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ORIGINAL ARTICLE

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Inverse association between 1,5-anhydroglucitol and neonatal diabetic complications

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Abstract

Purpose A glycemic control marker to predict neonatal diabetic complications is unavailable. We aimed to examine if 1,5-anhydroglucitol (1,5-AG) can predict neonatal complications in women with diabetes in pregnancy.

Methods Prospective observational study from December 2011 to August 2013. We recruited 105 women, 70 diabetic (gestational and pregestational) and 35 nondiabetic. 1,5-AG at birth was compared between the two groups.

In the diabetic group 1,5-AG, HbA1c, and fructosamine were measured before glycemic control initiation (first visit), after 4–6 weeks (second visit), and at delivery. Women were divided to poor (1,5-AG values below median at birth) and good (1,5-AG values at median and above) glycemic control groups. Mean daily glucose charts were collected. The primary outcome was a composite of neonatal diabetic complications: respiratory distress, hypoglycemia, polycythemia, hyperbilirubinemia, and large for gestational age.

Results Mean 1,5-AG in the nondiabetic group was similar to that of the diabetic group without the composite outcome and was significantly higher than in the diabetic group with the composite outcome.

The rate of the composite outcome was higher in the poor glycemic control group compared with the good glycemic control group (adjusted odds ratio (OR) 3.8 95% CI [1.2–12.3]). Only 1,5-AG was inversely associated with the composite outcome at all time points; the second visit was the only independent risk factor in multivariable logistic regression (OR 0.7 95% CI 0.54–0.91). The rest of the glycemic markers were not associated with neonatal composite outcome.

Conclusions 1,5-AG is inversely associated with neonatal diabetic complications and is superior to other glycemic markers in predicting those complications.

Keywords 1,5-anhydroglucitol · Neonatal complications · Hemoglobin A1c · Glycemic control · Gestational diabetes mellitus · Pregnancy

Introduction

The importance of glycemic control during pregnancy is primarily to prevent neonatal complications such as macrosomia, jaundice, hypoglycemia, and respiratory distress. Careful glucose control during pregnancy significantly reduces neonatal morbidity in those pregnancies [1, 2]. However, how to establish the level of glycemic control is

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challenging, since it should utilize sensitive markers of hyperglycemia and none of the available glucose control monitoring tests is ideal. Several glucose control monitoring techniques are available including daily self-monitoring blood glucose (SMBG), and maternal blood nonenzymatically glycosylated proteins, namely hemoglobin A1c (HbA1c) and fructosamine. Although those methods are commonly used for glucose control monitoring, they have concerning limitations. Mean blood glucose levels were shown to be a good predictor of perinatal outcome [2]; however, SMBG is uncomfortable, complicated, requires constant and repeating tests, and is inaccurate [3]. The tests are not performed at the appropriate times and in appropriate quantity, and false results are reported when compared with the memory of the device [4]. Nonenzymatically glycosylated proteins are acceptable tests to assess glycemic control and were shown to be good predictors for long-term vascular complications of type 1 and type 2 diabetes mellitus [4]. However, since HbA1c reflects the mean glucose concentration during the three preceding months [5], this glycemic marker is insensitive to recent treatment changes. The same limitations are seen for fructosamine, which reflects the mean glucose control during the last 2–3 weeks and its level depends on the level of plasma proteins [6]. Those limitations are probably the reason that the ability of those markers to predict neonatal complications was weak and not consistent through all studies [2, 7]. Fructosamine was not associated with neonatal complications, and only HbA1c > 8.0%, which is rarely seen and reflects extremely uncontrolled diabetes in pregnancies, significantly increased risk of neonatal morbidity and macrosomia [7]. This problem is emphasized in poorly compliant patients that fail to complete daily glucose charts, leaving the medical staff without any information regarding their glycemic control. Thus, searching for a good method to assess glycemic control that will be able to predict neonatal outcomes merits exploration.

Previously, 1,5-anhydroglucitol (1,5-AG) was introduced as an additional glycemic marker [6]. This is a 1-deoxy form of blood glucose that is supplied via certain foods (soy, rice, pasta, meat, fruit, and vegetables), with a minimal amount produced de novo within the body [8, 9]. The physiological role of 1,5-AG is unknown. In a normal state there is a balance between the absorption of 1,5-AG from the intestine and its consumption and excretion in the urine. Almost 99.9% is absorbed back through the kidneys [9]. The reabsorption is competitively inhibited by glucose, hence serum levels of 1,5-AG are inversely proportional to blood glucose and were shown to reflect the glucose level during the prior 1–2 weeks [10–14]. Moreover, 1,5-AG levels are sensitive to glucose fluctuations and therefore reflect postprandial hyperglycemia rather than only mean serum glucose [6]. An association between low levels of 1,5-AG and neonatal hypoglycemia and elevated birth weight was reported previously in retrospective studies [15, 16]. However, those diabetic complications and others such as respiratory distress and hyperbilirubinemia merit further investigation, preferably in prospective studies. We hypothesized that since 1,5-AG levels are more sensitive to short-term blood glucose fluctuations, given the time frame for monitoring and treatment of diabetes during pregnancy, they might serve as a better marker for hyperglycemic-related neonatal complications than HbA1c and fructosamine.

