


# Adverse Pregnancy Outcomes in Nondiabetic Patients with an Elevated Early Pregnancy HbA1c



Whitney R. Bender, MD<sup>1,2</sup>  Clare McCarthy, MPH<sup>3</sup> Michal Elovitz, MD<sup>1</sup> Samuel Parry, MD<sup>1</sup>  
Celeste Durnwald, MD<sup>1</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Maternal and Child Health Research Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

<sup>2</sup>Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Virginia Commonwealth University School of Medicine, Richmond, Virginia

<sup>3</sup>Maternal and Child Health Research Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

**Address for correspondence** Whitney R. Bender, MD, 1250 East Marshall Street, Richmond, VA 23298  
(e-mail: Whitney.bender@vcuhealth.org).

Am J Perinatol 2022;39:1496–1502.

## Abstract

**Objective** This study aimed to evaluate the impact of elevated early hemoglobin A1c (HbA1c) values on perinatal outcomes in patients without a diagnosis of diabetes or gestational diabetes.

**Study Design** This is a retrospective study of patients with a singleton pregnancy who underwent universal HbA1c screening in early pregnancy at an urban tertiary care center between December 1, 2016, and December 31, 2018. Patients with pregestational diabetes mellitus (DM) and gestational DM (GDM) were excluded from analysis. The exposure of interest was HbA1c of 5.7 to 6.4% as measured on routine prenatal bloodwork at or during 16 weeks' gestation. The following pregnancy outcomes were assessed: preterm delivery <37 weeks, hypertensive disorders of pregnancy, shoulder dystocia, macrosomia (birth weight >4,000 g), small or large for gestational age neonate, operative vaginal delivery, third- or fourth-degree lacerations, cesarean delivery, neonatal intensive care unit (NICU) admission, neonatal hypoglycemia, and neonatal hyperbilirubinemia. Multivariable regression was performed to assess the relationship between HbA1c and selected adverse outcomes while controlling for potential confounders

**Results** Of the 2,621 patients who met inclusion criteria, 334 (12.7%) had an elevated HbA1c of 5.7 to 6.4%. Patients with an elevated HbA1c were more likely to be older, Black, multiparous, publically insured, obese, or have chronic hypertension than patients with normal HbA1c values. In the unadjusted analysis, patients with an elevated HbA1c were less likely to deliver at term (84.7 vs. 92.4%,  $p = 0.006$ ), but more likely to undergo cesarean section (32.8 vs. 27.6%,  $p = 0.038$ ), develop hypertensive disorders of pregnancy (31.9 vs. 23.2%,  $p = 0.001$ ), or deliver a macrosomic infant (10.5 vs. 6.8%,  $p = 0.016$ ) than those with a normal A1c. After adjusting for race, body mass

## Keywords

- ▶ HbA1c
- ▶ preterm birth
- ▶ adverse outcomes
- ▶ glucose tolerance

received  
February 14, 2021  
accepted after revision  
June 3, 2022  
published online  
July 5, 2022

© 2022. Thieme. All rights reserved.  
Thieme Medical Publishers, Inc.,  
333 Seventh Avenue, 18th Floor,  
New York, NY 10001, USA

DOI <https://doi.org/10.1055/a-1877-8696>.  
ISSN 0735-1631.

index, insurance status, nulliparity, and age, however, only the relationship between HbA1c and spontaneous preterm birth remained significant (adjusted odds ratio [aOR] = 1.76, 95% confidence interval [CI]: 1.01–3.07).

**Conclusion** In our urban population, an elevated early HbA1c was associated with spontaneous preterm birth in nondiabetic patients

## Key Points

- In nondiabetic patients, early pregnancy HbA1c was associated with selected adverse outcomes.
- Rates of preterm birth, pregnancy-induced hypertension, cesarean section, and macrosomia were higher in patients with an elevated HbA1c.
- The relationship between early pregnancy HbA1c and spontaneous preterm birth remained significant after adjustment.

