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Original Article

Novel biochemical markers of glycemia to predict pregnancy outcomes in women with type 1 diabetes

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Abstract

Objective: The optimal method of monitoring glycemia in pregnant women with type 1 diabetes remains controversial. This study aimed to assess the predictive performance of HbA1c, continuous glucose monitoring (CGM) metrics, and alternative biochemical markers of glycemia to predict obstetric and neonatal outcomes.

Methods: 157 women from the CGM in pregnant women with type 1 diabetes trial (CONCEPTT) were included in this pre-specified secondary analysis. HbA1c, CGM data, and alternative biochemical markers (glycated CD59, 1,5 anhydroglucitol, fructosamine and glycated albumin) were compared at approximately 12, 24 and 34 weeks gestation using logistic regression and ROC curves to predict pregnancy complications (pre-eclampsia, preterm delivery, large-for-gestational-age, neonatal hypoglycemia, admission to neonatal intensive care unit).

Results: HbA1c, CGM metrics, and alternative laboratory markers were all significantly associated with obstetric and neonatal outcomes at 24 weeks gestation. More outcomes were associated with CGM metrics during the 1st trimester and with laboratory markers (area under ROC generally <0.7) during the third trimester. 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) were the most consistently predictive CGM metrics. HbA1c was also a consistent predictor of suboptimal pregnancy outcomes. Some alternative laboratory markers showed promise, but overall, they had lower predictive ability than HbA1c.

Conclusions: HbA1c is still an important biomarker for obstetric and neonatal outcomes in type 1 diabetes pregnancy. Alternative biochemical markers of glycemia and other CGM metrics did not substantially increase the prediction of pregnancy outcomes compared to widely available HbA1c and increasingly available CGM metrics (TIR and TAR).

Introduction

Type 1 diabetes in pregnancy is associated with obstetric and neonatal complications which are attributed to maternal hyperglycemia [1]. Affected women are more likely to develop pre-eclampsia and to experience instrumental or operative deliveries [1]. Their newborn babies may be affected by preterm delivery, large-for-gestational age (LGA; birthweight >90th centile) and neonatal hypoglycemia, which contribute to high rates of admission to the neonatal intensive care unit (NICU) [1].

Neonatal complications of type 1 diabetes pregnancy can be prevented or ameliorated by improved maternal glucose levels [2, 3]. However, the objective assessment of maternal glycemia throughout pregnancy is challenging. Gestational changes in red cell turnover and serum protein concentrations raise concerns about the validity of HbA1c as a glycemic marker [4, 5]. HbA1c measurements typically reflect glycemia over the preceding 2-3 months, which is also less suitable for intensive monitoring of 1-2 weekly glucose patterns during pregnancy [5].

Novel approaches to the assessment of glycemia in pregnancy include the use of continuous glucose monitoring (CGM) metrics and alternative laboratory markers, including glycated CD59 (gCD59), 1,5 anhydroglucitol (1,5-AG), fructosamine and glycated albumin [6-8]. During the continuous glucose monitoring in women with type 1 diabetes in pregnancy (CONCEPTT) trial, the use of CGM led to improved maternal glycemia and neonatal outcomes, with a substantial reduction in admissions to NICU[9]. This has resulted in widespread adoption of CGM in pregnant women with type 1 diabetes. Many women now have CGM data available throughout pregnancy, but it is unclear which metrics, at which time points, are most useful for pregnancy outcome prediction. Recent work has identified that lower time-in-range (TIR), higher mean glucose and glucose SD are associated with LGA [10]. Functional analysis of CGM data from CONCEPTT trial participants has identified that women whose offspring develop LGA have a higher mean glucose for 14-16 hours per day throughout pregnancy [11].

The aim of the current study was to assess the predictive performance of HbA1c, CGM metrics and alternative biochemical markers to identify women with type 1 diabetes at risk of suboptimal pregnancy outcomes.

Methods

The CONCEPTT trial which included women with type 1 diabetes recruited during pregnancy or while planning pregnancy is described elsewhere [9]. The trial was registered (ClinicalTrials.gov, number NCT01788527) and received ethical approval from the Health Research Authority, East of England Research Ethics Committee (12/EE/0310) for all UK sites and at each individual centre for all other sites. All participants gave written informed consent. The current study is a pre-specified secondary analysis approved by the CONCEPTT trial steering committee before trial completion.

Women were randomized to real-time CGM (Guardian REAL-Time or MiniMed Minilink system, both Medtronic, Northridge, CA) in addition to capillary glucose monitoring or capillary glucose monitoring alone for diabetes management. Women in the capillary glucose monitoring group also had short periods of masked CGM (iPro2 Professional CGM, Medtronic, Northridge CA, USA) to allow comparison of CGM metrics between groups. This study includes data from pregnant and pre-pregnant recruits who became pregnant and gave birth to a liveborn infant. Pre-specified obstetric and neonatal outcomes are: pre-eclampsia (systolic blood pressure of ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg on ≥ 2 occasions a minimum of 6 hours apart and proteinuria of ≥ 1+ dipstick or ≥300 mg per 24 hours), preterm delivery (<37 weeks), LGA (>90th centile) based on customised centiles, neonatal hypoglycemia requiring intravenous dextrose, and neonatal intensive care unit admission requiring a duration of at least 24 hours.

Blood Sampling and Laboratory Analysis

The HbA1c samples obtained at approximately 10-12 weeks, 24-25 and 34-35 weeks gestation were shipped at the end of pregnancy and were unavailable to participants and health-care teams during the trial. HbA1c measurements were done 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). Women were asked to give a voluntary additional serum sample for metabolic studies at the

same three time-points as trial HbA1c sampling. The sample was processed quickly and aliquotted for storage at -80ºC.

Analyses for 1,5-AG, fructosamine and glycated albumin were performed in batches in the Core Biochemical Assay Laboratory on the Cambridge Biomedical Campus. 1,5-AG was measured using commercially available reagents (Glycomark, USA) on a Randox Daytona+ analyser. Fructosamine was measured using a Randox kit on the Randox Daytona+ analyser. Glycated albumin was measured using commercially available reagents from Asahi Kasei Pharma (Japan) on a Randox Daytona+ analyser. Analyses for gCD59 were performed in the Laboratory for Translational Research, Harvard Medical School as described previously [12].

CGM metrics

The CGM metrics were derived from periods of 6 days at approximately 10-12 weeks, 24-25 and 34-35 weeks gestation. Definitions were consistent with international reporting recommendations and are defined in Table S1 [13].

Statistical Analysis

Continuous data were described as mean (SD) and categorical data as n (%) as appropriate). Pearson's correlation coefficients were used to assess relationships between CGM metrics and laboratory markers of glycemia. Unadjusted standardised bivariate logistic regression was used to identify associations between CGM metrics or glycemic markers with pregnancy outcomes, specifically pre-eclampsia, preterm birth, LGA, neonatal hypoglycemia and NICU admission. Outcomes were chosen to reflect maternal complications (pre-eclampsia), neonatal hyperinsulinemic complications (large-for-gestational age, neonatal hypoglycaemia) and outcomes with particular relevance for health economic outcomes (preterm birth, NICU admission). We chose to include unadjusted models only as these closely reflect decision making in clinical practice where glycemic targets are used consistently, and are not adjusted according to other patient characteristics.

In order to compare variables with different units, results were presented as standardised ORs with 95% CIs. We used receiver operator characteristic (ROCs) curves to compare the predictive ability of different metrics and glycemic markers individually.

Results

225 women enrolled in the CONCEPTT trial and gave birth to liveborn infants, of whom 157 participants gave at least one additional sample for laboratory testing of alternative markers of glycemia. Participants had a mean age of 32 years, with a BMI of 25.5 kg/m^2 and were predominantly of European or Mediterranean origin. Around 50% of women used insulin pump therapy. Overall, participants were similar to women who did not give an additional laboratory sample (n=70), although they were less likely to have previous diabetes complications (Table 1). Rates of pre-eclampsia (13%), preterm delivery (40%), LGA (62%), neonatal hypoglycemia (27%) and NICU admission (35%) were similar in women who did and did not participate.

