King's Research Portal

DOI:

[10.1089/dia.2018.0102](https://doi.org/10.1089/dia.2018.0102)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Maitland, R., Patel, N., Barr, S., Sherry, C., Marriage, B., Seed, P., Fernandez, L. G., Pedrosa, J. M. L., Murphy, H., Rueda, R., & Poston, L. (2018). A Slow-Digesting, Low-Glycemic Load Nutritional Beverage Improves Glucose Tolerance in Obese Pregnant Women Without Gestational Diabetes. *Diabetes Technology and Therapeutics*, 20(10), 672-680. <https://doi.org/10.1089/dia.2018.0102>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

1 A Slow-Digesting, Low-Glycaemic Load (SD-LGL) Nutritional Beverage
2 improves glucose tolerance in obese pregnant women without Gestational
3 Diabetes

4

5 Rahat Maitland MBChB¹, Nashita Patel MBBS¹, Suzanne Barr PhD¹, Christina
6 Sherry PhD, RD, MBA², Barbara Marriage PhD, RD², Paul Seed MSc¹,
7 Llenalia Garcia Fernandez PhD³, Jose M Lopez Pedrosa PhD⁴, Helen Murphy
8 MD⁵, Ricardo Rueda MD, PhD⁴, Lucilla Poston PhD¹

9

10 ¹ Department of Women and Children's Health, King's College London, 10th
11 Floor North Wing, St. Thomas' Hospital, London SE1 7EH, UK

12 ² Abbott Nutrition, 3300 Stelzer Road, Columbus, OH 43219, USA

13 ³ SEPLIN Statistical Solutions, Granada, Spain

14 ⁴ Abbott Nutrition, Strategic R&D, 68 Camino de Purchil, Granada 18004,
15 Spain

16 ⁵ University of Cambridge Metabolic Research Laboratories, Level 4, Box 289,
17 Addenbrooke's Hospital, Cambridge, CB2 0QQ, UK

18

19 Corresponding author: Dr Rahat Maitland, The Queen Elizabeth University
20 Hospital Glasgow, Scotland. (+44-7974940221) rahatmaitland@nhs.net

21

22 Funding was provided by Abbott Nutrition, Research and Development,
23 Granada, Spain.

24

25 Keywords: diabetes, pregnancy, obesity, glycaemic index

(ABSTRACT) word count: 248

Background: Obesity is a risk factor for gestational diabetes. Low glycaemic index diets attenuate hyperglycaemia. We designed a study to determine whether a slow-digesting low-glycaemic load (SD-LGI) beverage improves glucose tolerance in obese pregnant women without gestational diabetes (GDM).

Methods: This was a 3-arm comparison study comparing the effects of a SD-LGL nutritional beverage (glycaemic load [GL] 730), an isocaloric control beverage (GL 1124) and habitual diet on glycaemia in obese pregnant women. Sixteen women (mean BMI 37kg/m²) were recruited at 24-28 weeks' to receive either the SD-LGL or eucaloric control beverage. This was consumed with breakfast and as a mid-afternoon snack over 2 days with a controlled diet. Following a 2-day washout period of habitual diet, women completed 2 days on the alternative beverage with controlled diet. A 10h fast preceded each intervention phase. 24h glucose was measured using continuous glucose monitoring.

Results: Consumption of the lower glycaemic load beverage was associated with improved measures of glycaemia, compared to the control beverage and habitual diet at different time periods. Glucose estimates for control v SD-LGI at 24h (0.23mmol/l [0.16 to 0.31], $p<0.001$), daytime (0.26mmol/l [0.18 to 0.34], $p<0.001$) and night time (0.05mmol/l [-0.01 to 0.11] ($p=0.09$)). Post-

prandial glucose (PPG) was lower after breakfast but not after dinner,
compared to the control beverage (0.09mmol/l [0.01 to 0.18], p=0.03).

Conclusion: A slow digesting low glycaemic nutritional beverage may facilitate
improved glucose control in obese pregnant women. To address potential
benefit for clinical outcomes, a randomised controlled trial is warranted.

75 Introduction

76

77 Obese women have a 2-4 fold increased risk of developing gestational
78 diabetes (GDM) ¹ and maternal body mass index (BMI) is recognized as the
79 strongest potentially modifiable predictor of GDM ². Aberrant glucose
80 homeostasis is evident even amongst obese pregnant women who do not
81 meet the most rigorous of criteria for GDM diagnosis; in these, continuous
82 glucose monitoring (CGM) has revealed a delayed and greater post-prandial
83 peak glucose concentration (at 1h and 2h) ^{3, 4}. Fasting and post-prandial
84 glucose concentrations are also positively associated with greater fetal fat
85 mass in infants of obese women without GDM ⁵.

