee on Human Research at the University of California, San Francisco.

For a large proportion of women (51%) who received oral hypoglycemic agent, treatment was coded as 'oral hypoglycemic agent.' However, for women in whom the specific oral hypoglycemic agent was known, 99% received glyburide, while only 1% received metformin or other oral agents. Since most clinicians who used oral hypoglycemic agents chose glyburide during the study period [15], we designated those women who received 'oral hypoglycemic agents' as having received glyburide. Women were categorized as receiving glyburide or insulin based on the treatment modality at the last Sweet Success visit, unless they were placed on treatment at the first Sweet Success visit, in which case they were categorized by their treatment modality at the first visit. For example, women who were initially diet-controlled but subsequently placed on oral agents were designated as the glyburide group. Similarly, women who were initially diet-controlled but then placed on insulin by their last Sweet Success visit or those who were started on glyburide but were switched to and maintained on insulin by their last Sweet Success visit were assigned as the insulin group.

We explored maternal characteristics likely to be associated with glyburide use, including maternal age, race/ethnicity, parity, prepregnancy body mass index (BMI), education level, primary language, GA at which GDM was diagnosed, and GA at delivery. Maternal outcome examined included primary cesarean delivery. Neonatal outcomes examined included preterm delivery (PTD) <37weeks and <34 weeks, birthweight >4000 g and >4500 g, large-for-gestational-age (LGA, defined as birthweight >90th centile by GA according to the neonatal weight curves established by Babson et al. [16] and Williams et al. [17]), intrauterine fetal demise (IUFD), and admission to the neonatal intensive care nursery (NICU).

Treatment modality of GDM and perinatal outcomes were examined using chi-square test and multivariable logistic regression analysis to control for confounders. Final model covariates included maternal age, parity, race/ethnicity, prepregnancy BMI, GA at which GDM was diagnosed, gestational weight gain, and GA at delivery, primary language, and education level. Women treated with insulin were designated as the referent. Statistical significance was indicated by $p < 0.05$ and 95% CI. Statistical analysis was performed using STATA v9.0 (StataCorp, College Station, TX).

Results

Of the 10,682 women diagnosed with GDM meeting study criteria, 8609 (80.6%) were treated with subcutaneous insulin injections and 2073 (19.4%) received glyburide for glycemic control. The median GA at diagnosis of GDM was 27.1 weeks (intra-quartile range, IQR: 23.7–29.3 weeks) for women treated with subcutaneous insulin; it was 27.0 weeks (IQR: 24.0–29.0 weeks) for the glyburide group. Maternal characteristics associated with a higher frequency of glyburide use included nulliparity, African American or Asian, and prepregnancy BMI < 26.0 kg/m^2 ($p < 0.001$ for all; Table I). Women who received the diagnosis of GDM between 20 and 32 weeks were more likely to be treated with glyburide (21.3%) than those diagnosed prior to 20 weeks (19.7%) or after 33 weeks gestation (17.1%, $p = 0.001$). The use of glyburide was more frequent in women who did not attend college and in women whose primary language was not English (Table I). Further, in this cohort, we observed 225 women who were started on glyburide for treatment of GDM on initial visit, and 84 (37%) were switched from glyburide to insulin by the last CDAPP visit.

Maternal and neonatal outcomes associated with GDM treatment modality were examined using chi-square test and multivariable logistic regression analyses (Table II). Designating women who were treated with subcutaneous insulin as the referent, women who took glyburide had lower odds of overall cesarean delivery (aOR 0.77, 95% CI [0.65–0.91]) but no difference in primary cesarean delivery or PTD (Table II). On the contrary, women who received glyburide were more likely to have neonates with birthweight >4000 g (aOR = 1.29 [1.03–1.64]) and higher odds of admission to the NICU (aOR = 1.46 [1.07–2.00]; Table II) among term deliveries.