Measuring Glycemic status

CGM metrics and laboratory markers of glycemia varied across gestation (Table 2) and were significantly correlated (Table S2). Participants had an initial HbA1c of 51 mmol/mol (6.9%) in the first trimester which decreased to 46 mmol/mol (6.3%) at 24 weeks and slightly increased to 47 mmol/mol (6.4%) at 34 weeks gestation (Table 1). The corresponding CGM TIR (63-140mg/dl; 3.5-7.8mmol/l) was 52% in the first trimester, 50% at 24-25 weeks and 64% at 34-35 weeks (Table 2).

CGM Markers and Pregnancy Outcomes

Most CGM metrics were associated with one or more outcomes, including pre-eclampsia, preterm delivery, LGA, neonatal hypoglycemia and NICU admission (Figure 1; Table S3; standardised ORs). No CGM metrics in the first trimester or 34 weeks were associated with pre-eclampsia, but at 24 weeks associations were identified with CGM mean glucose, TIR (63-140 mg/dl; 3.5-7.8 mmol/l), time-above-range (TAR;

>140 mg/dl; >7.8 mmol/l), and glucose SD. For preterm birth, mean glucose, TIR and TAR showed associations in the first and second trimesters, but only TAR remained significant at 34 weeks gestation.

For LGA, CGM metrics showed consistent associations with TIR, TAR and SD at all time-points studied; mean glucose was also significant at 24 and 34 weeks. For neonatal hypoglycemia, mean glucose, TIR and TAR showed associations at 24 and 34 weeks, but only TIR had an association in the 1st trimester. For NICU admission, mean glucose, TIR, TAR and SD all showed associations at 24 weeks, but only TIR in the 1st trimester. There were no CGM metrics which could predict NICU admission at 34 weeks. Overall, CGM TIR and TAR showed the most consistent associations with neonatal outcomes.

Laboratory Markers and Pregnancy Outcomes

All laboratory markers of glycemia were associated with one or more outcomes. No laboratory markers were associated with pre-eclampsia in the first trimester, but we identified associations between pre-eclampsia and glycated albumin or gCD59 at 24 weeks, and fructosamine or 1,5-AG at 34 weeks gestation. HbA1c was not associated with pre-eclampsia but was associated with preterm birth at 24 and 34 weeks gestation. Preterm birth was also associated with 1,5-AG concentrations at 12 weeks and gCD59 concentrations at 24 weeks gestation.

All laboratory markers of glycemia were associated with LGA at one or more of the time-points studied. 1,5-AG in the first trimester and gCD59 at 34 weeks gestation demonstrated the strongest associations with LGA. Neonatal hypoglycemia was associated with gCD59 at all three time-points, with HbA1c at 24 and 34 weeks and with fructosamine and 1,5-AG at 24 weeks gestation. Admission to NICU was associated with gCD59 at 24 weeks and HbA1c at 24 and 34 weeks gestation. gCD59 showed the strongest associations with neonatal hypoglycemia and NICU admission at 24 weeks gestation.

The direction of most significant associations was towards a higher risk of complications with increased maternal hyperglycemia. The only exceptions were for 1,5-AG with preterm birth in the first trimester and fructosamine and 1,5-AG with pre-eclampsia at 34 weeks gestation.

Prediction of Pregnancy Outcomes using Glycemic Markers

ROC curves were used to compare the ability of the laboratory markers of glycemia with CGM metrics (mean glucose, TIR and TAR) to predict pregnancy outcomes (Figure 2, only including strongest CGM metrics; Table S4). However, as expected for inter-related glycemic markers, confidence intervals for ORs and AUROC were often overlapping (Tables S3 & S4). The strongest predictor (defined as having the highest AUROC) for pre-eclampsia was mean CGM glucose in the first trimester (AUROC 0.65), mean CGM glucose at 24 weeks (AUROC 0.72) and fructosamine at 34 weeks gestation (AUROC 0.76). For preterm birth, mean CGM glucose and TAR were equally predictive in the first trimester (AUROC 0.61 for both) while at 24 weeks, mean CGM glucose, TAR and gCD59 were equally predictive (AUROC 0.64). HbA1c was the strongest predictor of preterm birth at 34 weeks (AUROC 0.65).

For LGA, 1,5-AG and TIR were the strongest predictors in the first trimester (AUROC 0.64 for both), TIR, fructosamine and HbA1c were the strongest predictors at 24 weeks (AUROC 0.64 for each) and TAR at 34 weeks (AUROC 0.67). The strongest predictors of neonatal hypoglycemia were gCD59 in the first trimester and 24 weeks (AUROC 0.61 in the first trimester; 0.72 at 24 weeks) and HbA1c at 34 weeks (AUROC 0.68). There was no significant predictor for NICU admission in the first trimester; gCD59 was the strongest predictor at 24 weeks (AUROC 0.73) and HbA1c at 34 weeks gestation (AUROC 0.66).

Discussion

HbA1c, CGM metrics and alternative laboratory markers of glycemia can all be used to identify pregnancies at increased risk of suboptimal neonatal outcomes, even from the first trimester. However, neither laboratory markers nor CGM metrics were able to provide a strong prediction of any pregnancy outcome (AUROCs

mostly <0.70). In pregnant women with type 1 diabetes, the use of alternative laboratory markers did not appreciably increase the AUROC for prediction of suboptimal pregnancy outcomes beyond HbA1c, which is already widely available, or CGM metrics such as TIR and TAR.

HbA1c was consistently associated with pregnancy outcomes, suggesting that despite the known limitations of HbA1c for assessing antenatal glycemia [14], it is still a critically important biomarker for obstetric and neonatal health outcomes. While other laboratory biomarkers demonstrated some promise, none were able to significantly increase the AUROC, showing at best comparable prediction to HbA1c alone.

Glycated albumin and fructosamine (measuring total glycated serum proteins) provide a measure of glycemic status over the last 2-4 weeks and have been associated with the development of diabetes and microvascular complications in non-pregnant adults [15, 16]. Although fructosamine and glycated albumin are unaffected by altered hemoglobin concentration, potential disadvantages to the use of fructosamine include the variability of albumin and protein concentration due to the dilutional effects of pregnancy so that fructosamine falls with advancing gestational age [17]. Glycated albumin, expressed as a proportion of total albumin concentrations, shows less variation with gestational age and iron deficiency [14].

After initial interest in the use of glycated proteins for gestational diabetes screening [18], and later dismissal due to low sensitivity [19], few studies have assessed their relationship with pregnancy outcomes. A recent study in 301 gestational and pre-gestational diabetes pregnancies showed that fructosamine concentration at delivery was not associated with neonatal outcomes [20]. Glycated albumin may be more closely associated with HbA1c and mean capillary blood glucose compared to fructosamine [21]. Despite these findings, glycated albumin did not show strong associations with pregnancy outcomes in this study, even when outside pregnancy, it is associated with diabetes complications [22].

Another potential glycemic marker is 1,5-AG, a monosaccharide which is present in many foods, enters the body orally and is excreted gradually by the kidneys. In periods of hyperglycemia, glucose competes with re-uptake in the renal tubule, promoting excessive loss of 1,5-AG. Thus, 1,5-AG falls during hyperglycemia

and takes 2 weeks to re-stabilise once normoglycemia is restored [23]. 1,5-AG has been found to be inversely associated with birthweight, and with neonatal hypoglycemia in gestational diabetes [7, 24]. Nowak and colleagues identified that 1,5-AG was associated with mean glucose and a strong predictor of macrosomia in 58 women with type 1 diabetes [25]. Our results are consistent with these findings, as 1,5-AG was negatively associated with LGA in each trimester but it did not perform better than HbA1c values. A strong positive association between 1,5-AG and pre-eclampsia was observed at 34 weeks which was accompanied by a strong negative association of fructosamine and pre-eclampsia. Our observation of "improved" glycemic status at 34-35 weeks in women with pre-eclampsia (either already concurrent or to emerge within next weeks) could indicate early changes in renal function or placental dysfunction with ensuing lower insulin requirements (reverse causation) [26]. It is possible that these findings could be used to develop a predictive model in future.

CD59 is membrane protein inhibitor of the terminal complement cascade. Glycation of CD59 (yielding gCD59) abrogates its function as an inhibitor of complement, which likely plays a role in the pathogenesis of diabetes complications [27, 28]. gCD59 has been proposed as a novel marker of glycemic control which reflects changes within 2 weeks of a treatment intensification [6]. In a study of 1000 pregnant women, Ma and colleagues identified that GCD59 was a strong predictor of GDM (AUROC 0.92) and that higher levels of maternal gCD59 were associated with higher prevalence of LGA [6]. More recently, measurement of gCD59 at pregnancy week <20 identified early development of GDM and was strongly associated with LGA newborns [29]. In the current study, gCD59 measured at 24 weeks showed strong associations with neonatal hypoglycemia and NICU admission (AUROCs 0.72-0.73) and performed better than HbA1c (AUROCs 0.64-0.66) at this time-point. This suggests that if it was more widely available, gCD59 could potentially play a role in prediction of neonatal complications, particularly NICU admission and neonatal hypoglycemia.