In the present study we aimed to examine the association of 1,5-AG levels and neonatal diabetic complications. The association between mean blood glucose, HbA1c, fructosamine, and neonatal diabetic complications was assessed as well.

Materials and methods

Study design

A prospective observational cohort study was conducted at the diabetes in pregnancy clinic, the Maternal-Fetal Medicine Department, the delivery room, maternity ward, and neonatology departments at Emek Medical Center, a university teaching hospital in Afula, Israel, from December 2011 to August 2013. This study was authorized by the local review board at Emek Medical Center (approval EMC-121-10). Participants provided written informed consent.

In this study we investigated two issues:

1. The ability of 1,5-AG to assess glycemic control. To this end, we recruited a group of 35 pregnant women, above 18 years of age, without diabetes, who agreed to participate in the study. We used this group as a reference group to establish the normal mean values at birth of maternal 1,5-AG and cord 1,5-AG, glucose, fructosamine, insulin, and C-peptide. We compared the levels of those molecules with the levels in women with diabetes during pregnancy (inclusion and exclusion criteria and management of this study population are described in detail below).
2. The association between 1,5-AG, mean daily glucose, HbA1c, fructosamine, and neonatal diabetic complications in women with diabetes during pregnancy.

Women with diabetes in pregnancy

Women above 18 years old with diabetes during pregnancy (gestational or pregestational) at their first visit to

the diabetes in pregnancy clinic, prior to initiation of glycemic control treatments, were asked to participate in this study. Gestational diabetes mellitus (GDM) diagnosis was established using the two-step strategy in the following manner [17, 18]: women's plasma glucose was tested after a 50 g oral glucose load (glucose challenge test; GCT). If plasma glucose concentration one hour later was ≥200 mg/dL it was considered diagnostic for GDM. Women with glucose levels between 140 and 199 mg/dL performed the 100 g oral glucose tolerance test (OGTT). GDM was diagnosed when two or more abnormal values were presented using the Carpenter and Coustan criteria [19], or at least one abnormal value using the 1979 National Diabetes Data Group criteria [20]. Since the difference between the two criteria is only in the OGTT interpretation we used them simultaneously, and GDM diagnosis was established if at least one of them was fulfilled [17, 21–23]. Women with risk factors for GDM, such as polyhydramnios or estimated large for gestational age fetus, underwent OGTT as a single test without performing GCT.

Exclusion criteria included major fetal malformations, previous bariatric surgery, chronic kidney disease, active hepatic disease, severe anemia (hemoglobin < 8 g/dL), and women using Polygala, Tenuifolia, Senega syrup, or corticosteroids. Criteria for removal from the study were severe pre-eclampsia, intrauterine fetal death, delivery <37 weeks, clinical signs consistent with placental abruption, neonatal APGAR score < 7 after 5 min, arterial cord pH < 7.1, or suspected growth restriction with absent or reversed umbilical artery Doppler flows. Those criteria were chosen since they are strongly associated with neonatal complications and may serve as confounders. It should be noted, however, that only six women were excluded due to delivery before 37 weeks and none of the other criteria for study removal was met.

Women diagnosed with GDM or pre-GDM were invited to the diabetes in pregnancy clinic at Emek Medical Center. The initial visit included a full medical history by the clinic's attending physician and pre-pregnancy and current body mass index (BMI) recording. In addition, each participant was educated by a dietitian and by a trained nurse regarding the dietary, lifestyle, and management protocol recommendations for diabetic patients. All women were instructed on a diet ranging from 25 kcal/kg for overweight and obese women to 35 kcal/kg for women of normal weight, divided into three full meals and three snacks of 50% carbohydrates, 30% fat, and 20% protein. The women completed daily glucose charts—including seven measurements: three preprandial, three post prandial, and a 7th measurement at 10 p.m. The postprandial measurements were taken 90 min following meals, since this is the time interval for postprandial glucose to peak in diabetic pregnancy [24]. The glucose chart was completed daily 2–7 times per week according to the glycemic control. Daily glucose charts were sent to the clinic physician for review by fax or email at least once a week. Mean blood glucose was calculated and documented in the patient's data chart. Every 4–6 weeks all the participants arrived at the diabetes in pregnancy clinic for follow-up. Pharmacotherapy was initiated if repeated preprandial glucose values were >95 mg/dL, or repeated postprandial values were >130 mg/dL, or mean daily glucose was >100 mg/dL. Pharmacotherapy included glibenclamide, metformin, or insulin for gestational diabetes and insulin for pregestational diabetes. Serum 1,5-AG, HbA1c, and fructosamine were measured during the first visit to the gestational diabetes clinic before glycemic control treatments were initiated (baseline), after 4–6 weeks (second visit), and during delivery. Serum 1,5-AG was examined using the Glycomark kit (GlycoMark Inc.) as described previously [9, 14]. The GlycoMark kit intra-assay coefficients of variation were up to 5%. All the tests were performed in the same day using the same kit and therefore the inter-assay coefficient was not calculated. All tests' results of the controls supplied by the manufacturer were within the range reported by the manufacturer. The rest of the biochemical parameters are in standard use in our medical center laboratory for many years with commercial kits.

