CLINICAL TRIALS STUDY

Utility of a hemoglobin A1C obtained at the first prenatal visit

Lisa E Moore, Diana Clokey

Lisa E Moore, Diana Clokey, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of New Mexico, Albuquerque, NM 87131, United States

Author contributions: Moore LE designed the study, analyzed data, and wrote the paper; Clokey D recruited patients to the study, provided diabetic education to patients in the study and collected data.

Correspondence to: Lisa E Moore, MD, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of New Mexico, MSC105580, Albuquerque, NM 87131, United States. lemoore@salud.unm.edu

Telephone: +1-505-2726381 Fax: +1-505-2726386
Received: March 11, 2014   Revised: May 20, 2014
Accepted: June 10, 2014
Published online: August 10, 2014

Abstract

AIM: To evaluate the utility of the hemoglobin A1C (HbA1C) at the first prenatal visit as a triaging tool in patients at high risk for gestational diabetes (GDM).

METHODS: The HbA1C was obtained at the first prenatal visit prior to 20 wk. Women with a HbA1C ⩾ 6.5% (group one) were instructed on diet and daily self-monitoring of blood glucose. Women with a HbA1C between 5.7%-6.4% (group two) were offered testing or daily self-monitoring of blood glucose. Women with a HbA1C < 5.7% (group three) were tested at 24-28 wk. Patients were tested for GDM using the two step testing and Carpenter and Coustan values as cutoffs. Medication was started if patients failed to meet glycemic goals of fasting ⩽ 95 mg/dL (5.3 mmol/L) and 2 h postprandial ⩽ 120 mg/dL (6.7 mmol/L).

RESULTS: In group one (*n* = 16), 15/16 (95%) required medication to achieve euglycemia. The mean gestational age at which medication was required was early at 14 ± 6 wk. Postpartum, 14/16 patients (87%) remained diabetic. Group two contained 82 patients. Sixty-sixpatients (80%) were given a diagnosis of GDM

and 52 patients (64%) required medication. The mean gestational age at which medication was started in group two was 20 ± 7.8 wk. There were 205 patients in group three, 18 patients (8.7%) were diagnosed with GDM and 13 patients (6%) required medication. In comparison to group three, patients in group one were 220 times more likely to require medication (95%CI: 26.9- > 999, *P* < 0.0001). Patients in group two were 26 times more likely to require medication (95%CI: 12.5-54.3, *P* < 0.0001).

CONCLUSION: A HbA1C obtained at the first prenatal visit can be used to triage patients based on the level of glucose intolerance found.

Core tip: Hemoglobin A1C (HbA1C) has been endorsed by the World Health Organization for use in diagnosing diabetes and also for identifying degrees of glucose intolerance. This has not been validated in pregnancy. This study looks at a cohort of patients who received a HbA1C at the begining of pregnancy to see if the HbA1C can be used as a triaging tool for identifying patients with undiagnosed diabetes and for identifying a degree of glucose intolerance that would benefit from early intervention. HbA1C ⩾ 6.5% is consistent with preexisting diabetes. HbA1C between 5.7% and 6.4% demonstrates a level of glucose intolerance associated with risk of Gestational Diabetes which may benefit from early intervention.

Moore LE, Clokey D. Utility of a hemoglobin A1C obtained at the first prenatal visit. *World J Obstet Gynecol* 2014; 3(3): 130-133 Available from: URL: http://www.wjgnet.com/2218-6220/full/v3/i3/130.htm DOI: http://dx.doi.org/10.5317/wjog.v3.i3.130

INTRODUCTION

Gestational diabetes (GDM) is carbohydrate intolerance with onset or first recognition during pregnancy. A major limitation of this definition is the inclusion of women with undiagnosed preexisting diabetes who are at risk for complications different from women with diabetes occurring only during pregnancy.

Treatment of gestational diabetes is geared towards reducing glucose concentrations in order to reduce the risks to mothers and infants. The Hyperglycemia and Pregnancy Outcome (HAPO) study demonstrated that maternal hyperglycemia at levels lower than those diagnostic of diabetes were associated with increased birth weight and cord-blood serum C-peptide levels[1]. Other studies have shown that the offspring of diabetic mothers may be programmed to develop obesity and type 2 diabetes by the intrauterine environment[2,3].

Measurement of Hemoglobin A1C (HbA1C) has been endorsed by the American Diabetes Association (ADA) as a diagnostic and screening tool for diabetes but not for GDM[4]. The World Health Organization (WHO) has concluded that HbA1C can be used as a diagnostic test for diabetes if standardized assays are used[5].

Advantages of HbA1C are that it does not require fasting and is less prone to day to day variations. Disadvantages are possible racial differences and interference by anemia, hemoglobinopathies, and some medications. HbA1C reflects the average glucose over 2 to 3 mo.

