OBSTETRICS

Use of hemoglobin A1c as an early predictor of gestational diabetes mellitus

Alex Fong, MD; Allison E. Serra, MD, MPH; Lauryn Gabby, BSc; Deborah A. Wing, MD; Kathleen M. Berkowitz, MD

OBJECTIVE: The purpose of this study was to assess an early hemoglobin A1c (HgbA1c) value from 5.7-6.4% as an early predictor of progression to gestational diabetes (GDM).

STUDY DESIGN: A retrospective cohort study was performed on all women who delivered at a single institution over 2 years who had an early screening HgbA1c test performed at ≤20 weeks of gestation. Women with known preexisting diabetes mellitus or HgbA1c values ≥6.5% were excluded. The primary outcome was GDM development. Secondary outcomes included delivery route, maternal weight gain, birthweight, and neonatal morbidities. Women with an HgbA1c value of 5.7-6.4% were compared with those with an HgbA1c level of <5.7%.

RESULTS: Nearly one-third of those patients in the HgbA1c 5.7-6.4% group (27.3%) experience the development of GDM compared with only 8.7% in the HgbA1c <5.7% group (odds ratio, 3.9; 95% confidence level, 2.0—7.7). This 3-fold increase remained significant (adjusted odds ratio, 2.4) after adjustment for age, prepregnancy body mass index, gestational age at HgbA1c collection, gestational age at screening, ethnicity, and method of screening. There were no significant differences in the need for medical treatment, weight gain, delivery route, birthweight, macrosomia, or neonatal morbidities.

CONCLUSION: More than 10% of patients in our cohort had an early screening HgbA1c value of 5.7-6.4%. Women in this group have a significantly higher risk of progression to GDM compared with women with normal HgbA1c values and should be considered for closer GDM surveillance and possible intervention.

Key words: gestational diabetes mellitus, hemoglobin A1c

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Gestational diabetes mellitus (GDM) is an increasingly common maternal condition with proven maternal and fetal morbidity and a prevalence of approximately 6-8% in the United States.[1,2] The prevalence of GDM is even higher in obese pregnancies, ranging from 7-14%[3,4] Associated fetal risks of GDM include fetal death, macrosomia, shoulder dystocia, hypoglycemia, respiratory distress syndrome, and childhood obesity. Maternal risks include preeclampsia, cesarean delivery, and, importantly, increased risk of the development of type 2 diabetes mellitus later in life.[5-10] GDM also carries an economic burden that results in an increase of 25-34% in maternity care costs and a 49% increase in neonatal intensive care unit costs, compared with those pregnancies without GDM.[11,12] Identification and treatment of even mild GDM may reduce adverse pregnancy outcome, which underscores the need to screen properly for and diagnose this important comorbidity.[6,13]

Glycated hemoglobin (HgbA1c) is a form of hemoglobin that characterizes a patient's plasma glucose over a prolonged period of time.[14] It is typically used in the nonpregnant population as both a screening tool for diabetes mellitus and as a tool to assess the glycemic control of known diabetic patients.[15,16] HgbA1c has limited efficacy in the diagnosis of GDM in the third trimester and has demonstrated, at best, moderate sensitivity (85.7%), but poor specificity (61.1%).[17,18] Compared with maternal glucose levels, HgbA1c has been shown to be less predictive of certain adverse pregnancy outcomes.[19] In the United States, its use has not been standardized for GDM management by the American College of Obstetrics and Gynecology (ACOG) or the United States Preventive Services Task Force.[20,21] In contrast, organizations such as the American Diabetes Association (ADA) and the International Association of Diabetes in Pregnancy Study Group (IADPSG) support its use in pregnancy.[22]

Our practice uses an early GDM screening strategy whereby all patients, regardless of prepregnancy GDM risk, undergo an early screening HgbA1c at their first prenatal visit. If patients have HgbA1c value of ≥6.5%, they are diagnosed automatically as having overt diabetes mellitus and are referred

From the Department of Obstetrics and Gynecology, University of California, Irvine, Orange, CA (Drs Fong, Serra, and Wing); School of Medicine, University of California, Irvine, Irvine, CA (Ms Gabby); and Department of Obstetrics and Gynecology, MemorialCare Center for Women at Miller Children's Hospital Long Beach, Long Beach, CA (Dr Berkowitz).

