BMJ Open Diabetes Research & Care

Increased glycemic variability in pregnant women with Roux-en-Y gastric bypass compared with sleeve gastrectomy

Kleopatra Alexiadou,[1] Saleem Ansari,[1] Bryony Jones,[2] Christina Yu,[2] Anne Dornhorst,[1] Nick Oliver,[1] Christos Tsironis,[3] Sanjay Purkayastha,[3] Ahmed Ahmed,[3] Rochan Agha-Jaffar,[1] Bernard Khoo ,[4] Tricia M-M Tan [1]

To cite: Alexiadou K, Ansari S, Jones B, *et al*. Increased glycemic variability in pregnant women with Roux-en-Y gastric bypass compared with sleeve gastrectomy. *BMJ Open Diab Res Care* 2024;**12**:e003642. doi:10.1136/bmjdrc-2023-003642

KA and SA contributed equally.

Received 18 July 2023
Accepted 27 November 2023

[1]Department of Metabolism Digestion and Reproduction, Imperial College London, London, UK
[2]Queen Charlotte's and Chelsea Hospital, London, UK
[3]Surgery and Cancer, Imperial College Healthcare NHS Trust, London, UK
[4]Division of Medicine, University College London, London, UK

Correspondence to
Dr Tricia M-M Tan;
t.tan@imperial.ac.uk

ABSTRACT

Introduction Bariatric surgery is associated with adverse pregnancy outcomes such as reduced birth weight and premature birth. One possible mechanism for this is increased glycemic variability (GV) which occurs after bariatric surgery. The objective of this study was to compare the effect of Roux-en-Y gastric bypass (RYGB) versus vertical sleeve gastrectomy (SG) on GV during pregnancy and to investigate the relationships of GV, type of bariatric surgery and maternal and neonatal outcomes.

Research design and methods Fourteen pregnant women after RYGB and 14 after SG were investigated with continuous glucose monitoring in their second or third trimester in this observational study carried out as part of routine clinical care.

Results Pregnant women with RYGB had similar mean interstitial glucose values but significantly increased indices of GV and a lower %time in range 3.9–7.8 mmol/L (70–140 mg/dL), compared with SG.

Conclusions Pregnant women who have undergone RYGB have greater GV during pregnancy compared with those who have undergone SG. Further research is needed to establish the relationship between GV and pregnancy outcomes to determine the preferred bariatric operation in women of reproductive age, and whether interventions to reduce GV might improve outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (SG) are associated with adverse pregnancy outcomes and increased glucose variability (GV).
⇒ To date, no study has compared the relationships between GV, type of bariatric surgery (RYGB vs SG) and pregnancy outcomes.

WHAT THIS STUDY ADDS

⇒ RYGB was associated with increased GV and a lower %time in range (3.9–7.8 mmol/L) during pregnancy compared with SG.
⇒ Increased GV and %lower time in range (3.9–7.8 mmol/L) may be detrimental to feto-placental health.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Increased GV, reduced time in euglycemia and increased time in hyperglycemia is a possible mechanism affecting pregnancy outcomes in women who have had bariatric surgery.
⇒ Future prospective studies should investigate the effect of GV on pregnancy outcomes in women who have had bariatric surgery, to better inform the management of women of reproductive age with obesity and type 2 diabetes.

INTRODUCTION

Obesity and type 2 diabetes among women of reproductive age is a global health problem.[1] Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (SG) are successful in reducing obesity-associated complications.[2] As a result, bariatric surgery is increasingly performed in women of reproductive age. The reduction in bodyweight achieved with bariatric surgery improves fertility and reduces obesity-related pregnancy complications for both the mother and baby, such as hypertensive disorders in pregnancy and large-for-gestational age babies.[3 4] Adverse perinatal outcomes have also been reported in pregnant women who have undergone bariatric surgery[5 6] such as reduced fetal growth velocity, small for gestational age (SGA), peri-natal mortality, congenital anomalies, preterm birth and admission to neonatal intensive care.[7 8]

Bariatric surgery causes increased intraday glycemic variability (GV) due to accelerated delivery of nutrients to the small bowel, for example, via the gastrojejunal bypass after RYGB, leading to a sharp rise in glucose levels immediately after meal consumption, followed by a large insulinotropic response which leads to a rapid drop in blood glucose

levels. This drop in glucose can, if exaggerated, provoke postbariatric hypoglycemia[9 10] but whether this impacts fetal outcomes remains undetermined.[11] Furthermore, the impact of GV in pregnant women who have had bariatric surgery and whether this differs between the different types of bariatric surgery is also unknown as is the mechanism(s) by which GV may contribute to adverse pregnancy outcomes.

We hypothesised that the increased GV after bariatric surgery may be associated with adverse pregnancy outcomes. Our objective was to look at glycemic markers and GV assessed by continuous glucose monitoring (CGM) and home blood glucose monitoring (HBGM), and to compare these markers between pregnant women with RYGB and SG, and to correlate these glycemic markers with maternal and neonatal outcomes.