Poor and good glycemic control groups according to the 1,5-AG value

Participants were divided into two groups according to the 1,5-AG at delivery. Women with 1,5-AG value below the median were considered as the "poor glycemic control group". Women with the median or higher 1,5-AG value at birth comprised the "good glycemic control group".

Outcomes

The primary outcome was the rate of a composite of respiratory distress, hypoglycemia (defined as glucose levels <40 mg/dL on the first day and <50 mg/dL thereafter), polycythemia (defined as venous hematocrit > 65%), hyperbilirubinemia (diagnosis depended on gestational age as accepted), and large for gestational age neonates (defined as >90th percentile of the Dollberg growth curves, which are adjusted for the Israeli population [25]).

The secondary outcomes were individual components of the composite outcome, hypomagnesemia (defined as Mg < 1.5 mg/dL) and hypocalcemia (defined as Ca < 7 mg/dL). Neonatal birth weight and anthropometric indices were taken. Neonatal blood was taken to measure 1,5-AG,

fructosamine, glucose, C-peptide, insulin, calcium, magnesium, bilirubin, and hematocrit.

Blood tests for the neonatal outcomes were obtained from the umbilical cord. This was the only source for insulin and C-peptide levels due to their rapid clearance. Samples for the rest of the tests were also taken from neonatal blood in case of technical difficulty to obtain blood from the umbilical cord. Since the quantity of blood required to perform all the tests was ~20 mL, in some cases the amount of blood retrieved was not sufficient. Hence a system of prioritization was followed. Primarily, 1,5-AG and fructosamine were measured. Then, calcium and magnesium levels were tested. If the amount of blood was not sufficient to examine calcium and magnesium levels but there was a clinical suspicion for electrolyte imbalance, additional blood was taken. Hematocrit and bilirubin were examined using capillary blood and if the results were abnormal, venous blood was obtained to confirm the diagnosis of polycythemia and hyperbilirubinemia.

Statistical analysis

Sample size

Assuming 10 and 40% rates of the composite outcome in the good and poor glycemic control groups, respectively, according to maternal 1,5-AG level at birth, a total of 64 women are required (5% two-sided alpha, 80% power). This assumption was based on the study of Langer et al. who demonstrated an association between neonatal complications and glycemic control according to the daily glucose chart [2].

Groups were compared using the Student *t*-test (or the Wilcoxon two sample test) for continuous variables and χ^2 (or Fisher's exact test [two tailed]) for categorical variables. In cases of difference in maternal background characteristics, multiple logistic regressions were performed and adjusted OR with 95% confidence interval (CI) were presented for each of the study outcomes. Correlation between 1,5-AG and pre- and postprandial glucose values was assessed using the Spearman correlation coefficient.

Possible risk factors for the composite outcome were assessed by using stepwise multivariable logistic regression. This method also was used in order to calculate a prediction model equation for the probability of the composite outcome. The goodness of fit of the prediction model was evaluated using the C-statistic and Hosmer–Lemeshow goodness-of-fit test.

Statistical analyses were carried out with SAS version 9.4 (SAS Institute, Cary, NC, USA). Significance was set at a p value < 0.05.

