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1,5 Anhydroglucitol Evaluation as Glycemic Control Parameter of Diabetes Mellitus in Pregnancy

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ABSTRACT

Background: 1,5-Anhydroglucitol (1,5-AG) provides a reliable opportunity to assess the frequency and extent of intermittent hyperglycemic episodes. **Aim of the Work:** this study aimed to evaluate an alternative parameter to monitor blood glucose in pregnancies complicated with diabetes mellitus by studying the relationship between 1,5 Anhydroglucitol and self-monitoring of blood glucose level in pregnant women complicated with diabetes mellitus. **Patients and Methods:** this cross-sectional study with retrospective data was conducted on seventy pregnant women known to have pre-gestational or gestational diabetes mellitus attending Ain Shams University Maternity Hospital fulfilling the inclusion criteria of pre-gestational or gestational diabetes mellitus according to the criteria of the American Diabetes Association. **Results:** this study revealed a highly significant negative correlation between MMG (mean maximum glycemia) and 1,5 AG (r: -0.817, p-value: <0.001), also pre prandial blood glucose level (r: -0.500, p-value: <0.001) and a negative correlation and highly significant was found between post prandial blood glucose level and 1,5 AG (r: -0.640, p-value: <0.001). **Conclusion:** 1,5-AG is better than HbA1c as a tool for monitoring the glucose profile in pregnancies complicated by diabetes mellitus especially for the hyperglycemic episodes. **Recommendations:** as majority of interpretations for utility of 1,5-AG in pregnancy are based on scanty few clinical data so there is a scope of potential possibilities for its use in pregnancy and continuous research may allow its new applications and usefulness in pregnancy in the future.

Keywords: 1, 5 Anhydroglucitol, Glycemic Control Parameter, Diabetes Mellitus, Pregnancy.

INTRODUCTION

Diabetes mellitus (DM) during pregnancy can lead to serious risks for both mother and fetus. DM type1 and DM type 2 affect 1% of pregnancies, but this is probably an underestimation. Due to the increasing prevalence of DM type 2 caused by obesity in a younger age group, it is assumed that the prevalence of pregnancies complicated by DM type 2 will increase as well [(1)].The possible complications due to diabetes during pregnancy are severe. The mother has an increased risk of preeclampsia, infections, ketoacidosis, hypoglycemia and microvascular diseases such as retinopathy, nephropathy and neuropathy. In addition, there is an increased risk for miscarriage, still birth, congenital defects and neonatal morbidity and death [(2)]. For congenital defects, a dose-response relation is found: the poorer the peri-conceptional blood glucose control, the greater is the risk on congenital defects. Another major complication is macrosomia, which is a risk factor for instrumental delivery, caesarean section, shoulder dystocia during delivery and neonatal hypoglycemia after birth [(3)]. There is strong evidence that proper management of gestational diabetes mellitus (GDM) and pre-existing DM during pregnancy leads to better health outcomes for both mother and child [(4)]. The mechanisms of hemoglobin A1c discrepancy in pregnancy are not clear. It has been demonstrated that pregnant women may have lower hemoglobin A1c levels than non pregnant women [(5)]. Hemodilution and increased cell turnover have been postulated to account for the decrease. Iron deficiency has been presumed to cause the increase of hemoglobin A1c in the last trimester [(6)]. In current clinical practices, the common indexes to evaluate the blood glucose states are glycated hemoglobin (HbA1c) and fructosamine (FA). However, these can only reflect the integrated average blood glucose concentration of the preceding 8–12 weeks or 2–3 weeks, respectively, and potentially overlook the important hyperglycemic excursions that may be balanced out by hypo- glycaemia. Thus, neither HbA1c nor FA can reflect recent glycemic excursions sensitively. So, in addition to HbA1c and FA, there is an imperative need for more intensive and sensitive blood glucose monitoring markers to reveal not only blood glucose levels but also recent hyperglycemic excursions [(7)].1,5-Anhydroglucitol (1,5-AG), the 1-deoxy form of glucose, has been measured and used clinically in Japan for over a decade to monitor short-term glycemic control [(8)].1, 5-AG level in plasma reflects short-term (postprandial especially) changes in serum glucose and could be an excellent tool to achieve optimal glycemic control as an adjunct to HbA1c. 1,5-AG level monitoring is the useful method to identify otherwise well controlled patients with transient hyperglycemia – patients at high risk of

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macroangiopathic complications [9]. Another study had verified that 1, 5-AG values are sensitive to the changes in blood glucose and can reflect even transient elevations of glycaemia within a few days [7].This study aimed to evaluate an alternative parameter to monitor blood glucose in pregnancies complicated with diabetes mellitus by studying the relationship between 1,5 Anhydroglucitol and self-monitoring of blood glucose level in pregnant women complicated with diabetes mellitus.