Glucose intolerance in pregnancy increases the risk of adverse perinatal outcomes.<sup>1</sup> In patients with diabetes, higher hemoglobin A1c (HbA1c) values at the beginning of pregnancy are associated with an increased risk of spontaneous abortion, congenital malformations, preterm delivery, and preeclampsia.<sup>1</sup>

An elevated HbA1c in early pregnancy has also been found to be associated with an increased risk for gestational diabetes mellitus (GDM). Although GDM increases the risk of adverse pregnancy outcomes, whether impaired glucose tolerance in early pregnancy is also associated with an increased risk of adverse perinatal outcomes in patients who are not diagnosed with gestational diabetes is not well studied.

One large retrospective study in New Zealand of patients with an elevated HbA1c of >5.9% found an increased risk of preterm birth, hypertensive disorders of pregnancy, shoulder dystocia, large for gestational age infant, and perinatal death. These findings have not been confirmed in subsequent published reports.<sup>2–6</sup> Importantly, these studies have varied with respect to gestational age at the time of HbA1c measurement, the diversity of the population, and the inclusion of patients with GDM.

With these limitations in mind, the purpose of our study is to evaluate the association of early pregnancy HbA1c values and adverse pregnancy outcomes among nondiabetic patients.

## Materials and Methods

A retrospective cohort study was conducted at an urban tertiary care center of patients undergoing universal HbA1c screening at <17 weeks' gestation with a singleton pregnancy. The Institutional Review Board (IRB) at the University of Pennsylvania approved this study. Universal HbA1c screening was initiated in September 2016 as standard of care due to the high proportion of reproductive age patients entering pregnancy that met criteria for screening for prediabetes and diabetes based on American Diabetes Association (ADA) recommendations.<sup>7</sup> HbA1c level was measured using high performance liquid chromatography (HPLC). The Trinity Biotech Premier HB9210 analyzer was utilized for sample testing. This method is traceable to the International Federation of Clinical Chemistry (IFCC) method and is certified by the National Glycohemoglobin Standardization Program (NGSP). **Fig. 1** details the institutional protocol for GDM screening based on HbA1c screening value.

Patients were included in this study if they underwent HbA1c screening between December 1, 2016, and December 31, 2018. December 2016 was chosen, as this was the time at which all providers had accepted and implemented universal HbA1c screening approximately 3 months after roll out of the institution protocol change. Additionally, all patients who were screened at or after this date had all of their medical care documented in a single electronic medical record (EMR). Patients were excluded if they had preexisting DM, a screening HbA1c of  $\geq 6.5\%$ , were diagnosed with gestational diabetes as outlined in **Fig. 1**, or had their screening HbA1c drawn after 16 completed weeks of pregnancy. Patients who did not complete any glucose tolerance testing, who were pregnant with a multiple gestation, or who delivered at an outside institution were also excluded.

Demographic, obstetric, and pregnancy outcome data were collected from the EMR. Race and ethnicity were self-reported by the patient. Investigators were not blinded to the HbA1c results at the time of chart review.

The exposure of interest in this study was screening HbA1c value. An elevated HbA1c was defined as 5.7 to 6.4% consistent with impaired glucose tolerance or prediabetes as per the ADA standards of medical care.<sup>8</sup> HbA1c was analyzed as a dichotomous variable of normal versus abnormal. The following pregnancy outcomes were assessed: spontaneous abortion, intrauterine fetal demise (IUFD), preterm delivery at 24 to 37 weeks, hypertensive disorders of pregnancy,

### Universal HbA1c screening protocol

- HbA1c  $\geq 5.7\%$ : early two-step<sup>1</sup> GDM screening.
  - If abnormal<sup>2</sup>: early GDM diagnosed.
  - If normal: repeat two-step screening third trimester.<sup>3</sup>
- HbA1c < 5.7%: routine two-step<sup>1</sup> third trimester screening.
- HbA1c  $\geq 6.5\%$  - Diagnosis of type 2 DM

**Fig. 1** Universal HbA1c screening protocol. GDM, gestational diabetes mellitus; Hb, hemoglobin.

shoulder dystocia, macrosomia (birth weight >4,000 g), small (<10%) or large (>90%) for gestational age neonate, operative vaginal delivery, third- or fourth-degree lacerations, cesarean delivery, neonatal intensive care unit (NICU) admission, neonatal hypoglycemia (blood glucose <40 mg/dL) requiring intervention, and neonatal hyperbilirubinemia requiring phototherapy.