METHODS

We audited the glycemic parameters of 14 women with RYGB and 14 women with SG who attended the antenatal clinics of Queen Charlotte's and Chelsea and St Mary's Hospitals in London, UK between November 2019 and May 2022. Ethnicity was self-reported and classified according to our local electronic health record system. The glycemic assessments took place in the second or third trimester of pregnancy and our cohorts included women with and without gestational diabetes mellitus (GDM) in the current pregnancy, as well as women with or without history of type 2 diabetes presurgery or prepregnancy and after bariatric surgery. Pragmatically, GDM was defined by fasting blood glucose of ≥5.6 mmol/L (100 mg/dL) and/or postprandial blood glucose of >7.8 mmol/L (140 mg/dL) during 2 weeks of HBGM between weeks 24 and 28.[8] All women received routine obstetric antenatal care in terms of hospital visits, ultrasound scans and blood tests, and received input from bariatric physicians, bariatric dietitians, diabetologists and diabetes specialist midwives and nurses.

After consultation with Imperial College London and Imperial College Healthcare NHS Trust, as we are reporting on routinely collected clinical audit data, this study was not considered to be research under the UK Health and Social Care Research framework and did not require ethical approval.

We collected glycemic data from HBGM, oral glucose tolerance test (OGTT) and CGM during routine antenatal visits. The Dexcom G6 CGM sensors were inserted on the back of the upper arm for 10 days under free living conditions; this sensor position in the context of pregnancy has previously been validated.[12] The results were analyzed using the EasyGV V.10 calculator.[13] The main CGM metrics studied included mean interstitial glucose, SD of interstitial glucose, coefficient of variation of interstitial glucose (CV), continuous overlapping net glycemic action over 60 min (CONGA), mean amplitude of glucose excursions (MAGE) and percentage time in range (%TIR) for the following ranges: <3.0 mmol/L [54 mg/dl], <3.9 mmol/L [70 mg/dl], 3.9-7.8 mmol/L [70-140 mg/dl] and >7.8 mmol/L [140 mg/dl]. We also recorded maternal and neonatal outcomes in both cohorts. For birth weight, we used the absolute numerical values as well as centiles calculated using the UK Gestation Related Optimal Weight centile calculator (UK GROW), taking into account gestational age, ethnicity, parity, sex of the baby, maternal weight and height.[14] SGA babies were defined as <10th centile as per the Royal College of Obstetricians and Gynaecologists guidelines[15] and Large for Gestational Age (LGA) babies were defined as >90th centile.

Statistical analysis was performed using STATA V.15.1 (StataCorp). Distribution of data was assessed using Q-Q plots against an idealised normal distribution and kernel density plots. Unpaired two-tailed t-tests and Mann-Whitney U tests were used to compare continuous characteristics which were distributed in a Gaussian or non-Gaussian manner, respectively. Categorical characteristics were compared using a Fisher's exact test. Pearson's correlations were used to examine the association of birth weight, birthweight centile and gestational age at delivery with measures of GV and %TIR. A p value of <0.05 was considered statistically significant.

RESULTS

The clinical characteristics of the two cohorts of women are shown in table 1. There were no significant differences in age, body mass index (BMI) presurgery and prepregnancy, percentage weight loss, time between surgery and conception, weight gain and gestational age at assessment, glycated hemoglobin, diabetes presurgery and prepregnancy, diagnosis of gestational diabetes and hypertension, metformin and insulin use between the RYGB and SG groups.

Table 2 shows various indices of glycemia in both cohorts. Most participants did not routinely undergo OGTT during pregnancy to avoid any provoked hypoglycemia.[8] One woman with RYGB experienced hypoglycemia at 120 min during OGTT (2.5 mmol/L, 45 mg/dL) but recovered without any significant problem. No significant differences between cohorts in the baseline and 120 min glucose levels during the 75 g OGTT were seen in those who had undergone OGTT. HBGM was performed in most participants. The RYGB group was noted to have a slightly lower fasting glucose level on HBGM in comparison with SG group but no differences in postprandial values were recorded. The CGM results showed that mean interstitial glucose was not different between the two surgical groups however, RYGB was associated with significantly increased indices of GV including SD and CV of interstitial glucose (figure 1A), MAGE and CONGA per 60 min. With respect to %TIR, patients undergoing RYGB spent a significantly smaller %TIR 3.9–7.8 mmol/L than patients undergoing SG (figure 1B), with a numerically higher %TIR >7.8 mmol/L. No differences in %TIR

Table 1 Baseline characteristics of patients

	RYGB (n=14)	SG (n=14)	Mean difference (95% CI)	P value
Age (years)	34.5 (3.9)	32.9 (5.1)	1.64 (–1.88 to 5.17)	0.348
Ethnicity				
Asian/Asian British (%)	43	50	N/A	
Black British, African (%)	7	0	N/A	
Black British, Caribbean (%)	7	7	N/A	
Caucasian (%)	43	43	N/A	
BMI presurgery (kg/m^2)	43.4 (6.6)	41.1 (5.8)	2.37 (–2.50 to 7.23)	0.393
Total weight loss (%)	30.7 (9.8)	37.0 (9.2)	–6.31 (–13.71 to 1.01)	0.092
BMI prepregnancy (kg/m^2)	31.7 (4.8)	28.9 (4.9)	2.86 (–0.89 to 6.62)	0.129
Time between surgery and conception (months)	34.0 (30.0)	32.9 (23.1)	1.07 (–19.79 to 21.93)	0.916
Weight gain through pregnancy (kg)	5.8 (1.5)	6.6 (2.8)	–0.8 (–2.60 to 1.00)	0.368
HbA1c (mmol/mol)	36.2 (3.2)	34.4 (4.5)	1.87 (–1.25 to 5.00)	0.228
HbA1c (% points)	5.5% (0.29)	5.3% (0.41)	0.17% (–0.11 to 0.46)	
HbA1c in trimesters 1 and 2, respectively	11,2	14,0	N/A	
Diabetes presurgery	6/14	4/14	N/A	0.695
Duration of diabetes (months)	79.3 (40.0)	101.5 (86.3)	–22.17 (–113.78 to 69.44)	0.592
Diabetes prepregnancy	1/14	1/14	N/A	1.000
GDM	8/14	6/14	N/A	1.000
Diet controlled	1/8	2/7	N/A	0.438
Metformin controlled	7/8	2/7	N/A	0.119
Insulin controlled	5/8	4/7	N/A	0.077
Metformin plus insulin controlled GDM	5/8	1/7	N/A	1.000
Essential hypertension	1/14	1/14	N/A	1.000
Pre-eclampsia	0/14	0/14	N/A	1.000

