Flash glucose monitoring versus capillary glucose monitoring in type 1 diabetes pregnancy: efficacy on glycaemic control and pregnancy outcomes.

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ABSTRACT (no limite!)

Aims/hypothesis: The aim of the study was to assess whether the additional use of intermittently scanned continuous glucose monitoring (isCGM), compared to standard care (self-monitoring of blood glucose [SMBG]), could improve glycaemic control and pregnancy outcomes in women with type 1 diabetes and multiple doses of insulin therapy.

Methods: Multicentre cohort study of 300 pregnant women with type 1 diabetes in Spain (168 SMBG users vs. 132 isCGM users). Beyond HbA_{1c}, percentage of time spent within (TIR), below (TBR) and above (TAR) the pregnancy glucose target range (3.5–7.8 mmol/l) were also evaluated among women using isCGM. Logistic regression models were performed for adverse pregnancy outcomes adjusted for baseline maternal characteristics and centre.

Results: isCGM group had lower median HbA_{1c} in the second trimester (41 vs. 43.2 mmol/mol, p=0.034). In the third trimester, a higher increase from the second trimester was observed in isCGM group (median difference of HbA_{1c} of 2.2 vs. 1.1 mmol/mol, p=0.033) without between-group differences in the third trimester HbA_{1c} values (43.2 vs. 43.2mmol/mol).). Among isCGM users, HbA_{1c} was strongly inverse correlated with TIR and direct correlated with TAR throughout gestation (trimester 1: r= -0.568, r= 0.631; trimester 2: r=-0.689, r=0.745; trimester 3: r= -0.531, r=0,596; TIR and TAR, respectively). Regarding neonatal outcomes, newborns of women using isCGM were more likely to neonatal hypoglycaemia compared to non-sensor users (27.4% vs. 19.1%; $OR_{adjusted}$ 2.20, 95% CI 1.14 – 4.30) without differences in neonatal weight or prematurity. Focusing in isCGM users, large for gestational infants were related to percentage of TIR, TAR and TBR in the second trimester. Furthermore, a higher TBR in the first trimester was associated with lower risk of prematurity.

Conclusions/interpretation: isCGM use provided an initial improvement in glycaemic control but not further sustained. Furthermore, offspring of isCGM users were more likely to neonatal hypoglycaemia, despite no higher rates of macrosomia or prematurity.

RESEARCH IN CONTEXT

What is already known about this subject?

- Real-time continuous glucose monitoring (rtCGM) has demonstrated a reduction in neonatal morbidity (large-for-gestational age infants [LGA], neonatal hypoglycaemia and neonatal intensive care unit admissions) in pregnancies complicated by type 1 diabetes.
- Despite intermittently scanned continuous glucose monitoring (isCGM) is approved for its use during pregnancy, data about its impact on glycaemic control and pregnancy outcomes is scarce.

What is the key question?

- Does the addition of isCGM to routine antenatal care (monitoring only by SMBG) improve glycaemic control and adverse pregnancy outcomes in pregnant women with type 1 diabetes and multiple doses of insulin?

What are the new findings?

- isCGM use led to achieve a lower HbA_{1c} in the second trimester of gestation, however this improvement was not sustained, with similar third trimester HbA_{1c} to non-users.
- Offspring of pregnant women using isCGM were more like to neonatal hypoglycaemia without differences in neonatal weight or prematurity.
- Time within, above and below range in the second trimester of gestation were related to LGA. Furthermore, prematurity was associated with time below range in the first trimester.

How might this impact on clinical practice in the foreseeable future?

- Women with type 1 diabetes should be offered the use of rtCGM over isCGM during pregnancy.

Keywords: intermittently scanned continuous glucose monitoring, pregnancy, neonatal hypoglycaemia, type 1 diabetes

Abbreviations:

ADA American Diabetes Association

CGM Continuous glucose monitoring

CONCEPTT Continuous glucose monitoring in pregnant women with type 1 diabetes trial

isCGM intermittently scanned continuous glucose monitoring

LGA Large-for-gestational age infant

MDI Multiple doses of insulin

NICE National Institute for Health and Care Excellence

rtCGM Real-time continuous glucose monitoring

SGA Small-for-gestational age infant

SMBG Self-monitoring of blood glucose

INTRODUCTION

Despite of an improvement in glycaemic control, pregnant women with type 1 diabetes have a 3-5-fold greater risk of adverse perinatal and obstetric outcomes than the general population[1, 2]. In this context, the implementation of new technologies such as continuous glucose monitoring (CGM) could have a positive impact on maternal and neonatal morbidity as it has been shown in non-pregnant population[3, 4].

Since 2017, based on continuous glucose monitoring in pregnant women with type 1 diabetes trial (CONCEPTT) study results, CGM has been widely recommended for all pregnant women with type 1 diabetes for different international guidelines [5, 6]. CONCEPTT trial was the first RCT to demonstrate that real-time CGM (rtCGM) use during type 1 diabetes pregnancies led to significant reduction in large-for-gestational age infants (LGA), neonatal hypoglycaemia and neonatal intensive care unit admissions [7]. However, in contrast to rtCGM, data from RCT evaluating the effectiveness of the intermittent use of CGM in maternal and neonatal outcomes provided conflicting results[9–11]. Although Murphy et al. showed a decreased mean birthweight and a reduced risk of macrosomia in women randomized to intermittent use of retrospective CGM [10], GlucoMOMS study failed to replicate these benefits years later[11]. Moreover, when rtCGM was used intermittently throughout pregnancy, outcomes were not improved either [9]. In 2018, intermittently scanned CGM (isCGM, Freestyle libre system) was approved for its use in gestation (REF, 2018 scott). Nonetheless, to date, impact of isCGM on pregnancy outcomes has been scarcely studied [12, 13].