To further explore differences in GDM treatment modalities, GA of GDM diagnosis was stratified by diagnosis prior to or after 24 weeks. In women who were diagnosed with GDM prior to 24 weeks (n = 2248), the median GA at diagnosis was 17.0 weeks (IQR: 13.3–20.7 weeks). Among these women who were diagnosed early in gestation, those who received glyburide had a higher odds of birthweight >4000 g (aOR = 1.57 [1.01–2.45]) or LGA > 90th centile (aOR = 1.65 [1.10–2.48]), and IUFD (aOR = 4.68 [1.02–21.5]; Table III), as compared to those receiving insulin. In women diagnosed with GDM after 24 weeks (n = 6556), the median GA at diagnosis was 28.7 weeks (IQR: 27.0–30.6 weeks). Among this subgroup, women who received glyburide were more likely to have PTD < 34 weeks (aOR = 1.75 [1.02–3.03]) and NICU admissions, even when delivered at term (aOR = 1.50 [1.01–2.23]; Table III).

To examine whether educational level would influence the allocation of GDM treatment options, the cohort was stratified by years of education into two groups: <9 years (less than high school education), and ≥9 years (high school education and above). In women who did not complete high school education, treatment with glyburide, compared to insulin injections, was associated with a lower risk of cesarean delivery but higher risks of PTD and NICU admissions in term deliveries (Table IV). In women who attended high school or beyond (≥9 years of education), the risk of cesarean delivery was lower in the glyburide group but the risk of having an IUFD was 3-fold higher with glyburide treatment compared to insulin (aOR = 3.33 [1.14–9.74]; Table IV).

The association between GDM treatment modality and perinatal outcomes was examined with stratification by primary language: Spanish/other language, or English. For women who reported either Spanish/other as their primary language, glyburide, compared to insulin, was associated with higher PTD < 34 weeks (aOR = 2.04 [1.18–3.54]), LGA > 90th centile (aOR = 1.40 [1.02–1.94]), and NICU admissions (aOR = 2.54 [1.55–4.13]) but a lower risk of cesarean delivery (Table V). In women who reported English as their primary language, the risk of overall cesarean delivery was also lower with glyburide compared to insulin, but their risk of IUFD was more than 5-fold that of the insulin group (Table V).

Discussion

In a large population of women diagnosed with GDM requiring medical therapy, we report that treatment with glyburide is associated with increased risk of undesirable perinatal outcomes, including higher birthweight or macrosomia, neonatal admissions to the intensive care nursery, as well as PTD and IUFD in some subsets of higher-risk populations. While most prior studies which compared oral hypoglycemic agents to subcutaneous insulin have focused on the efficacy of glyburide for glycemic control in women with GDM [11–13,18], the association between glyburide and perinatal outcome has not been examined in depth. Some of these studies have reported higher rates of preeclampsia, neonatal hyperbilirubinemia requiring phototherapy, longer stay in the intensive care nursery [12], macrosomia, and neonatal hypoglycemia [13] in women who were treated with glyburide; however, these important findings were not further explored. Our study findings confirmed

that the use of glyburide in women with GDM is associated with several undesirable neonatal outcomes.

Although we observed a modest increase in the risk of macrosomia and NICU admissions in women treated with glyburide, we did not have information regarding the occurrence of neonatal hypoglycemia. Besides the short-term implications of macrosomia, it has been reported that children born to women with GDM who were LGA at birth are at significantly increased risk of childhood metabolic syndrome with an onset as early as 6 years of age [19]. With respect to clinical utility, we attempt to estimate the number needed to treat from the adjusted odds ratios of our regression model for macrosomia. According to this analysis, the baseline frequency of macrosomia was 13%; if women treated with oral agents have 29% greater odds of having infants with macrosomias compared to insulin, the number needed to treat in order to avoid one case of macrosomia is 30. While this estimate may not be generalizable across all population, it is a relatively small number that may potentially have large impact on the long-term health in the children of diabetic mothers.