Spontaneous abortion (SAB) was defined as a pregnancy loss as <20 weeks' gestation and IUD were defined as the absence of fetal cardiac activity after 20 weeks' gestation. Patients with these outcomes were excluded from analysis on the remaining pregnancy outcomes.

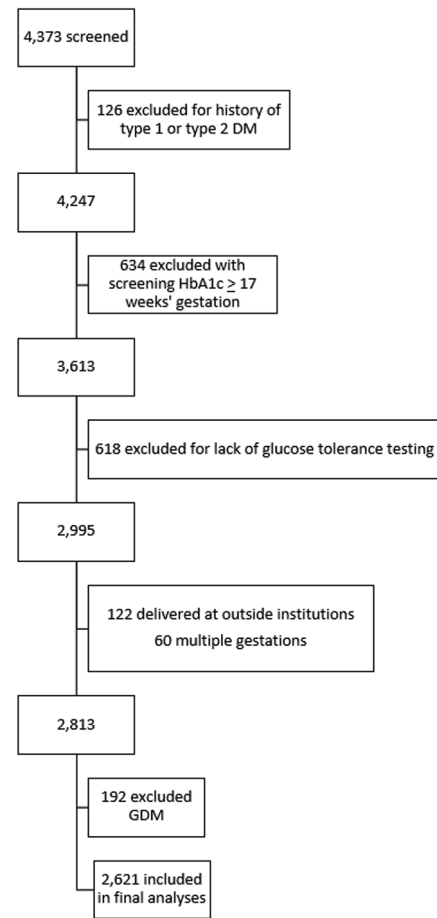
Preterm delivery was defined as delivery occurring between 24 and 37 weeks' gestation. Spontaneous preterm births included cases of preterm delivery following spontaneous onset of uterine contractions or rupture of membranes. Medically indicated preterm births included preterm delivery in the absence of labor or ruptured membranes. All incidents of preterm birth were adjudicated by the primary author (W.R.B.) to determine whether they were medically indicated or spontaneous.

Hypertensive disorders of pregnancy were defined in accordance with the American College of Obstetricians and Gynecologists (ACOG) recommendations.<sup>9</sup> Gestational hypertension was defined as the occurrence of two or more blood pressures of >140/90 at least 4 hours apart after 20 weeks' gestation. Preeclampsia was defined as gestational hypertension plus proteinuria ( $\geq 300$  mg of protein in 24-hour urine collection or urine protein/creatinine ratio  $\geq 0.3$ ). Preeclampsia with severe features was defined as gestational hypertension plus one of the following: thrombocytopenia with platelets <100,000, renal insufficiency with creatinine  $\geq 1.1$  or double patient's known baseline, liver dysfunction with transaminases  $\geq$  twice the upper limit of normal, pulmonary edema, or new-onset and intractable headache. The occurrence of shoulder dystocia, operative vaginal delivery, third- or fourth-degree lacerations and cesarean delivery were abstracted directly from delivery records.

The sample size was fixed based on the number of patients presenting for prenatal care within the study period. The association of categorical variables with binary outcomes was analyzed using Chi-square test or Fisher's exact test, where appropriate. The associations of continuous variables with binary outcomes were analyzed using Student's *t*-test or Wilcoxon's rank-sum test, as appropriate. Potential confounders were assessed using a backward selection process and included in the final model if they were clinically meaningful or altered the association of interest by >10%. Multivariable regression was performed to assess the relationship between HbA1c and selected adverse outcomes. A post hoc power calculation determined that this sample size, with an  $\alpha$  of 0.05, had 80% power to detect a 50% difference in the rate of spontaneous preterm birth.