Characteristics with Gaussian distribution presented as mean (SD) and unpaired t-test used for comparison. For non-Gaussian parameters, the medians (IQR) are shown and Mann-Whitney U test used for statistical comparison. Categorical characteristics analyzed using Fisher's exact test.
BMI, body mass index; GDM, gestational diabetes; N/A, not available; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

in the hypoglycemic ranges were noted between the two types of surgery.

We also performed an analysis between women with GDM (n=15) vs without GDM (n=13), independent of the type of surgery, which showed a significant increases in mean interstitial glucose (mean difference (95% CI) 0.63 mmol/L (0.20 to 1.06), p=0.006), SD (0.42 mmol/L (0.26 to 0.70), p=0.001), CV (6.42% (2.18 to 8.88), p=0.002), MAGE (1.23 mmol/L (0.60 to 1.91), p=0.003) and CONGA over 60 min (0.47 mmol/L (0.15 to 0.87), p=0.010) in the GDM group. The women with GDM had a significantly lower %TIR 3.9–7.8 mmol/L at 81.82% (77.51 to 87.51) vs those without GDM at 92.42% (89.12 to 94.88), mean difference 10.60% (5.02 to 14.77), p=0.001. Those with GDM had a significantly higher %TIR >7.8 mmol/L at 10.42% (5.69 to 15.76) vs those without GDM at 2.99% (1.51 to 5.83) mean difference 7.43% (2.67 to 11.54), p<0.001. However, there was no significant difference in birth weight in those with GDM versus those without (mean difference –161.1 g (–531.4 to 209.2), p=0.379).

Maternal and neonatal outcomes were also recorded (table 3). There was one miscarriage at 17 weeks' gestation in the RYGB group but none in the SG group. There were no differences between the RYGB and SG groups in relation to the number of women having spontaneous labor (RYGB=5, SG=5), medical induction of labor (RYGB=6, SG=4) and no labor (RYGB=2, SG=5). In a subgroup analysis of women with spontaneous labor independent of surgery type (n=10), there was no significant correlation between indices of GV (CV, SD, MAGE, CONGA) and gestational age at delivery. Indications for medical induction of labor included reduced fetal movements (SG=1, RYGB=2), GDM on glucose-lowering therapy (SG=1, RYGB=2), type 2 diabetes in pregnancy (SG=1), vaginal birth after cesarean section (SG=1), fetal compromise (RYGB=1) and maternal hypoglycemia (RYGB=1).

Four babies (two emergency, two elective) were delivered by cesarean section in the RYGB group and six (three emergency, three elective) in the SG group. One

Table 2 Glycemic parameters in pregnancy (OGTT, HBGM, CGM)

	RYGB	SG	Mean difference (95% CI)	P value
OGTT				
Number of patients	4	4	N/A	N/A
0 min glucose (mmol/L)	4.05 (0.17)	4.20 (0.22)	−0.15 (−0.49 to 0.19)	0.320
120 min glucose (mmol/L)	4.33 (1.96)	4.67 (0.51)	−0.33 (−3.58 to 2.92)	0.790
HBGM				
Number of patients	12	8	N/A	N/A
HBGM performed in trimesters 2 and 3, respectively	5, 7	4, 4	N/A	N/A
Fasting (mmol/L)	4.75 (0.39)	5.09 (0.42)	−0.34 (−0.72 to 0.05)	0.082
1 hour after breakfast (mmol/L)	7.71 (1.79)	6.28 (1.28)	1.42 (−0.35 to 03.20)	0.108
1 hour after lunch (mmol/L)	7.62 (1.61)	6.46 (1.08)	1.2 (−0.30 to 2.64)	0.112
1 hour after dinner (mmol/L)	7.10 (1.05)	6.46 (1.20)	−0.63 (−0.50 to 1.72)	0.238
CGM				
Number of patients	13	14	N/A	N/A
CGM in trimesters 1, 2 or 3	0, 9, 4	0, 7, 7	N/A	N/A
Mean interstitial glucose (mmol/L)	5.66 (0.70)	5.50 (0.56)	0.16 (−0.24 to 0.66)	0.52
SD (mmol/L)	1.57 (0.47)	1.18 (0.30)	0.38 (0.07 to 0.70)	0.018
Coefficient of variation (%)	27.30 (6.08)	21.21 (3.74)	6.08 (2.10 to 10.05)	0.004
Mean amplitude of glycemic excursion	4.22 (1.49)	2.93 (0.83)	1.29 (0.34 to 2.23)	0.009
Continuous overall net glycemic action per 60 min	2.35 (0.72)	1.64 (0.36)	0.72 (0.27 to 1.16)	0.003
%TIR 3.9–7.8 mmol/L (70–140 mg/dL)	81.77 (10.38)	89.63 (5.45)	−7.86 (−14.64 to 1.08)	0.026
%TIR <3.9 mmol/L (70 mg/dL)	4.34 (1.26, 5.71)	2.40 (0.82, 3.89)	N/A	0.466
%TIR <3.0 mmol/L (54 mg/dL)	0.32 (0.05, 1.08)	0.17 (0.00, 0.35)	N/A	0.279
%TIR >7.8 mmol/L (140 mg/dL)	8.64 (4.14,19.32)	3.60 (1.98, 11.78)	N/A	0.09