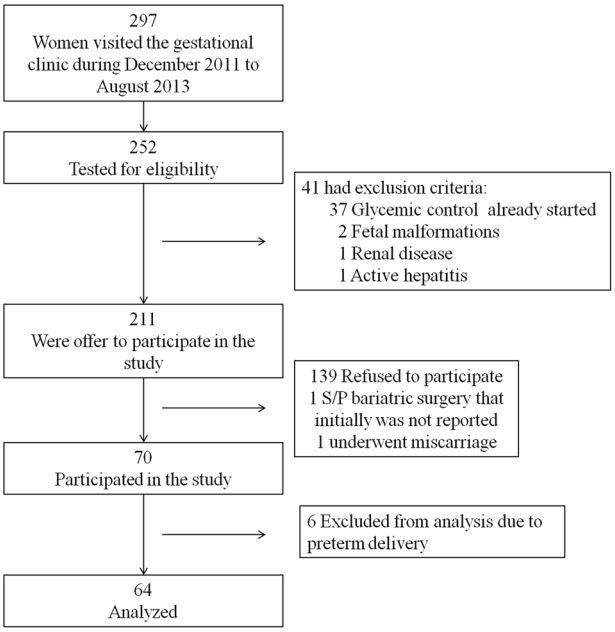

Fig. 1 Flow chart of patients

Results

The flow chart of patients is shown in Fig. 1. Seventy diabetic patients participated in this study. Of them, six women were excluded due to preterm delivery. Sixty-four women and their neonates were included in the analysis.

Table 1 describes the values of maternal 1,5-AG and cord 1,5-AG, glucose, insulin, and C-peptide at birth in women with diabetes during pregnancy and in women without diabetes. Women with diabetes had lower levels of serum and cord 1,5-AG and higher levels of cord insulin and C-peptide.

Next, we assessed the association between neonatal complications and poor versus good glycemic control using the median maternal 1,5-AG at birth for cutoff. Women with value below the median were considered the "poor glycemic control group" while women with median 1,5-AG value at birth or higher comprised the "good glycemic control group".

Table 2 describes the maternal background characteristics of women with good and poor glycemic control. BMI before pregnancy and at the first visit at the diabetes in pregnancy clinic were higher in the good glycemic control group. The rest of the maternal characteristics were not significantly different between the groups.

Pregnancy and neonatal outcomes are presented in Table 3. The rate of the composite outcome was higher in the poor glycemic control group compared with the good glycemic control group (21 (66%) versus 13 (41%), respectively, $p = 0.045$). This result remained statistically

Table 1 Maternal 1,5-AG, cord 1,5-AG, glucose, insulin, and C-peptide at delivery in women with diabetes versus healthy women

	Group		*p*-value
	Diabetes ($N = 64$)	Control ($N = 35$)	
Delivery week	38.3 ± 1.0 [37,38,41]	39.3 ± 1.4 [37,39,42]	0.0003
Maternal 1,5-AG (μg/mL)	8.9 ± 4.4 [1.7, 8.2, 21.1]	11.0 ± 4.4 [1.8, 10.9, 23.8]	0.02
Cord 1,5-AG (μg/mL)	7.5 ± 3.6 [1.4, 7.6, 16.8]	10.5 ± 4.6 [1.3, 10.3, 24.3]	0.003
Cord glucose (mg/dL)	82 ± 21.5 [33,78,118]	82 ± 19 [55,78,147]	0.90
Cord fructosamine (μmol/L)	178 ± 26.6 [119, 177, 232]	181 ± 17 [143, 183, 209]	0.47
Cord insulin (μIU/mL)	16.9 ± 14.5 [1, 11.7, 57]	6.8 ± 8.5 [1, 3.5, 34]	<0.0001
Cord C-peptide (ng/mL)	1.3 ± 0.7 [0.4, 1.3, 3.7]	0.8 ± 0.6 [0.05, 0.7, 3.5]	0.0008

Values are presented as mean ± standard deviation [minimum, median, maximum]

Cord blood for 1,5-AG, insulin, and C-peptide was available for 31 neonates. Cord glucose was available for 28 neonates and cord fructosamine was available for 29 neonates

significant after adjusting for BMI before pregnancy and in the first visit (adjusted OR 3.8 95% CI [1.2–12.3]).

In order to assess possible risk factors for the composite outcome, including other glycemic markers such as HbA1c, fructosamine, and mean daily glucose according to the daily glucose charts, we compared those parameters and others in women whose neonates had the composite outcome versus women without the composite outcome (Table 4). As can be seen, 1,5-AG values at the first visit, second visit, and at birth were statistically associated with the composite outcome. On the contrary, HbA1c, fructosamine and mean daily glucose were not associated with the composite outcome (Table 4). In subanalysis of women with GDM (excluding pregestational diabetes), the group with the composite outcome had higher levels of 1,5-AG values at the second visit compared with the group without the outcome (mean 11.1 (SD 4.9) [median 9.6, IQR 8.2–11.5] versus 7.1 (3.5) [6.7, 4.4–10.6], respectively, $p = 0.036$). The rest of the markers were not statistically different between the groups ($p > 0.05$ in all comparisons).

