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

4

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21

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24

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27

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

33

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

44

45 Results: Consumption of the lower glycaemic load beverage was associated  
46 with improved measures of glycaemia, compared to the control beverage and  
47 habitual diet at different time periods. Glucose estimates for control v SD-LGI  
48 at 24h (0.23mmol/l [0.16 to 0.31], p<0.001), daytime (0.26mmol/l [0.18 to  
49 0.34], p<0.001) and night time (0.05mmol/l [-0.01 to 0.11] (p=0.09). Post-

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

52

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

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75 Introduction

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77 Obese women have a 2-4 fold increased risk of developing gestational  
78 diabetes (GDM) <sup>1</sup> and maternal body mass index (BMI) is recognized as the  
79 strongest potentially modifiable predictor of GDM <sup>2</sup>. 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) <sup>3, 4</sup>. Fasting and post-prandial  
84 glucose concentrations are also positively associated with greater fetal fat  
85 mass in infants of obese women without GDM <sup>5</sup>.

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 <sup>6</sup>,  
91 <sup>7</sup> 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 <sup>5</sup>. Thus dietary strategies designed to reduce these biomarkers and  
98 postprandial hyperglycaemia from an early stage in obese pregnant women

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

101

102 Data from two systematic reviews are inconclusive to support universal  
103 recommendation of low glycaemic index (LGI) diets to prevent or treat GDM  
104 but have yielded important information regarding the safety of the approach <sup>8</sup>,  
105 <sup>9</sup>. Overall, pregnancy outcomes in LGI dietary RCTs have been unchanged  
106 but reported maternal benefits include reductions in gestational weight gain <sup>10</sup>,  
107 adiposity <sup>11</sup>, plasma glucose concentration <sup>10</sup> and progression to insulin  
108 therapy <sup>12</sup>.

109

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

117

## 118 RESEARCH DESIGN AND METHODS

119

### 120 Subjects and recruitment

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

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

133

134 A preliminary study was performed to examine the glycaemic effect  
135 (determined by incremental area under the curve [iAUC]) and assess the  
136 palatability of 2 SD-LGL beverages (71.6% of total CHO) compared to a  
137 eucaloric control composed of rapid digesting CHO (100% of total CHO) in 4  
138 categories of women (n=10 per group): lean non-pregnant (BMI  $\geq 18.5$ -  
139  $\leq 24.9$ kg/m<sup>2</sup>), obese non-pregnant (BMI  $\geq 30$ kg/m<sup>2</sup>), lean pregnant (pre-  
140 pregnancy BMI  $\geq 18.5$ - $\leq 24.9$ kg/m<sup>2</sup>) and obese pregnant (pre-pregnancy BMI  
141  $\geq 30$ kg/m<sup>2</sup>). The beverage selected for this study achieved the lowest glucose  
142 iAUC and greatest palatability scores across all groups of women (see  
143 Appendix).

144

145 Pre-study visit and randomisation

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

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

151

## 152 Study Protocol

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

- 157 • Days 1- 2 test/control beverage
- 158 • Days 3-4 habitual diet
- 159 • Days 5-6 test/control beverage

160

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

163

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

168

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

172



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

177

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

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

184

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

187

#### 188 Dietary Protocol

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

198 (3.7%). The glycaemic load (GL) of the test and control beverages was 730  
199 and 1124 respectively.

200

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

206

207 A standardised diet with a low residue and medium dietary GI reflecting the  
208 “average UK diet” <sup>16</sup> was provided for the two 48 hour controlled periods (days  
209 1-2 and day 5-6). On days 1 and 5, breakfast and lunch were provided in the  
210 CRF with remaining food and study beverages measured out by research  
211 staff. Women were advised to eat at similar times on each day.

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

214

#### 215 Continuous Glucose Monitoring

216 The CGM sensor was inserted on day 1 (0800h) and replaced on day 5  
217 (0800h). Mandatory calibrations (1, 2, 10, 24 and 72h) were performed using  
218 the inbuilt capillary glucometer and interstitial glucose measured every 10  
219 minutes for the duration of the study. For analysis of post-prandial glucose  
220 (PPG) glucose response, subjects were required to enter all meal times into  
221 the receiver, excluding the washout period when habitual data was recorded.  
222 CGM data was downloaded using the CoPilot® Health Management System

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

225

226 Plasma analyses

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

233

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

239

240 Analysis and Statistical power

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

248 for each 48h test phase as follows: 24h (0630h-0630h), daytime (0630h to  
249 2350h), night-time (0000h to 0620h [one night only]), fasting blood glucose  
250 (0600h to 0650h [one day only]) and post-prandial (1h, 2h and 3h after the  
251 meal marker).