For parameters in a Gaussian distribution, the means (SD) are displayed and two-tailed t-test used for statistical comparison of means: mean difference (95% CI) is shown. For non-Gaussian parameters, the medians (IQR) are shown and Mann-Whitney U test is used for statistical comparison.
CGM, continuous glucose monitoring; HBGM, home blood glucose monitoring; N/A, not available; OGTT, oral glucose tolerance test; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; %TIR, %time in range.

baby delivered by emergency cesarean section in the RYGB group was SGA. For this case, labor had been induced on the grounds of fetal compromise, an attempt was made at delivery using forceps, followed by operative delivery. The second baby delivered by emergency cesarean section in the RYGB group was due to failure of induction to progress to labor. Indications for delivery by emergency cesarean section in the SG group were reduced fetal movements (n=2) and breech presentation. No babies were admitted to the neonatal intensive care unit and there was no neonatal hypoglycemia recorded in either group.

The mean birth weight was lower for the RYGB group at 3037 g vs 3116 g for the SG group. The mean gestational age at delivery for the RYGB group (266 days) was significantly shorter than for the SG group (273 days, mean difference 7 days (95% CI 4 to 12), p=0.023; figure 1C). The birth weight correlated significantly with the gestational age at delivery (Pearson's correlation coefficient: 0.517, p=0.017; figure 1D). Using the UK GROW centile calculator[14] to adjust for gestational age at delivery, as well as maternal ethnic origin, height and weight, and sex of the baby, there was no significant difference in birthweight centile between the two groups, that is, the differences in birth weight were accounted for by differences in gestational age at delivery.

There was one LGA baby (in association with GDM) in the SG group. There were 17 babies that were appropriate for gestational age (AGA: RYGB=10/13, SG=7/14). There were 3/13 SGA babies after RYGB and 6/14 after SG. A subgroup analysis showed no differences in mean interstitial glucose between the SGA (n=9) and AGA (n=17) babies (5.4 vs 5.6 mmol/L, respectively, p=0.35).

DISCUSSION

To our knowledge, this is the first study to comprehensively profile glycemic patterns in pregnant women with