1,5-AG was suggested previously to be influenced by glucose fluctuations [14] and postprandial hyperglycemia [26, 27]. Thus, we examined the correlations between 1,5-AG and pre- and postprandial glucose values. There was a statistically significant correlation between 1,5-AG at the first visit and postprandial values (−0.3, $P = 0.02$). The rest of the correlations were not statistically significant. When mean 1,5-AG value at delivery in nondiabetic women (Table 1) was compared with the value of diabetic women with and without the neonatal composite outcome (Table 4), there was no statistically significant difference between the nondiabetic women and diabetic women without neonatal complications (11.0 ± 4.4 μg/mL versus 10.3 ± 4.2 μg/mL, respectively; $p = 0.52$). However, there was a statistically significant difference between nondiabetic women and diabetic women with the composite outcome (11.0 ± 4.4 μg/mL versus 7.7 ± 4.3 μg/mL, respectively; $p = 0.002$).

Multivariable analysis

We performed stepwise multivariable logistic regression in order to evaluate independent risk factors for the composite outcome. For this, we analyzed two regression models. The first incorporated all glycemic markers including 1,5-AG at the second visit. In the second model we did not include 1,5-AG at the second visit, which is missing in some of the women as explained in Table 2.

Regression model including 1,5-AG at the second visit: The value of 1,5-AG at the second visit (i.e., after 4–6 weeks of follow-up) was the only parameter that was found to be an inversely associated independent risk factor for the composite outcome (OR 0.7 95% CI 0.54–0.91). Based on this model we calculated a prediction model equation for the probability of the composite outcome. Since only 1,5-AG at the second visit was shown to be a statistically significant predictor, only this parameter was incorporated (c- statistic 81%, Hosmer–Lemeshow goodness of fit $p = 0.63$).

$$\text{Predictive probability of the composite neonatal outcome} = \frac{e^{(3.0583 - 0.3621 * 1{,}5-\text{AG value})}}{1 + e^{(3.0583 - 0.3612 * 1{,}5-\text{AG})}}$$

Calculator based on the model's equation is available upon request. For example, the risk for the composite outcome with 1,5-AG value of 11 μg/mL after 4–6 weeks of follow-up is 29% and increases to 78% with 1,5-AG value of 5 μg/mL.

Addition of the mean preprandial and postprandial daily glucose led to similar results (OR 0.7 95% CI 0.46–0.94, c-statistic 80%, Hosmer–Lemeshow goodness of fit $p = 0.24$).

Regression model without 1,5-AG at the second visit: The value of 1,5-AG at the first visit was the only parameter that was found to be an inversely associated independent risk factor for the composite outcome (OR 0.75 95% CI

Table 2 Characteristics of women with good and poor glycemic control according to median 1,5-AG at time of delivery

	N	Good glycemic control *N* = 32	Poor glycemic control *N* = 32	*p* value
Age (y)	64	35 (4) [33–38]	34 (6) [30–38]	0.81
Age ≥ 35	64	15 (47%)	18 (56%)	0.45
BMI before pregnancy	64	32.0 (5.4) [32.3, 27.2–35.4]	28.5 (5.8) [26.3, 24.4–31.2]	0.02
BMI at first visit	64	34.3 (5.6) [35.0, 29.3–36.8]	31.3 (5.7) [31.6, 26.5–34.0]	0.04
BMI at delivery	63	35.5 (5.9) [35.6, 31.6–38.8]	32.8 (5.7) [32.5, 28.3–36.7]	0.07
Week of GDM diagnosis	64	26.0 (9.1) [23–32]	28.4 (7.8) [30.5, 26.5–33.5]	0.27
<24 weeks	64	8 (25%)	5 (16%)	0.36
24–28 weeks		4 (13%)	8 (25%)	
>28 weeks		20 (63%)	19 (59%)	
Number of births	64	2.3 (1.5) [1–3]	2.4 (1.9) [1–3]	0.96
Primiparity	64	4 (13%)	4 (13%)	1
Number of children	64	2.2 (1.6) [1–3]	2.3 (1.6) [1–3]	0.96
Type of diabetes				
GDM-A1	64	8 (25%)	13 (41%)	0.10
GDM-A2		19 (59%)	11 (34%)	
Type 1		0 (0%)	3 (9%)	
Type 2		5 (16%)	5 (16%)	
Delivery week	64	38.4 (1.1) [38, 39]	38.2 (1.0) [38]	0.39
Cesarean delivery	64	15 (47%)	14 (44%)	0.80
Male	64	18 (56%)	14 (44%)	0.32
Markers				
1,5-AG (μg/mL)—at recruitment	64	12.8 (5.2) [11.4, 8.6–16.4]	5.8 (3.0) [5.3, 3.2–7.7]	<0.0001
1,5-AG (μg/mL)—second visit[a]	38	12.7 (4.4) [10.9, 9.6–13.9]	5.9 (2.8) [5.9, 3.5–7.5]	<0.0001
1,5-AG (μg/mL)—at birth	64	12.3 (3.4) [12.0, 9.4–13.7]	5.5 (2) [6.1, 3.5–7.3]	<0.0001
HbA1c (%)—at recruitment	62	5.7 (0.6) [5.7, 5.4–5.9]	6.0 (1.8) [5.6, 5.2–5.8]	0.47
HbA1c (%)—second visit[a]	45	5.5 (0.3) [5.4, 5.3–5.7]	5.7 (0.8) [5.5, 5.3–5.9]	0.45
HbA1c (%)—at birth	63	5.5 (0.4) [5.6, 5.2–5.8]	5.9 (1.0) [5.6, 5.4–6.2]	0.17
Fructosamine (μmol/L)—at recruitment	63	198 (21.7) [194, 186–212]	203 (40.5) [186, 177–213]	0.5
Fructosamine (μmol/L)—at second visit[a]	47	177 (32) [182, 175–197]	195 (36) [185, 172–198]	0.67
Fructosamine (μmol/L)—at birth	63	175 (18) [176, 163–187]	182 (27) [176, 165–191]	0.24
Mean daily glucose (mg/dL)	59	105 (11) [103, 98–111]	103 (14) [100, 95–104]	0.19