Relatively few studies have assessed the predictive ability of CGM metrics during pregnancy [30]. Mulla and colleagues found no associations between HbA1c or CGM metrics with birthweight or LGA in 41

pregnant women with type 1 diabetes [31]. Likewise, Panyakat and colleagues found no associations between third trimester CGM metrics and pregnancy outcomes in 47 women with gestational diabetes [32]. Dalfra et al reported that CGM glycaemic variability indexes were associated with ponderal index in the newborn offspring of 32 women with type 1 diabetes, but not in gestational diabetes[33]. Law and coworkers identified an association between nocturnal hyperglycemia and LGA, but with no associations identified with other CGM metrics, such as TIR or TAR in 162 women with gestational diabetes [34]. The same team identified associations between LGA and lower mean CGM glucose during the first trimester and a higher mean CGM glucose during the second and third trimesters in women with type 1 or type 2 diabetes [35]. Previous data from the CONCEPTT trial demonstrates particular diurnal periods, reflecting post-meal hyperglycemia, when mean CGM glucose is higher in women who deliver an LGA infant [11]. In this study, TAR was the CGM metric that showed the strongest association with pregnancy outcomes, followed by TIR which is the metric most commonly used in diabetes clinics due to its association with microvascular outcomes [36] and intuitive use both for patients and healthcare professionals [37]. Overall, these results indicate that TIR and TAR, in addition to aiding daily self-management of diabetes, can also offer insight into the pregnancy outcomes of women with type 1 diabetes, predictions that may be further improved with new generation CGM sensors yielding accurate CGM metrics for longer time periods throughout pregnancy. In regular CGM users, additional biomarkers including HbA1c, may not add to the assessment of maternal glycemia, but remain important for prediction of pregnancy outcomes.

These results also provide insight regarding relevant time-windows for pregnancy outcomes. Essentially, most associations including pre-eclampsia were more prominent in the second trimester, highlighting the importance of glycemic status in this period. Pre-eclampsia is generally agreed to commence in early pregnancy but current results are in line with other reports that also describe the association with maternal hyperglycemia as being only present or more marked in the second and third trimesters [38, 39].

This study provides detailed information about laboratory markers and CGM metrics in a well-characterized cohort during each trimester of pregnancy. The study design provided a near-complete dataset, albeit with

less third trimester data. In addition, we had a robust process for analysis of additional glycemic markers, with batch analysis for consistency. We also acknowledge the limitations. 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 glycemic markers and pregnancy outcomes. CGM metrics and glycemic biomarkers were only measured at three time-points, so it is possible that more frequent assessment, or use of CGM for longer than 6 days' duration and preferably continuously throughout pregnancy, may give further information and closer associations with obstetric and neonatal outcomes. Indeed, the optimal frequency of monitoring of CGM or laboratory biomarkers in pregnancy is unknown. This is particularly important for the novel laboratory markers, which have not been fully characterised in pregnant women and may show more dynamic changes than HbA1c. While pregnancy outcomes were adjudicated, the timing of delivery was determined by local policies, and we cannot exclude variation in local criteria used for NICU admission. The 34 week sampling time was chosen to include almost all women, but several deliveries occurred before 34 weeks, which may have also affected our results. We chose not to adjust for multiple testing in this analysis for several reasons. Firstly, adjustment of the threshold of significance is challenging where there are multiple inter-related variables and the options available do not facilitate a clear presentation of the data. Furthermore, as the analysis was primarily assessing the same question (associations between glycemia and outcomes), adjustment for multiple testing becomes less valid. We expected to find multiple significant associations and consider that our results are in line with the substantial body of evidence describing associations between maternal glucose and complications related to fetal hyperinsulinemia in type 1 diabetes pregnancy. We demonstrate that although some markers appeared stronger than others, there was a high degree of overlap of confidence intervals for prediction of pregnancy outcomes. This precludes a definitive conclusion about which single marker performed best, but is not unexpected since so many markers showed a high degree of statistical correlation.

In conclusion, this study provides a comprehensive assessment of measures of glycemia, using both CGM and laboratory markers to predict a range of outcomes in type 1 diabetes pregnancy. Despite the established importance of glycemia in type 1 diabetes pregnancy [9, 40], markers of glycemia were only moderate

predictors of outcomes (AUROC mostly <0.70). It is possible that the complexity of maternal hyperglycemia cannot be easily summarised by a single glycemic marker, or that other maternal, fetal and placental factors also contribute directly or indirectly, by mediating the relationship between glycemia and pregnancy outcomes. This is consistent with the finding that complications such as LGA have not substantially improved over recent decades, despite advances in diabetes management and technology [1, 9, 31]. Future work should seek to optimise maternal glucose levels before and during pregnancy and to identify what factors in addition to maternal hyperglycemia contribute to the variation in outcomes seen in type 1 diabetes pregnancy.

Table and Figures

Table 1: Characteristics of women participating in the CONCEPTT glycemic markers study

	Participants included in the glycemic markers study* n=157 Mean (SD) or n (%)	**Participants not included in the glycemic markers study n=70 Mean (SD) or n (%)**	**p**
Maternal Characteristics			
Randomization arm (CGM)	76 (48.4)	34 (48.6)	0.982
Age, years	31.6 (4.6)	31.2 (4.4)	0.575
BMI at study entry, kg/m^2	25.5 (4.3)	26.4 (5.1)	0.183
European origin	140 (89.2)	56 (80.0)	0.063
Post-secondary education	120 (76.9)	55 (78.6)	0.784
Smoking habit	15 (9.6)	7 (10.0)	0.916
Duration of diabetes, years	16.5 (8.0)	16.9 (7.1)	0.736
Diabetes complications >=1	28 (17.8)	31 (44.3)	0.000
Retinopathy	26 (16.6)	26 (37.1)	0.001
Nephropathy	1 (0.6)	7 (10)	0.000
Neuropathy	3 (1.9)	5 (7.1)	0.048
Severe hypoglycemia in past year	13 (8.3)	7 (10)	0.673
Severe hypoglycemia 1st trimester	7 (4.5)	5 (7.1)	0.410
HbA_{1c} at entry, %	6.85 (0.60)	7.01 (0.63)	0.118
HbA_{1c} at entry, mmol/mol	51.4 (6.6)	53.1 (6.9)	0.118
Insulin pump	79 (50.3)	32 (45.7)	0.522
Total insulin dose (IU/kg per day)	0.688 (0.249)	0.739 (0.250)	0.160
Primiparous	64 (40.8)	26 (37.1)	0.606
Pre-conception folic acid	85 (54.1)	32 (45.7)	0.241
Pre-conception multivitamin	54 (34.4)	23 (32.9)	0.821
Gestational age, weeks	10.3 (2.3)	10.6 (2.6)	0.308
Pregnancy outcomes			
Pre-eclampsia	20 (12.7)	8 (11.4)	0.782
Caesarean section	106 (67.5)	49 (70.0)	0.710
Preterm delivery	63 (40.1)	22 (38.6)	0.825
LGA	97 (61.8)	42 (61.8)	0.998
Neonatal hypoglycemia	42 (26.8)	15 (22.1)	0.457
NICU admission	55 (35.0)	28 (41.2)	0.380

*with all CGM and laboratory glycemic markers measured in the first trimester and delivering a livebirth at ≥20 weeks

