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Brief report

Lack of validity of the glucose management indicator (GMI) in type 1 diabetes in pregnancy

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Running title: **GMI in type 1 diabetes in pregnancy**

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Twitter summary (200 characters): Does the #CGM glucose management indicator (GMI) perform well in pregnancy? @ClaireMeek5 et al found that GMI is less accurate and less clinically-useful compared to time-in-range in #T1D pregnancy.

Abstract 147

Objective: The glucose management indicator (GMI) is widely used as a replacement for HbA1c, but information in pregnancy is very limited. We assessed the accuracy of GMI and associations with pregnancy outcomes in type 1 diabetes.

Research Design & Methods: We compared HbA1c, continuous glucose monitoring (CGM) metrics, GMI at 12, 24 and 34 weeks' gestation and outcomes in 220 women from the CGM in pregnant women with type 1 diabetes (CONCEPTT) trial using logistic/ linear regression and Bland-Altman plots.

Results: GMI equations performed less accurately in pregnancy, with higher bias, especially in first and third trimesters. GMI and mean CGM glucose had equivalent predictive capability over pregnancy outcomes. GMI did not offer additional predictive capability over time-in-range (63-140 mg/dl; 3.5-7.8 mmol/l), time-above-range (>140 mg/dl; >7.8 mmol/l) and average CGM glucose.

Conclusions: GMI is not an accurate replacement for HbA1c in pregnancy in women with type 1 diabetes.

Article Highlights (<130 words)

- Why did we undertake this study?

The glucose management indicator (GMI), an arithmetic calculation using average glucose from continuous glucose monitoring (CGM), is used to approximate HbA1c. However, the GMI has not been extensively tested in pregnancy.

- What question we wanted to answer?

Is the GMI valid and clinically-useful in pregnancies with type 1 diabetes?

- What did we find?

GMI performed less accurately as an approximation of HbA1c in pregnancy; associations and bias varied according to trimester. GMI predicted similar outcomes to average glucose. At 34 weeks, GMI predicted fewer pregnancy outcomes compared to HbA1c.

- What are the implications of our findings?

The GMI is not accurate in pregnancy. HbA1c or alternative CGM metrics, such as time-in-range or time-above-range, offer similar or better predictive capability for pregnancy outcomes.

Type 1 diabetes in pregnancy is associated with perinatal complications which can be predicted using laboratory HbA1c and continuous glucose monitoring (CGM) metrics such as average CGM glucose, time-in-range (TIR; 63-140 mg/dl; 3.5-7.8 mmol/l) and time-above-range (TAR; >140 mg/dl; >7.8 mmol/l)[1]. However, CGM reports also offer the glucose management index (GMI), an estimation of HbA1c calculated from an equation using at least six days of average CGM glucose data[2]. The accuracy of the GMI equation has not been formally assessed in pregnancy.

Accurate assessment of maternal glycemia in pregnancy is vital to inform management decisions and prevent neonatal morbidity and mortality [3]. However, the relationship between HbA1c and mean blood glucose is known to be influenced by pregnancy[4]. Previous work in 89 women with type 1 diabetes suggests that the usual GMI formula is not an acceptable HbA1c substitute during pregnancy, but did not evaluate its association with outcomes[4, 5]. A trimester-specific GMI has been proposed by Ling et al, using data from 98 women [6], but associations with pregnancy outcomes were not assessed

Since HbA1c changes over a period of 1-3 months, metrics representing maternal glucose status in a short-term period, such as 6-day GMI, could be valuable alternatives in pregnancy where glycemia is reviewed 1-2 weekly. We previously identified robust associations between HbA1c or CGM metrics, particularly TIR, TAR and average CGM glucose, with clinical outcomes in women with type 1 diabetes in pregnancy[1]. However, we did not examine GMI. The aim of the current study was therefore to assess if GMI is a reliable approximation of HbA1c and can improve prediction of relevant perinatal outcomes in women with type 1 diabetes in pregnancy.

Methods

The CGM in pregnant women with type 1 diabetes trial (CONCEPTT) is described elsewhere [7](ClinicalTrials.gov; NCT01788527). The trial received ethical approval from the Health Research Authority, East of England Research Ethics Committee (12/EE/0310) for all UK sites and at individual centres for all other sites. Written informed consent was taken from all participants in advance.