The American Diabetes Association (ADA) has cautioned that the use of glyburide for the treatment of GDM awaits larger studies to establish its safety [6], and the most recent ACOG practice guidelines state that subcutaneous insulin remains as the standard of care in women with GDM requiring medical therapy [1]. Yet, the utilization of oral hypoglycemic agents, particularly glyburide, has become an increasingly common practice [20]. Nearly one in five women with GDM was treated with glyburide in our cohort. Maternal characteristics associated with higher use of oral hypoglycemic agents included multiparity, Asian race/ethnicity, normal or low BMI, GA at GDM diagnosis between 20 and 32 weeks, less than high school education, and non-English as primary language. Further, in this cohort, we observed that a high proportion (39%) of women who were started on glyburide for treatment of GDM on initial visit was eventually placed on insulin therapy. While the precise reason for this crossover is uncertain, it is likely due to either intolerance of side effect or suboptimal glycemic control as previously reported by other studies [11,12]. Thus, it appeared that for the cohort of high-risk women who likely have overt hyperglycemia requiring medical therapy at time of GDM diagnosis, there is a high likelihood of need for insulin therapy.

Likely, treatment allocation is not random and clinicians may be more inclined to prescribe oral hypoglycemic agents to women considered at lower risk of insulin resistance given the reported ‘failure’ rate of glyburide of around 20% [11,15]. As our study was not a randomized trial, this difference in treatment allocation made the use of multivariable regression paramount in examining the outcomes associated with glyburide as compared to insulin.

In women who were diagnosed with GDM early in gestation (<24 weeks), glyburide use, compared to insulin, was associated with higher risk of macrosomia/LGA and IUFD. In this high-risk population, we speculate that suboptimal glycemic control and adverse outcomes are more likely with glyburide use.

We observed that the two groups of women who either did not attend high school, or do not speak English as their primary language, were more likely to receive glyburide as opposed to insulin. While it may be that these women were more likely to decline insulin therapy secondary to socio-cultural differences or perceptions regarding insulin, we also speculate that providers may have lacked the resources to adequately teach insulin administration to non-English speakers and/or were concerned about the ability of these women to self-administer insulin injections once appropriately taught. Despite these differences, when the subsets of women with lower education or who did not report English as their primary

language were analyzed, those treated with glyburide had worse perinatal outcome compared to those who received insulin.

Our study has limitations. First, treatment for a large proportion of the women in this cohort was designated as 'oral hypoglycemic agents;' however, of the women for whom we did have such information, nearly 99% were treated with glyburide. Prior to and during the study period, most studies on oral agents focused on glyburide, as no other agents have been shown to be safe and effective [1] until a recent large study on metformin use in GDM became available in 2008 [21]. Therefore, we speculate that nearly all women in this cohort who were treated with oral hypoglycemic agents received glyburide, with very few receiving metformin or other oral hypoglycemic agents. Of note, this limitation would only appear to bias our results toward the null as the most recent randomized controlled trial of metformin versus insulin was adequately powered and demonstrated no differences in outcomes between the two groups. Another limitation of our study is that there are a number of factors and outcomes often associated with diabetes in pregnancy which we could not examine, including prior history of macrosomia, presence of coexisting medical morbidity such as chronic hypertension, details of labor/delivery, and complications often related to hyperglycemia. While preexisting medical condition would have been interesting to examine as potential effect modifiers, we believe that they would not be associated with the exposure of interest (treatment modality of GDM for our study), and thus, by definition of confounding bias, they would likely not have biased our study results. Additionally, we did not have information regarding the degree of glycemic control or whether treatment was changed during pregnancy, since treatment groups were categorized based on treatment modality at the last Sweet Success visit. Thus, a small proportion of women who were initially started on oral hypoglycemic agents but subsequently switched to insulin were analyzed as belonging to the insulin group. Although this misclassification could be bi-directional, likely much fewer women who were started on insulin would be switched to oral agents. In this setting, the misclassification likely should bias our results toward the null. Since we consistently observed that glyburide was associated with undesirable outcomes, our findings are likely valid and may underestimate the true differences.

Our observational study design may be prone to confounding bias. Although we used statistical techniques to control for potential confounders, there may be residual confounding for which we could not observe or did not control for. Ideally, a large, double-blinded, randomized controlled trial would more accurately evaluate the causal association between glyburide for the treatment of GDM and perinatal outcomes. Specifically, assuming a 50% risk reduction, with a probability of event at 10%, the RCT would require 686 women in each arm to achieve 80% power. Until such information is available, the efficacy of glyburide remains debatable and subcutaneous insulin should remain the standard of care for the treatment of women with GDM requiring medical therapy.