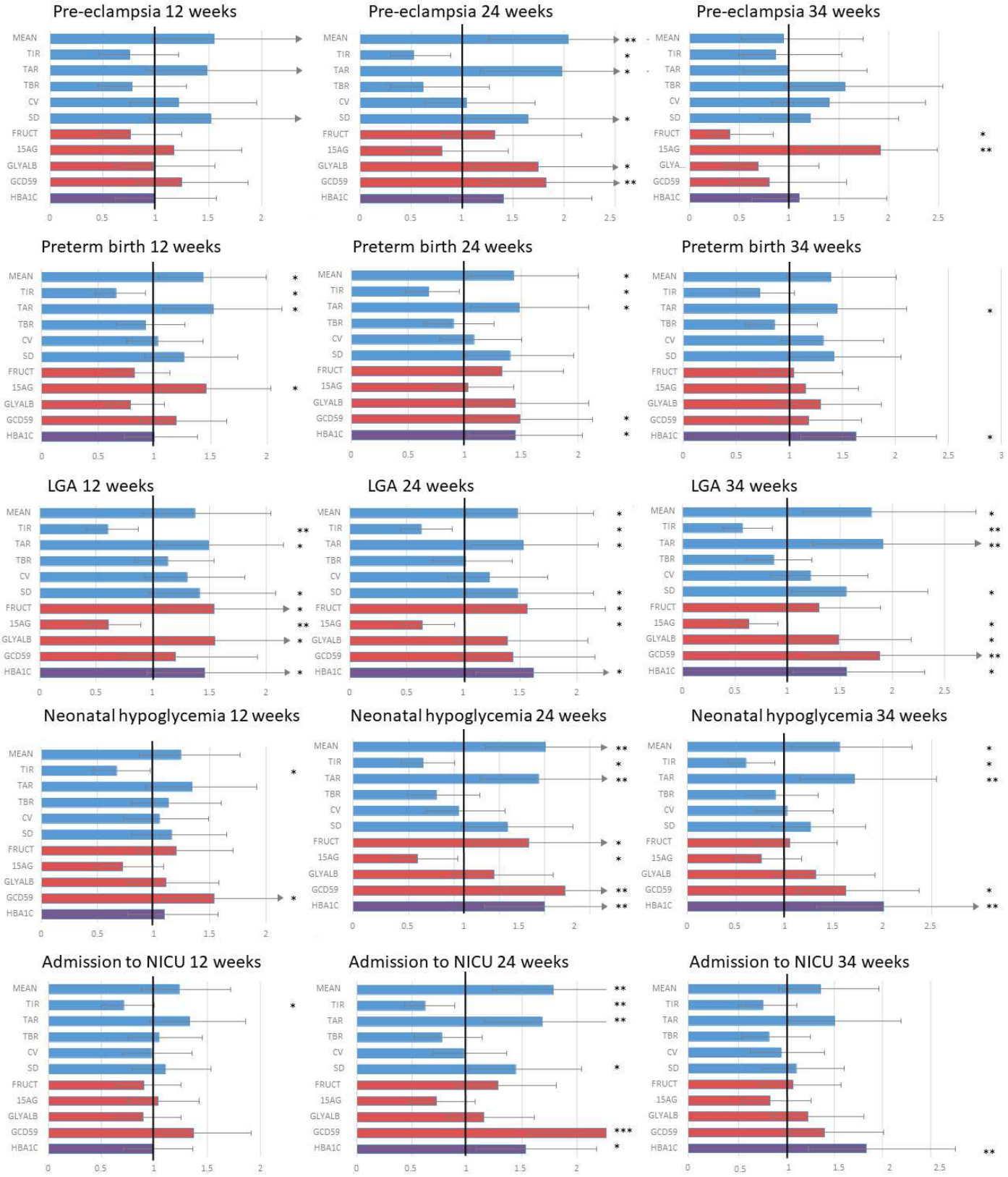
Abbreviations: CGM: continuous glucose monitoring;; HbA_{1c}: glycated haemoglobin; LGA: large for gestational age; NICU: neonatal intensive care unit; SD: standard deviation

Table 2: Continuous glucose monitoring metrics and laboratory glycemic markers at 12, 24 and 34 weeks.

	12 weeks n=157	**24 weeks n=150**	**34 weeks n=134**
Continuous Glucose Monitoring	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Mean glucose (mmol/l)	7.49 (1.15)	7.72 (1.28)	6.89 (1.01)
Mean glucose (mg/dl)	135 (20.6)	139 (23.1)	124 (18.2)
TIR 3.5-7.8 mmol/L (%)	51.6 (12.7)	50.4 (15.4)	64.1 (15.1)
TAR >7.8 mmol/l (%)	40.1 (14.0)	44.2 (16.9)	30.9 (15.1)
TBR <3.5 mmol/l (%)	8.3 (6.5)	5.4 (5.5)	5.0 (4.7)
CV (%)	41.6 (7.14)	36.3 (6.53)	33.5 (7.00)
Glucose SD (SD)	3.13 (0.76)	2.81 (0.67)	2.33 (0.66)
Laboratory Glycemic Markers			
Fructosamine (umol/l)	449 (80.1)	361 (64.5)	276 (45.7)
1,5-AG (ug/dl)	3.62 (2.03)	2.83 (1.64)	3.50 (1.92)
Glycated albumin (%)	19.8 (2.93)	19.0 (3.46)	16.0 (1.96)
GCD59 (SPU)	7.07 (4.84)	7.15 (4.76)	5.44 (3.10)
HbA_{1c} (%)	6.85 (0.60)	6.34 (0.62)	6.43 (0.63)
HbA_{1c} (mmol/mol)	51.4 (6.6)	45.8 (6.8)	46.7 (6.90)

Abbreviations: 1,5-AG: 1,5 anhydroglucitol; CGM: continuous glucose monitoring; CV: coefficient of variation; GCD59: Glycated complement protein CD59; HbA_{1c}: glycated haemoglobin; SD: standard deviation; SPU: standard peptide units; TAR: time above range; TIR: time in range

Figure 1: Prediction of pregnancy outcomes using laboratory glycemic markers and CGM metrics data at 12, 24 and 34 weeks using unadjusted standardised odds ratios between with pregnancy outcomes. Data are given in table S3. * p<0.05; ** p<0.01; *** p<0.001. X axis indicates OR per 1 SD



Abbreviations: 1,5-AG: 1,5 anhydroglucitol; CGM: continuous glucose monitoring; CV: coefficient of variation; FRUCT: fructosamine; GCD59: Glycated complement protein CD59; GlyAlb: glycated albumin; HbA_{1c}: glycated haemoglobin; LGA: large for gestational age; MEAN: mean CGM glucose; NICU: neonatal

intensive care unit; OR: odds ratio; SD: standard deviation; TAR: time above range; TBR: time below range; TIR: time in range

Figure 2: Receiver operator curves (ROCs) showing ability of laboratory markers and strongest CGM metrics to predict pregnancy outcomes. Data are shown in table S4. Markers showing a negative association with outcomes are shown in the lower right section of the graph, below the reference line, to enable these to be distinguished from positively-associated markers.