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Corresponding author: Alex Fong, MD. alex_fong@pediatrix.com

immediately for diabetic counseling and treatment. If their HgbA1c value is <6.5%, they do not typically undergo any additional GDM testing until 24-28 weeks of gestation, at which time they undergo routine oral glucose tolerance testing.

O'Connor et al[23] investigated normal values for HgbA1c in pregnancy in nondiabetic women and identified a normal reference interval of 4.3-5.4% in the first trimester. In the nonobstetric population, it has been shown that an HbgA1C value of 5.7-6.4% indicates impaired glucose tolerance and a high risk of future diabetes.[24] HgbA1c levels of 5.5-6.0% have been associated with a 5-year cumulative incidence of diabetes mellitus that range from 12-25%.[15] This study aims to correlate early HgbA1c levels and the subsequent development of GDM. Given the evidence that an HgbA1C level of 5.7-6.4% indicates impaired glucose tolerance and is associated with development of diabetes mellitus in nonpregnant patients, we hypothesized that those patients with HgbA1C levels of 5.7-6.4% are at increased risk for the development of GDM when compared with those patients with an HgbA1c level of <5.7%. We also sought to assess differences in pregnancy and neonatal outcomes between these 2 groups.

Materials and Methods

This was a retrospective study of a cohort of patients from MemorialCare Center for Women at Miller Children's Hospital in Long Beach, CA. Women were included if they had a screening HgbA1c test at ≤20 0/7 weeks of gestation and had been delivered by our practice from January 2011 to January 2013. Women were excluded if they had known pregestational diabetes mellitus, their HgbA1c result was ≥6.5% (which indicates overt diabetes mellitus), they never underwent GDM screening or assessment, or ultimately did not deliver at our institution. The MemorialCare Health Systems Institutional Review Board approved the study. A comprehensive prenatal chart review was performed with the use of both inpatient and outpatient data.

The 2 groups that were used for our comparative analyses were patients with HgbA1c levels of 5.7-6.4% vs those with HgbA1c levels of <5.7%. The primary outcome was the development of GDM. Secondary outcomes included other maternal and delivery characteristics (route of delivery, weight gain, and glucose values at time of GDM screening). Neonatal outcomes included a composite of adverse outcomes such as neonatal intensive care unit admission, neonatal hypoglycemia, hyperbilirubinemia, transient tachypnea, or acute respiratory distress. Other neonatal outcomes included 5-minute Apgar score <7, birthweight, macrosomia (defined as birthweight >4 kg), small for gestational age (defined as birthweight <10th percentile), and intrauterine fetal death.

Recent Los Angeles and Orange County healthcare surveys have demonstrated the prevalence of GDM to be 7-12% in our area.[25,26] Based on these figures, we estimated that patients with an HgbA1c level of <5.7% would have a lower GDM prevalence of approximately 5%, which is slightly lower than the local GDM prevalence. To detect a clinically significant increase in GDM prevalence from 5% in the group with an HgbA1c level of <5.7% to 15% in the group with an HgbA1c level of 5.7-6.4%, a sample size of at least 55 women in each group would be required when we used an alpha error of .05 and 80% power.

We used the Mann-Whitney *U* test and the Student *t* test for comparison of continuous variables and Pearson's chi-square or Fisher exact test for discrete variables. We also performed multivariable logistic regression analysis and analysis of covariance to perform adjustment for confounders in determining maternal outcomes. Adjustments were made for age, race/ethnicity, prepregnancy body mass index (BMI), gestational age at HgbA1c sample collection, gestational age at GDM screening/diagnosis, and method of GDM screening (2-step vs 1-step screening). Two-step screening entailed a 1-hour 50-g glucose test, which, if >140 mg/dL, was followed by a 3-hour 100-g glucose according to Carpenter-Coustan criteria. Women screened by the 1-step screening were given a 2-hour 75-g glucose test.[21,22] Results were expressed in odds ratios (ORs), 95% confidence intervals (CIs), and mean ± standard deviation. Significance was defined as a probability value of < .05. SPSS software (version 20.0; IBM Corporation, Armonk, NY) was used for statistical analysis.

Results

There were 526 women who met inclusion criteria during the study period: 471 of the women had an HgbA1c level of <5.7%; 55 women had an HgbA1c level of 5.7-6.4%. An HgbA1c sample was drawn at gestational ages that ranged from 2 5/7 to 20 0/7 weeks of gestation, with a mean gestational age of 9.6 weeks.