The ADA and WHO recommend using HbA1C $\geq$ 6.5% as a cut point for the diagnosis of diabetes. Using the ADA guidelines, patients with HbA1C between 5.7%-6.4% are at an increased risk for diabetes and microvascular complications and are designated as having impaired glucose tolerance[4]. The WHO expert group made no formal recommendations on the interpretation of HbA1C levels below 6.5%[5]. However, as the HbA1C rises, the risk of diabetes increases disproportionately in a curvilinear fashion.

It is not known whether HbA1C between 5.7% and 6.4% confers an increased risk of GDM as it does for type 2 diabetes. The use of HbA1C $\geq$ 6.5% for the diagnosis of diabetes has not been validated during pregnancy.

We sought to determine if a HbA1C at the first prenatal visit, in women at high risk for GDM, was useful in identifying women with undiagnosed diabetes or impaired glucose tolerance who may benefit from early testing and intervention for gestational diabetes.

MATERIALS AND METHODS

All patients received a HbA1C as part of routine prenatal labs at the first prenatal visit. Patients with a HbA1C $\geq$ 6.5% were counseled on diet, exercise and daily self-monitoring of blood glucose and were referred to the diabetes in pregnancy clinic. Patients with HbA1C between 5.7%-6.4% were given the choice of immediate testing for GDM or to begin daily self-monitoring of blood glucose. Additionally, they were counseled on diet and exercise and tested for GDM at 24-28 wk if necessary. Patients with a HbA1C < 5.7% were tested for gestational diabetes at 24-28 wk. Testing for GDM was performed using the standard two step testing and Carpenter and Coustan values were used as cutoffs. Patients with GDM performed self-monitoring of blood glucose four times a day: fasting and two hours after each meal. Glycemic goals were fasting $\leq$ 95mg/dL (5.3 mmol/L) and two hour postprandials $\leq$ 120 mg/dL (6.7 mmol/L). Medication was started if 20% of values over a two week period exceeded these goals. Medications used included insulin and oral antidiabetic agents. All patients with the first prenatal visit prior to 20 wk were eligible for inclusion. Determination of HbA1C values was done using the TOSOH G8 AutoHPLC (High Performance Liquid Chromatograph). This method is approved by the National Glycohemoglobin Standardization Program (NGSP) and is not affected by the presence of hemoglobinopathies or anemia. This method is subject to interference from the presence of haemoglobin E (HbE). HbE is a hemoglobin variant most common in persons of Thai, Cambodian, Vietnamese or Laotian descent. The enrollment period was from October 2011 to March 2012. Patients with known diabetes were excluded. Data was collected by chart review after delivery. This study was approved by the Institutional Review Board at the University of New Mexico as a retrospective cohort study.

Statistical analysis

Statistical analysis was performed using the SAS package version 9.3. Sample size was chosen assuming that the incidence of GDM in patients with HbA1C $\geq$ 5.7 was 15%. In patients with HbA1C < 5.7% the incidence of GDM was assumed to be 5%. A 2:1 ratio of patients with HbA1C < 5.7% to patients with HbA1C $\geq$ 5.7% was used to compensate for the comparatively low incidence of GDM in the former group. Desired enrollment numbers were 98 patients with HbA1C $\geq$ 5.7 % and 196 patients with HbA1C < 5.7%. The study was powered to have an 80% probability of detecting a difference in the incidence of GDM between patients with HbA1C < 5.7% compared to patients with HbA1C $\geq$ 5.7% at a significance level of 0.05. Logistic Regression was used to calculate odds ratios and ANOVA was used to determine the effect of group on the use of medication and the week medication was started.

RESULTS

Three-hundred-three patients had sufficient data for analysis. This included 98 patients with HbA1C $\geq$ 5.7% and 205 patients with HbA1C < 5.7% Ethnicity was determined by patient self-reporting; 78% were Hispanic of Mexican descent, 15% Caucasian, 3% Native American, 1% Asian, 1% African American and 0.68% other. Patient demographics including age, parity, BMI and ethnicity are shown in Table 1.

Patients were assigned to groups based on HbA1C.

Table 1 Patient demographics

	A1C ≥ 6.5% (*n* = 16)	A1C = 5.7%-6.4% (*n* = 82)	A1C < 5.7% (*n* = 205)
Age	32 ± 6.6 yr	28 ± 4.7 yr	25 ± 4.4 yr
Parity	2.9 ± 1.7	1.7±1.1	0.86 ±. 0.78
BMI	37.3 ± 6.9	32.1 ± 7.7	28.8 ± 6.1
Ethnicity	Hispanic = 14	Hispanic = 61	Hispanic = 162
	Caucasian = 0	Caucasian = 8	Caucasian = 38
	Native Am. = 2	Native Am. = 6	Native Am. = 2
	African Am. = 0	African Am. = 4	African Am. = 0
	Asian = 0	Asian = 3	Asian = 1
	Other = 0	Other = 0	Other = 2

All values are ± SD.