PATIENTS AND METHODS

This cross-sectional study with retrospective data was conducted on seventy pregnant women known to have pre-gestational or gestational diabetes mellitus attending Ain Shams University Maternity Hospital fulfilling the inclusion criteria of pre-gestational or gestational diabetes mellitus according to the criteria of the American Diabetes Association.

Inclusion criteria

Pregnant women were included between 18 and 45 years old with pre-gestational diabetes mellitus or gestational diabetes mellitus.

Exclusion criteria

- Renal and liver diseases Since 1,5 Anhydroglucitol levels can be altered in chronic renal and liver diseases.
- Hypertensive disorders in pregnancy (including preeclampsia)
- High risk pregnancy by any disease other than diabetes (e.g cardiac diseases, asthmatic patients on steroids..etc)
- Acute and chronic infections.
- Patients on parenteral nutrition.

Pre-gestational diabetes mellitus which is defined according to The American Diabetes Association as presence and establishment of diabetes prior to pregnancy.

Gestational diabetes mellitus is defined as any degree of glucose intolerance with onset or first recognition during pregnancy.

Diagnostic criteria for gestational diabetes mellitus according to The American Diabetes Association guidelines 2015: by two-step strategy.

- **Step one:** using **50** grams **glucose test** and if 1 h after load is ≥140 mg/dL
- Proceed to step two which is **100** grams **Oral Glucose Tolerance Test (OGTT)**
- **Step 2:** performed while patient is fasting. Gestational diabetes Diagnosis made when two or more patient blood glucose level values meet or exceed: **Fasting:** (95 mg/dL), **1 hr:** (180 mg/dL), **2 hr:** (155 mg/dL) **or 3 hr:** (140 mg/dL)

Ethical consideration

The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.

All patients were subjected to:

1. Full history taking laying stress on: age, parity, history of repeated infection, co-morbid disease, previous invasive medical procedures and family history of diabetes mellitus.
2. Self-monitoring of blood glucose (SMBG) of capillary blood glucose for one week using the intensive European expert panel according to the European Association for the Study of Diabetes (**Fig. 3**):

	Breakfast		Lunch		Dinner		
	pre	post	pre	post	pre	post	night
Mon	×	×	×	×	×	×	×
Tue	×	×	×	×	×	×	×
Wed	×	×	×	×	×	×	×
Thur	×	×	×	×	×	×	×
Fri	×	×	×	×	×	×	×
Sat	×	×	×	×	×	×	×
Sun	×	×	×	×	×	×	×

Figure 1: self-monitoring of blood glucose (SMBG) of capillary blood glucose for one week

Glycemic control targets according to The American Diabetes Association recommendations in 2015:

- Premeal blood glucose: 60-99 mg/dl.
- Peak postprandial blood glucose: 100-129 mg/dl.

The mean maximum glycaemia is defined as the average of the daily maximum blood glucose level over 7 days, the mean of daily glycemia (MDG) is defined as the average of all values of blood glucose level over 7 days ; pre-prandial and post-prandial glycemia were expressed as mean ± SD (standard deviation) and they were calculated.

1. At the end of the week, blood samples were taken for assessment of:
   - HbA1c from whole blood samples via a turbidimetric inhibition immunoassay (Tina-Quant; Roche Diagnostics), automated on the Hitachi 917.
   - 1,5- anhydroglucitol immuno-enzymatically by using ELISA kits.

Then assessment of correlation between all indices was done.

Sample Size Justification

Sample size was calculated using Stata program, setting the type-1 error (α) at 0.05 and the power (1-β) at 0.8. Results from a previous study (N. Nowak et al., 2013) showed that correlation

coefficient between1,5- anhydroglucitol and the mean maximum glycaemia was -0.58. Calculation according to these values produced a minimal sample size of 45 cases.

Reference for program:

- Stata Corp. 2001. Statistical Software: Release 7.0. College Station, TX:
- Stata Corporation.