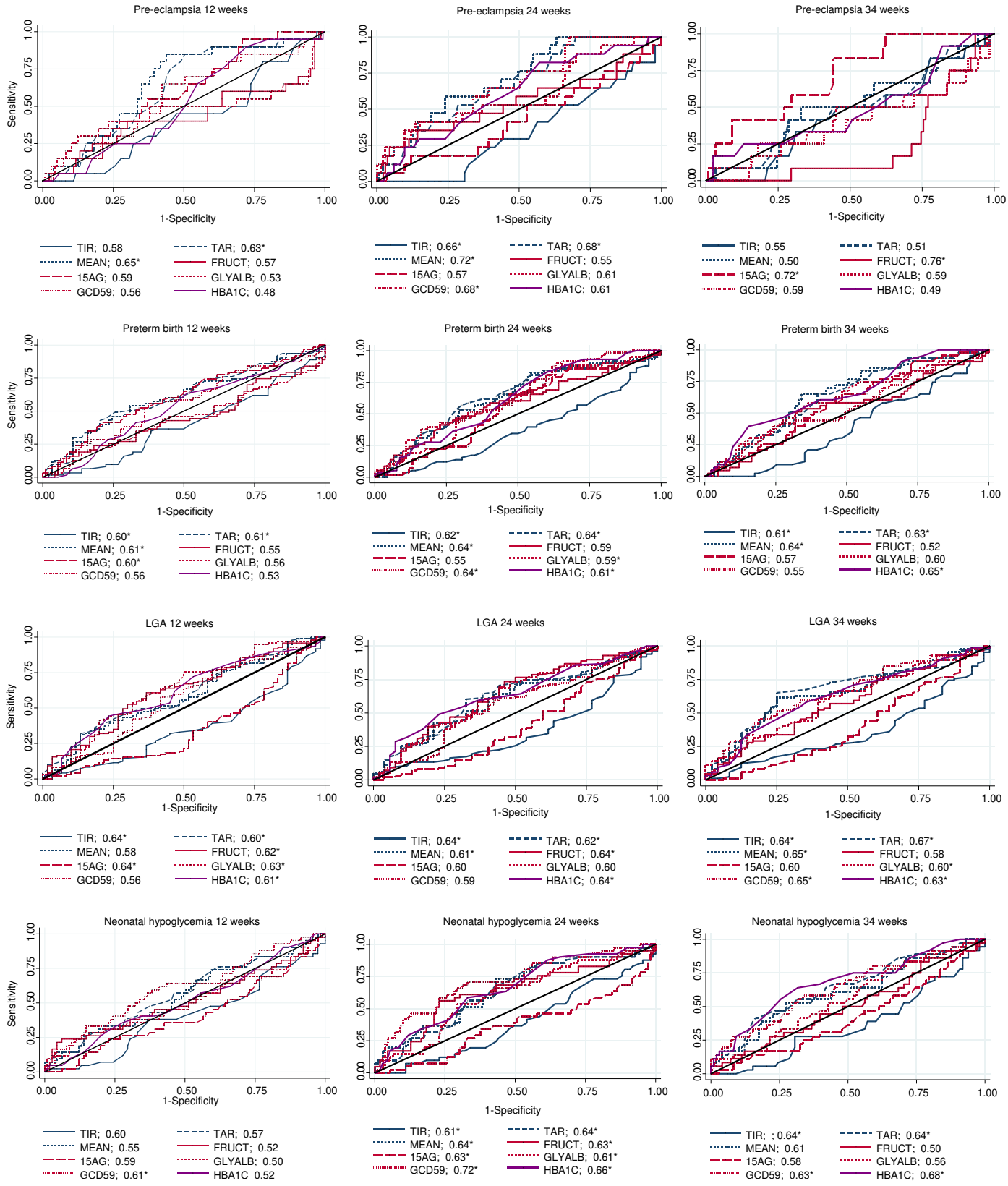
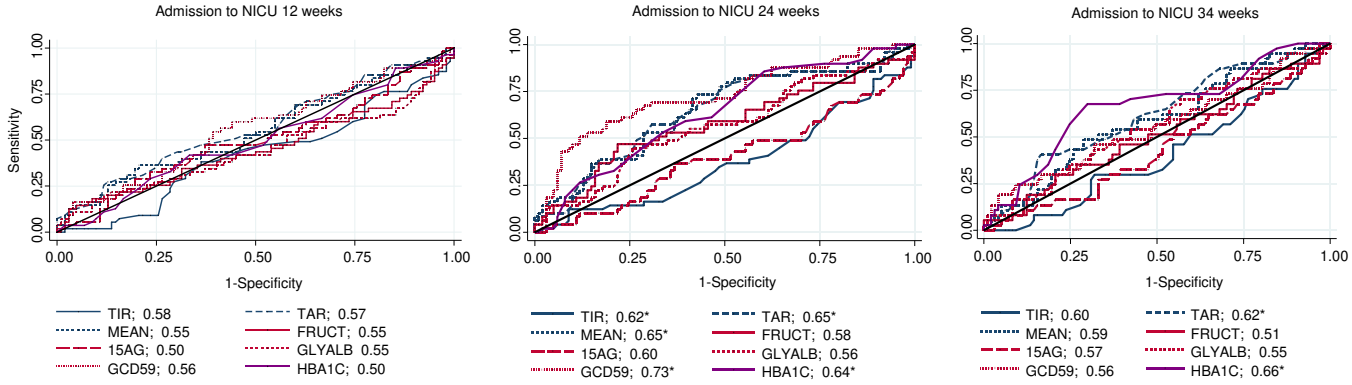


Figure 2 (continued)



Abbreviations: 1,5-AG: 1,5 anhydroglucitol;; Fruct: fructosamine; GCD59: Glycated complement protein CD59; GlyAlb: glycated albumin; HbA_{1c}: glycated haemoglobin; LGA: large for gestational age; MEAN: mean CGM glucose; NICU: neonatal intensive care unit; TAR: time above range; TIR: time in range

Supplementary Material

Table S1: Definitions of continuous glucose monitoring (CGM) metrics used in this study

CGM MARKERS	
Mean glucose, mg/dl; mmol/l	Average glucose concentration given for the whole time with CGM output.
Time in range (TIR, 63-140 mg/dl; 3.5-7.8 mmol/l, %	Time in minutes spent in the range given, expressed as a percentage of all time with CGM output.
Time above range (TAR >140mg/dl; >7.8 mmol/l), %	Time in minutes spent >140 mg/dl (>7.8 mmol/l), expressed as a percentage of all time with CGM output.
Time below range (TBR, <63 mg/dl; <3.5 mmol/l), %	Time in minutes spent <63 mg/dl (<3.5 mmol/l), expressed as a percentage of all time with CGM output.
Glucose CV, %	Coefficient of Variation – the standard deviation divided by the mean, expressed as percentage.
Glucose SD	Standard deviation of glucose concentrations

Table S2: Pearson correlations between laboratory and CGM markers of glycemia used in this study, at 12, 24 and 34 weeks.
* p<0.05; ** p<0.01; *** p<0.001.

12 weeks	CGM MEAN GLUCOSE	CGM TIR	CGM TAR	CGM TBR	CGM CV	CGM SD	Fructosamine	1,5-AG	Glycated Albumin	gCD59
CGM MEAN GLUCOSE	1									
CGM TIR	-0.82***	1								
CGM TAR	0.97***	-0.89***	1							
CGM TBR	-0.50***	-0.03	-0.43***	1						
CGM CV	0.13	-0.47***	0.14	0.61***	1					
CGM SD	0.72***	-0.82***	0.69***	0.10	0.78***	1				
Fructosamine	0.42***	-0.34***	0.41***	-0.22**	-0.01	0.25**	1			
1,5-AG	-0.38***	0.36***	-0.37***	0.11	-0.24**	-0.40***	-0.45***	1		
Glycated Albumin	0.44***	-0.40***	0.43***	-0.16	0.07	0.320***	0.91***	-0.42***	1	
gCD59	0.34***	-0.28***	0.35***	-0.21*	0.01	0.21**	0.40***	-0.26**	0.35***	1
HbA1c	0.52***	-0.45***	0.50***	-0.22**	0.14	0.41***	0.56***	-0.41***	0.59***	0.19*
24 weeks										
CGM MEAN GLUCOSE	1									
CGM TIR	-0.88***	1								
CGM TAR	0.96***	-0.95***	1							
CGM TBR	-0.48***	0.11	-0.42***	1						
CGM CV	-0.03	-0.22**	-0.02	0.68***	1					
CGM SD	0.65***	-0.72***	0.61***	0.15	0.73***	1				
Fructosamine	0.43***	-0.42***	0.41***	-0.10	0.03	0.31***	1			
1,5AG	-0.35***	0.42***	-0.38***	-0.02	-0.13	-0.32***	-0.38***	1		
Glycated Albumin	0.45***	-0.41***	0.42***	-0.16	0.02	0.32***	0.82***	-0.30***	1	
gCD59	0.36***	-0.30***	0.31***	-0.12	-0.03	0.24**	0.27**	-0.22**	0.25**	1
HbA1c	0.58***	-0.54***	0.55***	-0.16*	0.08	0.45***	0.57***	-0.39***	0.57***	0.30***

Table S2 continued.