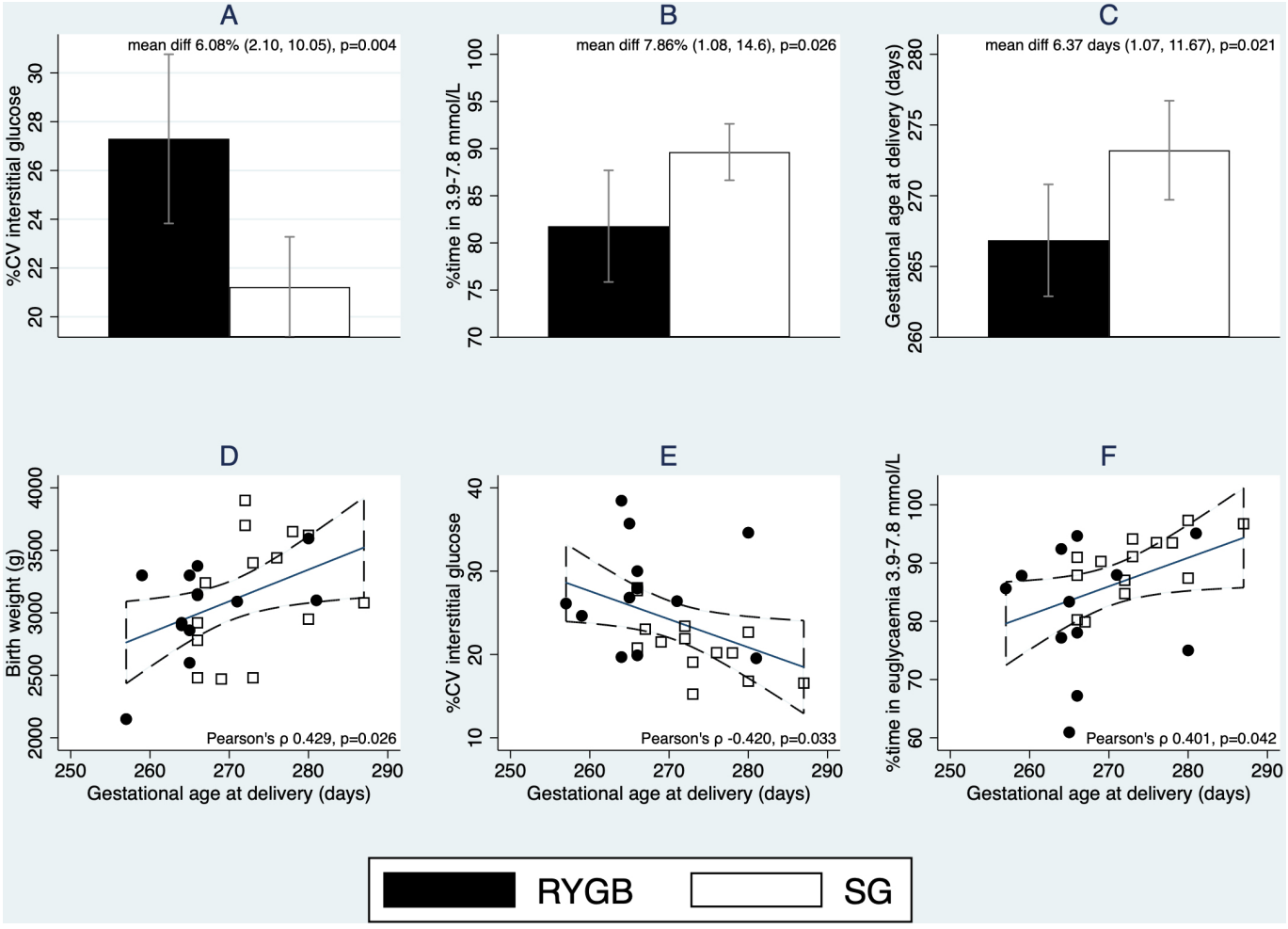

Figure 1 Relationship of surgical type (Roux-en-Y gastric bypass (RYGB); sleeve gastrectomy (SG)) to outcome measures. (A) Bar chart showing glucose variability (GV), expressed as %coefficient of variation (CV) of interstitial glucose, is higher with RYGB than SG; (B) bar chart showing percentage time spent in euglycemia (3.9–7.8 mmol/L, 70–140 mg/dL) is lower with RYGB than SG; (C) bar chart showing that gestational age at delivery is shorter with RYGB than with SG. For (A–C), means plotted for RYGB (filled bar) and SG (unfilled bar) and 95% CI indicated by error bars. Mean difference, 95% CI for difference, p value for unpaired two-tailed Student's t-test is displayed on the top right-hand corner of the graph. (D) Scatter plot showing positive correlation of birth weight (y-axis) with gestational age at delivery (x-axis); (E) scatter plot showing negative correlation between %CV of interstitial glucose (y-axis) with gestational age at delivery (x-axis); (F) scatter plot showing negative correlation between percentage time spent in euglycemia (y-axis) with gestational age at delivery (x-axis). For (D–F), RYGB=filled circles, SG=unfilled squares. Line represents best-fit linear regression line and dashed lines the 95% CI of the regression line. Pearson's correlation coefficient and p value indicated in the lower right-hand corner of the graph.

RYGB and SG using CGM and HBGM. Our findings showed that pregnant women who have undergone RYGB displayed increased GV (as evidenced by increased SD, CV, MAGE and CONGA) compared with those who have undergone SG. In addition, RYGB women spent a significantly smaller %TIR 3.9–7.8 mmol/L compared to pregnant women who had undergone SG, with numerically higher %TIR >7.8 mmol/L. No differences in %TIR in hypoglycemic ranges were noted between the two types of surgery.

Although RYGB has hitherto been regarded as the gold-standard procedure for obesity and type 2 diabetes, SG is becoming increasingly more popular due to its comparative simplicity and similar clinical results to RYGB in terms of weight loss and diabetes remission, as seen here.

There is a general paucity of data regarding GV in pregnant women with bariatric surgery. Stentebjerg *et al*[11] prospectively investigated 23 pregnant women with RYGB and 23 BMI-matched and parity-matched pregnant women without RYGB using a Dexcom G6 CGM system for 10 days; the characteristics of their women with RYGB are similar to our RYGB cohort in terms of mean age, presurgery and prepregnancy BMI and percentage total weight loss. Pregnant women with RYGB in both studies had similar mean interstitial glucose levels (5.7 vs 5.4-5.6 mmol/L) and displayed the greatest GV with comparable results for CV (27.5% vs 26.0%–27.0%) and SD (1.6 vs 1.4–1.5 mmol/L) measured in trimesters 2 and 3. In terms of GV metrics, both cohorts demonstrated the greatest time in hyperglycemia (>7.8 mmol/L)