252

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

255

256 All analyses were carried out at a 5% significance level using SPSS version  
257 19 & Stata, version 11.2 (StataCorp, College Station, Texas) and 95%  
258 confidence intervals were obtained for the estimates.

259

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

266

267 Results

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

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

274

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

280

281 Estimates of 24h mean glucose concentration for study day 1, 2 and 5 were  
282 lower for the test beverage compared to the control. On the final day, day 6,  
283 no difference was found (day 1: 4.56 v 4.68 mmol/l,  $p < 0.001$ , day 2: 4.75mmol  
284 v 4.84mmol/l,  $p = 0.001$ , day 5: 4.47 v 4.73,  $p < 0.001$  and day 6: 4.72 v  
285 4.78mmol/l,  $p = 0.51$ ).

286 Predicted mean blood glucose concentrations were consistently lower for the  
287 test beverage throughout the day (Figure 1B), with the estimates for the  
288 habitual diet (0.25mmol/l [0.19 to 0.31],  $p < 0.001$ ) and control beverage  
289 (0.04mmol/l [0.18 to 0.34],  $p < 0.001$ ) being significantly greater than the test  
290 beverage (Table 2). No difference was observed between glucose estimates  
291 measured in the CRF versus home study days (-0.02mmol/l [-0.08 to 0.04],  
292  $p = 0.54$ ).

293

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

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

302

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

309

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

317

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

321 following the test supplement (difference in arithmetic means 0.05 [95%CI  
322 0.00 to 0.10],  $p=0.049$ ).

323

324 Conclusion

325

326 We tested two dietary beverages of identical macronutrient composition as  
327 part of a calorie-controlled diet in obese pregnant women considered to be at  
328 high risk of GDM. The supplements differed only by CHO composition (Table  
329 1).

330

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

335

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

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

351

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

361

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



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

377

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

384

385 Most adequately powered studies comparing responses to dietary advice,  
386 designed to increase the consumption of low GI foods in women with <sup>28-31</sup> and  
387 without GDM <sup>10, 29</sup>, have been carried out in women with BMI 24-27kg/m<sup>2</sup> with  
388 equivocal results. Moses et al., reported improved obstetric outcomes (birth  
389 weight, ponderal index and incidence of LGA) comparing LGI to a “high-fibre  
390 moderate-to-high GI (HGI)” diet in healthy women without GDM (n=62, mean  
391 BMI 25.5kg/m<sup>2</sup>, mean GI 51 v 58 for LGI and HGI respectively) but did not  
392 replicate these findings in a larger RCT (mean BMI 24.5kg/m<sup>2</sup>) <sup>29, 32</sup>. In both  
393 studies a relatively small albeit significant reduction in GI was achieved in the  
394 intervention arm compared to the control with a greater GI point difference  
395 reported in the former <sup>29, 32</sup>.

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/m<sup>2</sup>) reported a reduction in GL and 1h  
400 glucose following a 50g glucose challenge test <sup>10</sup>. 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 <sup>33</sup>. A  
407 reduction in GDM, the primary outcome, was also not met in the exclusively  
408 obese UPBEAT study (mean BMI 36.3kg/m<sup>2</sup>) 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 <sup>11</sup>.

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 1<sup>st</sup> clinical consultation ([nice.org.uk/guidance/ph27](http://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

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

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

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

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

448

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

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

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

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

470 Glucose concentrations were generally lower on the 1<sup>st</sup> day compared to the  
471 2<sup>nd</sup> of each 48h test period for both beverages. Visits on these days were  
472 conducted in the CRF, a highly controlled environment, with limited ability to  
473 exercise. This could indicate issues with non-adherence to the prescribed  
474 diet on “home” days or could reflect a chance finding although several  
475 methods to improve compliance were adopted: participants being requested  
476 to return all empty food packets/drink cartons and complete a food and  
477 exercise diary.

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

487

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501

502

503 Duality of Interest

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

505

506 Author Contributions

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

508 C.S., B.M, J.M.L.P., H.M., R.R. and L.P. edited and contributed to the

509 manuscript. R.M. and S.B. designed the study protocol. P.S. and L.G.F.

510 provided statistical analysis of the data and review of the manuscript.

511

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