Poor and good glycemic control were established using the median maternal 1,5-AG at birth as cutoff; Women with value below the median were considered as the "poor glycemic control group" while women with the median 1,5-AG value at birth or higher comprised the "good glycemic control group"

Values are presented as mean (SD) [median, IQR) or number (percent)

1,5-AG 1,5-anhydroglucitol, *BMI* body mass index, *GDM* gestational diabetes mellitus

[a]Thirty-eight women had a second visit. Of the 26 women that did not arrive, 12 women gave birth before the scheduled second visit and 14 women refused to arrive to the scheduled visit. More women had available results of HbA1c and fructosamine than 1,5-AG since those tests were also taken in the community clinic

0.62–0.91, c-statistic 80%, Hosmer–Lemeshow goodness of fit $p = 0.42$). Since the difference between the two regression models was only in the significance of 1,5-AG at the first versus second visit, we compared the values of 1,5-AG at the first visit in women with and without 1,5-AG value in the second visit (8.2 (5.2) [7.8, 5.0–11.4] versus 9.9 (5.9)

Table 3 Maternal and neonatal outcomes of women with good and poor glycemic control according to median 1,5-AG at birth

	N	Good glycemic control N = 32	Poor glycemic control N = 32	p value
Neonatal outcomes				
Birth weight (g)	64	3360 (512) [3470, 2951–3720]	3474 (508) [3368, 3092–3755]	0.81
Weight percentile	64	64 (30) [43–90]	72 (22) [53–93]	0.31
AGA	64	22 (69%)	23 (72%)	0.62
LGA		8 (25%)	9 (28%)	
SGA		2 (6%)	0 (0%)	
Macrosomia > 4000 g	64	3 (9%)	5 (16%)	0.71
Length (cm)	57	50 (2.2) [48–51]	50 (1.8) [49–51]	0.5
Head circumference (cm)	64	35 (1.2) [34–36]	34 (1.3) [34,35]	0.54
Abdominal circumference (cm)	57	31 (2.4) [31–33]	32 (1.7) [31–33]	0.43
Shoulders distance (cm)	57	11 (1.0) [10,11]	11 (1.1) [10–12]	0.34
Cord/neonatal blood				
Calcium (mg/dL)	52	9.7 (0.7) [9.6, 9.3–10.3]	9.8 (0.6) [9.9, 9.5–10.3]	0.4
Magnesium (mg/dL)	53	2.1 (0.2) [2.1, 1.9–2.3]	2.1 (0.3) [2.1, 1.9–2.2]	0.85
Hyperbilirubinemia	64	6 (19%)	13 (41%)	0.056
Phototherapy	64	4 (13%)	5 (16%)	1
Hypoglycemia	64	2 (6%)	2 (6%)	1
Respiratory distress	64	0 (0%)	4 (13%)	0.11
Polycythemia	64	4 (13%)	4 (13%)	1
composite outcome	64	13 (41%)	21 (66%)	0.045
1,5-AG—neonatal blood[a] (μg/mL)	58	8.2 (3.5) [9.5, 7.9–11.6]	4.5 (1.9) [4.4, 2.7–5.8]	<0.0001

Values are presented as mean (SD) [median,IQR) or number (percent)

1,5-AG 1,5-anhydroglucitol, *AGA* appropriate for gestational age, *HCT* hematocrit, *LGA* large for gestational age, *SGA* small for gestational age

[a]Neonatal 1,5-AG was taken from cord blood or the neonates if cord blood was not available due to technical reasons

[8.6, 4.8–15.1], respectively, $p = 0.46$). This result suggests that the group with 1,5-AG at the second visit probably represents the entire cohort.