During the CONCEPTT trial, women in the intervention arm received real-time CGM (Guardian REAL-Time or MiniMed Minilink system, both Medtronic, Northridge, CA) and women in the control group had masked CGM (iPro2

Professional CGM, Medtronic, Northridge CA, USA) for ~6 days at approximately 12 weeks, 24 and 34 weeks. Pre-specified obstetric and neonatal outcomes were as previously defined[7].

The HbA1c was taken and CGM was sited at the same research visit. HbA1c was measured at approximately 12 weeks, 24 and 34 weeks using the turbidimetric inhibition immunoassay for haemolysed whole blood on the Cobas Integra 700 platform (Roche, Basel, Switzerland) at a central laboratory (DynaCare, Brampton, ON, Canada). CGM metrics were derived from periods of ~6 days starting at approximately 12, 24 and 34 weeks gestation, in the period of blood withdrawal for HbA1c[8], since ~6 days of data were available from both control and intervention participants. GMI was calculated using the published equation[2]: GMI (%) = 0.02392 x [CGM mean glucose mg/dl] + 3.31.

Statistical Analysis

Unadjusted standardised bivariate logistic regression was used to identify associations between GMI, CGM metrics or HbA1c (analysed as continuous variables) with pregnancy outcomes as previously defined[7], chosen for consistency with our previous work[1]. We chose to include unadjusted models only, presented as standardised ORs with 95% CIs, to reflect decision making in clinical practice. Results are presented as scatter plots showing the proposed GMI equations per trimester, and Bland-Altman plots showing the degree of bias with glucose concentration.

Results

220 women were included in this analysis (table 1).

Associations between GMI, HbA1c and CGM metrics

At 12 weeks' gestation (figure 1a-b), mean CGM glucose and HbA1c showed a linear relationship with a gradient of 0.01474 and an intercept of 4.910. The relationship between mean CGM glucose and HbA1c varied with each trimester (Figure 1 a,c,e) but the gradient was smaller in all trimesters of pregnancy compared to the standard GMI equation (gradient 0.02392). On Bland-Altman plots (Figure 1 b,d,f), the difference between HbA1c and GMI (bias)

varied with each trimester and within the concentration range. At average concentrations of 8.0% (64 mmol/mol), HbA1c was on average 1% (11 mmol/mol) higher than GMI at 12 and 34 weeks, while the average bias was 0 at this concentration at 24 weeks. In trimesters 1, 2 and 3, HbA1c was higher than GMI in 161/221 (72.8%), 48/197 (24.4%) and 108/172 (62.8%) of cases respectively (Figure 1). There was a high degree of scatter and biases of ±0.5% were common throughout the concentration range in all trimesters.

GMI and Pregnancy Outcomes

HbA1c, GMI, mean glucose, TIR, and TAR were all inconsistently associated with various outcomes of interest. Since they are linearly related, GMI and mean CGM glucose had equivalent predictive capability over pregnancy outcomes (Figure 2). GMI did not offer additional predictive capability over TIR , TAR and HbA1c.

Discussion

GMI using the standard equation is a less accurate reflection of HbA1c in pregnancy and commonly showed biases of +/- 0.5%. In addition, it does not offer benefits in the prediction of suboptimal pregnancy outcomes over HbA1c, CGM average glucose, TIR and TAR. There is no additional benefit to calculating GMI.

Strengths and weaknesses

This study provides detailed information on glucose control in a well-characterized cohort longitudinally during pregnancy[7]. However, women with HbA1c <6.5% (48 mmol/mol) or >10.0% (86 mmol/mol) at baseline were excluded from the CONCEPTT trial, which may have reduced the strength of association between GMI, other CGM markers and HbA1c with pregnancy outcomes. This is consistent with previous work showing reduced GMI performance in euglycemic populations[9]. Our analysis used the same approach as that used in our previous publication[1], providing consistency across publications and over time. We recognise that our cohort does not provide extensive ethnic diversity, which may influence the results. We used ~6 days of CGM data since this was available on all participants regardless of control or intervention allocation. Using a longer duration of data may improve predictive capability for GMI but also for other CGM markers.