34 weeks	CGM MEAN GLUCOSE	CGM TIR	CGM TAR	CGM TBR	CGM CV	CGM SD	Fructosamine	1,5-AG	Glycated Albumin	gCD59
CGM MEAN GLUCOSE	1									
CGM TIR	-0.89***	1								
CGM TAR	0.96***	-0.95***	1							
CGM TBR	-0.24**	-0.17	-0.14	1						
CGM CV	0.23**	-0.50***	0.28**	0.71***	1					
CGM SD	0.68***	-0.81***	0.68***	0.41***	0.87***	1				
Fructosamine	0.49***	-0.48***	0.51***	-0.05	0.11	0.33***	1			
1,5-AG	-0.27**	0.30***	-0.30***	0.02	-0.09	-0.21*	-0.22**	1		
Glycated Albumin	0.64***	-0.62***	0.65***	-0.07	0.16	0.44***	0.82***	-0.35***	1	
gCD59	0.35***	-0.30***	0.34***	-0.12	0.09	0.24**	0.29**	-0.21*	0.33***	1
HbA1c	0.60***	-0.59***	0.62***	-0.08	0.19*	0.43***	0.41***	-0.31***	0.65***	0.33***

Abbreviations: 1,5-AG: 1,5 anhydroglucitol; CGM: continuous glucose monitoring; CV: coefficient of variation;; gCD59: glycated complement protein CD59; HbA_{1c}: glycated haemoglobin;MEAN: mean CGM glucose; NICU: neonatal intensive care unit; OR: odds ratio; SD: standard deviation; TAR: time above range; TBR: time below range; TIR: time in range

Table S3. Unadjusted standardised odds ratios showing associations between glycemic laboratory markers and CGM metrics with pregnancy outcomes. Data are displayed in figure 1. *significant associations are displayed in bold characters

	Pre-eclampsia OR per 1SD (95%CI)	Pre-eclampsia p	Preterm birth OR per 1SD (95%CI)	Preterm birth p	LGA OR per 1SD (95%CI)	LGA p	NH OR per 1SD (95%CI)	NH p	NICU Admission OR per 1SD (95%CI)	NICU Admission p
12 WEEKS										
Mean glucose, mmol/L	1.55 (0.96-2.51)	0.075	**1.43 (1.03-1.99)**	**0.035**	1.37 (0.98-1.92)	0.063	1.24 (0.87-1.77)	0.245	1.23 (0.88-1.72)	0.219
TIR 3.5-7.8 mmol/L, %	0.75 (0.46-1.21)	0.239	**0.66 (0.47-0.92)**	**0.015**	**0.60 (0.42-0.85)**	**0.004**	**0.67 (0.46-0.97)**	**0.036**	**0.71 (0.50-<1.00)**	**0.048**
TAR >7.8 mmol/L, %	1.48 (0.91-2.40)	0.117	**1.52 (1.08-2.13)**	**0.015**	**1.49 (1.06-2.08)**	**0.022**	1.34 (0.93-1.92)	0.119	1.33 (0.95-1.86)	0.099
TBR <3.5 mmol/L, %	0.77 (0.45-1.29)	0.320	0.92 (0.66-1.27)	0.595	1.13 (0.81-1.57)	0.479	1.13 (0.80-1.60)	0.493	1.04 (0.75-1.45)	0.804
CV, %	1.21 (0.75-1.95)	0.435	1.03 (0.75-1.43)	0.838	1.30 (0.93-1.80)	0.126	1.05 (0.73-1.49)	0.810	0.97 (0.70-1.35)	0.876
Glucose SD, SD	1.52 (0.94-2.46)	0.091	1.26 (0.91-1.74)	0.170	**1.41 (1.01-1.97)**	**0.046**	1.16 (0.81-1.65)	0.417	1.10 (0.79-1.53)	0.569
Fructosamine, umol/l	0.76 (0.47-1.24)	0.274	0.82 (0.59-1.14)	0.243	**1.54 (1.09-2.19)**	**0.015**	1.20 (0.84-1.71)	0.321	0.90 (0.65-1.25)	0.530
1,5-AG, ug/dl	1.17 (0.76-1.81)	0.474	**1.46 (1.04-2.03)**	**0.027**	**0.61 (0.43-0.86)**	**0.004**	0.72 (0.48-1.09)	0.124	1.03 (0.74-1.42)	0.880
Glycated albumin, %	0.97 (0.61-1.56)	0.911	0.79 (0.57-1.09)	0.154	**1.55 (1.09-2.21)**	**0.015**	1.11 (0.78-1.58)	0.556	0.89 (0.64-1.25)	0.505
Glycated CD59, SPU	1.24 (0.82-1.87)	0.312	1.19 (0.87-1.64)	0.282	1.20 (0.85-1.69)	0.306	**1.54 (1.09-2.18)**	**0.016**	1.37 (0.98-1.91)	0.064
HbA_{1c}, %	0.98 (0.61-1.57)	0.938	1.00 (0.73-1.38)	0.989	**1.46 (1.03-2.05)**	**0.032**	1.10 (0.77-1.57)	0.591	0.98 (0.71-1.36)	0.909
24 WEEKS										
Mean glucose, mmol/L	**2.04 (1.26-3.32)**	**0.004**	**1.43 (1.02-2.00)**	**0.041**	**1.48 (1.02-2.15)**	**0.038**	**1.73 (1.19-2.52)**	**0.004**	**1.78 (1.23-2.57)**	**0.002**
TIR 3.5-7.8 mmol/L, %	**0.52 (0.30-0.89)**	**0.017**	**0.68 (0.48-0.95)**	**0.025**	**0.63 (0.44-0.90)**	**0.011**	**0.63 (0.43-0.91)**	**0.015**	**0.62 (0.43-0.89)**	**0.009**
TAR >7.8 mmol/L, %	**1.98 (1.17-3.37)**	**0.011**	**1.48 (1.05-2.09)**	**0.026**	**1.53 (1.07-2.19)**	**0.021**	**1.67 (1.14-2.45)**	**0.009**	**1.68 (1.16-2.42)**	**0.006**
TBR <3.5 mmol/L, %	0.62 (0.30-1.27)	0.191	0.90 (0.64-1.26)	0.535	1.02 (0.73-1.43)	0.909	0.75 (0.49-1.14)	0.177	0.77 (0.52-1.14)	0.194
CV, %	1.04 (0.63-1.72)	0.882	1.08 (0.78-1.50)	0.653	1.23 (0.86-1.74)	0.256	0.95 (0.66-1.37)	0.787	0.97 (0.69-1.36)	0.844
Glucose SD, SD	**1.65 (1.02-2.66)**	**0.040**	1.40 (1.00-1.96)	0.053	**1.48 (1.03-2.15)**	**0.036**	1.39 (0.97-1.98)	0.075	**1.44 (1.02-2.04)**	**0.040**
Fructosamine, umol/l	1.32 (0.80-2.17)	0.278	1.33 (0.95-1.87)	0.096	**1.56 (1.08-2.25)**	**0.018**	**1.58 (1.09-2.30)**	**0.017**	1.28 (0.91-1.81)	0.161
1,5-AG, ug/dl	0.80 (0.45-1.45)	0.465	1.03 (0.74-1.43)	0.871	**0.64 (0.45-0.92)**	**0.014**	**0.58 (0.36-0.94)**	**0.027**	0.72 (0.48-1.07)	0.100
Glycated albumin, %	**1.75 (1.09-2.80)**	**0.020**	1.45 (1.00-2.09)	0.050	1.39 (0.93-2.10)	0.111	1.27 (0.90-1.80)	0.181	1.15 (0.82-1.61)	0.418
Glycated CD59, SPU	**1.82 (1.19-2.78)**	**0.006**	**1.49 (1.05-2.13)**	**0.027**	1.44 (0.95-2.16)	0.084	**1.91 (1.29-2.82)**	**0.001**	**2.41 (1.55-3.75)**	**0.000**
HbA_{1c}, %	1.41 (0.87-2.27)	0.163	**1.45 (1.03-2.04)**	**0.032**	**1.62 (1.11-2.38)**	**0.013**	**1.72 (1.18-2.50)**	**0.004**	**1.53 (1.08-2.18)**	**0.018**
34 WEEKS										
Mean glucose, mmol/L	0.94 (0.51-1.74)	0.849	1.39 (0.97-2.01)	0.077	**1.80 (1.15-2.80)**	**0.010**	**1.56 (1.06-2.30)**	**0.025**	1.31 (0.90-1.89)	0.155
TIR 3.5-7.8 mmol/L, %	0.86 (0.49-1.53)	0.612	0.72 (0.50-1.05)	0.084	**0.57 (0.38-0.86)**	**0.008**	**0.60 (0.41-0.89)**	**0.012**	0.74 (0.50-1.07)	0.111
TAR >7.8 mmol/L, %	0.98 (0.54-1.78)	0.934	**1.45 (1.003-2.10)**	**0.048**	**1.91 (1.24-2.93)**	**0.003**	**1.71 (1.15-2.55)**	**0.008**	1.45 (0.99-2.11)	0.056
TBR <3.5 mmol/L, %	1.56 (0.95-2.54)	0.078	0.86 (0.58-1.26)	0.426	0.87 (0.61-1.23)	0.417	0.90 (0.60-1.34)	0.600	0.80 (0.53-1.21)	0.291
CV, %	1.40 (0.82-2.37)	0.218	1.32 (0.92-1.89)	0.135	1.22 (0.84-1.77)	0.298	1.02 (0.70-1.49)	0.919	0.92 (0.62-1.35)	0.656
Glucose SD, SD	1.21 (0.70-2.10)	0.500	1.42 (0.99-2.05)	0.059	**1.56 (1.04-2.34)**	**0.032**	1.26 (0.87-1.82)	0.232	1.07 (0.73-1.55)	0.743
Fructosamine, umol/l	**0.40 (0.19-0.84)**	**0.015**	1.04 (0.72-1.50)	0.830	1.30 (0.90-1.89)	0.163	1.05 (0.71-1.53)	0.817	1.04 (0.71-1.52)	0.829
1,5-AG, ug/dl	**1.92 (1.19-3.10)**	**0.007**	1.15 (0.81-1.65)	0.430	**0.63 (0.44-0.91)**	**0.014**	0.76 (0.49-1.17)	0.214	0.81 (0.53-1.22)	0.310
Glycated albumin, %	0.69 (0.37-1.30)	0.250	1.29 (0.90-1.87)	0.172	**1.49 (1.01-2.18)**	**0.043**	1.31 (0.89-1.92)	0.173	1.19 (0.82-1.74)	0.366
Glycated CD59, SPU	0.80 (0.41-1.58)	0.525	1.18 (0.82-1.68)	0.373	**1.88 (1.19-2.97)**	**0.007**	**1.62 (1.11-2.37)**	**0.012**	1.35 (0.94-1.94)	0.109
HbA_{1c}, %	1.10 (0.62-1.98)	0.743	**1.63 (1.11-2.39)**	**0.012**	**1.56 (1.05-2.31)**	**0.026**	**2.01 (1.32-3.05)**	**0.001**	**1.77 (1.19-2.65)**	**0.005**