## Results

Of the 4,373 patients who underwent HbA1c screening during the 2-year study, 2,621 (58.7%) met inclusion criteria



**Fig. 2** Study population. DM, diabetes mellitus; GDM, gestational DM; Hb, hemoglobin.

(**Fig. 2**). As noted in the **Fig. 2**, gestational diabetes was diagnosed in 192 patients, 71 (37%) of which had an early elevated A1c. These patients were excluded from the analysis. Of the 2,621 patients included in the final analysis, 334 (12.7%) had an elevated HbA1c of 5.7 to 6.4%.

Clinical characteristics of the population stratified by normal or elevated HbA1c are presented in **Table 1**. The mean gestational age at which the HbA1c blood draw occurred was 10 weeks (range: 3.6–16.9 weeks). Patients with an elevated early HbA1c were more likely to be older, Black, multiparous, publically insured, obese, or have chronic hypertension than patients with normal early HbA1c values.

Pregnancy outcomes are presented in **Table 2**. Eight patients had an IUD at >20 weeks' gestation, and 11 patients had a spontaneous abortion before 20 weeks' gestation. All of the patients who experienced an IUD had a normal HbA1c in early pregnancy. In contrast, all 11 patients who experienced a spontaneous abortion had an elevated HbA1c (median = 5.8%, range: 5.7–6.4%). These women were excluded from analysis on additional pregnancy outcomes.

As shown in **Table 2**, patients with elevated early HbA1c were more likely to be diagnosed with a hypertensive disorder of pregnancy, deliver preterm, and undergo cesarean delivery compared with their counterparts with normal early HbA1c values. They were also more likely to have a

<b>Table 1</b> Clinical characteristics among women with normal versus elevated screening HbA1c value ( <i>n</i> = 2,621)			
	Normal screening HbA1c (<5.7%) <i>n</i> = 2,287 <i>n</i> (col %)	Elevated screening HbA1c (5.7–6.4%) <i>n</i> = 334 <i>n</i> (column%)	<i>p</i> -Value
Maternal age (y) Mean (SD)	29.8 (5.6)	30.8 (5.9)	0.004 <sup>a</sup>
Gestational age at HbA1c screening Mean (SD)	10.2 (2.5)	10.3 (2.4)	0.55 <sup>a</sup>
Maternal race <sup>b</sup>			<0.001
White	648 (28.8)	30 (9.1)	
Black	1,203 (53.4)	253 (76.9)	
Asian	233 (10.4)	23 (7.0)	
Other	168 (7.5)	23 (7.0)	
Maternal ethnicity <sup>c</sup>			0.28
Non-Hispanic/non-Latino	2,172 (95.0)	318 (95.2)	
Hispanic/Latino	111 (4.9)	14 (4.2)	
Nulliparous	1,184 (51.8)	116 (34.7)	<0.001
Insurance status			<0.001
None	58 (2.5)	11 (3.3)	
Medicaid	1,247 (54.5)	141 (42.2)	
Private	942 (41.2)	175 (52.4)	
Other	40 (1.8)	7 (2.1)	
BMI at first prenatal visit (kg/m <sup>2</sup> ) Mean (SD) <sup>d</sup>	27.2 (6.8)	32.1 (8.1)	<0.001 <sup>a</sup>
BMI at first prenatal visit (kg/m <sup>2</sup> )			<0.001
Underweight/normal (<25)	1,065 (46.7)	65 (19.5)	
Overweight (25–30)	583 (25.6)	87 (26.1)	
Obese (≥30)	631 (27.7)	181 (54.4)	
Chronic hypertension	109 (4.8)	26 (8.1)	0.013

Abbreviations: BMI, body mass index; Hb, hemoglobin; SD, standard deviation.