Data Management and Analysis:

The collected data were revised, coded, tabulated and introduced to a PC using Statistical Package for Social Science (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Data was presented as Mean and Standard deviation (± SD) for quantitative parametric data, and Median and Interquartile range for quantitative non parametric data. Frequency and percentage were used for presenting qualitative data. Suitable analysis was done according to the type of data obtained. Student T-Test or Mann Whitney test was used to analyze quantitative data while chi square test and fisher exact test was used to analyze qualitative data.

- P- value: level of significance
- -P>0.05: Non significant (NS).
- -P< 0.05: Significant (S).
- -P<0.01: Highly significant (HS).

RESULTS

Table 1: demographic data distribution of the studied group.

Demographic Data	Total (N=65)
Age (years)	18-45 [32.82±6.66]
Type of DM	
Gestational (GES)	17 (26.15%)
DM Type one (ONE)	7 (10.77%)
DM Type two (TWO)	41 (63.08%)
Trimester	
First	4 (6.15%)
Second	13(20%)
Third	48 (73.45%)
Body Mass Index (BMI)(kg/m2)	26-36(30.45±3.8)
Parity	
1	14 (21.54%)
2	16 (24.62%)
3	10 (15.38%)
4	9 (13.85%)
5	4 (6.15%)
6	2 (3.08%)
7	1 (1.54%)
PG(Primi Gravida)	9 (13.85%)
Family History	
Positive	38 (58.46%)
Negative	27 (41.54%)

This demographic data table showed that the mean age of patients was 32 yrs old, the main type of DM was type 2 (63.08%), majority of patients were in their third trimester of pregnancy (73.45%), Body Mass Index (BMI) (kg/m^2) ranged from 26-36 with mean (30.45±3.8), various distribution in parity and most of them have positive family history (58.46%).

Self-monitoring of blood glucose for one week was done for every woman to get the values of the Mean Maximum Glycaemia (MMG),Mean of Daily Glycemia (MDG),Pre-prandial and Post prandial glycemia. Then at the end of the week 1,5Anhydroglucitol (1,5 AG) and Hemoglobin A1c (HbA1C) were measured to get the correlation between them.

Table 2: descriptive data of the studied group.

	Min.	Max.	Mean	±SD
HbA1C	5.2	8	6.45	0.60
1,5 AG	3.5	6.55	4.87	0.84
MMG	180	296	217.34	22.62
MDG	111	278	195.23	25.81
Pre prandial	87	187	120.78	21.91
Post prandial	121	280	204.68	24.11

This table showed that the:

- HbA1C Ranged (5.2-8) and Mean±SD (6.45±0.6)
- 1.5 AG Ranged (3.5-6.55) and Mean±SD (4.87±0.84)
- MMG Ranged (180-296) and Mean±SD (217.34±22.62)
- MDG Ranged (111-278) and Mean±SD (195.23±25.81)
- Pre-prandial Ranged (87-187) and Mean±SD (120.78±21.91)
- Post prandial Ranged (121-280) and Mean±SD (204.68±24.11)

Table 3: correlation between MMG and HbA1C, 1,5 AG, using Pearson correlation Coefficient in the studied group.

		HbA1C	1,5 AG
MMG	**r**	0.367	-0.817
	p-value	0.003	<0.001

This table showed positive significant correlation and between MMG with HA1C, but highly significant negative correlation was detected between MMG and 1,5 AG

Table 4:correlation between HA1C and 1,5 AG with pre prandial, post prandial and MDG, using Pearson Correlation Coefficient.

		HA1C	1,5 AG
Pre prandial	r	0.265	-.500
	p-value	0.033	<0.001
Post prandial	r	0.116	-0.640
	p-value	0.358	<0.001
MDG	r	0.298	-0.733
	p-value	0.016	<0.001

This table showed significant positive correlation between HbA1C with pre prandial, post prandial and MDG.

Also, there was highly significant negative correlation between 1,5 AG with pre prandial, post prandial and MDG.

Table 5: correlation between HbA1C and 1,5 AG, using Pearson Correlation Coefficient.

		1,5 AG
HbA1C	r	-0.246
	p-value	0.048

There was a significant negative correlation between HbA1C and 1,5 AG, using Pearson Correlation Coefficient.