Despite growing evidence supporting rtCGM use in pregnancy over isCGM, the economic-burden of rtCGM systems for the different National Health Systems has limited its implantation. Indeed, in Spain, isCGM is the main government-funded CGM system for pregnant women with type 1 diabetes and multiple doses of insulin (MDI) therapy. Therefore, the aim of the study was to assess whether the additional use of isCGM,

compared to standard care (only monitored by daily SMBG), could improve maternal glycaemic control and pregnancy outcomes in a cohort of women with type 1 diabetes and MDI.

MATERIAL AND METHODS

Study population

We performed an observational, retrospective, multicentre cohort study in women with type 1 diabetes attended at 7 tertiary university hospitals in Spain between 2011 and 2021. Inclusion criteria were: (1) Age > 18 years (2) type 1 diabetes; (3) MDI therapy; (4) singleton pregnancy. Women with pregnancy loss < 20 weeks of gestation or use of insulin pump during pregnancy were excluded for the analysis. No additional exclusion criteria were used. Information was obtained from Spanish Diabetes and Pregnancy Study Group database or medical records in place. The study was approved by the ethics committee at each participating centre.

Management of diabetes in pregnancy

All women received routine clinical care, with antenatal visits every 2 to 4 weeks. According to current national guidelines [14], women were advised to perform SMBG both before and one hour after meals, at bedtime, and occasionally at night. The goals were to achieve pre-prandial capillary glucose levels <5.3 mmol/l, 1-hour post-prandial capillary glucose <7.8 mmol/l and HbA1c < 48 mmol/mol (<6.5%). In Spain, the use of isCGM is reimbursed in type 1 diabetes for all women in pregnancy since 2019 [15]. In addition to isCGM, SMBG measurements were recommended prior to insulin dose adjustment or correction to hypoglycaemia to verify CGM accuracy. HbA_{1c} was measured every 4 to 8 weeks during pregnancy and a value of each trimester was selected (first trimester: 10-14 weeks' gestation; second trimester: 24-28 weeks' gestation; and third trimester: 32-36 weeks' gestation). HbA_{1c} analysis was performed in each local laboratory according to standard procedures.

CGM system

The isCGM device used was the Freestyle Libre system (Abbott Diabetes Care, Alameda, CA, USA), which measures subcutaneous interstitial glucose concentration every 60 s and generates a glucose value every 15 min (with 96 recordings per day). The device requires no calibration by the user. Since June 2020, Freestyle Libre 2 was implanted and in contrast to previous version, Freestyle Libre 2 has optional alarms that warn the user if the glucose is in hypoglycaemia or hyperglycaemia. The dataset for each pregnancy was obtained from Libreview software. We followed the recently published consensus on use of CGM and required that there was a minimum of 14 consecutive days of data [16]. CGM-data derived included the percentage of time spent within (TIR), below (TBR) and above (TAR) the pregnancy glucose target range (3.5–7.8 mmol/l) of each trimester of gestation (first trimester: 10-14 weeks' gestation; second trimester: 24-28 weeks' gestation; and third trimester: 32-36 weeks' gestation). A 60.6% of isCGM users were CGM naïve at the first antenatal visit.

Maternal and neonatal data

We assessed baseline demographic characteristics (age at time of delivery, parity, self-reported prepregnancy weight and BMI), diabetes-related characteristics (diabetes duration at booking, presence of micro/macrovascular complications), smoking habit, attending to prepregnancy care programme and folic acid supplementation.

The primary outcome of interest was LGA, which was defined as birth weight >90th centile according to Spanish fetal growth charts that take into account sex and gestational age [17]. Gestational age at delivery was defined as the number of completed weeks based on the last menstrual period or on the earliest ultrasound assessment if discordant. Secondary outcomes evaluated were maternal severe hypoglycaemia during pregnancy (events requiring third party assistance), preeclampsia (blood pressure 140/90 mmHg plus proteinuria 300 mg/day[18]) caesarean section, preterm and early

preterm delivery (delivery < 37 and <34 weeks, respectively), small-for-gestational age infant (SGA, birth weight <10th centile), macrosomia (birth weight > 4000 g), neonatal hypoglycaemia (glycemia <2.2 mmol/l in the first 24 h after delivery requiring treatment [19]), respiratory distress (any distress requiring treatment), congenital anomalies classified according EUROCAT[20] and perinatal mortality (foetal and infant death from 20 weeks of gestation to 4 weeks after birth [21]).

Statistical analysis

Continuous data were compared using t-tests or the Mann-Whitney compared test and categorical data using chi-square tests. Wilcoxon and McNemar tests were used to evaluate changes throughout pregnancy of HbA_{1c} levels and percentage of HbA_{1c} attainment according American Diabetes Association (ADA) and National Institute for Health and Care Excellence (NICE) guidelines. ADA indicates HbA_{1c}<48 mmol/mol (6.5%) as prepregnancy target and first trimester and <42 mmol/mol (6.0%) in the second and third trimesters[5], and NICE indicates HbA_{1c}<48 mmol/mol (6.5%) in all trimesters[6]. Time trend analyses were performed using multivariate linear regression, including glucose monitoring system as independent variable. Due to the observational design of this study, logistic regression analysis was fitted to characterize the strength of association between adverse pregnancy outcomes with a prevalence > 20% and glucose monitoring system. The regression model was adjusted for baseline characteristics such as maternal age, pregestational BMI, smoking habit, centre, HbA_{1c} at first trimester and gestational age at first antenatal visit. HbA_{1c} at first trimester could be a reflection of baseline status rather than isCGM effect itself due to the high proportion of women who are naïve to isCGM at first antenatal visit; hence, this variable was included in the adjusted model. The regression models were not adjusted for the intermediate variables such as HbA_{1c} at second and third trimesters, gestational age or maternal gestational weight gain[22]. However, its known that LGA and preterm infants are more likely to

neonatal hypoglycaemia[23, 24], thus a sensitivity analysis was performed in groups without prematurity and LGA.