Note: Data presented as *n* (col %), Chi-square *p*-value, unless otherwise indicated.

<sup>a</sup>Two-sided *t*-test.

<sup>b</sup>*n* = 40 missing race.

<sup>c</sup>*n* = 6 missing ethnicity.

<sup>d</sup>*n* = 9 missing BMI at first prenatal visit.

macrosomic infant. Conversely, patients with elevated early HbA1c were less likely to have a third- or fourth-degree laceration. There was no difference in overall birth weight, neonatal hypoglycemia, or neonatal hyperbilirubinemia.

In the unadjusted analysis, the odds of a preterm birth were nearly two-time higher among patients with an elevated early HbA1c compared with those patients with normal early HbA1c (95% confidence interval [CI]: 1.25–2.60; **Table 3**). After adjusting for race, first prenatal visit body mass index (BMI), insurance status, nulliparity, and age, only spontaneous preterm birth remained significant. The odds of spontaneous preterm birth among patients with an elevated early HbA1c were 1.76 times that of patients with normal early HbA1c values (95% CI: 1.01–3.07). Of the patients who had a spontaneous preterm birth, the mean gestational age among patients with an elevated HbA1c was 34.2 compared with 34.7 weeks' gestation in patients with normal HbA1c values (*p* = 0.42). There was, however, no difference in NICU admission between the two groups.

Patients with elevated early HbA1c had higher odds of both cesarean delivery and a diagnosis of hypertensive disorder of pregnancy in the unadjusted analysis compared with patients with normal early HbA1c. Neither of these relationships remained statistically significant in the adjusted analysis.

## Discussion

We have shown that elevated early HbA1c values between 5.7 and 6.4% are associated with an increased risk of preterm birth at <37 weeks in nondiabetic patients. Patients with elevated HbA1c screening values remained at increased risk of spontaneous preterm birth after adjustment for confounders, including age, race, insurance status, nulliparity, and initial BMI. This finding highlights the potential for metabolic abnormalities below current thresholds for diabetes diagnosis, independent of other commonly associated

**Table 2** Pregnancy and delivery characteristics among women with by normal versus elevated screening HbA1c value ( $n = 2,602$ )<sup>a</sup>

	Normal screening HbA1c (<5.7%) $n = 2,287$ $n$ (col %)	Elevated screening HbA1c (5.7–6.4%) $n = 334$ $n$ (col %)	$p$ -Value
Birth outcome <sup>b</sup>			0.006
Spontaneous preterm birth	79 (3.5)	18 (5.6)	
Medically indicated preterm birth	87 (3.8)	22 (6.8)	
Term	2,113 (92.7)	283 (87.6)	
Gestational age at delivery (wk) Mean (SD)	39.1 (1.7)	38.7 (2.2)	0.001 <sup>c</sup>
Mode of delivery			0.038
Cesarean	628 (27.6)	106 (32.8)	
Spontaneous vaginal	1,523 (66.8)	207 (64.1)	
Operative vaginal	128 (5.6)	10 (3.1)	
Indication for cesarean <sup>d</sup>			0.633
Planned repeat	152 (31.5)	28 (37.8)	
Malpresentation	27 (5.6)	3 (4.1)	
Nonreassuring fetal status	124 (25.7)	17 (23.0)	
Labor arrest (first or second stage)	97 (20.1)	11 (14.9)	
Other/unknown	82 (31.5)	15 (20.3)	
Shoulder dystocia <sup>e</sup>	46 (2.8)	9 (4.2)	0.28 <sup>f</sup>
Third-/fourth-degree laceration <sup>e</sup>	108 (6.5)	4 (1.8)	0.004 <sup>f</sup>
Preeclampsia/gestational HTN	531 (23.2)	103 (31.9)	0.001
Maternal length of stay (d) Median [IQR]	2 [2,3]	2 [2,3]	0.19 <sup>g</sup>
Birth weight (g) Mean (SD)	3,257.7 (825.8)	3,203.5 (582.6)	0.25 <sup>c</sup>
Large for gestational age infant	115 (5.1)	19 (5.9)	0.52
Small for gestational age infant	630 (27.6)	99 (30.7)	0.26
Macrosomia <sup>h</sup>	156 (6.8)	35 (10.5)	0.016
Neonatal Intensive care unit admission	237 (10.4)	38 (11.8)	0.46
Neonatal hypoglycemia	106 (4.7)	17 (5.3)	0.63
Neonatal hyperbilirubinemia	173 (7.6)	20 (6.2)	0.37
Neonatal length of stay (d) Median [IQR]	2 [2,3]	2 [2,3]	0.55 <sup>g</sup>