Table 1 shows the baseline characteristics between women with HgbA1c levels of <5.7% vs 5.7-6.4%. Women in the HgbA1c 5.7-6.4% group trended towards being older, to have a higher prepregnancy BMI, to have higher HbgA1C values, and to be at a slightly earlier gestational age at testing. A lower proportion was screened by the 2-step method, and a higher proportion had a previous pregnancy that had been complicated by GDM.

Table 2 demonstrates the maternal outcomes between the groups. After adjustments were made for age, prepregnancy BMI, gestational age at HgbA1c sample collection, gestational age at screening/diagnosis, race/ethnicity, and method of screening, women with HgbA1c levels of 5.7-6.4% were found to have a 2.4-fold higher odds of the development of GDM when compared with their HgbA1c <5.7% counterparts (27.3% vs 8.7%; adjusted OR, 2.38; 95% CI, 1.01−5.63). There was no statistically significant difference between the groups in terms of those who needed medical treatment or the type of medical treatment (insulin vs oral hypoglycemic). There were no differences in cesarean delivery rates or weight gain. The mean 1-hour 50-g glucose tolerance value was significantly higher in the HgbA1c 5.7-6.4% group (130.2 vs 114.3 mg/dL; $P = .02$), as was the fasting glucose tolerance value (90.6 vs 81.1 mg/dL; $P < .001$).

TABLE 1
Baseline characteristics between women with a hemoglobin A1c value <5.7% vs 5.7-6.4%

Baseline characteristic	Hemoglobin A1c value <5.7% (n = 471)	Hemoglobin A1c value 5.7-6.4% (n = 55)	*P* value
Age, y[a]	28.8 ± 6.4	30.8 ± 6.8	.06
Prepregnancy body mass index, kg/m^2[b]	26.5 (22.5–30.8)	30.3 (23.9–35.4)	.002
Body mass index ≥30 kg/m^2, n/N (%)	129/465 (27.7)	30/55 (54.5)	< .001
Gestational age at delivery, wk[a]	39.2 ± 1.9	39.0 ± 2.1	.95
Hemoglobin A1c value[a]	5.2 ± 0.3	5.9 ± 0.2	< .001
Gestational age at hemoglobin A1c testing, wk[a]	11.4 ± 3.7	9.7 ± 2.7	.003
Gestational age at diabetes screen/diagnosis, wk[a]	26.2 ± 1.9	24.3 ± 5.4	.08
Race/ethnicity, n (%)			.03
African American	69 (14.6)	17 (30.9)	
Hispanic	264 (56.1)	29 (52.7)	
White	73 (15.5)	3 (5.5)	
Asian	58 (12.3)	5 (9.1)	
Other	7 (1.5)	1 (1.8)	
Parity, n (%)			.68
0	206 (43.7)	23 (41.8)	
1-4	250 (53.1)	29 (52.7)	
>4	15 (3.2)	3 (5.5)	
Method of screening (2-step), n/N (%)	366/471 (77.7)	30/52 (57.7)	.001
Previous pregnancy complicated by gestational diabetes mellitus, n/N (%)	14/265 (5.3)	5/32 (15.6)	.02
Pregnancy conceived with assisted reproductive technology, n (%)	7 (1.5)	0	—

[a] Data expressed as mean ± standard deviation; [b] Data are expressed as median (interquartile range).

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Three of the women in our cohort (early screening HgbA1c values of 6.1%-6.3%) were diagnosed immediately with GDM by their providers after their HgbA1c values (samples drawn at 9 0/7 to 11 6/7 weeks of gestation) were reviewed. These patients were initiated immediately on self-blood glucose monitoring and thus never underwent glucose screening at 24-28 weeks of gestation. All 3 women demonstrated evidence of hyperglycemia. Dietary and exercise modifications were initiated, but 2 of the 3 women ultimately required medical treatment.

Neonatal outcomes are listed in Table 3. There were no differences between the 2 groups with respect to composite adverse neonatal outcome (including neonatal intensive care admission, hypoglycemia, hyperbilirubinemia, transient tachypnea, or acute respiratory distress), low 5-minute Apgar score, birthweight, macrosomia, small for gestational age, or intrauterine fetal death.