Table 2 Diagnosis of gestational diabetes and medication use by group

	GDM diagnosis *n*%	Required meds *n*%[1] %[2]	Mean gestation at initiation of medication
Group 1[3] (*n* = 16)	16 (100)	15 (95) (95)	14 ± 6 wk
Group 2[4] (*n* = 82)	66 (80)	52 (64) (80)	20 ± 7.8 wk
Group 3[5] (*n* = 205)	18 (8.7)	13 (6) (72)	31 ± 4.3 wk

[3]HbA1C ≥ 6.5%; [4]HbA1C: 5.7%-6.4%; [5]HbA1C < 5.7%; [1]Percentage of the group that required medication; [2]Percentage of patients in the group with a diagnosis of gestational diabetes (GDM) that required medication. HbA1C: Hemoglobin A1C.

Group one (*n* = 16) had a HbA1C ≥ 6.5%. Group two (*n* = 82) had a HbA1C between 5.7% and 6.4%. Group three (*n* = 205) had a HbA1C < 5.7%.

We identified 16/303 patients (5.4%) who met criteria for overt diabetes diagnosed during pregnancy. Ninety-five percent or 15/16 patients with a HbA1C ≥ 6.5% (group one) required medication to achieve euglycemia during pregnancy. Postpartum, 14/16 patients in group one (87%) were diagnosed with type 2 diabetes based on a 75 g two hour challenge test.

Fifty-one patients in group two were diagnosed based on testing. An additional 15 patients in group two were given the diagnosis of GDM because daily self-monitoring of glucose demonstrated a need for medication to achieve glycemic goals.

All patients in group one, 66 patients (80%) in group two, and 18 patients (8.7%) in group three were given a diagnosis of GDM. To achieve glycemic goals, 94% of patients in group one, 64% of the patients in group two and 6% of the patients in group three required medication. Within each group, of the patients who required medication, the mean gestational age at which medication was started was 14 ± 6.0 wk in group one (range 6-28 wk), 20 ± 7.8 wk in group two (range 8-35 wk) and 31 ± 4.3 wk in group three (range 19-36 wk) as shown in Table 2.

Based on group alone, the odds of requiring medication to control blood glucose in comparison to group thee patients who had normal HbA1C values, was 220 times higher in group one (95%CI: 26.9- >999, $P < 0.0001$) and 26 times higher in group two (95%CI: 12.5-54.3, $P < 0.0001$).

DISCUSSION

An A1C drawn at the first prenatal visit is convenient for the both the patient and provider. The test can be done as part of routine prenatal labs and does not require the time commitment of the standard two step testing and does not require fasting. Our data indicates that the HbA1C performed at this time will also provide useful information for the management of the patient who is at high risk for gestational diabetes.

In patients with overt diabetes, HbA1C has been correlated with average glucose concentration as measured by daily evaluation of capillary blood glucose levels. However, during pregnancy HbA1C levels have not been used to manage patients because HbA1C levels perform poorly in differentiating women with normal pregnancies from those with GDM. A secondary analysis of the HAPO data was undertaken to determine if HbA1C measurement could provide an alternative to the oral glucose tolerance test in pregnant women[6]. HbA1C measurements were taken at the time of the oral glucose tolerance test (OGTT). Birthweight > 90th percentile, primary cesarean section and clinical neonatal hypoglycemia, preterm delivery, preeclampsia and cord C-peptide > 90th percentile were evaluated. The authors concluded that HbA1C was not a useful alternative to the OGTT because it was not predictive of these adverse outcomes. Our data suggests that the HbA1C at the first prenatal visit, if prior to 20 wk, rather than at the time of the OGTT, can be used to identify women with a level of glucose intolerance that will benefit from early modification of diet and exercise and early testing or self-monitoring of blood glucose. In support of the previous statement, the mean gestational age of medication initiation in groups one and two of our study, was lower than the gestational age at which routine testing for GDM is performed.

In our study we divided patients into three groups based on the recommendations of the ADA for diagnosis: patients with overt diabetes of pregnancy (HbA1C > 6.5%); patients with impaired glucose tolerance (HbA1C between 5.7%-6.4%) and normal glucose tolerance (HbA1C < 5.7%). Our study appears to support the clinical relevance of these categories in pregnancy. Ninety-five percent of patients with HbA1C of 6.5% or greater and 64% of patients with a HbA1C between 5.7 and 6.4 required medication to achieve euglycemia. This is consistent with a study by Balaji looking at 255 Asian women at risk for GDM reported that high (> 6.1%) and intermediate (5.3%-6%) HbA1C in the first trimester was associated with an elevated risk of GDM[7]. In that study 100% of patients with HbA1C > 6% and 23% of the patients with intermediate range HbA1C developed GDM. González-Quintero *et al*[8] found that HbA1C of 6% at the time of diagnosis of GDM was associated with a 61% increase in the odds of insulin use.