Abbreviations: 1,5-AG: 1,5 anhydroglucitol; CGM: continuous glucose monitoring; CI: confidence interval; CV: coefficient of variation; CI: confidence interval; CD59: Complement protein CD59; HbA_{1c}: glycated haemoglobin; LGA: large for gestational age; MEAN: mean CGM glucose; NH: neonatal hypoglycemia. NICU: neonatal intensive care unit; OR: odds ratio; SD: standard deviation; SPU: standard peptide units; TAR: time above range; TBR: time below range; TIR: time in range

Table S4. Area under the ROC curves on bivariate unadjusted analysis relating glycemic biomarkers and pregnancy outcomes (data shown in figure 2).

	Pre-eclampsia AUROC (95% CI)	**Preterm birth AUROC (95% CI)**	**LGA AUROC (95% CI)**	**Neonatal hypoglycemia AUROC (95% CI)**	**NICU admission AUROC (95% CI)**
12 WEEKS					
Mean glucose, mmol/L	**0.65 (0.54-0.77)**	**0.61 (0.51-0.70)**	0.58 (0.49-0.67)	0.55 (0.45-0.66)	0.55 (0.45-0.64)
TIR 3.5-7.8 mmol/L, %	0.58 (0.46-0.71)	**0.60 (0.51-0.69)**	**0.64 (0.55-0.73)**	0.60 (0.49-0.70)	0.58 (0.48-0.67)
TAR >7.8 mmol/L, %	**0.63 (0.51-0.74)**	**0.61 (0.52-0.70)**	**0.60 (0.51-0.69)**	0.57 (0.47-0.67)	0.57 (0.47-0.66)
TBR <3.5 mmol/L, %	0.58 (0.44-0.72)	0.53 (0.44-0.62)	0.54 (0.45-0.64)	0.53 (0.43-0.63)	0.51 (0.41-0.61)
CV, %	0.53 (0.41-0.66)	0.51 (0.42-0.60)	0.56 (0.46-0.65)	0.51 (0.41-0.61)	0.50 (0.41-0.60)
Glucose SD, SD	**0.63 (0.51-0.75)**	0.56 (0.47-0.65)	**0.60 (0.51-0.70)**	0.54 (0.44-0.64)	0.53 (0.44-0.63)
Fructosamine, umol/l	0.57 (0.41-0.73)	0.55 (0.45-0.64)	**0.62 (0.53-0.71)**	0.52 (0.41-0.63)	0.55 (0.45-0.65)
1,5-AG, ug/dl	0.59 (0.47-0.71)	**0.60 (0.51-0.70)**	**0.64 (0.55-0.73)**	0.59 (0.49-0.69)	0.50 (0.40-0.59)
Glycated Albumin, %	0.53 (0.36-0.71)	0.56 (0.46-0.65)	**0.63 (0.54-0.72)**	0.50 (0.39-0.62)	0.55 (0.45-0.66)
Glycated CD59, SPU	0.56 (0.43-0.69)	0.56 (0.47-0.66)	0.56 (0.46-0.65)	**0.61 (0.50-0.71)**	0.56 (0.46-0.65)
HbA_{1c}, %	0.48 (0.36-0.60)	0.53 (0.43-0.62)	**0.61 (0.52-0.70)**	0.52 (0.41-0.62)	0.50 (0.41-0.60)
24 WEEKS					
Mean glucose, mmol/L	**0.72 (0.60-0.83)**	**0.64 (0.55-0.73)**	**0.61 (0.51-0.70)**	**0.64 (0.55-0.74)**	**0.65 (0.56-0.75)**
TIR 3.5-7.8 mmol/L, %	**0.66 (0.53-0.78)**	**0.62 (0.53-0.71)**	**0.64 (0.54-0.73)**	**0.61 (0.51-0.71)**	**0.62 (0.53-0.72)**
TAR >7.8 mmol/L, %	**0.68 (0.56-0.80)**	**0.64 (0.55-0.73)**	**0.62 (0.53-0.72)**	**0.64 (0.54-0.74)**	**0.65 (0.55-0.74)**
TBR <3.5 mmol/L, %	0.61 (0.47-0.75)	0.51 (0.42-0.61)	0.50 (0.41-0.60)	0.57 (0.47-0.67)	0.54 (0.44-0.64)
CV, %	0.51 (0.37-0.66)	0.53 (0.44-0.62)	0.55 (0.46-0.65)	0.49 (0.39-0.59)	0.50 (0.40-0.60)
Glucose SD, SD	**0.65 (0.53-0.76)**	0.59 (0.49-0.68)	**0.63 (0.54-0.73)**	0.59 (0.49-0.70)	0.59 (0.50-0.69)
Fructosamine, umol/l	0.55 (0.38-0.72)	0.59 (0.49-0.68)	**0.64 (0.54-0.73)**	**0.63 (0.53-0.74)**	0.58 (0.48-0.68)
1,5-AG, ug/dl	0.57 (0.42-0.72)	0.55 (0.45-0.64)	0.60 (0.50-0.70)	**0.63 (0.53-0.74)**	0.60 (0.50-0.70)
Glycated Albumin, %	0.61 (0.45-0.76)	**0.59 (0.501-0.68)**	0.60 (0.50-0.70)	**0.61 (0.50-0.71)**	0.56 (0.46-0.66)
Glycated CD59, SPU	**0.68 (0.55-0.81)**	**0.64 (0.55-0.73)**	0.59 (0.49-0.68)	**0.72 (0.62-0.81)**	**0.73 (0.64-0.82)**
HbA_{1c}, %	0.61 (0.48-0.75)	**0.61 (0.52-0.70)**	**0.64 (0.55-0.73)**	**0.66 (0.56-0.75)**	**0.64 (0.54-0.73)**
34 WEEKS					
Mean glucose, mmol/L	0.50 (0.32-0.67)	**0.64 (0.55-0.74)**	**0.65 (0.56-0.75)**	0.61 (0.50-0.72)	0.59 (0.48-0.69)
TIR 3.5-7.8 mmol/L, %	0.55 (0.39-0.71)	**0.61 (0.51-0.71)**	**0.64 (0.55-0.74)**	**0.64 (0.53-0.74)**	0.60 (0.49-0.70)
TAR >7.8 mmol/L, %	0.51 (0.33-0.68)	**0.63 (0.54-0.73)**	**0.67 (0.58-0.77)**	**0.64 (0.54-0.75)**	**0.62 (0.51-0.72)**
TBR <3.5 mmol/L, %	0.66 (0.48-0.84)	0.53 (0.42-0.63)	0.54 (0.44-0.65)	0.52 (0.41-0.63)	0.56 (0.45-0.66)
CV, %	0.64 (0.49-0.80)	**0.60 (0.50-0.70)**	0.55 (0.45-0.65)	0.53 (0.43-0.63)	0.49 (0.39-0.59)
Glucose SD, SD	0.60 (0.45-0.74)	**0.63 (0.54-0.73)**	**0.61 (0.51-0.71)**	0.56 (0.45-0.67)	0.53 (0.43-0.63)
Fructosamine, umol/l	**0.76 (0.65-0.87)**	0.52 (0.42-0.63)	0.58 (0.48-0.68)	0.50 (0.39-0.62)	0.51 (0.40-0.62)
1,5-AG, ug/dl	**0.72 (0.59-0.85)**	0.57 (0.48-0.67)	0.60 (0.50-0.71)	0.58 (0.47-0.69)	0.57 (0.46-0.67)
Glycated Albumin, %	0.59 (0.41-0.77)	0.60 (0.50-0.71)	**0.60 (0.50-0.70)**	0.56 (0.45-0.67)	0.55 (0.44-0.67)
Glycated CD59, SPU	0.59 (0.40-0.78)	0.55 (0.44-0.66)	**0.65 (0.56-0.75)**	**0.63 (0.52-0.74)**	0.56 (0.44-0.67)
HbA_{1c}, %	0.49 (0.31-0.67)	**0.65 (0.55-0.74)**	**0.63 (0.53-0.73)**	**0.68 (0.57-0.78)**	**0.66 (0.56-0.77)**

