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

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Keywords: diabetes, pregnancy, obesity, glycaemic index
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.
Introduction

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

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

Throughout pregnancy, obese women have greater concentrations of plasma insulin, triglycerides (TGs) and free fatty acids (FFAs) compared to lean controls, contributing to the multifactorial common pathway of insulin resistance. Thus dietary strategies designed to reduce these biomarkers and 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 approach. Overall, pregnancy outcomes in LGI dietary RCTs have been unchanged but reported maternal benefits include reductions in gestational weight gain, adiposity, plasma glucose concentration and progression to insulin therapy.

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 (BMI≥30Kg/m²) 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 ≥6.1mmol/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–≤24.9kg/m$^2$), obese non-pregnant (BMI ≥30kg/m$^2$), lean pregnant (pre-pregnancy BMI ≥18.5–≤24.9kg/m$^2$) and obese pregnant (pre-pregnancy BMI ≥30kg/m$^2$). 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 dietician 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 dietician 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. 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...
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)\(^\text{15}\).

A standardised diet with a low residue and medium dietary GI reflecting the “average UK diet”\(^\text{16}\) 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 unthawed 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/m², 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, will undoubtedly influence PPG concentration. 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.\textsuperscript{15}

Consensus methodology for the calculation of GI, requires the measurement
blood glucose 120 minutes after food consumption.\textsuperscript{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.\textsuperscript{20} In this study we evaluated the effect of the 2
beverages on PPG to 180 minutes. 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.\textsuperscript{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/m\(^2\) 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/m\(^2\), mean GI 51 v 58 for LGI and HGI respectively) but did not replicate these findings in a larger RCT (mean BMI 24.5kg/m\(^2\)) \(^29, 32\). 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 \(^29, 32\).
Of those dietary advice intervention studies undertaken in women of a higher BMI, the ROLO study (Low glycaemic index diet in pregnancy to prevent macrosomia RCT) (mean BMI 26.8kg/m²) reported a reduction in GL and 1h glucose following a 50g glucose challenge test\textsuperscript{10}. In the heterogeneous overweight and obese population of the LIMIT trial (n=2212) (The effects of antenatal dietary and lifestyle advice for women who are overweight or obese on maternal diet and physical activity), a lifestyle intervention designed to reduce LGA infants in overweight and obese women, general dietary advice led to a small reduction in the GL but no change in the primary outcome or GDM, although the number of infants with macrosomia was reduced\textsuperscript{33}. A reduction in GDM, the primary outcome, was also not met in the exclusively obese UPBEAT study (mean BMI 36.3kg/m²) but, GI and GL were reduced in the intervention group as was consumption of CHO, total fat, saturated fat and total energy. Daily intake of fibre and protein was increased, and gestational weight gain and maternal adiposity were significantly less at the time of the oral glucose tolerance test and over the entire pregnancy\textsuperscript{11}.

Considering the potential therapeutic benefits of low GI and GL diets in pregnancy, improving glycaemic control using a low GI beverage in high-risk obese women to attenuate glucose intolerance warrants further exploration. Current UK National Institute for Health and Care Excellence (NICE) recommendations include general dietary advice for all obese pregnant women at the 1\textsuperscript{st} clinical consultation (nice.org.uk/guidance/ph27) and the most recent economic evaluation of non-pharmacological approaches to weight management outside of pregnancy reported lower costs associated
with dietary compared to physical interventions. 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. 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.

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. 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. 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. 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.

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Duality of Interest


Author Contributions

R.M. researched data, wrote the manuscript and edited the final version. N.P.,
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.

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