Table 3 Maternal and neonatal outcomes as of October 2022

	RYGB	SG	Mean difference (95% CI)	P value
Maternal outcomes				
Delivered	13/14	14/14	N/A	1.000
Miscarriage	1/14	0/14	N/A	
Premature delivery (<37 weeks)	0/14	1/14	N/A	
Spontaneous labor	5/14	5/14	N/A	1.000
Induction of labor	6/14	4/14	N/A	0.385
No labor	2/14	5/14	N/A	0.385
Delivery mode				
Vaginal	9/14	8/14	N/A	1.000
Elective cesarean section	2/14	3/14	N/A	1.000
Emergency cesarean section	2/14	3/14	N/A	1.000
Maternal complications	2/14	0/14	N/A	0.482
Postpartum hemorrhage	1/14	0/14	N/A	
Shoulder dystocia	1/14	0/14	N/A	
Maternal infection	1/14	0/14	N/A	
Neonatal outcomes				
Number of offspring	13	14	N/A	
Gestational age at delivery (days)	266 (7)	273 (6)	−6 (−12 to 1)	0.021
Birth weight (g)	3036 (369)	3150 (487)	−113 (−455 to 228)	0.666
Birthweight centile	32.4 (26.9)	31.40 (29.6)	1.0 (−21.4 to 23.5)	0.925
SGA	3/13	6/14	N/A	0.659
AGA	10/13	7/14	N/A	0.236
LGA	0/13	1/14	N/A	
Neonatal complications				
Hypoglycemia	0/13	0/14	N/A	
Admission to NICU	0/13	0/14	N/A	

Birthweight centile calculated using GROW centile calculator.[14] SGA is defined as <10th percentile. LGA is defined as >90th percentile. For Gaussian distributed parameters, the means (SD) are displayed and two-tailed t-test used for statistical comparison of means. For non-Gaussian parameters, the medians (IQR) are shown and Mann-Whitney U test used for statistical comparison. Categorical characteristics analyzed using Fisher's exact test (not shown for outcomes where there are ≤1 total events recorded).
AGA, appropriate for gestational age; GROW, Gestation Related Optimal Weight; LGA, large for gestational age; N/A, not available; NICU, neonatal intensive care unit; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; SGA, small for gestational age.

and least time in euglycemia, but our cohort spent less %TIR >7.8 mmol/L (7.51% vs 9.4%–9.5%) and %TIR <3.0 mmol/L (0.36 vs 1.0%–1.1%). One possible reason for this difference is that all pregnant women in the present study were offered specialist nutritional advice by bariatric physicians and dietitians, aiming to reduce GV.

Bonis *et al*[16] used short-term (3–7 days) CGM to study 35 pregnant women with RYGB. This study showed increased GV (based on a mean CV of ~31%) and a mean %TIR >7.8 mmol of 6.6% and <2.7 mmol/L (50 mg/dL) of 4.9%. Leutner *et al*[17] also studied 17 pregnant women post-RYGB with CGM for up to 7 days and found the %TIR <3.0 mmol/L varied between 0.2% and 4.1% and %TIR >7.8 mmol/L between 7.5% and 15% (depending on the time of day). This is indicative of higher GV in comparison with their control groups of pregnant women with and without obesity, although no validated metrics of GV were reported in that study. Gohier *et al*,[18] from the same center as Bonis *et al*[16] reported on a larger set of 122 pregnant women who had RYGB and who underwent CGM for 3–7 days (mean 3.9 days). The CV of interstitial glucose was 28% on average. The women in this study had a mean %TIR in the euglycemic range of 3.3–7.8 mmol/L (60–140 mg/dL) at 86.9%. The median %TIR >7.8 mmol/L was 5.4% and %TIR <3.3 mmol/L (60 mg/dL) was 3.1%. Our patients undergoing RYGB did show respective median %TIR >7.8 mmol/L of 7.51%, <3.9 mmol/L of 5.01% and <3.0 mmol/L of 0.36%, that is, our patients undergoing RYGB had a lower %TIR in low-range hypoglycemia of 2.7–3.3 mmol/L (50–60 mg/dL). Of note, the studies by Bonis *et al*, Leutner *et al* and Gohier *et al* used obsolete Medtronic CGMS Gold or

iPro 2 systems which were not validated for use in pregnancy.[16–18] Like Stentebjerg *et al*,[11] we used Dexcom G6 CGM systems which are currently used and validated in pregnancy.[12]

In our study, we demonstrate that RYGB is associated with higher GV and lower %TIR 3.9–7.8 mmol/L relative to SG in pregnant women, which may be detrimental to feto-placental health. Women who have had RYGB deliver earlier in comparison with a control group of BMI-matched women without surgery.[8] Gohier *et al*,[18] in their dataset of pregnant women after RYGB, found that there were statistically significant associations between premature delivery (<37 weeks or 259 days gestation) and higher hypoglycemic %TIR <3.3 mmol/L as well as insufficient weight gain during pregnancy (<5 kg), although the latter was the only significant predictor in an multivariate analysis. Gohier *et al*[18] also reported that a higher %TIR <3.3 mmol/L was associated with SGA (<10th centile) but the reference growth curves used for this study did not adjust for gestational age at delivery. Stentebjerg *et al*[11] reported that women with RYGB who gave birth to SGA neonates (n=6) had lower mean interstitial glucose levels compared with those who did not give birth to SGA neonates (n=17) but this was statistically significant only in the second trimester for a short period of time between 12:00 and 16:00 hours. In the present study, there was no difference in mean interstitial glucose levels between SGA (n=9) and AGA (n=17) babies delivered by women with RYGB and SG.