Abbreviations: Hb, hemoglobin; HTN, hypertension; IQR, interquartile range; SD, standard deviation; SAB, spontaneous abortion.

Note: Data presented as  $n$  (col %), Chi-square  $p$ -value, unless otherwise indicated.

<sup>a</sup>Applies to patients who did not have intrauterine fetal demise or SAB ( $n = 2,602$ )

<sup>b</sup>Preterm birth defined as a live birth at <37 weeks' gestational age.

<sup>c</sup>Two-sided  $t$ -test.

<sup>d</sup>Among patients who had a cesarean section ( $n = 734$ ).

<sup>e</sup>Among patients who had a vaginal delivery ( $n = 1,868$ ).

<sup>f</sup>Fisher's exact  $p$ -value.

<sup>g</sup>Wilcoxon's rank-sum test.

<sup>h</sup>Birth weight >4,000 g.

comorbidities, to impact obstetric outcomes and adds to a growing body of literature on this subject.

In a prospective cohort study of HbA1c screening with initial prenatal laboratories in New Zealand, Hughes et al showed that early elevated A1c of  $\geq 5.9\%$  was associated with an increased risk of preterm delivery at <37 weeks, pre-

eclampsia, major congenital anomalies, shoulder dystocia, large for gestational age, and perinatal death.<sup>2</sup> Although they excluded patients diagnosed with GDM in their analysis similar to our study, their findings are limited by an ethnically homogeneous group of patients, a smaller number of patients with elevated A1c and lack of adjustment for

**Table 3** Association between HbA1c  $\geq 5.7\%$  and selected adverse outcomes

	Crude OR (95% CI)	aOR (95% CI)
Preterm birth <37 weeks <sup>a,b</sup>	1.80 (1.25–2.60)	1.47 (1.00–2.18)
Spontaneous preterm birth <sup>a,c</sup>	1.70 (1.00–2.88)	1.76 (1.01–3.07)
Medically indicated preterm birth <sup>a,d</sup>	1.89 (1.16–3.06)	1.26 (0.75–2.12)
Cesarean delivery <sup>a,b</sup>	1.29 (1.00–1.66)	0.94 (0.72–1.24)
Hypertensive disorders of pregnancy <sup>a,b,e</sup>	1.55 (1.21–2.00)	1.26 (0.95–1.66)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; Hb, hemoglobin.

<sup>a</sup>Adjusted for race, body mass index (BMI), and insurance status, nulliparity, and age unless otherwise indicated. Missing  $n = 36$  for race and  $n = 9$  for BMI.

<sup>b</sup> $n = 2,602$ .

<sup>c</sup> $n = 2,493$  ( $n = 109$  medically indicated preterm births [PTBs] excluded).

<sup>d</sup> $n = 2,505$  ( $n = 97$  spontaneous PTBs excluded).