DISCUSSION

The prevalence of diabetes continues to increase globally. Diabetes in pregnancy (DIP) provides an opportunity to intervene early in the life course for mother and child. Pregnancies complicated by diabetes (pre-existing and gestational diabetes) pose a challenge for management, as timely diagnosis and implementation of best-practice care have implications for both maternal and foetal outcomes [(10)]**.** Pregnancy complicated by type 1 diabetes mellitus requires tight glycaemic control. Clinical guidelines include HbA1c targets for affected women. A growing number of type 1 diabetic women achieve the recommended HbA1c goal; however, the prevalence of macrosomia remains high; this may be because HbA1c, a long-term glycaemic marker, does not reflect short excursions [(11)]**.**

The current study was conducted at Ain Shams University Maternity Hospital during the period between June and December 2016. A total of 65 diabetic pregnant women in various trimesters were included in the study. Self-monitoring of blood glucose for one week was done for every woman to get the values of the Mean Maximum Glycaemia (MMG) (defined as the average of the daily maximum blood glucose level over 7 days), the mean of daily glycemia (MDG) (defined as the average of all values of blood glucose level over 7 days), pre-prandial and Post-prandial glycemia then results were expressed as mean ± SD (standard deviation) and they were calculated. At the end of the week 1,5 anhydroglucitol (1,5 AG) and hemoglobin A1c (HbA1C) were measured to get the correlation between them and the above values. This study showed that the mean age of included women was 32.82±6.66years (range: 18 -45years). the range of parity was mostly between P1 to P3, type of DM was mostly pre gestational type 2 DM (63.08% of cases), most of cases were in the third trimester (73.45%),mean of BMI (Body Mass Index) was (30.45±3.8) and lastly (58.46%) had a positive family history of DM while (41.54%) had a negative family history of DM. In this study HbA1C ranged from5.2-8 and mean±SD (6.45%±0.6),1.5 AG was ranged from 3.5-6.55 and mean±SD (4.87µg/mL ±0.84), MMG was ranged (180-296) and mean±SD (217.34 mg/dL ±22.62), MDG was ranged (111-278) and mean±SD (195.23 mg/dL ±25.81),pre-prandial was ranged from 87-187 and mean±SD (120.78 mg/dL ±21.91), post prandial was ranged from 121-280) and mean±SD (204.68 mg/dL ±24.11).A significant positive correlation was found between MMG (mean maximum glycemia) and HA1C (r: 0.367, p-value: 0.003). These results agree with the results of **Nowak *et al.* [(11)];Sun *et al.* [(12)]** and **Dworacka and Winiarska [(13)]** who reported a positive correlation between MMG and HA1C.

- A highly significant negative correlation was detected between MMG (mean maximum glycemia) and 1,5 AG (r: -0.817, p-value: <0.001).

These results agree with the results of **Wang *et al.* [(7)]** and **Nowak *et al.* [(11)]** who reported a highly significant negative correlation between MMG and 1,5 AG.

- A significant positive correlation was found between pre prandial blood glucose level and HA1C (r: 0.265, p-value: 0.033) and a significant positive correlation was realized between post prandial blood glucose level and HA1C (r: 0.116, p-value: 0.358).These results agree with the results of Sun Jie et al. [(12)], who reported a positive correlation of HA1C with pre and post prandial blood glucose level values.
- A negative correlation and highly significant was found between 1,5 AG and pre prandial blood glucose level (r: -0.500, p-value: <0.001) and a negative correlation and highly significant was found between post prandial blood glucose level and 1,5 AG (r: -0.640, p-value: <0.001)

These results agree with the results of **Wang *et al.*** [7] and **Sun *et al*.** [12] who reported a highly significant negative correlation of 1,5 AG with pre and post prandial blood glucose level values.

- A significant positive correlation was found between MDG (Mean of Daily glycemia) and HA1C (r: 0.298, p-value: 0.016).

These results agree with the results of **Nowak *et al.*** [11]**; Sun *et al.*** [12] and **Suk *et al*.** [14] who reported a positive correlation between MDG and HA1C.