86

87 Rising rates of obesity combined with lower glucose thresholds for diagnosis
88 of GDM as recommended by the International Association of Diabetes
89 Pregnancy Study Groups (IADPSG), World Health Organisation (WHO) and
90 American Diabetes Association (ADA) has led to a tripling of incident cases ⁶,
91 ⁷ necessitating a review of traditional therapeutic approaches to the
92 prevention and management of GDM.

93

94 Throughout pregnancy, obese women have greater concentrations of plasma
95 insulin, triglycerides (TGs) and free fatty acids (FFAs) compared to lean
96 controls, contributing to the multifactorial common pathway of insulin
97 resistance ⁵. Thus dietary strategies designed to reduce these biomarkers and
98 postprandial hyperglycaemia from an early stage in obese pregnant women

provide a novel and logical approach to improve glucose control and avoid adverse pregnancy outcomes.

Data from two systematic reviews are inconclusive to support universal recommendation of low glycaemic index (LGI) diets to prevent or treat GDM but have yielded important information regarding the safety of the approach⁸.⁹. Overall, pregnancy outcomes in LGI dietary RCTs have been unchanged but reported maternal benefits include reductions in gestational weight gain¹⁰, adiposity¹¹, plasma glucose concentration¹⁰ and progression to insulin therapy¹².

In this study, we undertook a proof of principle, 3-arm randomised comparison study in obese pregnant women without GDM to evaluate the effects of a slow-digesting low glycaemic load (SD-LGL) beverage on measures of glycaemic control using continuous glucose monitoring (CGM) and selected biomarkers implicated in the pathogenesis of insulin resistance. Comparison was made to a control beverage composed of rapidly digesting carbohydrate CHO and habitual diet.

RESEARCH DESIGN AND METHODS

Subjects and recruitment

Obese pregnant women ($\text{BMI} \geq 30 \text{ Kg/m}^2$) with a singleton pregnancy and no history of GDM attending antenatal clinics at Guy's and St. Thomas' NHS Foundation Trust, London, UK, were recruited at 24⁺⁰-28⁺⁶ weeks' gestation,

prior to routine 75g oral glucose tolerance test (OGTT) at 28 weeks'. Exclusions included any dietary intolerance, eating disorder and medical conditions known to independently influence weight, body composition or biochemistry. To exclude undiagnosed type 2 diabetes or impaired fasting glycaemia (IFG) subjects were excluded if fasting plasma glucose was ≥ 6.1 mmol/l at first visit. Ethical approval was granted by the Riverside Research Ethics Committee, London, UK (Integrated Research Applications System [IRAS]: 12/LO/0307). An online database was designed and managed by Medscinet® (www.medscinet.net).

A preliminary study was performed to examine the glycaemic effect (determined by incremental area under the curve [iAUC]) and assess the palatability of 2 SD-LGL beverages (71.6% of total CHO) compared to a eucaloric control composed of rapid digesting CHO (100% of total CHO) in 4 categories of women (n=10 per group): lean non-pregnant (BMI ≥ 18.5 - ≤ 24.9 kg/m²), obese non-pregnant (BMI ≥ 30 kg/m²), lean pregnant (pre-pregnancy BMI ≥ 18.5 - ≤ 24.9 kg/m²) and obese pregnant (pre-pregnancy BMI ≥ 30 kg/m²). The beverage selected for this study achieved the lowest glucose iAUC and greatest palatability scores across all groups of women (see Appendix).

Pre-study visit and randomisation

Subjects were naïve to CGM technology thus a pre-study visit including a trial wearing the sensor (Abbott FreeStyle® Navigator, Alameda, CA, USA) was undertaken. Computerised randomisation, using the SQL Server

Randomisation function integrated in the online study database was adopted and concealed until the study day.

Study Protocol

This was a 3-arm randomised comparison design. Study visits were held in a clinical research facility (CRF) equipped with a metabolic kitchen, a research dietitian and physician. The study was performed over 6 consecutive days divided into three 48h periods with CRF visits on days 1 and 5:

- Days 1- 2 test/control beverage
- Days 3-4 habitual diet
- Days 5-6 test/control beverage

Preparation instructions for test days included example menus for a 30-50g CHO meal with overnight fast from 2200h.

All meals and snacks including the nutritional beverages (packaged in standard drink cartons) for days 1-2 and 5-6 were provided. Women were advised to consume their normal diet during the washout period with no restriction to physical activity levels.

Empty food packets and drink cartons were returned and a food and physical activity diary completed. This was reviewed with the dietitian at each CRF visit.

Day 1-2. Following CGM calibration and fasting venous blood sampling, the prescribed breakfast and test/control beverage were consumed, and venous sampling then carried out every 15 minutes for 3.5h. The importance of adherence to the controlled diet until midnight on day 2 was reiterated.