Lastly, a sub-analysis was performed among isCGM users. Spearman correlation was performed to estimate the association between CGM-metrics and HbA_{1c}. Logistic regression models were used to estimate OR (95% CI) for adverse pregnancy outcomes (LGA, prematurity, neonatal hypoglycaemia and caesarean section). Variables included in the model were: CGM-metrics (time spent within, above or below range), pregestational BMI and smoking habit. HbA_{1c} was not included in the model because was strongly correlated with CGM-metrics.

All analyses were performed using STATA version 14.0 (Stata Corp., College Station, TX, USA). A two-sided -value of $P < 0.05$ was considered statistically significant. Based on the size of the cohort, our analyses had 80% of power at the 5% level to detect a 16% difference in LGA rates between participants with or without isCGM use during pregnancy.

RESULTS

Subjects' characteristics

A total of 300 pregnant women were recruited, 132 (44%) of women were isCGM users. The mean age of study participants was 34.1±5.3 years with a median of 16 (9.5-23) years of diabetes duration without differences between groups. A 10.6% of isCGM group used Freestyle Libre 2. As shown in table 1, no differences between-group were observed in smoking habit, pregestational weight, parity, rates of diabetes complications, folic use or prepregnancy care.

Glycaemic control

Whole cohort showed a significant decrease in HbA_{1c} levels from the pregestational period to the second trimester (median difference of 8.7 mmol/mol [0.8%], p<0.001) with a slightly increase in the third trimester (median difference of HbA_{1c} 1.1 mmol/mol [0.1%], p<0.001). The same pattern was observed in both groups throughout pregnancy, but isCGM group had a significantly higher increase in HbA_{1c} levels from the second to the third trimester (median difference of 2.2 mmol/mol [0.2%] vs. 1.1 mmol/mol [0.1%], isCGM vs. SMBG, p=0.033) compared to control group (Figure 1). When cross-sectional evaluation in each trimester was performed, HbA_{1c} levels in the second trimester were lower in isCGM users (41mmol/mol [5.9%] vs. 43.2 mmol/mol [6.1%], isCGM vs. SMBG, p=0.034), without differences in other periods (Table 1, Figure 1). Rates of severe hypoglycaemia were not different between groups (Table 1).

Figure 2 depicts the attainment of HbA_{1c} targets according to international guidelines. When NICE goals were applied, there were no trimester-specific differences in proportion of women fulfilling HbA_{1c} targets. However, when the proportion of achievement of ADA goals was evaluated, significant differences were observed between groups in the second trimester (56% vs. 42.6%, isCGM vs. SMBG, p=0.024) with a higher decrease of these rates from the second to the third trimester in isCGM group (mean difference of 19.6% vs. 5.9%, p=0.034).

Pregnancy outcomes

The median gestational age at the first antenatal visit was 8.4 (6.9-10) weeks without differences between glucose monitoring systems. As shown in Table 2 (unadjusted analysis), there was no significant difference in adverse pregnancy outcomes between groups. Nevertheless, when logistic regression was performed adjusted for well-known confounders (such as maternal age, centre, diabetes duration, smoking habit, pregestational BMI and HbA_{1c} at first trimester), isCGM users had higher risk of neonatal hypoglycaemia compared to SMBG group ($OR_{adjusted}$ 2.20, 95% CI 1.14 – 4.30). Glucose

monitoring system was not associated with LGA, prematurity or caesarean section (Figure 3). In addition, a sensitivity analysis was performed among pregnancies without LGA or prematurity leading the same results on neonatal hypoglycaemia (Supplemental table 1).

CGM-derived metrics among women with isCGM

HbA_{1c} was strongly inverse correlated with TIR (first trimester: r= -0.568, p<0.01; second trimester: r=-0.689, p<0.01; third trimester: r= -0.531, p<0.01) and direct correlated with TAR (first trimester: r= 0.631, p<0.01; second trimester: r=0.745, p<0.01; third trimester: r= 0.596, p<0.01). In contrast, a weak correlation between HbA_{1c} and TBR was observed in all trimesters (first trimester: r= -0.382, p<0.01; second trimester: r=-0.289, p=0.01; third trimester: r= -0.265, p=0.01).

Table 3 showed changes in times of range throughout pregnancy. Percentage of TIR step-increased during pregnancy as percentage of TAR step-decreased. However, TBR decreased from the first to the second trimester, with no significant changes in the third trimester. Lastly, an exploratory analysis was performed to evaluate the relationship among time spent within, above or below range and adverse pregnancy outcomes: prematurity, caesarean section, LGA and neonatal hypoglycaemia. After adjustment for confounders, metrics from second trimester were associated with LGA (per 1% increase; TIR: $OR_{adjusted}$ 0.97, CI 95% 0.94 - 0.99; TAR: $OR_{adjusted}$ 1.05, CI 95% 1.02 – 1.08; and TBR: $OR_{adjusted}$ 0.76, CI 95% 0.65 – 0.89) as well as TBR in the first trimester with prematurity (per 1% increase, $OR_{adjusted}$ 0.79, CI 95% 0.66 – 0.93) (Supplemental table 2).

DISCUSION

In the present multicentre cohort study, the addition of isCGM use to routine clinical practice (SMBG alone) in pregnancies complicated by type 1 diabetes led to achieve a

better metabolic control in the second trimester, however this improvement was not sustained over time, with similar third trimester HbA_{1c} to non-users. We also found that offspring of pregnant women using isCGM were more like to neonatal hypoglycaemia without significant differences in other neonatal outcomes. To the best of our knowledge, this is the largest cohort study evaluating the effect on pregnancy of a new CGM system as isCGM versus current clinical practice, using SMBG alone, in women with type 1 diabetes and MDI.