Comparative accuracy of glycemic markers in pregnancy: a theoretical framework

Assessment of the accuracy of markers of glycemia requires a perspective on pre-analytical, analytical and post-analytical (interpretive) sources of variability in results. HbA1c has few preanalytical problems and can be analysed very accurately, with international standardisation. However, post-analytical challenges in HbA1c interpretation are abundant in pregnancy, due to variability related to red cell turnover, gestational age and concomitant iron deficiency and supplementation [10-13]. Despite these challenges, overall HbA1c provides strong associations with pregnancy outcomes and is a meaningful test to patients and clinicians. CGM conversely has some pre-analytical challenges, related to temperature and skin condition, and offers a more frequent but less analytically precise measurement of glycemia compared to optimal laboratory measurement. However, the real benefit of CGM lies in the postanalytical phase: interpretation of CGM metrics such as TIR, TAR and average CGM glucose guiding treatment modification and at the same time, is accessible to patients and clinicians, supporting widespread adoption of the technology. Using GMI combines the preanalytical and analytical variability of measurement inherent in CGM metrics, with the variation inherent in the post-analytical interpretation of HbA1c.

The history of assessing accuracy of GMI in non-pregnant populations

Fundamentally, the GMI is only useful if it is reliable enough to support safe clinical decision making[14, 15]. Original accuracy data suggest that around 50% of GMI values are +/- >0.3%, and around 20% of values are +/- >0.6% compared to the HbA1c concentration[2], meaning that changes in GMI can often be due to chance. GMI was initially developed in a population of young adults with type 1 diabetes and stable glycemic control over 1-3 months, in order to give an approximation of the HbA1c using CGM data[2, 16]. The standard equation for GMI has been widely adopted, is now reported after 6-7 days' CGM use[14] and has not been updated to reflect increasing CGM accuracy. Even after recent advances in CGM accuracy, intra-individual differences still exist, for example, after a sensor change[17]. Although GMI was developed in type 1 diabetes, it is now widely used in many other populations, such as pregnant women[18], children[19], people with type 2 diabetes[14] and healthy people, with reduced accuracy[9, 20].

Accuracy of GMI in pregnancy

In this study we demonstrate that the standard GMI equations for non-pregnancy populations are less accurate when used in pregnancy, with high degrees of bias across the concentration range, especially in trimesters 1 and 3.

In clinical use, if the GMI result is lower than the latest measured HbA1c, some consider that this suggests recent improvements in glycemia. However, in this study, only half of participants had a GMI below the HbA1c in the third trimester, although the vast majority showed an overall improvement in glycemia. Using the GMI to assess progress instead of more accurate longitudinal measures such as mean CGM glucose, TIR or TAR risks providing false reassurance, missing opportunities to optimise treatment.

In conclusion, GMI is inaccurate as an approximation of HbA1c in pregnancy. Clinicians should use HbA1c, CGM TIR and mean CGM glucose to inform management decisions in pregnant women with type 1 diabetes.

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*Dr Lois Jovanovic died during the preparation of this manuscript

This manuscript arose following a discussion at the meeting of the National Glycohemoglobin Standardisation Panel advisory group at the American Diabetes Association Scientific Sessions 2023.

Contribution Statement

CLM identified the study question, designed the study, analysed and interpreted the data, wrote and revised the manuscript. RC designed the study, contributed to data analysis and reviewed and revised the manuscript. HRM, and DSF identified the study question, contributed to data analysis and discussion, and reviewed and revised the manuscript. ES provided expertise on analysis of CGM data. All authors reviewed the final version of the manuscript prior to publication.

Conflict of interest

CLM has received research funding and reduced-cost equipment from Dexcom Inc.

DSF has received honoraria for speaking engagements from Medtronic and has been on an Advisory Board for Novo Nordisk.

EMS has received honoraria for speaking engagements with Eli-Lilly and Abbott Diabetes Care and has been on advisory boards for Abbott Diabetes Care

HRM has received honoraria for speaking engagements from Medtronic, Roche, Novo Nordisk, Eli-Lilly and is a member of the Medtronic European Advisory Board.

RC has received honorary for speaking engagements with Lilly and Novo Nordisk and has been on an Advisory Board for Novo Nordisk and Abbott.

Guarantor

CLM is the guarantor of this work and, as such, has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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HRM conducts independent research supported by the National Institute for Health Research (Career Development Fellowship, CDF-2013-06-035), and is supported by Tommy's charity. CLM is supported by the Diabetes UK Harry Keen Intermediate Clinical Fellowship (DUK-HKF 17/0005712) and the European Foundation for the Study of Diabetes – Novo Nordisk Foundation Future Leaders' Award (NNF19SA058974).