Day 3-4. The habitual diet was adopted until 2200h on day 4, after which participants fasted in preparation for day 5.

Day 5-6. The prescribed breakfast and the beverage (cross over: control if previously test, test if previously control) were consumed with venous sampling as above at the CRF. The controlled diet together with the test/control beverage was consumed until midnight on day 6.

Subjects were excluded from data analysis if non-adherence to the controlled diet was identified from CGM downloads (n=3).

Dietary Protocol

Macronutrient composition and caloric value were equivalent for the test and control beverage (percentage total energy (%E) CHO 60.7%, fat 20.8%, protein 18.5%; total energy and 303Kcal/8oz carton/24-h) (Table 1), in line with dietary recommendations from the American Diabetes and Heart Associations for prevention of diabetes and reduction of cardiovascular risk in non-pregnant subjects ^{13, 14}. The concentration of CHO sub-groups, known to affect absorption differed significantly, with the test product composed of more slow-digesting, low-GL carbohydrates (SG-LGL) (72% v 0%), less rapid digesting CHO (8.4% v 100%), resistant starch (16.3%) and indigestible fiber

(3.7%). The glycaemic load (GL) of the test and control beverages was 730 and 1124 respectively.

Beverages were provided in 8oz (237ml) cartons; 4oz consumed with breakfast and 4oz as an afternoon snack (1500h). Addition of the nutritional beverage to the controlled diet did not exceed recommended daily energy requirements for the gestational age range of participants (24h total calorie content 2014kcal inclusive of beverage) ¹⁵.

A standardised diet with a low residue and medium dietary GI reflecting the “average UK diet” ¹⁶ was provided for the two 48 hour controlled periods (days 1-2 and day 5-6). On days 1 and 5, breakfast and lunch were provided in the CRF with remaining food and study beverages measured out by research staff. Women were advised to eat at similar times on each day.

Menu choices developed by the research dietician using standard food tables and WISP® (Tinuviel) dietary software are supplied in the appendix.

Continuous Glucose Monitoring

The CGM sensor was inserted on day 1 (0800h) and replaced on day 5 (0800h). Mandatory calibrations (1, 2, 10, 24 and 72h) were performed using the inbuilt capillary glucometer and interstitial glucose measured every 10 minutes for the duration of the study. For analysis of post-prandial glucose (PPG) glucose response, subjects were required to enter all meal times into the receiver, excluding the washout period when habitual data was recorded. CGM data was downloaded using the CoPilot® Health Management System

(Abbott Diabetes Care, Alameda, CA USA) and checked by 2 diabetes physicians.

Plasma analyses

Plasma insulin and C-peptide were measured at 15 time points (0-3.5h) and analysed using manual ELISA kits (Mercodia, Uppsala, Sweden). Plasma triglyceride and non-esterified fatty acid (NEFA) concentrations were measured in plasma samples (0, 60, 120, 180, 210 min) using a clinically validated automated platform (Clinical Analyser ILab 650, Instrumentation Laboratories, Warrington, UK) using IL Triglyceride and Randox (FA115) kits.

All standards, controls and samples were assayed in duplicate and quality control (QC) was performed. The inter-assay coefficient of variation for all assays was <5%. Analyses were performed on previously unfrozen EDTA and samples stored -80°C. Technical staff were blinded to the identity of the samples.

Analysis and Statistical power

Linear mixed model regression method including trigonometric terms up to order $k=3$ was employed in the CGM data analysis to take into account the high intra-day variability and non-linear structure of CGM data. A linear mixed model (LMM) assuming a normally distributed error term was fitted to the data. Further addition of a random effect within the model to take into account study period (hospital v home) and randomisation were assessed using the likelihood ratio test. CGM data was analysed in clinically relevant time periods

for each 48h test phase as follows: 24h (0630h-0630h), daytime (0630h to 2350h), night-time (0000h to 0620h [one night only]), fasting blood glucose (0600h to 0650h [one day only]) and post-prandial (1h, 2h and 3h after the meal marker).

Logarithmic transformations were performed for insulin and C-peptide only, following standard distributional checks.

All analyses were carried out at a 5% significance level using SPSS version 19 & Stata, version 11.2 (StataCorp, College Station, Texas) and 95% confidence intervals were obtained for the estimates.

The study protocol recommended that 22 subjects be randomised, conservatively assuming a correlation of no more than 0.3 between repeated measurements of glucose. However, as initial analyses demonstrate a correlation of 0.7, a decision was made to recruit 16 subjects, giving a power of 96% to detect a difference in glucose between test and control beverage with 95% confidence ($p < 0.05$).

