The utility of novel CGM metrics in the LGA newborn prediction in women with type 1 diabetes – assessment of the cut-off values

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ABSTRACT

Background: Pregnant women with type 1 diabetes (T1D) are at high risk of multiple pregnancy-related complications associated with poor glycemic control and pathologically raised insulin resistance that continuously increases throughout the pregnancy. The use of continuous glucose monitoring (CGM) devices significantly reduces the incidence of large-for-gestational-age (LGA) newborns in individuals with T1D.

Objective: We aimed to assess the utility and determine optimal novel CGM metrics cut-off values in the early prediction of LGA in pregnancies with T1D.

Methods: The study cohort included 75 pregnant women with T1D treated with insulin pumps with CGM devices. We measured the HbA1c and collected the anthropometric and CGM data in each trimester. Analyzing the first and second-trimester raw CGM data, we calculated several CGM indices reflecting the measure of short and long-term glycemic fluctuations. We assessed their utility in the early prediction of LGA risk and estimated optimal cut-off points in a receiver operating characteristic curve (ROC) analysis.

Results: Even though most of the patients achieved target HbA1c and time-in-range (TIR) values throughout the pregnancy, 33% of babies were born LGA. The ROC analysis revealed that the calculated CGM parameters were significantly associated with the LGA. In most cases, area under the curve (AUC) values attributed to the metrics of glycemic fluctuations exceeded 0.7. TIR values lower than 77% had about 90% sensitivity and 50% specificity in the LGA prediction.

Conclusion: Several novel CGM metrics of glucose fluctuations may be applicable in the LGA prediction in patients with T1D; however, more extensive clinical trials are necessary.

BACKGROUND and AIM

The results of randomized controlled trials revealed that CGM use in pregnancy significantly improves maternal long-term glycemic control pronounced by glycated hemoglobin measurements and reduces the risk of neonatal complications such as LGA, hypoglycemia, and prolonged hospitalization.

In our recent publications, we reported that the risk of LGA is associated with several CGM metrics reflecting high glycemic fluctuations [1,2]. In this study, we aimed to conduct ROC analysis and establish optimal CGM metrics' cut-off values predicting the risk of LGA.

MATERIAL and METHODS

We conducted a single-center retrospective cohort study. Study group included 75 pregnant patients with type 1 diabetes treated with insulin pumps and CGM devices (Medtronic REAL-Time 722 insulin pumps and Medtronic MiniMed™ Paradigm Veo™ and Medtronic MiniLink™ REAL-Time transmitters and Enlite™ sensors).

Recruited patients met the following inclusion criteria: age 18-45 years, had a documented history of type 1 diabetes for at least 12 months at the enrollment and were at 13 weeks and six days' gestation or less at baseline. We excluded patients in multiple pregnancies and individuals with early pregnancy loss.

We measured the patients' weight gain and HbA1c values in the three consecutive trimesters of pregnancy (the first visit scheduled at 13 weeks and six days' gestation or less, second between 20 and 24 weeks, and third between 33 and 39 weeks' pregnancy) and collected the data about pregnancy complications and perinatal outcomes (gestational age, macrosomia > 4000 g, LGA births > 90th centile, and LGA births > 97,7th centile). Calculated percentiles were adjusted for - maternal ethnicity, weight, height, parity, and the infant's sex and gestational age using GROW v.8.0.6.1 calculator [3].

We used data obtained from the CGM sensors to calculate glycemic control parameters - mean glucose values; time spent in (TIR), above (TAR), and below target range (TBR); %CV; MAGE; MODD; GRADE; GRADE attributed to hypo-, and hyperglycemia; CONGA; LBGI, and HBGI – using the GlyCulator2 application [4].

RESULTS

1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS AT BASELINE

Parameter; unit	Mothers of non-LGA infants (n -50)	Mothers of LGA infants (n - 25)	p - value
Maternal age; years	30.0 (4.5)	30.1 (4.3)	0.94#
Duration of diabetes; years	12.6 (7.6)	13.1 (6.3)	0.78#
Age at diagnosis; years	17.3 (8.1)	17.0 (7.1)	0.85#
Pre-pregnancy BMI; kg/m^2	23.0 (21.0 - 26.0)	24.4 (21.6 - 26.8)	0.33^

- Student's t-test, ^ - Mann Whitney U test; p values are statistically significant when P < 0.05

3. NEONATAL RESULTS IN CGM USERS

Clinical characteristics	CGM group (n - 75)
Gestational age; (days)	268 (262 - 271)
Preterm births <37 weeks; (n)	10
Neonatal birth weight; (g)	3520 (3130 - 3840)
LGA > 90th centile	25/75 (33%)
LGA > 97,7th centile	16/75 (21%)
Macrosomia (>4000 g)	14/75 (19%)
SGA <10th centile	6/75 (8%)