<sup>e</sup>Hypertensive disorders of pregnancy including gestational hypertension, preeclampsia, superimposed preeclampsia, and severe preeclampsia.

additional confounders that could have contributed to the heightened risk of adverse perinatal outcomes. In our study, the relationship between early elevated HbA1c and spontaneous preterm birth persisted after adjustment for important cofounders. In contrast, risk of medically indicated preterm birth, hypertensive disorders of pregnancy, and cesarean delivery were no longer statistically significant. Additionally, their utilization of 5.9% rather than the clinically accepted cut-off value of 5.7% to indicate impaired glucose tolerance limits applicability. This same cut-off value was utilized in a Spanish study by Mane et al that found an increased rate of macrosomia and preeclampsia in the 48 patients with an HbA1c of  $>5.9\%$ .<sup>3</sup> In contrast, a retrospective cohort study of 504 patients in Greenland found no association between HbA1c of  $>5.7\%$  and birth weight.<sup>6</sup> These findings are limited by inclusion of patients with a diagnosis of GDM and a small sample size.

The hyperglycemia and pregnancy outcome (HAPO) study found an association between elevated HbA1c values and birth weight of  $>90$  percentile, cesarean section, preterm birth, and preeclampsia in nondiabetic patients.<sup>10</sup> In this study, HbA1c was drawn at 24 to 32 weeks' gestation at the time of glucose tolerance testing, thereby limiting their ability to draw conclusions regarding the importance of prepregnancy or early pregnancy impaired glucose tolerance. Furthermore, in this study, 4.8% of patients had an HbA1c of  $\geq 5.5\%$ ; they do not specify the exact number of patients meeting the clinically accepted cut-off value of 5.7%. In contrast, our study focused on early pregnancy HbA1c to determine the impact of glucose intolerance (defined using the ADA cut-off of 5.7%) on adverse pregnancy outcomes in nondiabetic patients.

In a large retrospective cohort from the Kaiser Permanente Washington, Chen and colleagues compared maternal and neonatal outcomes in 7,020 patients with HbA1c screening prior to 20 weeks' gestation. In their adjusted analysis, they found no difference in preterm delivery, preeclampsia, or cesarean delivery in patients with HbA1c  $>5.7\%$  compared with patients with normal screening HbA1c.<sup>5</sup> Similar to prior studies, the analysis included patients diagnosed with GDM when evaluating the association between screening HbA1c and adverse perinatal outcomes. Despite a large number of

patients studied, only 239 (3.4%) had an A1c of 5.7 to 6.4%. In contrast, in our study, 334 patients had an HbA1c consistent with impaired glucose tolerance which accounted for 12% of our study population after excluding those diagnosed with GDM. Clinical characteristics of the patients studied were also different. In the Kaiser study, only 6.6% of the patients studied were Black race compared with 55% of patients in our study. We also had a higher proportion of obese women (31%) compared with the Kaiser study (21.1%).

## Strengths and Limitations

This study has several strengths compared with those previously described. We examined a large, diverse cohort of patients with a high rate of impaired glucose tolerance (12%) at the beginning of pregnancy. We used the ADA definition of impaired glucose tolerance for HbA1c measurement which is a standardized and clinically useful measure of metabolic dysfunction. All patients in this retrospective cohort study had universal HbA1c screening performed per institution protocol, thereby limiting clinician bias as to who should undergo early screening for GDM. We then excluded patients diagnosed with GDM and controlled appropriately for additional cofounders in our analyses to assess the relationship between HbA1c and adverse outcomes independent of GDM.

This is a single-center study; therefore, despite the diverse population, these results may not be widely generalizable. This study is also limited by exclusion of patients who underwent A1c screening beyond the 17th week of the pregnancy and those who did not complete any glucose screening. Therefore, we are unable to comment on the metabolic status or pregnancy outcomes of these patients and cannot determine the impact of their exclusion on our results. We evaluated the relationship of HbA1c to multiple adverse obstetric and neonatal outcomes and must acknowledge the potential for type-1 error to account for our findings. The use of multiple primary outcomes could increase the chance of finding a significant difference by chance, yet we felt that it was necessary to separate the outcomes, as the physiologic pathway between HbA1c and different adverse outcomes in pregnancy could vary significantly. Importantly,

we did not have data on whether prior preterm births were spontaneous or iatrogenic, so were unable to adequately control for history of spontaneous preterm birth. Furthermore, although we were able to control for several clinically significant confounders, there may be residual confounding for which we were unable to account. Lastly, although no clinical recommendations were made to patients with an elevated HbA1c, we cannot guarantee that lifestyle modifications were not made independently by these patients. If this occurred, however, it would bias our results to the null. Therefore, its potential occurrence only serves to strengthen the primary results of our study.