In the present study, the gestational age at delivery was shorter in women with RYGB compared with women with SG; however, over 60% of women in our study had induction of labor or delivery by cesarean section with the remaining women entering labor spontaneously. Of the 10 women that delivered spontaneously, gestational age at delivery was not associated with GV metrics. Buschur *et al*[19] have reported that in pregnant women with type 1 diabetes, increased MAGE was associated with an earlier mean gestational age at delivery (36.6 weeks) however this may be at least partly explained by their high rates of pre-eclampsia (28.6%). Unlike Gohier *et al*,[18] we did not find an association between our measures of hypoglycemic %TIR <3.0 and <3.9 mmol/L with gestational age at delivery but note that in comparison with their dataset, our pregnant women spent little time in low-range hypoglycemia <3.0 mmol/L. Previous studies have compared so-called 'malabsorptive' procedures such as RYGB to 'restrictive' procedures such as laparoscopic adjustable gastric banding and SG and have found some evidence that RYGB is associated with lower birth weights,[20] but the comparator cohort mostly had laparoscopic adjustable gastric banding, gestational age at delivery was not controlled for, nor were the possible mechanisms for the differences in outcome interrogated.

In the present study, GDM was defined on a pragmatic basis using HBGM observations, the standard diagnostic OGTT being deprecated in this context due to the common side effect of dumping syndrome and hypoglycemia which occurs when the glucose load rapidly transits and is absorbed by the small bowel, leading to a rapid spike in blood glucose, subsequent insulin secretion and an 'overswing' of blood glucose from the hyperglycemic to the hypoglycemic range.[21] We highlight the fact that this definition was associated with higher mean interstitial glucose and GV, as well as a higher %TIR >7.8 mmol/L in our dataset, but the diagnosis of GDM was not influential on birth weight. It is not presently clear whether CGM might be used as an alternative method for diagnosing GDM, nor are there agreed target CGM metrics for treatment of GDM at present.[22]

Currently, the impact of GV on fetal growth and perinatal outcomes in pregnant women with bariatric surgery remains of unknown clinical significance. The prepregnancy weight loss after bariatric surgery is however associated with a reduction in obesity-related pregnancy outcomes when compared with pregnant women with obesity but without bariatric surgery.[3 4] There are also bariatric surgery-specific complications that can present in pregnancy, especially in the third trimester due to the gravid uterus such as internal small bowel hernia in RYGB[23] and severe gastroesophageal reflux disease with SG.[24]

A limitation of our study is a lack of control groups. A control group of pregnant women without bariatric surgery matched for presurgery BMI would allow the investigation of bariatric surgery on obesity-related pregnancy outcomes whereas a control group matched for prepregnancy BMI would allow the investigation of bariatric surgery on perinatal outcomes. Preconception data on glycemia in our participants would have allowed us to describe the impact that pregnancy has on GV in women with bariatric surgery. We are currently undertaking a prospective study collecting CGM data in pregnant controls that are matched according to presurgery and prepregnancy BMI, as well as capturing preconception CGM.

As an observational study of a small cohort of patients, our results should be regarded as hypothesis-generating. Data on nutritional status were not collected routinely, although we note that there do not appear to be major differences in nutritional status between RYGB and SG during pregnancy in studies.[25] It would also be of interest to characterise the longitudinal trajectory of maternal weight gain and fetal growth during pregnancy. We also acknowledge that we derived the CGM data from recordings up to 10 days; optimally 14 days of data or more would be used based on studies of CGM datasets from type 1 diabetics,[26] but we note that the studies of Bonis *et al*, Leutner *et al* and Gohier *et al* used even shorter recordings.[16–18]

CONCLUSION

We hypothesise that the increased GV, reduced time in euglycemia and increased time in hyperglycemia observed in pregnant women with RYGB compared with

SG may be associated with adverse perinatal outcomes. We propose that this hypothesis be tested in prospective studies to determine whether SG is truly associated with better pregnancy outcomes than RYGB, whether SG might be the preferred bariatric procedure in women of reproductive age and lastly whether interventions to reduce GV (eg, dietary changes) might be used to improve pregnancy outcomes.

Acknowledgements This work was supported by the UK National Institute for Health Research (NIHR) Imperial Biomedical Research Centre. TM-MT, KA and SA had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Contributors TM-MT led the project. KA and SA collected the data. BK, KA, SA, NO, RA-J and TM-MT analyzed the data. KA, SA, BK and TM-MT wrote the manuscript. BJ, CY, RA-J, TM-MT, KA, SA, AD, CT, SP and ARA were all involved in clinical care of the patients. All authors have reviewed and approved the current version of the manuscript. TM-MT is the guarantor of this work and, as such, 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.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval After consultation with Imperial College London and Imperial College Healthcare NHS Trust, as we are reporting on routinely collected clinical audit data, this study was not considered to be research under the UK Health and Social Care Research framework and did not require ethical approval.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

ORCID iDs
Bernard Khoo http://orcid.org/0000-0002-4223-9736
Tricia M-M Tan http://orcid.org/0000-0001-5873-3432