Results

Analysis was performed with data from 16 subjects randomised to receive the test or control beverage at the first visit [(BMI 37kg/m^2 , range 31-46, SD 4.7) (age 31 years, range 21-39, SD 4.8)]. Twelve were of Black ethnicity, 2 White European and 2 of unclassified ethnicity. Three subjects were excluded from

analysis: 2 for non-adherence to the controlled diet (n=2) and 1 who was unable to wear the sensor.

When considering the overall performance of the supplement throughout the study period (2 days and one night), the glucose curve derived from the LMM was lower than both habitual diet and control periods as shown in (Figure 1A). Glucose estimates for habitual diet and control days were significantly greater ($p<0.001$ for both) (Table 2).

Estimates of 24h mean glucose concentration for study day 1, 2 and 5 were lower for the test beverage compared to the control. On the final day, day 6, no difference was found (day 1: 4.56 v 4.68 mmol/l, $p<0.001$, day 2: 4.75mmol v 4.84mmol/l, $p=0.001$, day 5: 4.47 v 4.73, $p<0.001$ and day 6: 4.72 v 4.78mmol/l, $p=0.51$).

Predicted mean blood glucose concentrations were consistently lower for the test beverage throughout the day (Figure 1B), with the estimates for the habitual diet (0.25mmol/l [0.19 to 0.31], $p<0.001$) and control beverage (0.04mmol/l [0.18 to 0.34], $p<0.001$) being significantly greater than the test beverage (Table 2). No difference was observed between glucose estimates measured in the CRF versus home study days (-0.02mmol/l [-0.08 to 0.04], $p=0.54$).

Review of CGM downloads in association with the food diaries indicated lack of adherence to the protocol, with uncontrolled food consumption after midnight on the 2nd night of each 48h test period. This data was excluded

and analysis of nocturnal data included the 1st night only (day 1 and day 5). No difference was observed overnight between the test and control beverages overnight ($p=0.09$) but glucose concentrations were significantly greater during the habitual period compared to the test beverage overnight ($p<0.001$) (Table 2) (Figure 1C).

Analysis of fasting glucose (0600-0650h) demonstrated a reduction in glucose estimates until 0620h (before breakfast) for the test, control and habitual phases, with a progressive rise thereafter (Figure 1D). Fasting CGM concentrations recorded over this 50 minute period were significantly lower for the test beverage compared to the habitual period ($p<0.001$) but no different to the control ($p=0.22$) (Table 2).

Postprandial data (up to 3h) excluded the habitual washout period since women were not requested to record meal markers. Glucose concentration was significantly lower following consumption of the test beverage at breakfast only ($p=0.03$) (Table 2). Postprandial glucose (PPG) concentrations were generally lower on hospital days in the CRF compared to the second day at home for all meals in both arms (breakfast $p<0.001$, lunch $p=0.80$ and dinner $p=0.43$) (Table 2).

Linear regression analysis found no detectable effect of the test beverage compared to control for concentrations of plasma insulin, C-peptide and TGs (Table 3). A marginally higher concentration of plasma NEFA was observed

following the test supplement (difference in arithmetic means 0.05 [95%CI 0.00 to 0.10], $p=0.049$).

Conclusion

We tested two dietary beverages of identical macronutrient composition as part of a calorie-controlled diet in obese pregnant women considered to be at high risk of GDM. The supplements differed only by CHO composition (Table 1).

Using CGM, we demonstrated that consumption of a SD-LGL beverage, specifically developed for use in pregnancy, significantly reduced glucose concentration over a 24 hour period in addition to day and night periods when examined separately, compared to habitual living ($p<0.001$ for all).

Numerous factors including meal composition, pre-meal glucose concentration, physical activity, insulin secretion, gastric emptying and hepatic glucose metabolism determine post-prandial glucose (PPG). Hence, the reduction in PPG observed following traditional CHO restriction, may be explicable only in part by the lower total CHO load. Since the rate of gastric emptying is delayed by fat, the observed increase in percentage energy from fat to approximately 45% following traditional dietary strategies recommended by the American College of Obstetricians and Gynaecologists ¹⁷, will undoubtedly influence PPG concentration ¹⁸. We demonstrated improvements in PPG concentrations without a reduction in CHO load or increase in

percentage of energy from fat, excluding this mechanism as a confounder and thus supporting an independent role of CHO modification. Importantly in this obese population, the addition of the nutritional supplement to the controlled diet did not exceed recommended daily energy requirements for the gestational age period studied ¹⁵.

Consensus methodology for the calculation of GI, requires the measurement blood glucose 120 minutes after food consumption.¹⁹ Recent use of CGM in GI studies has revealed potential limitations of this long-standing approach. Following the consumption of mixed meals, Chlup et al. confirmed changes in glycemia exceeding 120 minutes with a prolonged return to baseline glucose at 210 minutes and beyond ²⁰. In this study we evaluated the effect of the 2 beverages on PPG to 180minutes. With the advantage of this minimally invasive approach, inclusion of CGM in future dietary studies may yield important novel information on the impact of different food groups on PPG.