CGM systems extrapolates blood glucose concentration from measurements of interstitial subcutaneous glucose, thus accuracy and reliability of these systems are key factors. Recently, the accuracy, safety and user acceptability of the isCGM (Freestyle libre 1) in pregnant women with diabetes were demonstrated [8]. Nonetheless, although acceptable correlation has been shown between estimates from interstitial glucose and reference blood glucose measurements (mean absolute relative difference of 11.8%), the discrepancy is more pronounced in the extremes of glucose ranges, both in pregnant and non-pregnant population[25–27]. Indeed, despite similar mean glucose sensor was observed when simultaneously measured by isCGM and rtCGM, more glucose readings were classified as TBR by isCGM among 20 pregnant women with type 1 diabetes in early pregnancy[26]. Therefore, the overestimation of hypoglycaemia during pregnancy, when a tight glycaemic control is recommended, could have clinical consequences. In fact, these could explain, in part, the greater increase in HbA_{1c} levels from the second to the third trimester in isCGM users in our cohort. Between 24 and 34 weeks of gestation insulin requirements are higher[28], however women using isCGM which spend large proportion of time (3-10%) below target may have conflicting decisions to prevent or treat hypoglycaemia (for example snacking) and to change insulin dosage. Furthermore, the international consensus on use of CGM recommended to all pregnant women with type 1 diabetes spend < 4% of TBR regardless of CGM system[16]. Thus, the overestimation

of this parameter by isCGM system could led a decision-making more conservative, not only for pregnant women, but also for their physicians in order to achieve this goal.

Surprisingly, unlike previous studies, isCGM use during pregnancy showed an increased risk of neonatal hypoglycaemia compared to those without isCGM. Nonetheless, only one previous RCT compared isCGM versus SMBG but was unpowered for neonatal outcomes due to the low number of participants included (n=34 women with type 1 diabetes)[12]. In a larger cohort study from Sweden (n=187), isCGM users were only compared with rtCGM users, without differences in pregnancy outcomes either[13]. Interestingly, the rtCGM group had higher rates of insulin pump therapy. A prespecified analysis of CONCEPTT study revealed that insulin pump during pregnancy was associated with poor metabolic control at gestational age 34 as well as poor neonatal outcomes (including neonatal hypoglycaemia) compared to MDI [29]. Thus, the higher rates of insulin pumps among rtCGM group from Sweden study could have interfered in the results, due to isCGM group was directly compared with a high-risk group. On the other hand, it has been described that high glucose levels during peripartum period also plays a role in neonatal hypoglycaemia [23, 24]. In our cohort, no between-group difference in the HbA_{1c} values in the third trimester was observed but isCGM users started with significant lower levels in the second trimester, which leads to hypothesize that further increase on glucose levels in the isCGM group could be present weeks/days before delivery, and consequently, leading to increase the risk of neonatal hypoglycaemia. In contrast, this better glycaemic control in the second trimester in isCGM group could have avoid a deleterious repercussion on foetal growth in which the glycaemic control not only at the end, but also throughout gestation is important [30]. Overall, these results highlighted the needed of a tight glycaemic control until the end of the delivery.

Focusing in the isCGM cohort, CGM-derived metrics showed a strong correlation with HbA_{1c} levels, especially with TAR and TIR, in all trimesters equally. Our results showed a slightly higher correlation than recent studies in this field (r= 0.6-0.7 vs r=0.4-0.5, respectively) [31, 32]. Beyond HbA_{1c}, our data suggest an association of all 3 CGM-metrics of the second trimester (TIR, TBR and TAR) with higher risk of LGA. The relationship between metrics related to hyperglycaemia and LGA has been previously observed both in isCGM and rtCGM users and confirmed by our results[13, 31, 33, 34]. In contrast to previous, we found an inverse association with TBR and risk of LGA as well as prematurity [33, 34]. Recently, despite Sibiak et al. did not find any relationship with TBR, but a measure of glycaemic variability, such as Glycaemic Risk Assessment in Diabetes Equation attributed to hypoglycaemia, was related to LGA [33]. Taken together, these data confirm the role of maternal hyperglycaemia triggering excessive insulin production by foetal pancreas.

Our study has strengths and limitations. Among the strengths, this is a multicentre study including 300 pregnant women with type 1 diabetes and MDI. To date, this is the largest cohort study evaluating the effect of isCGM during a critical period as pregnancy in a real clinical setting. Until data, most of the studies evaluating CGM in type 1 diabetes included not only women with MDI, but also with pump therapy[13, 33, 35] leading a bias. Thus, we carefully selected only women with MDI. Furthermore, these data came from university hospitals with expertise in both CGM systems and obstetric management of diabetes pregnancies. And in addition to well-known maternal risk factors, adjusted logistic regression models included centre of inclusion due to the possible variation between centres in their clinical practices. Nonetheless, limitations should also be acknowledged. First, this was an observational study, which precludes us from making causal inferences. However, pragmatic trials have external validity, since it was a reflection of what happens in real practice beyond RCT [36]. This study highlighted the limitations observed in real clinal practice (such as the worsening glycaemic control in

the third trimester of gestation). And on the other hand, the wide availability of isCGM system for all pregnant with type 1 diabetes, in order to facilitate self-management of glucose control, will make practically and ethically difficult to perform a RCT with standard care (SMBG alone) as comparator. Second, evaluation of metabolic control was only performed by HbA_{1c} levels, but despite its limitation in pregnancy[37], it was stronger correlated with scans per day [38] and still is a robust predictor of adverse pregnancy outcomes[39]. And lastly, frequency of SMBG in isCGM group is missing. Although this information could have help to a elucidate which percentage of decisions were performed only by glucose sensor, beyond RCT, usually this information could be difficult to obtain[40, 41].

In conclusion, the addition of isCGM to standard care in pregnancies complicated by type 1 diabetes and MDI therapy provided an initial improvement in glycaemic control but not further sustained. This worsening late in pregnancy could explain the higher risk of neonatal hypoglycaemia. Further studies are needed to confirm our results in isCGM, as well as with the new version of isCGM (Freestyle libre 2) currently available. Nevertheless, until data, rtCGM should be the gold standard of CGM therapy in pregnant women with type 1 diabetes and MDI.