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Table and Figures

Table 1: Characteristics of women from the CONCEPTT trial included in this analysis*. Data are presented as Mean (SD) or n (%).

	Maternal Characteristics
	n=220
Age, years	31.4 (4.6)
BMI at study entry, kg/m²	25.7 (4.6)
European origin	189/220 (85.9%)
Post-secondary education	169/220 (76.8%)
Smoking habit	20/220 (9.1%)
Primiparous	111/220 (50.5%)
Duration of diabetes, years	16.4 (7.8)
Insulin pump	105/220 (47.7%)
Randomization arm (CGM)	110/220 (50.0%)
Pregnancy outcomes	
Gestational age, weeks	37.0 (1.6)
Pre-eclampsia	27/220 (12.3%)
Caesarean section	150/220 (68.2%)
Customised Centile (GROW)	82.3 (25.5)
LGA (GROW)	135/220 (61.4%)
Neonatal hypoglycemia	55/220 (25.0%)
NICU admission	81/220 (36.8%)

*with all CGM markers measured in the first trimester and delivering a livebirth at ≥20 weeks
Abbreviations: CGM: continuous glucose monitoring; LGA: large for gestational age; NICU: neonatal intensive care unit; SD: standard deviation

Table 2: Continuous glucose monitoring metrics, GMI and HbA1c at 12, 24 and 34 weeks in women with type 1 diabetes in pregnancy.

	12 weeks	24 weeks	34 weeks
	n=220	n=198	n=172
Continuous Glucose Monitoring	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Mean CGM glucose (mg/dl)	135 (21.6)	138.6 (23.4)	122.4 (18)
Mean CGM glucose (mmol/l)	7.5 (1.2)	7.7 (1.3)	6.8 (1.0)
TIR 63-140 mg/dl; 3.5-7.8 mmol/l (%)	51.7 (13.1)	51.4 (15.2)	64.8 (14.2)
TAR >140 mg/dl; 7.8 mmol/l (%)	39.7 (14.3)	43.3 (16.9)	30.1 (14.3)
TBR <63 mg/dl; 3.5 mmol/l (%)	8.5 (7.1)	5.2 (5.4)	5.1 (5.0)
CV (%)	0.4 (0.1)	0.4 (0.1)	0.3 (0.1)
Glucose SD (SD)	3.1 (0.8)	2.8 (0.7)	2.3 (0.6)
Glucose Management Indicator (GMI)			
GMI %	6.5 (0.5)	6.6 (0.5)	6.2 (0.4)
Laboratory Glycemic Markers			
HbA_{1c} (%)	6.9 (0.6)	6.3 (0.6)	6.4 (0.6)
HbA_{1c} (mmol/mol)	51.7 (6.7)	45.4 (6.7)	46.6 (6.6)

Abbreviations: CGM: continuous glucose monitoring; CV: coefficient of variation; GMI: glucose management indicator; HbA_{1c}: glycated hemoglobin; SD: standard deviation; TAR: time above range; TBR: time below range; TIR: time in range.

Figures

Figure 1: Associations between CGM mean glucose and HbA1c, and Bland-Altman plot of bias in pregnant women with type 1 diabetes at 12 weeks (a-b), 24 weeks (c-d) and 34 weeks (e-f). Average refers to the average of HbA1c and GMI, both expressed as a percentage. Difference refers to the difference between HbA1c and GMI, both expressed as a percentage.

Abbreviations: CGM: continuous glucose monitoring; GMI: glucose management indicator; HbA_{1c}: glycated hemoglobin; RMSE: root mean squared error; SD: standard deviation.

Figure 2: Associations between CGM metrics, HbA1c and GMI at 12, 24 and 34 weeks' gestation with pregnancy outcomes.

Abbreviations: CI: confidence interval; CV: coefficient of variation; GMI: glucose management indicator; HbA_{1c}: glycated haemoglobin; LGA: large for gestational age, >90th centile using GROW centiles; MEAN: mean glucose on continuous glucose monitoring; NICU: neonatal intensive care unit admission; SD: standard deviation; TAR: time above range; TBR: time below range; TIR: time in range. * $p<0.05$; ** $p<0.01$; *** $p<0.001$.