Post-prandial glucose was significantly lower following the test beverage compared to the control and habitual diet at breakfast. Clinically, this presents the most challenging period to achieve adequate glycaemic control for women with diabetes in pregnancy due to the physiological secretion of insulin counter-regulatory hormones coupled with high concentrations of processed CHO contained in breakfast foods ²¹. This often results in the use of higher insulin doses, associated with greater risks of hypoglycaemia or the practice of excluding CHO from the meal entirely, a potentially challenging option typically resulting in greater fat consumption. Increased concentrations of

maternal TGs and NEFA, correlated with dietary intake, are strong predictors of excess fetal fat accretion ^{5, 22}, therefore therapeutic interventions utilising resistant or LGL CHO to attenuate postprandial hyperglycaemia, which also limit dietary fat, may have a role not only in the management of diabetes in pregnancy but also in obese non-diabetic pregnant women who have a 2-5 fold increased risk of delivering a large for gestational age (LGA) infant ²³.

Obese pregnant women are at increased risk of lipotoxicity and its metabolic sequelae. This occurs as a consequence of increased hydrolysis of dietary TGs and expanded adipose depots generating FFAs, contributing to insulin resistance ^{24, 25}. Low GI and GL diets may therefore be more effective in obese compared to lean women as they are likely to be more insulin resistant ^{26, 27}.

Most adequately powered studies comparing responses to dietary advice, designed to increase the consumption of low GI foods in women with ²⁸⁻³¹ and without GDM ^{10, 29}, have been carried out in women with BMI 24-27kg/m² with equivocal results. Moses et al., reported improved obstetric outcomes (birth weight, ponderal index and incidence of LGA) comparing LGI to a “high-fibre moderate-to-high GI (HGI)” diet in healthy women without GDM (n=62, mean BMI 25.5kg/m², mean GI 51 v 58 for LGI and HGI respectively) but did not replicate these findings in a larger RCT (mean BMI 24.5kg/m²) ^{29, 32}. In both studies a relatively small albeit significant reduction in GI was achieved in the intervention arm compared to the control with a greater GI point difference reported in the former ^{29, 32}.

396

397 Of those dietary advice intervention studies undertaken in women of a higher
398 BMI, the ROLO study (Low glycaemic index diet in pregnancy to prevent
399 macrosomia RCT) (mean BMI 26.8kg/m²) reported a reduction in GL and 1h
400 glucose following a 50g glucose challenge test ¹⁰. In the heterogeneous
401 overweight and obese population of the LIMIT trial (n=2212) (The effects of
402 antenatal dietary and lifestyle advice for women who are overweight or obese
403 on maternal diet and physical activity), a lifestyle intervention designed to
404 reduce LGA infants in overweight and obese women, general dietary advice
405 led to a small reduction in the GL but no change in the primary outcome or
406 GDM, although the number of infants with macrosomia was reduced ³³. A
407 reduction in GDM, the primary outcome, was also not met in the exclusively
408 obese UPBEAT study (mean BMI 36.3kg/m²) but, GI and GL were reduced in
409 the intervention group as was consumption of CHO, total fat, saturated fat and
410 total energy. Daily intake of fibre and protein was increased, and gestational
411 weight gain and maternal adiposity were significantly less at the time of the
412 oral glucose tolerance test and over the entire pregnancy ¹¹.

413 Considering the potential therapeutic benefits of low GI and GL diets in
414 pregnancy, improving glycaemic control using a low GI beverage in high-risk
415 obese women to attenuate glucose intolerance warrants further exploration.
416 Current UK National Institute for Health and Care Excellence (NICE)
417 recommendations include general dietary advice for all obese pregnant
418 women at the 1st clinical consultation ([nice.org.uk/guidance/ph27](https://www.nice.org.uk/guidance/ph27)) and the
419 most recent economic evaluation of non-pharmacological approaches to
420 weight management outside of pregnancy reported lower costs associated

with dietary compared to physical interventions ³⁴. This advice is generalised and at present not adopted across the UK; pragmatically, therefore, we would recommend habitual diet and activity as the control in future studies of LGI diets in pregnancy as opposed to specific dietary recommendations for 'healthy eating'.