The mechanism by which an elevated HbA1c would increase the risk of spontaneous preterm birth is unknown. In patients with diabetes, an elevated HbA1c results in microvascular and macrovascular complications. It is unclear if impaired glucose tolerance below current diagnostic thresholds for either GDM or type-2 diabetes has the potential to alter biological processes that may contribute to the pathogenesis of preterm birth such as altered vascularity or cervicovaginal microbiota. An elevated HbA1c may also be indicative of a metabolic syndrome phenotype beyond the standard comorbidities that we adjusted for in this analysis. The inflammation associated with this disorder could contribute to preterm birth.

Basic and translational research assessing the mechanistic association between milder degrees of altered glucose metabolism and spontaneous preterm birth is warranted. The association between HbA1c and spontaneous preterm birth in our study population should be explored more thoroughly to identify and describe clinical characteristics and/or environmental factors, such as dietary patterns or social stressors, that may also influence this relationship. Additional research is warranted to determine the efficacy of lifestyle modifications or medication to alter adverse pregnancy outcomes in patients with an elevated early HbA1c.

## Conclusion

In conclusion, this retrospective cohort study found a 1.7-fold increased risk of spontaneous preterm birth in

nondiabetic patients with an elevated HbA1c in early pregnancy. Although the mechanisms of this association remain uncertain, this is an important area of future research as the rate of impaired glucose tolerance is expected to continue to rise among reproductive-aged patients.

## Conflict of Interest

None declared.

## References

- 1 American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin no. 201: pregestational diabetes mellitus. *Obstet Gynecol* 2018;132(06):e228–e248
- 2 Hughes RC, Moore MP, Gullam JE, Mohamed K, Rowan J. An early pregnancy HbA1c  $\geq$ 5.9% (41 mmol/mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes. *Diabetes Care* 2014;37:2953–2959
- 3 Mañé L, Flores-Le Roux JA, Gómez N, et al. Association of first-trimester HbA1c levels with adverse pregnancy outcomes in different ethnic groups. *Diabetes Res Clin Pract* 2019;150:202–210
- 4 Osmundson SS, Zhao BS, Kunz L, et al. First trimester hemoglobin A1c prediction of gestational diabetes. *Am J Perinatol* 2016;33(10):977–982
- 5 Chen L, Pocobelli G, Yu O, et al. Early pregnancy hemoglobin A1c and pregnancy outcomes: a population-based study. *Am J Perinatol* 2019;36(10):1045–1053
- 6 Rasmussen KV, Nielsen KK, Pedersen ML. No association between early maternal HbA1c and offspring birthweight among women without pre-existing diabetes in Greenland. *Int J Circumpolar Health* 2020;79(01):1702798
- 7 American Diabetes Association. 14. management of diabetes in pregnancy: Standards of Medical Care in Diabetes-2019. *Diabetes Care* 2019;42(Suppl 1):S165–S172
- 8 American Diabetes Association. 2. classification and diagnosis of diabetes: Standards of Medical Care in Diabetes-2018. *Diabetes Care* 2018;41(Suppl 1):S13–S27
- 9 ACOG Practice Bulletin No. 202: gestational hypertension and preeclampsia. *Obstet Gynecol* 2019;133:1
- 10 Lowe LP, Metzger BE, Dyer AR, et al; HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: associations of maternal A1c and glucose with pregnancy outcomes. *Diabetes Care* 2012;35(03):574–580