Subanalysis for women with GDM and type 2 diabetes (excluding type 1 diabetes)

Both GDM and type 2 diabetes represent similar pathogenesis derived from insulin resistance which is different than type 1 diabetes. Therefore, we also performed subanalysis in which we excluded women with type 1 diabetes ($N = 3$). The results are presented in Tables S1, S2, and S3. We performed stepwise multivariable logistic regression in order to evaluate independent risk factors for the composite outcome.

Similarly to the total analysis, the value of 1,5-AG at the second visit (i.e., after 4–6 weeks of follow-up) was the only parameter that was found to be an inversely associated independent risk factor for the composite outcome (OR 0.71 95% CI 0.55–0.93, c-statistic 79%, Hosmer–Lemeshow goodness of fit $p = 0.83$).

Discussion

In the present study we aimed to examine the association between 1,5-AG and other glycemic markers with neonatal composite outcome of respiratory distress, hypoglycemia, polycythemia, hyperbilirubinemia, and large for gestational age. We found that poor glycemic control that was determined using the median 1,5-AG level at birth was associated with the composite outcome. In addition, after assessing several possible risk factors including other glycemic markers such as HbA1c, fructosamine, and characteristics of the daily glucose charts, only 1,5-AG at all times it was tested, was associated with the neonatal composite outcome. Stepwise multivariable logistic regression demonstrated that 1,5-AG at the second visit was an independent risk factor for the composite outcome. This result is important since it demonstrates that a single test can be used to evaluate the effect of glycemic control treatment after 4–6 weeks when there is enough time to change the treatment and management if those are required and to provide reassurance to the physician and patient in case the glycemic control is adequate.

It should be noted that mean 1,5-AG in the diabetic group without complications was similar to the value of the healthy non-diabetic women during delivery, suggesting that good glycemic control according to 1,5-AG reflects the normoglycemic state of those individuals.

Data regarding the association of low levels of 1,5-AG and neonatal complications is scarce. Low levels of 1,5-AG were shown to be associated with increased neonatal complications, particularly elevated birth weight and neonatal hypoglycemia in two retrospective studies [15, 16] and one prospective study that examined the association of 1,5-AG with birth weight in women with type 1 diabetes mellitus [28]. To our knowledge, our study is the first that examined prospectively the association of 1,5-AG with diabetic neonatal complications in pregnant women, most of whom had gestational diabetes. This is also the first study to address the association with a composite of neonatal diabetic complications other than only hypoglycemia or birth

Table 4 Characteristics of women with and without neonatal composite outcome

	N	Composite outcome		*p* value
		No *N* = 30	Yes *N* = 34	
Age (y)	64	35 (5) [32–38]	35 (5) [34.5, 32–37]	0.95
Age ≥ 35	64	16 (53%)	17 (50%)	0.80
BMI before pregnancy	64	29.5 (4.7) [28.6, 25.4–33.8]	30.9 (6.7) [31.0, 26.0–35.4]	0.46
BMI at first visit	64	31.5 (4.2) [31.9, 28.3–35.3]	33.9 (6.8) [33.8, 28.1–39.0]	0.17
BMI at delivery	63	32.7 (4.6) [33.0, 29.0–35.3]	35.6 (6.7) [36.3, 29.8–40.1]	0.06
Recruitment week	64	26.1 (8.7) [23–32]	28.1 (8.3) [27–34]	0.23
<24 weeks		8 (27%)	5 (15%)	0.37
24–28 weeks		4 (13%)	8 (24%)	
>28 weeks		18 (60%)	21 (62%)	
Number of births	64	2.2 (1.9) [1–3]	2.5 (1.6) [1–4]	0.28
Primiparity	64	5 (17%)	3 (9%)	0.46
Number of children	64	2.1 (1.7) [1–3]	2.4 (1.5) [1–4]	0.37
Type of diabetes				
GDM-A1	64	9 (30%)	12 (35%)	0.12
GDM-A2		18 (60%)	12 (35%)	
Type 1		0 (0%)	3 (9%)	
Type 2		3 (10%)	7 (21%)	
Delivery week	64	38.5 (1.1) [38, 39]	38.1 (0.9) [38]	0.13
Cesarean delivery	64	12 (40%)	17 (50%)	0.42
Male	64	15 (50%)	17 (50%)	1
Markers				
1,5-AG (μg/mL)—at recruitment	64	11.0 (6.1) [9.9, 6.5–15.9]	7.8 (4.4) [8.1, 4.4–10.2]	0.0495
1,5-AG (μg/mL)—second visit	38	11.4 (5.0) [10.0, 8.2–13.9]	6.5 (3.5) [6.1, 2.7–10.1]	0.003
1,5-AG (μg/mL)—at birth	64	10.3 (4.2) [9.0, 7.2–12.5]	7.7 (4.3) [7.3, 4–10.9]	0.02
HbA1c (%)—at recruitment	62	5.7 (0.6) [5.7, 5.2–5.8]	6.1 (1.8) [5.6, 5.4–5.9]	0.99
HbA1c (%)—second visit	45	5.5 (0.3) [5.4, 5.2–5.7]	5.8 (0.8) [5.6, 5.4–6]	0.18
HbA1c (%)—at birth	63	5.5 (0.5) [5.6, 5.2–5.9]	5.9 (0.9) [5.6, 5.5–6.1]	0.29
Fructosamine (μmol/L)—at recruitment	63	199 (22) [197, 186–205]	202 (40) [186, 180–213]	0.35
Fructosamine (μmol/L)—at second visit	47	183 (15) [182, 174–196]	191 (47) [185, 174–208]	0.48
Fructosamine (μmol/L)—at birth	63	173 (18) [174, 161–181]	184 (26) [178, 169–192]	0.14
Mean daily glucose (mg/dL)	59	104 (11) [103, 98–108]	104 (14) [101, 94–106]	0.57
Mean pre-prandial daily glucose (mg/dL)	45	91 (9) [85–94]	91 (8) [85–94]	0.99
Mean postprandial daily glucose (mg/dL)	45	110 (13) [108, 101–116]	115 (13) (115, 108–120]	0.16