*significant AUROCs are displayed in bold characters

Abbreviations: 1,5-AG: 1,5 anhydroglucitol; CD59: Complement protein CD59; CI: confidence interval; CV: coefficient of variation; HbA_{1c}: glycated haemoglobin; LGA: large for gestational age; MEAN: mean CGM glucose; NICU: neonatal intensive care unit; ROC: receiver operating characteristic; SD: standard deviation; SPU: standard peptide units; TAR: time above range; TBR: time below range; TIR: time in range

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*Dr Lois Jovanovic died during the preparation of this manuscript

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Conflict of interest/ Disclosures

CLM, DT, DM and JMY have no conflicts of interest to declare.

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

JAH has a financial interest in Mellitus LLC. Mellitus has licensed intellectual property for the technology used in this research and in developing diagnostic tools for diabetes. The interests of J.A.H. are reviewed and are managed by Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict of interest policies.

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.

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.

Reagents for analysis of glycated albumin were kindly provided by Asahi Kasei Pharma Corporation through Spinreact. Reagents for 1,5 anhydroglucitol were kindly provided by Hirotaka Ishibashi at Glycomark Inc. Laboratory analysis for these analytes was performed in the NIHR Core biochemistry assay

laboratory in Cambridge Biomedical Research Campus, Cambridge, UK. Reagents and laboratory analysis for gCD59 were provided by Prof Jose Halperin.

Contribution Statement

CLM designed the study, arranged laboratory analysis for 1,5 anhydroglucitol, fructosamine and glycated albumin, collated, analysed and interpreted the data, wrote and revised the manuscript. RC identified the study question, designed the study, contributed to data analysis and discussion 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. DT contributed to the analysis and interpretation of the data. ES provided expertise on analysis of CGM data. JY contributed to quality control of the database. DM and JH analysed the samples for gCD59, and contributed to the discussion. All authors reviewed the final version of the manuscript prior to publication.

Appendix 1 - CONCEPTT Collaborative Group (listed according to recruitment numbers):

Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK: Helen Murphy, Jeannie Grisoni, Carolyn Byrne, Sandra Neoh, Katy Davenport, (43); Alberta Health Services, University of Calgary, Calgary, Canada: Lois Donovan, Claire Gougeon, Carolyn Oldford, Catherine Young (39); King's College Hospital, London, UK: Stephanie Amiel, Katharine Hunt, Louisa Green, Helen Rogers, Benedetta Rossi (29); Mount Sinai Hospital, Toronto, Canada: Denice Feig, Barbara Cleave, Michelle Strom (22); Hospital de la Santa Creu i Sant Pau, Barcelona, Spain and CIBER-BBN, Zaragoza, Spain: Rosa Corcoy, Alberto de Leiva, Juan María Adelantado, Ana Isabel Chico, Diana Tundidor (22); The Ottawa Hospital General Campus, Ottawa, Canada: Erin Keely, Janine Malcolm, Kathy Henry (15); Ipswich Hospital NHS Trust, Ipswich, UK: Damian Morris, Gerry Rayman, Duncan Fowler, Susan Mitchell, Josephine Rosier (13); Norfolk and Norwich University Hospital, Norwich, UK: Rosemary Temple, Jeremy Turner, Gioia Canciani, Niranjala Hewapathirana, Leanne Piper (13); St. Joseph's Health Centre, London, Canada: Ruth McManus, Anne Kudirka, Margaret Watson (13); Niguarda ca' Granda Hospital, Milano, Italy: Matteo Bonomo, Basilio Pintaudi, Federico Bertuzzi, Giuseppina Daniela Corica, Elena Mion (12); Sunnybrook Health Sciences Centre, Toronto, Canada: Julia Lowe, Ilana Halperin, Anna Rogowsky, Sapida Adib (11); Glasgow Royal Infirmary, Glasgow, UK: Robert Lindsay, David Carty, Isobel Crawford, Fiona Mackenzie, Therese McSorley (10); McMaster University, Hamilton, Canada: John Booth, Natalia McInnes, Ada Smith, Irene Stanton, Tracy Tazzeo (8); Centre hospitalier universitaire de Québec, Quebec City, Canada: John Weisnagel (6); Queen's Medical Centre, Nottingham, UK: Peter Mansell, Nia Jones, Gayna Babington, Dawn Spick (6); Royal Victoria Infirmary, Newcastle Upon Tyne, Newcastle, UK: Malcolm MacDougall, Sharon Chilton, Terri Cutts, Michelle Perkins (6); Leeds Teaching Hospitals NHS Trust, Leeds, UK: Eleanor Scott, Del Endersby (6); Royal Infirmary of Edinburgh, Edinburgh, UK: Anna Dover, Frances Dougherty, Susan Johnston (6); Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK: Simon Heller, Peter Novodorsky, Sue Hudson, Chloe Nisbet (6); Izaak Walton Killam Health Sciences Centre (IWK), Halifax, Canada: Thomas Ransom, Jill Coolen, Darlene Baxendale (5); University Hospital Southampton NHS Foundation Trust, Southampton, UK: Richard Holt, Jane Forbes, Nicki Martin, Fiona Walbridge (6); Galway University Hospitals, Galway, Ireland: Fidelma Dunne, Sharon Conway, Aoife Egan, Collette Kirwin (4); Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK: Michael Maresh, Gretta Kearney, Juliet Morris, Susan Quinn (4); South Tees Hospitals, NHS Foundation Trust, Middlesbrough, UK: Rudy Bilous, Rasha Mukhtar (4); Centre de Recherche du Centre Hospitalier de Université de Montréal (CR-CHUM), Montreal, Canada: Ariane Godbout, Sylvie Daigle (3); The Dudley Group NHS FT, Russells Hall Hospital, Dudley, UK: Alexandra Lubina Solomon, Margaret Jackson, Emma Paul, Julie Taylor (3); Kingston General Hospital, Queen's University, Kingston, Canada: Robyn Houlden, Adriana Breen (3); Guys and St Thomas' NHS Foundation Trust, London, UK: Anita Banerjee, Anna Brackenridge, Annette Briley, Anna Reid, Claire Singh (2); Royal University Hospital, Saskatoon, Canada: Jill Newstead-Angel, Janet Baxter (2); Grampian Diabetes Centre, Aberdeen, UK: Sam Philip, Martyna Chlost, Lynne Murray (2); William Sansum Diabetes Center, Santa Barbara, USA: Kristin Castorino, Lois Jovanovic*, Donna Frase (2). The Centre for Clinical Trial Support (CCTS) at the Sunnybrook Research Institute, Toronto, Canada: Sonya Mergler, Kathryn Mangoff, Johanna Sanchez, and Gail Klein. The Jaeb Center for Health Research, Tampa, USA: Katrina Ruedy and Craig Kollman. Juvenile Diabetes Research Foundation (non-clinical collaborators): Olivia Lou and Marlon Pragnell.

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