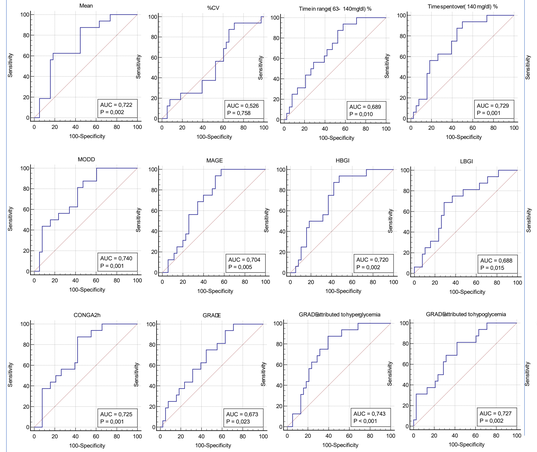
2. MATERNAL GLYCEMIC CONTROL

Parameter; unit	Mothers of non-LGA infants (n - 50)	Mothers of LGA infants (n - 25)	p-value
HbA1C; %			
I trimester	6,00 (5,63 - 6,35)	6,45 (6,10 - 6,73)	0,01^
II trimester	5,30 (0,60)	5,59 (0,47)	0,06#
III trimester	5,67 (0,61)	5,86 (0,57)	0,20#
TAR (>140 mg/dl); %			
I	17,9 (11,6 - 26,2)	27,9 (21,6 - 31,2)	0,009^
II	19,5 (13,4 - 31,1)	30,2 (20,2 - 36,5)	0,01^
III	19,7 (13,8 -26,4)	29,7 (20,7 - 36,0)	0,03^
TIR (63-140 mg/dl); %			
I	76,2 (70,2 - 83,2)	70,4 (64,7 - 76,5)	0,03^
II	74,2 (11,5)	68,1 (8,7)	0,04#
III	79,1 (69,2 -84,0)	67,6 (63,2 -77,1)	0,03^
TBR (<63 mg/dl); %			
I	3,8 (1,6 - 5,5)	1,8 (0,6 - 3,9)	0,03^
II	2,5 (1,3 - 4,7)	2,0 (0,8 - 3,6)	0,31^
III	1,7 (0,4 - 3,4)	1,0 (0,6 - 2,7)	0,47^
TBR (<54 mg/dl); %			
I	1,0 (0,4 - 2,1)	0,3 (0,04 - 1,4)	0,03^
II	0,8 (0,2 - 1,9)	0,5 (0,2 - 1,0)	0,38^
III	0,5 (0,1 - 0,9)	0,2 (0,1 - 0,7)	0,41^

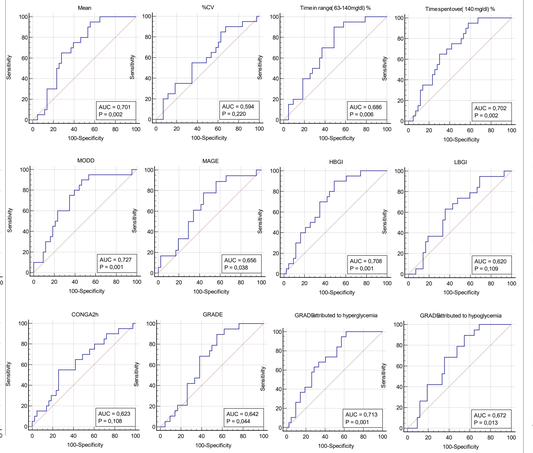
- Student's t-test, ^ - Mann Whitney U test; p values are statistically significant when P < 0.05

4. CGM METRICS IN THE LGA PREDICTION – ROC ANALYSIS GRAPHS

FIRST TRIMESTER



SECOND TRIMESTER



Abbreviations: %CV; coefficient of variation, **CONGA 2h**; continuous overall net glycemic action 2-hour interval, **GRADE;** glycemic risk assessment in diabetes equation, **GRADE hypo;** GRADE attributed to hypoglycemia, **GRADE hyper;** GRADE attributed to hyperglycemia, **HBGI**; high blood glucose index, **LBGI**; low blood glucose index, **MAGE**; mean amplitude of glycemic excursions, **MODD**; mean of daily differences, **TAR**; time above range, **TIR**; time in range

RESULTS

5. CGM METRICS IN THE LGA PREDICTION – ROC ANALYSIS, CUT-OFF VALUES

1st Trimester CGM metric	Cut-off value, (sensitivity; specificity)	2nd Trimester CGM metric	Cut-off value, (sensitivity; specificity)
Mean	**>121.4 mg/dl (62.5%; 81.6%)**	**Mean**	**>109.6 mg/dl (95.0%; 44.2%)**
%CV	>28.8 (93.7%; 28.9%)	%CV	>27.4 (90.0%; 32.6%)
TIR	**≤78.3% (93.7%; 42.1%)**	**TIR**	**≤77.5% (90.0%; 51.2%)**
TAR	**>16.7% (93.7%; 50.0%)**	**TAR**	**>16.7% (95.0%; 41.9%)**
MODD	**>33.4 (87.5%; 52.6%)**	**MODD**	**>33.5 (90.0%; 53.5%)**
MAGE	**>84.8 (100%; 42.9%)**	**MAGE**	**>89.6 (77.8%; 56.1%)**
HBGI	**>1.18 (93.7%; 52.6%)**	**HBGI**	**>1.17 (90.0%; 51.2%)**
LBGI	**≤1.50 (68.7%; 71.1%)**	LBGI	≤1.48 (63.2%; 64.3%)
CONGA2h	**>28.3 (87.5%; 57.9%)**	CONGA2h	>29.7 (55.0%; 74.4%)
GRADE	**>3.1 (93.7%; 36.8%)**	**GRADE**	**>3.2 (89.5%; 45.2%)**
GRADE hypo	**≤15.0 (81.2%; 57.9%)**	**GRADE hypo**	**≤22.0 (89.5%; 45.2%)**
GRADE hyper	**>56.6 (87.5%; 60.5%)**	**GRADE hyper**	**>45.2 (100%; 38.1%)**

*bold values are statistically significant, P < 0.05

SUMMARY and CONCLUSIONS

Our study proved that several CGM metrics attributed to increased glucose fluctuations are associated with the LGA risk and may be used as additional markers to predict the risk of LGA births in patients with T1D with near-normal glycated hemoglobin levels. Nonetheless, their efficacy should be further tested in larger randomized-controlled clinical trials.

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