Using a similar design as in the present investigation, Hernandez et al. conducted a study to determine whether reducing the fat content of a complex carbohydrate traditional 'GDM' diet in obese pregnant women with GDM would improve glucose control, using CGM in controlled and free living environments ³⁵. No difference in mean glucose between the lower and control higher fat diets were observed but the glucose AUC was significantly greater in those on the lower fat diet for daytime and 24-hour periods. The clinical relevance of the increase in glucose exposure reported, together with the modest reductions observed in our study on pregnancy outcomes, requires assessment. We found no difference following the SD-LGL beverage in the concentration of relevant biomarkers (plasma insulin, C-peptide and TGs) but a small increase in NEFA. It would be of interest in future studies to determine whether glucose-independent pathways contributing to insulin resistance, as assessed by a targeted metabolome are influenced by this dietary intervention ³⁶.

Limitations of the study include the small sample size and short duration. This was a proof of concept study and we would recommend future studies of the SD-LGI beverage extend until delivery and include evaluation of neonatal outcomes. It is unclear whether the small reduction in glucose estimates

observed, would correspond to a clinically significant reduction in HbA1c or adverse neonatal outcomes including macrosomia but analysis of alternative measures of glycaemia utilising CGM is warranted.

We recruited a high number of women from Black ethnic minorities who are recognised to have a significantly greater risk of GDM and type 2 diabetes compared to White European women of equivalent BMI ³⁷. It is possible that reductions in glucose observed may not be as pronounced in a Caucasian population. Conversely, the results indicate that those at greatest risk of GDM may stand to gain the greatest benefit, as suggested by Louie et al. ³⁰. OGTT was not performed at recruitment therefore in the absence of biochemical evidence of glucose intolerance, “high risk for GDM” was defined by BMI on entry in keeping with similar LGI studies in pregnancy.

Participation in dietary studies may introduce a degree of bias or confounding as a consequence of the “observer” or “Hawthorn effect,” when individual behaviours are modified in response to an awareness of being observed. In this study however, the greatest differences in glycaemia were observed between the test beverage with controlled diet and habitual diet for all time periods examined suggesting that diet was not specifically modified on the habitual days.

The CONCEPTT study demonstrated improvements in maternal glycaemia and neonatal outcomes in women with T1DM who used CGM ³⁸. It is possible that CGM plus dietary advice in this high risk obese population may improve

maternal glycaemia or reduce progression to GDM but to the best of our knowledge there are no studies specifically examining this.

Glucose concentrations were generally lower on the 1st day compared to the 2nd of each 48h test period for both beverages. Visits on these days were conducted in the CRF, a highly controlled environment, with limited ability to exercise. This could indicate issues with non-adherence to the prescribed diet on “home” days or could reflect a chance finding although several methods to improve compliance were adopted: participants being requested to return all empty food packets/drink cartons and complete a food and exercise diary.

In conclusion, we have demonstrated in obese women at high risk of GDM that consumption of a SD-LGL beverage when compared to habitual diet reduces glucose concentration over a 24-hour period, and that this includes differences during both day and night time. In contrast to previously reported low GI diets in obese pregnant women, the beverage comprised both a low GI CHO and slow digesting CHO, which could have additive clinical benefit. A reduction in post-prandial glucose at breakfast is also of particular clinical relevance. Evaluation of this dietary approach in a RCT to reduce incidence of GDM in high-risk obese women is justified.

Acknowledgements

The authors acknowledge the support of all participants and Erini Platsa (research midwife) for her assistance with all aspects of the study. We thank Laima Juodvirsiene (MedSciNet) for technical support with the database, staff of the CRF at Guy's and St.Thomas' NHS Foundation Trust (GSTFT) London

and the laboratory staff at King's College London for their excellent technical input: Dr Carolyn Gill, Dr Jo Gill and Anne-Catherine Perz. We also acknowledge the support of the NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London. LP was supported by Tommy's Charity and the European Union's 7th Framework Programme (FP7/2007–2013), project EarlyNutrition under grant agreement no. 289346.

Duality of Interest

B.M, C.S., J.M.L.P and R.R. are employed by Abbott Nutrition.

Author Contributions

R.M. researched data, wrote the manuscript and edited the final version. N.P., C.S., B.M, J.M.L.P., H.M., R.R. and L.P. edited and contributed to the manuscript. R.M. and S.B. designed the study protocol. P.S. and L.G.F. provided statistical analysis of the data and review of the manuscript.

References

1. Athukorala C, Rumbold A, Willson K, Crowther C. The risk of adverse pregnancy outcomes in women who are overweight or obese. *BMC Pregnancy and Childbirth*. 2010;10(1):56.
2. Zhang C, Tobias DK, Chavarro JE, et al. Adherence to healthy lifestyle and risk of gestational diabetes mellitus: prospective cohort study. *BMJ*. 2014;349:g5450.
3. Yogev Y, Ben-Haroush A, Chen R, Rosenn B, Hod M, Langer O. Diurnal glycemic profile in obese and normal weight nondiabetic pregnant women. *Am J Obstet Gynecol*. Sep 2004;191(3):949-953.