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Table I

Maternal characteristics associated with women with GDM who were treated with either subcutaneous insulin or glyburide.

	Insulin injections (%), (*n* = 8609)	**Glyburide (%), (*n* = 2073)**	***p* value**
Parity			
Nulliparas (*n* = 2037)	77.5	22.5	$p < 0.001$
Multiparas (*n* = 8167)	81.5	18.5	
Age			
Maternal age < 19 (*n* = 104)	82.7	17.3	$p < 0.001$
Maternal age 20–34 (*n* = 5676)	79.1	20.9	
Maternal age >35 (*n* = 4484)	82.5	17.5	
Race/Ethnicity			
White (*n* = 2278)	81.9	18.1	$p < 0.001$
African American (*n* = 385)	77.7	22.3	
Latina/Hispanic (*n* = 5450)	81.1	18.9	
Asian (*n* = 1616)	75.1	24.9	
Other (*n* = 488)	83.2	16.8	
Body mass index (kg/m^2)			
<19.8 (*n* = 48)	75	25	$p < 0.001$
19.8–26.0 (*n* = 1774)	77.3	22.7	
26.1–29.0 (*n* = 2719)	79.3	20.7	
>29.0 (*n* = 5475)	82.2	17.8	
Gestational age at GDM diagnosis			
< 20 weeks (*n* = 1004)	80.3	19.7	$p = 0.001$
20–32 weeks (*n* = 3985)	78.7	21.3	
≥33 weeks (*n* = 147)	82.9	17.1	
Education (years)			
0–8 years (<high school; *n* = 1619)	80	20	$p < 0.001$
9–12 years (high school; *n* = 4934)	77.8	22.2	
>12 years (college and above; *n* = 2964)	83.4	16.6	
Primary language			
English (*n* = 5594)	82.9	17.2	$p < 0.001$
Spanish (*n* = 3848)	79.6	20.4	
Other (*n* = 1056)	73.9	26.1	

Table II

Maternal and neonatal outcomes associated with treatment modality of women diagnosed with GDM: Glyburide compared to subcutaneous insulin.

	Insulin injections (%) (*n* = 8609)	Glyburide (*n* = 2073)	Adjusted odds ratio* (aOR)	95% CI
Maternal outcome				
Cesarean delivery				
Overall cesarean (*n* = 4367)	44.9	38.8	0.77	0.65–0.91
Primary cesarean (*n* = 2251)	22.7	22.6	0.84	0.67–1.03
Neonatal outcome				
Preterm delivery				
<37 weeks (*n* = 1241)	11.5	12.2	0.97	0.75–1.24
<34 weeks (*n* = 221)	1.95	2.56	1.26	0.72–2.22
Birthweight				
>4000 g (*n* = 1307)	13.1	13.4	1.29	1.03–1.64
>4500 g (*n* = 358)	3.64	3.73	1.32	0.78–1.90
Birthweight >90th centile (*n* = 1833)	19	17.6	1.03	0.89–1.20
Intrauterine fetal demise (*n* = 37)	0.32	0.49	1.82	0.53–6.22
Neonatal intensive care admission† (*n* = 324)	6.47	8.12	1.46	1.07–2.00

Reference comparison group: women treated with subcutaneous insulin injections.

*Multivariable logistic regression controlling for potential confounding covariates including maternal age, parity, ethnicity, education status, gestational age at GDM diagnosis, gestational weight gain, primary language, education level, and prepregnancy BMI.

†In term pregnancies (gestational age at delivery > 37 weeks) only.

Table III

Subgroup analysis stratified by gestational age at GDM diagnosis (<24 and ≥24 weeks): Multivariable logistic regression analysis* of maternal and neonatal outcomes associated with glyburide compared to subcutaneous insulin.