REFERENCES

1 Poston L, Caleyachetty R, Cnattingius S, *et al*. Preconceptional and maternal obesity: epidemiology and health consequences. *Lancet Diabetes Endocrinol* 2016;4:1025–36.
2 Schauer PR, Bhatt DL, Kirwan JP, *et al*. Bariatric surgery versus intensive medical therapy for diabetes - 5-year outcomes. *N Engl J Med* 2017;376:641–51.
3 Kwong W, Tomlinson G, Feig DS. Maternal and neonatal outcomes after Bariatric surgery; a systematic review and meta-analysis: do the benefits outweigh the risks. *Am J Obstet Gynecol* 2018;218:573–80.
4 Johansson K, Cnattingius S, Näslund I, *et al*. Outcomes of pregnancy after Bariatric surgery. *N Engl J Med* 2015;372:814–24.
5 Adams TD, Hammoud AO, Davidson LE, *et al*. Maternal and neonatal outcomes for pregnancies before and after gastric bypass surgery. *Int J Obes (Lond)* 2015;39:686–94.
6 Akhter Z, Rankin J, Ceulemans D, *et al*. Pregnancy after Bariatric surgery and adverse perinatal outcomes: A systematic review and meta-analysis. *PLoS Med* 2019;16:e1002866.
7 Maric T, Kanu C, Johnson MR, *et al*. Maternal, neonatal insulin resistance and neonatal Anthropometrics in pregnancies following Bariatric surgery. *Metabolism* 2019;97:25–31.
8 Maric T, Kanu C, Muller DC, *et al*. Fetal growth and Fetoplacental circulation in pregnancies following Bariatric surgery: a prospective study. *BJOG* 2020;127:839–46.
9 Ilesanmi I, Tharakan G, Alexiadou K, *et al*. Roux-en-Y gastric bypass increases Glycemic variability and time in Hypoglycemia in patients with obesity and Prediabetes or type 2 diabetes: A prospective cohort study. *Diabetes Care* 2021;44:614–7.
10 Lee D, Dreyfuss JM, Sheehan A, *et al*. Glycemic patterns are distinct in post-Bariatric Hypoglycemia after gastric bypass (PBH-RYGB). *J Clin Endocrinol Metab* 2021;106:2291–303.
11 Stentebjerg LL, Madsen LR, Støving RK, *et al*. Roux-en-Y gastric bypass increases Glycemic excursions during pregnancy and postpartum: A prospective cohort study. *Diabetes Care* 2023;46:502–10.
12 Castorino K, Polsky S, O'Malley G, *et al*. Performance of the Dexcom G6 continuous glucose monitoring system in pregnant women with diabetes. *Diabetes Technol Ther* 2020;22:943–7.
13 Moscardó V, Giménez M, Oliver N, *et al*. Updated software for automated assessment of glucose variability and quality of Glycemic control in diabetes. *Diabetes Technol Ther* 2020;22:701–8.
14 Customised Centile Calculator. Version 8.0.6.1 (UK). gestation network. 2020. Available: https://www.gestation.net/
15 Robson SC, Martin WL, Morris RK. *Guidelines Committee of the Royal College of Obstetricians and Gynaecologists. Small-for-Gestational-Age Fetus, Investigation and Management (Green-top Guideline no.31*). Royal College of Obstetricians and Gynaecologists, Available: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg31/
16 Bonis C, Lorenzini F, Bertrand M, *et al*. Glucose profiles in pregnant women after a gastric bypass: findings from continuous glucose monitoring. *Obes Surg* 2016;26:2150–5.
17 Leutner M, Klimek P, Göbl C, *et al*. Glucagon-like peptide 1 (GLP-1) drives postprandial Hyperinsulinemic Hypoglycemia in pregnant women with a history of Roux-en-Y gastric bypass operation. *Metabolism* 2019;91:S0026-0495(18)30224-5:10–7.:.
18 Gohier H, Guyard-Boileau B, Tuyeras G, *et al*. Glucose abnormalities and inappropriate weight gain predict negative pregnancy outcomes after gastric bypass surgery. *Obes Surg* 2021;31:3123–9.
19 Buschur EO, Campbell K, Pyle L, *et al*. Exploratory analysis of Glycemic control and variability over gestation among pregnant women with type 1 diabetes. *Diabetes Technol Ther* 2021;23:768–72.
20 Chevrot A, Kayem G, Coupaye M, *et al*. Impact of Bariatric surgery on fetal growth restriction: experience of a perinatal and Bariatric surgery center. *Am J Obstet Gynecol* 2016;214:S0002-9378(15)02346-7.
21 Göbl CS, Bozkurt L, Tura A, *et al*. Assessment of glucose regulation in pregnancy after gastric bypass surgery. *Diabetologia* 2017;60:2504–13.
22 Battelino T, Danne T, Bergenstal RM, *et al*. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International consensus on time in range. *Diabetes Care* 2019;42:1593–603.
23 Vannevel V, Jans G, Bialecka M, *et al*. Internal Herniation in pregnancy after gastric bypass: A systematic review. *Obstet Gynecol* 2016;127:1013–20.
24 Yeung KTD, Penney N, Ashrafian L, *et al*. Does sleeve Gastrectomy expose the distal esophagus to severe reflux?: A systematic review and meta-analysis. *Ann Surg* 2020;271:257–65.
25 Mead NC, Sakkatos P, Sakellaropoulos GC, *et al*. Pregnancy outcomes and nutritional indices after 3 types of Bariatric surgery performed at a single institution. *Surg Obes Relat Dis* 2014;10:1166–73.
26 Herrero P, Alalitei A, Reddy M, *et al*. Robust determination of the optimal continuous glucose monitoring length of intervention to evaluate long-term Glycemic control. *Diabetes Technol Ther* 2021;23:314–9.