We performed a series of additional subgroup analyses. First, we restricted cases to those who had an HgbA1c sample drawn at a gestational age of ≤14 0/7 weeks to evaluate the use of HgbA1c in the first trimester. A total of 413 women remained: 25.5% of the women (13/51) with an HgbA1c level of 5.7-6.4% experienced GDM; 7.7% of the women (28/362) with an HgbA1c level of <5.7% experienced GDM. This finding remained significant even after the same covariate adjustment that was used in the primary analysis (adjusted OR, 2.54; 95% CI, 1.02–6.36).

A second subgroup analysis isolated women who were identified as having a prepregnancy BMI in the obese range (≥30 kg/m^2). A total of 159 obese women were identified. Two-fifths of the obese women (12/30; 40.0%) with an HgbA1c level of 5.7-6.4% experienced GDM; 16 of 129 the women (12.4%) in the HgbA1c <5.7% group experienced GDM. This result remained statistically significant after covariate adjustment (adjusted OR, 4.57; 95% CI, 1.48–14.15). In the remaining women with nonobese prepregnancy weight (BMI, <30 kg/m^2), 3 of 25 of the women (12.0%) with an HgbA1c level of 5.7-6.4% experienced GDM; 24 of 336 of the women (7.1%) with an HgbA1c level of <5.7% experienced GDM. This finding was not found to be statistically significant (OR, 1.77; 95% CI, 0.50–6.35).

Comment

At present, there is no effective method of prediction of which patients ultimately will experience GDM. Current screening methods that are used by many practitioners use risk stratification that was designed solely to detect patients with overt 'pregestational' diabetes mellitus. For example, IADPSG and ADA recommend that patients in certain high-risk populations (those with obesity, a history of GDM, and polycystic ovary syndrome) should be screened at their first prenatal visit and with positive results (HgbA1c, ≥6.5%; fasting glucose, >126 mg/dL; random glucose, >200

TABLE 2
Maternal outcomes between women with a hemoglobin A1c value <5.7% vs 5.7-6.4%

Outcome	Hemoglobin A1c value		Crude odds ratio (95% confidence interval)	*P* value	Adjusted odds ratio[a] (95% confidence interval)	*P* value
	<5.7% (n = 471)	5.7-6.4% (n = 55)				
Development of gestational diabetes mellitus, n (%)	41 (8.7)	15 (27.3)	3.93 (2.00–7.72)	< .001	2.38 (1.01–5.63)	.048
Development of class A2 diabetes mellitus, n (%)	17 (41.5)	8 (53.3)	1.61 (0.49–5.30)	.43	1.43 (0.19–11.02)	.73
Insulin treatment, n (%)	12 (70.6)	6 (75.0)	1.25 (0.19–8.44)	.82	1.60 (0.09–29.71)	.75
Oral hypoglycemic treatment, n (%)	5 (29.4)	2 (25.0)	0.80 (0.12–5.40)	.82	1.23 (0.09–18.19)	.86
Cesarean delivery (nonelective), n/N (%)	107/443 (24.2)	14/52 (26.9)	1.16 (0.60–2.22)	.66	0.94 (0.43–2.06)	.88
Weight gained, lb[b]	29.7 ± 17.0	27.2 ± 15.1	—	.30	—	.70
Weight gain exceeding Institute of Medicine guidelines, n/N (%)	228/465 (49.0)	24/55 (43.6)	0.81 (0.46–1.41)	.45	0.90 (0.48–1.70)	.75[c]
1-hr 50-g glucose tolerance test result, mg/dL[b]	114.5 ± 30.3	128.9 ± 28.9	—	.01	—	.04[c]
Fasting value from glucose tolerance test result, mg/dL[b]	81.2 ± 11.1	89.1 ± 19.4	—	.004	—	.003[c]

[a] Adjusted for age, prepregnancy body mass index, race/ethnicity, gestational age at HgbA1c collection, gestational age at screening/diagnosis, and method of screening; [b] Data are expressed as mean ± standard deviation; [c] From an analysis of covariance model adjusted for age and race.