- 522 4. IADPSG. International Association of Diabetes and Pregnancy Study
523 Groups Recommendations on the Diagnosis and Classification of
524 Hyperglycemia in Pregnancy. *Diabetes Care*. March 1, 2010
525 2010;33(3):676-682.
- 526 5. Harmon KA, Gerard L, Jensen DR, et al. Continuous Glucose Profiles in
527 Obese and Normal-Weight Pregnant Women on a Controlled Diet.
528 *Diabetes Care*. October 1, 2011 2011;34(10):2198-2204.
- 529 6. Duran A, Saenz S, Torrejon MJ, et al. Introduction of IADPSG criteria for
530 the screening and diagnosis of gestational diabetes mellitus results in
531 improved pregnancy outcomes at a lower cost in a large cohort of
532 pregnant women: the St. Carlos Gestational Diabetes Study. *Diabetes Care*.
533 Sep 2014;37(9):2442-2450.
- 534 7. Mayo K, Melamed N, Vandenberghe H, Berger H. The impact of adoption
535 of the international association of diabetes in pregnancy study group
536 criteria for the screening and diagnosis of gestational diabetes. *Am J*
537 *Obstet Gynecol*. 2015;212(2):224.e221-224e.229.
- 538 8. Han S, Crowther CA, Middleton P, Heatley E. Different types of dietary
539 advice for women with gestational diabetes mellitus. *Cochrane Database*
540 *Syst Rev*. 2013;3:CD009275.
- 541 9. Tieu J, Crowther CA, Middleton P. Dietary advice in pregnancy for
542 preventing gestational diabetes mellitus. *Cochrane Database Syst Rev*.
543 2008(2):CD006674.
- 544 10. Walsh JM, McGowan CA, Mahony R, Foley ME, McAuliffe FM. Low
545 glycaemic index diet in pregnancy to prevent macrosomia (ROLO study):
546 randomised control trial. *BMJ*. 2012;345:e5605.
- 547 11. Poston L, Bell R, Croker H, et al. Effect of a behavioural intervention in
548 obese pregnant women (the UPBEAT study): a multicentre, randomised
549 controlled trial. *Lancet Diabetes Endocrinol*. Oct 2015;3(10):767-777.
- 550 12. Moses RG, Barker M, Winter M, Petocz P, Brand-Miller JC. Can a low-
551 glycemic index diet reduce the need for insulin in gestational diabetes
552 mellitus? A randomized trial. *Diabetes Care*. Jun 2009;32(6):996-1000.
- 553 13. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle
554 management to reduce cardiovascular risk: a report of the American
555 College of Cardiology/American Heart Association Task Force on Practice
556 Guidelines. *J Am Coll Cardiol*. Jul 1 2014;63(25 Pt B):2960-2984.
- 557 14. Sheard NF, Clark NG, Brand-Miller JC, et al. Dietary carbohydrate (amount
558 and type) in the prevention and management of diabetes: a statement by
559 the american diabetes association. *Diabetes Care*. Sep 2004;27(9):2266-
560 2271.
- 561 15. Rasmussen K, Yaktine A. Institute of Medicine (IOM). Weight Gain During
562 Pregnancy: Reexamining the Guidelines. . *The National Academies Press*.
563 2009.
- 564 2009.
- 565 16. Aston LM, Gambell JM, Lee DM, Bryant SP, Jebb SA. Determination of the
566 glycaemic index of various staple carbohydrate-rich foods in the UK diet.
567 *Eur J Clin Nutr*. Feb 2008;62(2):279-285.
- 568 17. Practice Bulletin No. 137: Gestational Diabetes Mellitus. *Obstet Gynecol*.
569 2013;122(2, PART 1):406-416
570 410.1097/1001.AOG.0000433006.0000409219.f0000433001.