	GDM diagnosis <24 weeks, (*n* = 2248)		GDM diagnosis ≥24 weeks, (*n* = 6556)	
	aOR	**95% CI**	**aOR**	**95% CI**
Maternal outcome				
Cesarean delivery				
Overall cesarean	0.74	0.60–0.91	0.74	0.64–0.85
Primary cesarean	0.79	0.61–1.62	0.84	0.71–1.01
Neonatal outcome				
Preterm delivery				
<37 weeks	1.30	0.94–1.81	0.99	0.78–1.24
<34 weeks	1.51	0.79–2.88	1.75	1.02–3.03
Birthweight				
>4000 g	1.57	1.01–2.45	1.03	0.83–1.30
>4500 g	1.55	0.91–2.65	0.92	0.59–1.44
Birthweight >90th centile	1.65	1.10–2.48	1.02	0.85–1.25
Intrauterine fetal demise	4.68	1.02–21.5	0.78	0.09–6.88
Neonatal intensive care unit admission†	1.39	0.71–2.71	1.50	1.01–2.23

Reference comparison group: women treated with subcutaneous insulin injections.

*Multivariable logistic regression controlling for potential confounding covariates, including maternal age, parity, ethnicity, education status, gestational weight gain, primary language, education level, and prepregnancy BMI.

†In term pregnancies (gestational age at delivery > 37 weeks) only.

Table IV

Subgroup analysis stratified by maternal education (less than high school [<9 years] and at least some high school [≥9 years]): Multivariable logistic regression analysis* of maternal and neonatal outcomes associated with glyburide compared to subcutaneous insulin.

	Education <9 years, (*n* = 1517)		Education ≥9 years, (*n* = 7435)	
	aOR	**95% CI**	**aOR**	**95% CI**
Maternal outcome				
Cesarean delivery				
Overall cesarean	0.72	0.54–0.97	0.81	0.71–0.92
Primary cesarean	0.87	0.58–1.31	0.92	0.79–1.08
Neonatal outcome				
Preterm delivery				
<37 weeks	1.65	1.08–2.52	1.03	0.84–1.26
<34 weeks	2.05	0.88–4.83	1.43	0.91–2.27
Birtdweight				
>4000 g	1.14	0.76–1.72	1.07	0.88–1.31
>4500 g	0.9	0.11–1.90	1.19	0.83–1.70
Birthweight >90th centile	1.17	0.83–1.67	1.06	0.89–1.26
Intrauterine fetal demise	0.82	0.09–7.72	3.33	1.14–9.74
Neonatal intensive care unit admission†	3.47	1.70–7.08	1.13	0.77–1.65

Reference comparison group: women treated with subcutaneous insulin injections.

*Multivariable logistic regression controlling for potential confounding covariates, including maternal age, parity, ethnicity, gestational age at GDM diagnosis, gestational weight gain, primary language, and prepregnancy BMI.

†In term pregnancies (gestational age at delivery >37 weeks) only.

Table V

Subgroup analysis stratified by primary language (English and Spanish/Other): Multivariable logistic regression analysis* of maternal and neonatal outcomes associated with oral hypoglycemic agents compared to subcutaneous insulin

	Spanish/Other (*n* = 4,335)		English (*n* = 5,273)	
	aOR	**95% CI**	**aOR**	**95% CI**
Maternal Outcome				
Cesarean delivery				
Overall cesarean	0.78	0.63–0.94	0.82	0.68–0.98
Primary cesarean	0.95	0.73–1.24	0.90	0.73–1.11
Neonatal Outcome				
Preterm delivery				
<37 weeks	1.12	0.83–1.53	0.99	0.75–1.31
<34 weeks	2.04	1.18–3.54	1.11	0.56–2.17
Birthweight				
>4,000gm	1.09	0.83–1.44	1.09	0.83–1.43
>4,500gm	1.07	0.65–1.76	1.12	0.68–1.83
Birth weight >90th centile	1.40	1.02–1.94	1.00	0.79–1.27
Intrauterine fetal demise	0.94	0.17–4.95	5.31	1.06–26.5
Neonatal intensive care unit admission†	2.54	1.55–4.13	0.86	0.48–1.56

Reference comparison group: women treated with subcutaneous insulin injections.

*Multivariable logistic regression controlling for potential confounding covariates, including maternal age, parity, ethnicity, gestational age at GDM diagnosis, gestational weight gain, education level, and prepregnancy BMI.

†In term pregnancies (gestational age at delivery >37 weeks) only.