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mg/dL) diagnosed as overt diabetes mellitus.[22] However, there is controversy regarding whether this practice should be the norm; although ACOG now supports early screening in high-risk populations, other groups such as the United States Preventive Services Task Force have not recommended it.[20,21]

Our findings suggest that early universal screening with HgbA1c values may help to identify those women at highest risk of the development of GDM in our patient population. More than 10% of the women had an early HgbA1c level of 5.7-6.4%. These patients ultimately had a nearly 1 in 3 chance of the development of GDM compared with less than one-tenth of patients with HgbA1c levels <5.7%. This result remained significant even after adjustment for a number of confounders. This impact was even more pronounced when restricted to obese patients. Finally, we performed a subgroup analysis on women who had HgbA1c samples drawn <14 weeks of gestation, when the first prenatal visit often occurs. The positive results signify that its use in the first trimester may be helpful in treating women at higher risk of GDM.

We limited HgbA1c values to those obtained ≤20 0/7 weeks of gestation so that the physiologic insulin resistance that develops during pregnancy would be less likely to affect our HgbA1c levels. One of the proposed reasons for increased insulin resistance in pregnancy is a rise in placental hormones such as human placental lactogen. Human placental lactogen has been shown to cause glucose intolerance and has a marked rise beginning in the late second trimester.[27,28] However, it is unlikely that a difference in HgbA1c levels was strictly due to an increased human placental lactogen effect in the HgbA1c 5.7-6.4% group because their HgbA1c samples were drawn, on average, 1.7 weeks earlier than the HgbA1c <5.7% group.

After limiting the cohort to obese women (prepregnancy BMI, ≥30 kg/m^2), there was an even more marked predictive value of HgbA1c, with nearly one-half of those in the HgbA1c 5.7-6.4% group experiencing GDM. Obesity is a well-known risk factor for the

TABLE 3
Neonatal outcomes between women with hemoglobin A1c values of <5.7% vs 5.7-6.4%

Outcome	Hemoglobin A1c value		Odds ratio (95% confidence interval)	*P* value
	<5.7% (n = 471)	5.7-6.4% (n = 55)		
Composite adverse neonatal outcome, n (%)	108 (22.9)	11 (20.0)	0.84 (0.42–1.68)	.62
Neonatal intensive care admission, n (%)	77 (71.3)	6 (54.5)	0.48 (0.14–1.70)	.48
Neonatal hypoglycemia, n (%)	5 (4.6)	1 (9.1)	2.06 (0.22–19.41)	.52
Neonatal hyperbilirubinemia, n (%)	56 (51.9)	8 (72.7)	2.48 (0.62–9.84)	.19
Transient tachypnea, n (%)	4 (3.7)	0	—	—
Acute respiratory distress, n (%)	5 (4.6)	0	—	—
5-minute Apgar score <7, n (%)	3 (0.6)	1 (1.8)	2.89 (0.30–28.26)	.36
Birthweight, g[a]	3325 ± 526	3306 ± 629	—	.81
Macrosomic infant (>4 kg birthweight), n (%)	40 (8.5)	5 (9.1)	1.08 (0.41–2.86)	.88
Small-for-gestational-age infant, n (%)	8 (1.7)	2 (3.6)	2.18 (0.45–10.55)	.28
Intrauterine fetal death, n (%)	1 (0.2)	1 (1.8)	8.70 (0.54–141.15)	.20

[a] Data expressed as mean ± standard deviation.

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development of GDM, a fact that amplifies the importance of GDM assessment in our population, given that nearly one-third of our cohort was obese.[29,30] There is literature that suggests that obese patients have a 2- to 4-fold higher risk of the development of GDM than nonobese parturients; however, no effective method yet exists for specific targeting of obese patients with the highest risk of GDM.[3] Our data suggest that an early HgbA1c sample may be useful in targeting which patients from this already high-risk population will benefit the most from vigilance in GDM screening and treatment.

There was a more modest difference in GDM development in nonobese women. This finding may have been due to insufficient power to detect a difference in this subgroup, with only 3 of 25 women (12.0%) experiencing GDM in women with an HgbA1c level of 5.7-6.4% vs 24 of 336 women (7.1%) experiencing GDM in women with an HgbA1c level of <5.7%. With the use of our same sample size error assumptions, the number of women in a nonobese cohort who would be needed to detect a difference would be 222 women per group, which is a number that we did not achieve in our cohort. Thus, although HgbA1c level may still be predictive of GDM in nonobese patients, our study was not powered sufficiently to detect this difference.