Data availability

Data are available on request from the authors.

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Authors'relationships and activities

The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Author contributions

VP, MJP, AM, MG, AMW, BV, MDM and IV made substantial contributions to the conception or design of the work and the acquisition, analysis, or interpretation of data. All authors participated in drafting the work or revising it critically for important intellectual content. The final version of this manuscript was approved by all authors, who agree to be accountable for all aspects of the work. VP and IV are the guarantors of this work. They 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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Table 1. Maternal characteristics according to glucose monitoring system

	Overall (n=300)	**SMBG (n=168)**	**isCGM (n=132)**	***p* value**
Age (years)	34.1±5.3	34.4±5.3	33.5±5.1	0.110
Current smoker	52 (17.1)	32 (21.4)	22 (17.1)	0.371
European descent	273 (90.7)	156 (92.3)	117 (88.7)	0.277
Diabetes duration (years)	16 (9.5-23)	16 (9.5-23)	17 (9.2-23.5)	0.725
Diabetes-related complications				
Retinopathy	60 (19.9)	28 (16.5)	32 (24.2)	0.098
Nephropathy	14 (4.6)	7 (4.1)	7 (5.3)	0.635
Neuropathy	8 (2.7)	6 (3.6)	2 (1.5)	0.276
Cardiovascular disease	1 (0.34)	1 (0.6)	0	0.375
Primipara	134 (44.5)	70 (41.4)	64 (48.5)	0.221
Prepregnacy care programme	142 (47.3)	87 (51.2)	55 (42.3)	0.128
Folic acid use	132/204 (64.7)	82/123 (67.7)	50/83 (60.2)	0.287
Pregestational BMI (Kg/m^2)	23.7 (21.6 - 26.7)	23.7 (21.6 - 26.9)	23.6 (21.8 - 26.4)	0.928
Gestational weight gain (Kg)	13.5 (9.3-6.3)	13.3 (9.5-16)	13.5 (9.1-16.8)	0.514
HbA_{1c}				
Pregestational, mmol/mol	50.8 (45.3 – 61.7)	51.1 (46.4 – 61.7)	50.8 (44.3 – 60.6)	0.811
%	6.8 (6.3 – 7.8)	6.8 (6.4 – 7.8)	6.8 (6.2 – 7.7)	
Trimester 1, mmol/mol	46.4 (40.9 - 53)	47.5 (42.1 – 54.1)	45.9 (39.9 – 51.9)	0.218
%	6.4 (5.9 - 7)	6.5 (6 – 7.1)	6.4 (5.8 – 6.9)	
Trimester 2, mmol/mol	42.1 (36.6 – 47.5)	43.2 (37.7 – 47.5)	41 (35.5 – 46.4)	0.034
%	6 (5.5 – 6.5)	6.1 (5.6 – 6.5)	5.9 (5.4 – 6.4)	
Trimester 3 mmol/mol	43.2 (39.9 – 47.5)	43.2 (39.9 – 47.5)	43.2 (39.9 – 47.5)	0.943
%	6.1 (5.8 – 6.5)	6.1 (5.8 – 6.5)	6.1 (5.7 – 6.5)	
Severe hypoglycaemia during pregnancy	19 (6.5)	8 (4.9)	11 (8.5)	0.208

Results are given as n(%), n/N (%), mean ± SD or median (Q1-Q3)
Abbreviations: BMI: body mass index; isCGM: intermittently scanned continuous glucose monitoring; SMBG: self- monitoring of blood glucose.

Table 2. Pregnancy outcomes according to glucose monitoring system

	Total (n=300)	**SMBG (n=168)**	**isCGM (n=132)**	***p* value**
GA at first antenatal visit (weeks)	8.4 (6.9 – 10)	8.1 (6.7 – 10)	8.9 (7.1 – 10)	0.285
GA at delivery (weeks)	38 (37 – 38.9)	38 (37 - 39)	38 (36.9 – 38.9)	0.654
Preterm birth				
Preterm < 37 weeks	78 (26)	41 (24.9)	36 (27.3)	0.636
Early preterm < 34 weeks	12 (4)	6 (3.6)	6 (4.6)	0.693
Caesarean section	158 (52.7)	82 (48.8)	76 (57.6)	0.131
Preeclampsia	35 (11.7)	23 (13.8)	12 (9.1)	0.204
Birthweight				
Birthweight (g)	3380±634	3358±661	3408±599	0.495
SGA	9 (3.1)	7 (4.2)	2 (1.6)	0.184
LGA	126 (43.2)	74 (45.1)	52 (40.6)	0.441
Macrosomia (≥4000g)	52 (17.6)	28 (17)	24 (18.4)	0.738
Neonatal hypoglycemia	65 (22.7)	31 (19.1)	34 (27.4)	0.098
Respiratory distress	37 (13.1)	19 (12.5)	18 (13.7)	0.774
Congenital anomaly	18 (6.2)	7(4.4)	11 (8.5)	0.148
Perinatal mortality	3 (1.05)	1 (0.7)	2 (1.5)	0.481

Results are given as n(%), median (Q1-Q3) or mean ± standard deviation as appropriate.
Abbreviations: GA: gestational age; isCGM: intermittently scanned continuous glucose monitoring; LGA: large-for-gestational age infant (>90th centile); SMBG: self- monitoring of blood glucose; SGA: small-for-gestational age infant (<10th centile)

Table 3. CGM-derived metrics in each trimester of gestation in women with iCGM use

	First trimester	**Second trimester**	**Third trimester**	**p***
TIR 3.5–7.8 mmol/L	N= 76	N= 100	N=103	
median %	61 (51- 67.5)	60 (51 – 73.5)	69 (60 - 79)	<0.001
TIR >70%, n (%)	14 (18.4)	31 (31)	44 (42.7)	0.003
TBR <3.5 mmol/L	N= 75	N = 95	N=100	
median %	9 (5-15)	5 (2 – 9)	5.5 (3 - 10)	0.002
TBR < 4%, n (%)	16 (21.3)	36 (37.9)	27 (27)	0.051
TAR >7.8 mmol/L	N=87	N= 109	N= 113	
median %	29 (18 - 41)	32 (21 - 44)	22 (13 - 32)	0.001
TAR < 25%, n (%)	32 (36.7)	36 (33)	66 (58.4)	<0.001
Sensor use (%)	N=73 97 (91-100)	N= 91 97 (91 – 97)	N= 92 98 (94.5 – 100)	0.008

Data are presented as median (Q1-Q3) or n(%) as appropriate * p between trimesters
Abbreviations: TAR: Time-above-range; TBR: Time-below-range; TIR: Time-in-range.