- 571 18. Marathe CS, Rayner CK, Jones KL, Horowitz M. Relationships Between
572 Gastric Emptying, Postprandial Glycemia, and Incretin Hormones.
573 *Diabetes Care*. May 1, 2013 2013;36(5):1396-1405.
- 574 19. Wolever TM, Jenkins DJ. The use of the glycemic index in predicting the
575 blood glucose response to mixed meals. *The American Journal of Clinical*
576 *Nutrition*. January 1, 1986 1986;43(1):167-172.
- 577 20. Chlup R, Peterson K, Zapletalova J, Kudlova P, Seckar P. Extended prandial
578 glycemic profiles of foods as assessed using continuous glucose
579 monitoring enhance the power of the 120-minute glycemic index. *J*
580 *Diabetes Sci Technol*. May 1 2010;4(3):615-624.
- 581 21. Porcellati F, Lucidi P, Bolli GB, Fanelli CG. Thirty Years of Research on the
582 Dawn Phenomenon: Lessons to Optimize Blood Glucose Control in
583 Diabetes. *Diabetes Care*. December 1, 2013 2013;36(12):3860-3862.
- 584 22. Schaefer-Graf UM, Graf K, Kulbacka I, et al. Maternal lipids as strong
585 determinants of fetal environment and growth in pregnancies with
586 gestational diabetes mellitus. *Diabetes Care*. Sep 2008;31(9):1858-1863.
- 587 23. Bowers K, Laughon SK, Kiely M, Brite J, Chen Z, Zhang C. Gestational
588 diabetes, pre-pregnancy obesity and pregnancy weight gain in relation to
589 excess fetal growth: variations by race/ethnicity. *Diabetologia*. Jun
590 2013;56(6):1263-1271.
- 591 24. Catalano PM, Hauguel-De Mouzon S. Is it time to revisit the Pedersen
592 hypothesis in the face of the obesity epidemic? *Am J Obstet Gynecol*.
593 2011;204(6):479-487.
- 594 25. Jarvie E, Hauguel-de-Mouzon S, Nelson SM, Sattar N, Catalano PM,
595 Freeman DJ. Lipotoxicity in obese pregnancy and its potential role in
596 adverse pregnancy outcome and obesity in the offspring. *Clin Sci (Lond)*.
597 Aug 2010;119(3):123-129.
- 598 26. Catalano PM. Management of obesity in pregnancy. *Obstet Gynecol*. Feb
599 2007;109(2 Pt 1):419-433.
- 600 27. Langer O, Yogev Y, Xenakis EM, Brustman L. Overweight and obese in
601 gestational diabetes: the impact on pregnancy outcome. *Am J Obstet*
602 *Gynecol*. Jun 2005;192(6):1768-1776.
- 603 28. Louie JC, Markovic TP, Ross GP, Foote D, Brand-Miller JC. Effect of a low
604 glycaemic index diet in gestational diabetes mellitus on post-natal
605 outcomes after 3 months of birth: a pilot follow-up study. *Matern Child*
606 *Nutr*. May 3 2013.
- 607 29. Moses RG, Casey SA, Quinn EG, et al. Pregnancy and Glycemic Index
608 Outcomes study: effects of low glycemic index compared with
609 conventional dietary advice on selected pregnancy outcomes. *The*
610 *American Journal of Clinical Nutrition*. March 1, 2014 2014.
- 611 30. Louie JCY, Markovic TP, Perera N, et al. A Randomized Controlled Trial
612 Investigating the Effects of a Low-Glycemic Index Diet on Pregnancy
613 Outcomes in Gestational Diabetes Mellitus. *Diabetes Care*. November 1,
614 2011 2011;34(11):2341-2346.
- 615 31. Moreno-Castilla C, Hernandez M, Bergua M, et al. Low-carbohydrate diet
616 for the treatment of gestational diabetes mellitus: a randomized
617 controlled trial. *Diabetes Care*. Aug 2013;36(8):2233-2238.

- 618 32. Moses RG, Luebcke M, Davis WS, et al. Effect of a low-glycemic-index diet
619 during pregnancy on obstetric outcomes. *Am J Clin Nutr.* Oct
620 2006;84(4):807-812.
- 621 33. Dodd JM, Turnbull D, McPhee AJ, et al. Antenatal lifestyle advice for
622 women who are overweight or obese: LIMIT randomised trial. *BMJ.*
623 2014;348:1285.
- 624 34. NICE. *National Institute for Health and Care Excellence. Obesity Prevention*
625 *[CG43]*. London 2006.
- 626 35. Hernandez TL, Van Pelt RE, Anderson MA, et al. A higher-complex
627 carbohydrate diet in gestational diabetes mellitus achieves glucose
628 targets and lowers postprandial lipids: a randomized crossover study.
629 *Diabetes Care.* May 2014;37(5):1254-1262.
- 630 36. White SL, Pasupathy D, Sattar N, et al. Metabolic profiling of gestational
631 diabetes in obese women during pregnancy. *Diabetologia.* Oct
632 2017;60(10):1903-1912.
- 633 37. Ferrara A. Increasing Prevalence of Gestational Diabetes Mellitus: A public
634 health perspective. *Diabetes Care.* July 1, 2007 2007;30(Supplement
635 2):S141-S146.
- 636 38. Feig DS, Donovan LE, Corcoy R, et al. Continuous glucose monitoring in
637 pregnant women with type 1 diabetes (CONCEPTT): a multicentre
638 international randomised controlled trial. *Lancet.* Nov 25
639 2017;390(10110):2347-2359.
- 640