Values are presented as mean (SD) [median,IQR) or number (percent)

1,5-AG 1,5-anhydroglucitol, *BMI* body mass index, *GDM* gestational diabetes mellitus

weight. It should be noted that the sample size in this study was not sufficient to examine each component of the composite outcome individually and in larger studies an association to those outcomes might be demonstrated. HbA1c was less reliable as a predictor of neonatal complications in this study and in others [15, 16, 28]. It was

hypothesized that since 1,5-AG is influenced by glucose fluctuations [14] rather than mean serum glucose, it is more sensitive to postprandial hyperglycemia [26, 27], which was shown to be more associated with neonatal complications than the pre-prandial values [29]. The significant correlation between 1,5-AG at the first visit and postprandial glucose values while no correlation was found with the pre-prandial glucose values, supports that assumption. An additional explanation is that 1,5-AG levels are determined mostly by its renal reabsorption, which is a relatively rapid process, while glycosylation is a long process and therefore it is less suitable for the time frame that is required to assess glycemic control during pregnancy. It should be noted that in this study, 1,5-AG was a better predictor for neonatal complications than the mean postprandial daily glucose, which did not reach statistical significance. A reason for that may be that postprandial glucose is represented in the daily glucose chart by only three measurements while 1,5-AG is affected by glucose fluctuations throughout the day. This also might be the reason why the degree of correlation between those parameters was low.

Using 1,5-AG levels to evaluate glycemic control during pregnancy may be important for several indications. First, 1,5-AG levels can be used for patients that do not complete daily glucose charts properly, or if there is a suspicion that false results are reported. This population, which is at the highest risk for diabetic neonatal complications, lacks a reliable method for glycemic control monitoring. Assessment of glycemic control by hospitalizing those patients is also not ideal, since many of them refuse to be admitted, hospital service entails additional costs, and the meals are supplied by the institution, so glycemic control during hospitalization gives only limited information regarding glycemic control for poorly compliant patients. A second clinical use for 1,5-AG may be to assist in choosing the settings for glycemic control treatment; women with low 1,5-AG levels should be the focus of more intensive medical surveillance including counseling regarding proper diet, lifestyle changes, and even admission for glycemic control, while women with higher values can be managed with regular management in an outpatient clinic. The third clinical use is to detect patients with a higher risk for complications despite apparent normoglycemia, as the mean daily glucose chart failed to predict the probability for the neonatal composite outcome. Normoglycemic women, with low levels of 1,5-AG according to the daily glucose charts, should be the focus of more intense medical intervention including diet, lifestyle modifications, and initiating or changing pharmacotherapy.

The strengths of this study are its prospective design, tests of glycemic control performed at several time points, and addressing several neonatal outcomes. The limitations of this study are small sample size to examine the components of the composite outcomes individually and the fact that there was a small sample size of women with pregestational diabetes, which did not allow performing subanalysis of this population. Larger studies should be conducted in the future to elucidate the role of 1,5-AG in glycemic control of women with either GDM or pregestational diabetes during pregnancy.

Conclusions

Altogether, the results of this study suggest that 1,5-AG can be used to assess glycemic control during pregnancy and it is superior to other glycemic markers in predicting the probability of neonatal complications in pregnancies complicated with diabetes mellitus. Therefore, this marker can be used to evaluate glycemic control during pregnancy. Future studies with larger sample size should be conducted to further evaluate the predictive ability of 1,5-AG on the neonatal composite outcome and its individual components.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent All participants in the study gave signed an informed consent form.

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