Figure 1. HbA_{1c} levels according to glucose monitoring system and gestational age. First trimester: 10-14 weeks' gestation; second trimester: 24-28 weeks' gestation; and third trimester: 32-36 weeks' gestation.

* P-value <0.05 SMBG vs. isCGM. ** P-value <0.05 for change in HbA_{1c} levels between second and third trimesters SMBG vs. isCGM.

Abbreviations. isCGM: intermittently scanned continuous glucose monitoring; SMBG: self-monitoring of blood glucose.

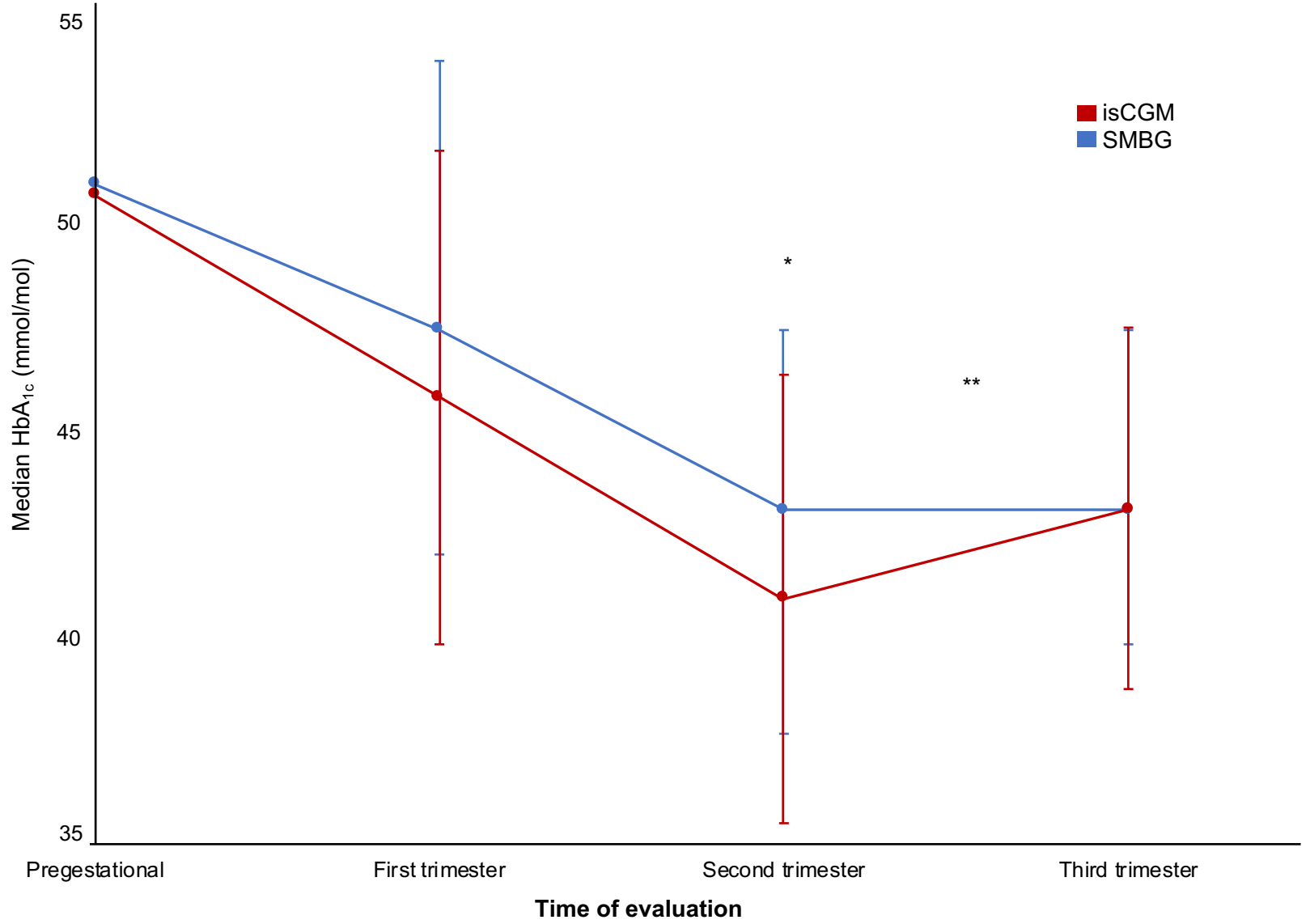
Figure 2. Percentage of women fulling HbA_{1c} target according NICE and ADA criteria. ADA indicates HbA_{1c}<48 mmol/mol (6.5%) as prepregnancy target and first trimester and < 42 mmol/mol (6.0%) in the second and third trimesters. NICE indicates HbA_{1c}<48 mmol/mol (6.5%) in all trimesters. First trimester: 10-14 weeks' gestation; second trimester: 24-28 weeks' gestation; and third trimester: 32-36 weeks' gestation.

P-value* for change over time SMBG vs. isCGM.