- A highly significant negative correlation was detected between MDG(Mean of Daily glycemia) and 1,5 AG (r: -0.733, p-value: <0.001). These results agree with the results of **Wang *et al.*** [7]***;*** **Sun *et al.*** [12]***;*** **Nowak and Skupien *et al.*** [11] ***and*** **Suk *et al.*** [14] who reported a negative and significant correlation between MDG and 1,5 AG.
- A significant negative correlation was observes between HbA1C and 1,5 AG (r: -0.246, p-value: 0.048).These results agree with the results **of Mcgill *et al*.** [15] who reported a significant negative correlation a between HbA1C and 1,5 AG. In our study, although HbA1C was positively correlated with all glycemic indices; 1,5 AG was correlated significantly and sensitively with all glycemic indices more than HbA1C.

This is in line with results of **Dworacka and Winiarska** [13] who reported that glycated hemoglobin is not sensitive for short-lasting, transient hyperglycaemia. The capability of HbA1c to capture a hike in blood glucose level immediately after meals is weak and most of currently used tests for HbA1c estimation not coordinate with thus transient hyperglycaemia, postprandial or whichever acute one, so transient hyperglycemia may not be able to change HbA1c level. Alternatively, 1,5-AG concentration fall in the plasma reflects not only chronic, but also short-lasting hyperglycaemic episodes in a much sensitive way. Also 1,5 AG showed a more sensitivity to hyperglycemic indices especially (either MMG (Mean maximum glycemia) or post prandial glycemia.

This is in line with results of **Wang *et al.*** [7] who reported that 1,5-AG could be a useful index of glycaemic excursions in patients with reasonably well-controlled diabetes (mean HbA1c: 7.1%). The 1,5-AG marker reflects glycaemic excursions, often in the postprandial hyperglycaemic state, more accurately than HbA1c ,This demonstrated that 1,5-AG was not only a marker for the state of hyperglycaemia, but also for postprandial hyperglycaemia in their study and more others ,so 1,5-AG can be a marker of hyperglycaemia and blood glucose excursions for 3–7 days patients with DM. If 1,5 AG measurements can be used regularly, in addition to HbA1c , it would be extremely helpful for adjusting treatment regemines to reduce the hazards that occur with hyperglycaemia and the hyperglycaemic excursions and ultimately effectively improve the prognosis of patients with DM. Also this is in line with the published results of **Sun *et al.*,** [12] which reported that 1,5-AG was superior to HbA1c and GA (glycated albumin) as a marker of glycemic excursions and can better evaluate the postprandial glycemic state, especially for diabetic patients whose blood glucose levels fluctuate less sharply.

Conclusion

1,5-AG is better than HbA1c as a tool for monitoring the glucose profile in pregnancies complicated by diabetes mellitus especially for the hyperglycemic episodes.Plasma AG is as good as other glycemic markers in short-term evaluation of long standing pregnant diabetic women with fluctuating glycemic control. Believing that 1,5-AG is a sensitive marker for the hyper glycemic episodes especially and the fact that controlling blood glucose in the non fasting state, especially the postprandial period can reduce the risk of macroangiopathic complications of diabetes and the risk of maternal and fetal complications in pregnancy suggest that The determination of 1,5-AG should be considered for clinical use of monitoring and evaluating diabetic pregnant women in addition to HbA1c as low HbA1c level is not sufficient to decrease risk of macrovascular complications, especially risk of coronary heart disease and the fetal complications in pregnancy.

1,5-AG level monitoring is the useful method to identify otherwise well controlled patients with transient hyperglycaemia – patients at high risk of macroangiopathic complications. Utilizations of 1,5-AG as an index of glycemic control in pregnancy and otherwise has several advantages, including retained metabolic inertness, steady state levels in all tissues, and negligible influence of sampling conditions such as collection time, body weight, age, and food intake of the pregnant women. Based on the fact that renal function during pregnancy is characterized by considerable changes in filtration and tubular reabsorption, dependent on gestational age and the time of a day which may create differences in renal glucose threshold and so theoretically limit the usefulness of 1,5-AG as a reliable marker of glycemic control in pregnant women , this study agrees with many studies which suggested that the deviation in renal threshold for glucose is an important

constraint for the use of 1,5-AG for diabetes screening, but not for diabetes monitoring; and this marker may be used as a useful tool of daily glucose monitoring in pregnant women with diabetes beside HbA1C monitoring and can provide valuable information regarding effectiveness of treatment. As majority of interpretations for utility of 1,5-AG in pregnancy are based on scanty few clinical data so there is a scope of potential possibilities for its use in pregnancy and continuous research may allow its new applications and usefulness in pregnancy in the future.

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