One limitation of the study is its retrospective design.

Retrospective studies in general are subject to selection bias. We attempted to ameliorate this effect by including all patients who met inclusion criteria and for whom there was sufficient data for analysis. A second limitation is that 15 patients in group 2, who were labeled as gestational diabetic, did not receive an oral glucose tolerance test. These patients performed daily monitoring of blood glucose and despite counseling on diet and exercise failed to meet glycemic goals and required medication indicating a degree of glucose intolerance consistent with the diagnosis.

The HbA1C ≥ 6.5% identifies women with a degree of hyperglycemia consistent with preexisting diabetes who have a high risk of requiring medication to achieve euglycemia and who may benefit from dietary counseling and daily monitoring of blood glucose. HbA1C between 5.7%-6.4% identifies women with a degree of glucose intolerance who may benefit from early testing. These women are also at high risk of requiring medication to achieve euglycemia if diagnosed with GDM. HbA1C < 5.7% is associated with minimal risk of GDM.

COMMENTS

Background
Gestational Diabetes and preexisting diabetes in pregnancy are becoming increasingly more common. Early identification allows intervention with resultant improved outcomes.

Research frontiers
There is current controversy on the best method of screening for and diagnosing gestational diabetes and preexisting diabetes in pregnancy. In this study the authors evaluate a hemoglobin A1C (HbA1C) obtained at the first prenatal visit as a tool for identification of patients who may benefit from early intervention for glucose intolerance.

Innovations and breakthroughs
This is the first study to look at the use of the HbA1C specifically in pregnant patients and to use the HbA1C to determine a course of management.

Applications
Data from this study can be used to create protocols for the management of patients based on the value of the HbA1C obtained at the first prenatal visit.

Terminology
Gestational diabetes: Glucose intolerance with onset or first recognition during pregnancy. HbA1C: a measure of the amount of glycated hemoglobin. HbA1C gives a picture of glycemic control over the preceeding 3 mo.

Peer review
The manuscript studied the utility of HbA1C at the first prenatal visit to detect the gestational diabetes (GDM) in local population. The study used the ADA and WHO cutoff to divide over 300 subjects based on HbA1C levels and determine the risk of GDM and subsequent management. The study identified significant high detection rate of GDM with high Hb1AC group with over 200 time more likely to require medication. The results are interesting.

REFERENCES

1. **Metzger BE**, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva Ad, Hod M, Kitzmiler JL, Lowe LP, McIntyre HD, Oats JJ, Omori Y, Schmidt MI. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010; **33**: 676-682 [PMID: 20190296 DOI: 10.2337/dc09-1848]
2. **Hillier TA**, Pedula KL, Schmidt MM, Mullen JA, Charles MA, Pettitt DJ. Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. *Diabetes Care* 2007; **30**: 2287-2292 [PMID: 17519427 DOI: 10.2337/dc06-2361]
3. **Gillman MW**, Rifas-Shiman S, Berkey CS, Field AE, Colditz GA. Maternal gestational diabetes, birth weight, and adolescent obesity. *Pediatrics* 2003; **111**: e221-e226 [PMID: 12612275 DOI: 10.1542/peds.111.3.e221]
4. **American Diabetes Association.** Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010; **33** Suppl 1: S62-S69 [PMID: 20042775 DOI: 10.2337/dc10-S062]
5. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus (World Health Organization 2011, WHO reference# WHO/NMH/CHP/CPM/11.1). Available from: URL: http://www.who.int/diabetes/publications/report-hba1c_2011.pdf
6. **Lowe LP**, Metzger BE, Dyer AR, Lowe J, McCance DR, Lappin TR, Trimble ER, Coustan DR, Hadden DR, Hod M, Oats JJ, Persson B. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations of maternal A1C and glucose with pregnancy outcomes. *Diabetes Care* 2012; **35**: 574-580 [PMID: 22301123 DOI: 10.2337/dc11-1687]
7. **Balaji V**, Madhuri BS, Ashalatha S, Sheela S, Suresh S, Seshiah V. A1C in gestational diabetes mellitus in Asian Indian women. *Diabetes Care* 2007; **30**: 1865-1867 [PMID: 17416790 DOI: 10.2337/dc06-2329]
8. **González-Quintero VH**, Istwan NB, Rhea DJ, Tudela CM, Flick AA, de la Torre L, Stanziano GJ. Antenatal factors predicting subsequent need for insulin treatment in women with gestational diabetes. *J Womens Health* (Larchmt) 2008; **17**: 1183-1187 [PMID: 18774897 DOI: 10.1089/jwh.2007.0667]

Baishideng®