Strengths of our study include a large cohort of women screened by HgbA1c sample, detailed information regarding maternal sociodemographics and maternal/neonatal outcomes, and a statistical analysis that accounted for multiple confounding factors. The prevalence of GDM in our population was 8.7% in women with an HgbA1c level of <5.7%, which is similar to published rates of GDM in California.[1] Nevertheless, several limitations deserve mention. External validity of our study may be limited, given that our population was primarily an Hispanic population with a high prevalence of obesity and thus may differ from the demographic makeup of other populations.

Another limitation is the use of 2 different methods of GDM screening in our population. ACOG recommends GDM screening with a '2-step' method, whereas the ADA/IADPSG recommend a '1-step' screening method.[22,31] We found that 42.9% of the HgbA1c 5.7-6.4% group were screened by the 1-step ADA method vs only 22.7% in the HgbA1c <5.7% group. Our delivery practice predominantly used the 1-step method at the time of the study's initiation. ACOG published a committee opinion on GDM screening in September 2011 that recommended against use of the 1-step method; thereafter, the 1-step method was phased out in favor of the 2-step method.[31] ACOG has cited concern regarding the ADA/IADPSG method, given that, with the use of this method, a potentially higher percentage (18%) of pregnant patients will receive a diagnosis of GDM.[21] We accounted for this difference by adjusting for method of screening in our statistical model. Furthermore, if we assumed a theoretic GDM detection rate of 8% by the 2-step method and an 18% GDM detection rate using the 1-step method and applied it to our population using the actual numbers screened by each method in both groups respectively, we would achieve a prevalence of 10.2% GDM in the HgbA1c <5.7% group and only 13.8% in the HgbA1c 5.7-6.4% group. Thus, such a marked disparity in our results (27.3% vs 8.7% GDM prevalence) is not likely explained solely by a difference in GDM screening modality. As of now, early screening and treatment of GDM has not yet been

proved to improve maternal or fetal outcome. However, some organizations throughout California have actually begun treating women with an HgbA1c level of 5.7-6.4% as having early GDM. The California Diabetes and Pregnancy Program (CDAPP) Sweet Success is a state-funded organization that performs GDM management and education in various medical clinics and centers throughout California. Per CDAPP's 2011 algorithm, if a patient's HgbA1c level falls between 5.7-6.4%, CDAPP actually diagnoses these patients as having GDM and recommends immediate referral and treatment.[32] Although our practice adapted CDAPP guidelines in the use of HgbA1c as a universal screening tool, we differed by not automatically treating HgbA1c 5.7-6.4% as GDM. Instead, we treated these cases as routine and performed GDM screening at 24-28 weeks of gestation.

Although the benefits of immediate diagnosis and treatment in this population are unclear, there is a proven dose-dependent response between HgbA1c level and adverse pregnancy outcomes in patients with known type 1 diabetes mellitus. Nielsen et al[33] found that, when using an HgbA1c level of $\leq$7.0% as a referent group, increasing HgbA1c levels above this level were associated with complications such as spontaneous and therapeutic abortion, stillbirth, neonatal death, or major congenital abnormalities. The Hyperglycemia and Adverse Pregnancy Outcomes study demonstrated a continuous graded relationship between maternal glucose levels in later gestational ages and adverse pregnancy outcome such as cesarean delivery, macrosomia, and neonatal hypoglycemia.[10]

There are some practical benefits to the use of HgbA1c as a tool for early GDM risk assessment. It does not require a fasting state, requires only a single blood draw, and is interpreted by a single value. Conversely, HgbA1C is more expensive to analyze than plasma glucose. Current evidence is also insufficient to recommend its use in universal (or even targeted) screening. Future research endeavors could include confirmation of our findings in a larger study population powered to identify maternal/neonatal differences. The most informative study would involve universal screening for GDM with HgbA1c with subsequent randomization of those women with an HgbA1c level of 5.7-6.4% to early GDM screening/treatment vs expectant treatment.

Our data demonstrate that, in our unselected population, an HgbA1c level of 5.7-6.4% is an effective means of identifying patients at the highest risk of the development of GDM. It may be most prognostic in an obese population. Its efficacy has been demonstrated when the sample is drawn during the first trimester and may be effective up to 20 weeks of gestation. This information may help providers target the patients who will benefit the most from GDM screening and treatment. ■

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