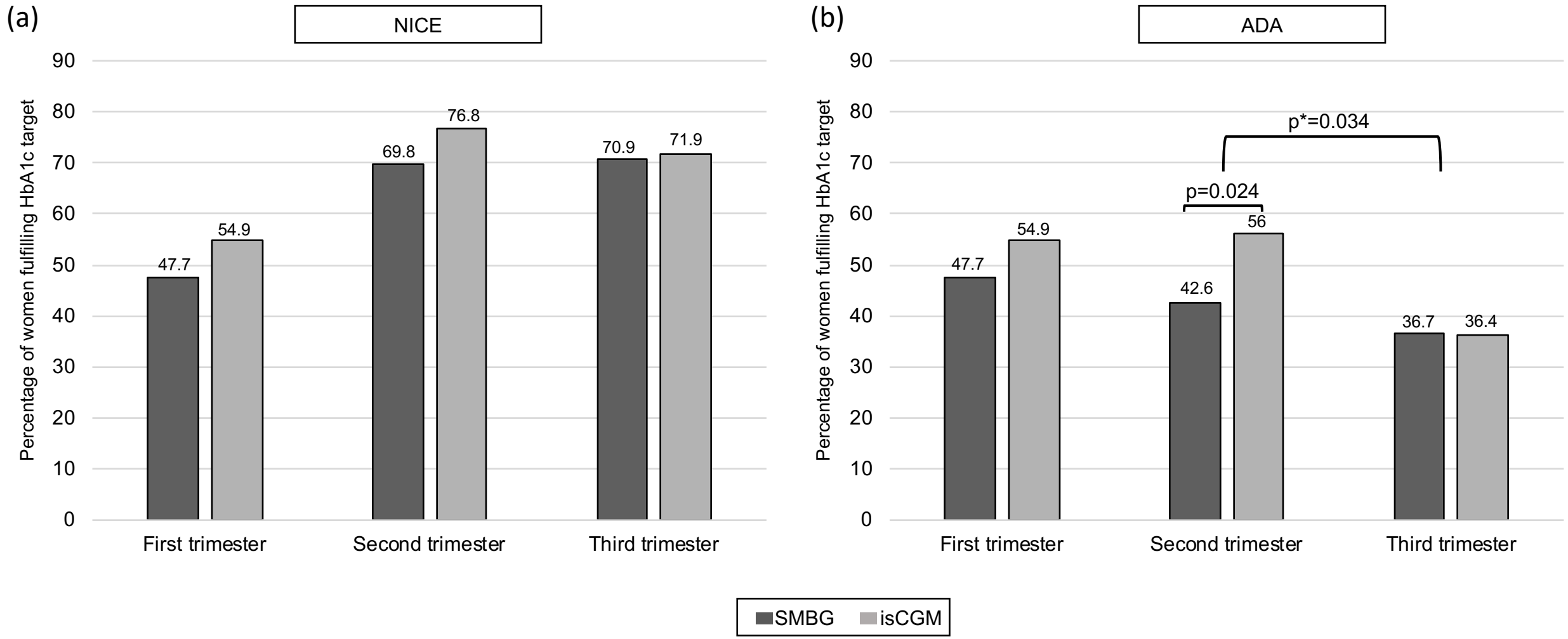
Abbreviations. ADA: American Diabetes Association; NICE: National Institute for Health and Care Excellence.

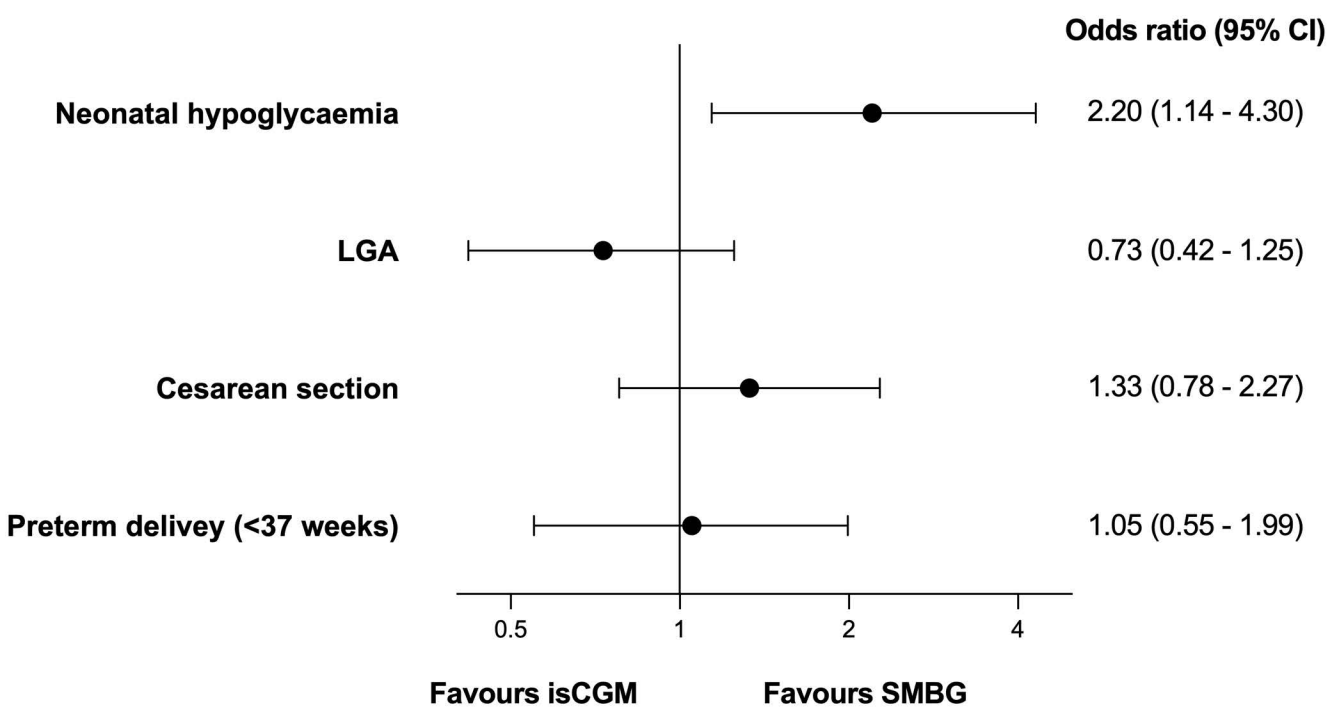
Figure 3. Binary logistic regression models for the most prevalent adverse pregnancy outcomes including SMBG group as reference group. All models were adjusted for the same variables: maternal age, pregestational body mass index, smoking habit, centre, HbA_{1c} at first trimester and gestational age at first antenatal visit.

Abbreviations. isCGM: intermittently scanned continuous glucose monitoring; LGA: large-for-gestational age infant (>90^{th} centile); SMBG: self-blood glucose monitoring.



Participants assessed				
SMBG	160	151	162	158
isCGM	123	122	125	121


(a)
NICE
Percentage of women fulfilling HbA1c target
90
80
70
60
50
40
30
20
10
0
47.7
54.9
69.8
76.8
70.9
71.9
First trimester
Second trimester
Third trimester
(b)
ADA
p*=0.034
p=0.024
47.7
54.9
42.6
56
36.7
36.4
SMBG
isCGM


Odds ratio (95% CI)
Neonatal hypoglycaemia
2.20 (1.14 - 4.30)
LGA
0.73 (0.42 - 1.25)
Cesarean section
1.33 (0.78 - 2.27)
Preterm delivey (<37 weeks)
1.05 (0.55 - 1.99)
0.5
1
2
4
Favours isCGM
Favours SMBG

Supplemental table 1. Binary logistic regression models for neonatal hypoglycaemia including SMBG group as reference group stratifying according LGA or prematurity presence.

	Model (OR (95% CI)	
	Crude	**Adjusted**
LGA presence		
LGA -	**2.34 (1.07-5.10)**	**2.63 (1.01-6.91)**
LGA +	1.08 (0.47-2.48)	2.44 (0.78-7.62)
Prematurity presence		
Preterm -	1.73 (0.87-3.47)	**2.52 (1.12-5.67)**
Preterm +	1.31 (0.49-3.49)	1.54 (0.42-5.8)

All models were adjusted for the same variables: maternal age, pregestational body mass index, smoking habit, centre, HbA1c at first trimester and gestational age at first antenatal visit.
+/- indicates presence or absence

Supplemental table 2. Logistic regression analysis of CGM-derived metrics tested for associations with adverse pregnancy outcomes

	CGM-derived metrics					
	Percentage of time in range (3.5–7.8 mmol/l)		**Percentage of time above range (>7.8 mmol/l)**		**Percentage of time below range (<3.5 mmol/l)**	
	Crude model	Adjusted model	Crude model	Adjusted model	Crude model	Adjusted model
Large-for-gestational age infant						
Trimester 1	0.98 (0.94-1.01)	0.98 (0.94-1.03)	1.02 (0.99-1.05)	1.02 (0.99-1.05)	0.96 (0.89-1.02)	0.94 (0.87-1.02)
Trimester 2	**0.97 (0.95-0.99)**	**0.97 (0.94-0.99)**	**1.04 (1.02-1.07)**	**1.05 (1.02-1.08)**	**0.80 (0.71-0.91)**	**0.76 (0.65-0.89)**
Trimester 3	0.99 (0.96-1.02)	0.98 (0.95-1.01)	1.01 (0.98-1.03)	1.02 (0.99-1.05)	0.95 (0.90-1.02)	0.96 (0.89-1.02)
Prematurity						
Trimester 1	0.98 (0.94-1.01)	1.01 (0.96-1.06)	**1.03 (1.00-1.06)**	1.01 (0.98-1.05)	**0.86 (0.78-0.95)**	**0.79 (0.67-0.92)**
Trimester 2	0.98 (0.96-1.01)	1.00 (0.97-1.03)	1.02 (0.99-1.04)	1.01 (0.98-1.04)	0.94 (0.86-1.03)	0.93 (0.83-1.04)
Trimester 3	0.99 (0.96-1.01)	1.01 (0.97-1.04)	1.02 (0.99-1.05)	1.02 (0.99-1.04)	0.92 (0.83-1.01)	0.90 (0.80-1.01)
Neonatal hypoglycaemia						
Trimester 1	0.99 (0.95-1.03)	0.99 (0.95-1.05)	1.00 (0.97-1.03)	1.00 (0.97-1.04)	0.95 (0.89-1.03)	096 (0.89-1.03)
Trimester 2	0.99 (0.96-1.01)	0.99 (0.96-1.02)	1.01 (0.98-1.04)	1.00 (0.98-1.04)	0.99 (0.92-1.06)	0.99 (0.93-1.06)
Trimester 3	0.99 (0.96-1.02)	0.99 (0.96-1.03)	1.01 (0.98-1.04)	1.00 (0.98-1.03)	0.98 (0.91-1.04)	0.98 (0.92-1.05)
Cesarean section						
Trimester 1	1.02 (0.98-1.05)	1.01 (0.9-1.06)	0.98 (0.95-1.01)	0.99 (0.96-1.02)	**1.07 (1.00-1.13)**	1.07 (0.99-1.14)
Trimester 2	1.00 (0.98-1.03)	0.99 (0.97-1.02)	0.99 (0.98-1.02)	1.00 (0.98-1.03)	1.02 (0.96-1.07)	1.02 (0.95-1.08)
Trimester 3	1.00 (0.97-1.02)	0.99 (0.96-1.02)	1.00 (0.98-1.02)	1.00 (0.98-1.03)	1.02 (0.96-1.08)	1.01 (0.95-1.08)

Odds ratio and 95% confidential interval for adverse pregnancy outcomes including each metrics (per 1% increase) as dependent variable. The adjusted model included pregestational body mass index and smoking habit.