Impact of a Low Glycemic Index Diet in Pregnancy on Markers of Maternal and Fetal Metabolism and Inflammation

Reproductive Sciences
2014, Vol. 21(11) 1378-1381
© The Author(s) 2014
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1933719114525275
rs.sagepub.com

Jennifer M. Walsh, MB, PhD¹, Rhona M. Mahony, MD¹,
Marie Culliton, MSc¹, Michael E. Foley, MD¹,
and Fionnuala M. McAuliffe, MD¹

Abstract

This is a secondary analysis of 621 women in ROLO study, a randomized control trial of low glycemic index (GI) diet in pregnancy to prevent the recurrence of macrosomia, which aims to assess the effect of the diet on maternal and fetal insulin resistance, leptin, and markers of inflammation. In early pregnancy and at 28 weeks, serum was analyzed for insulin, leptin, tumor necrosis factor α (TNF- α), and interleukin 6 (IL-6). At delivery, cord blood concentrations of leptin, TNF- α , IL-6, and C-peptide were recorded. We found no difference between those who did or did not receive low GI advice with respect to the concentrations of any marker in early pregnancy, at 28 weeks or in cord blood. Women in the intervention arm of the study did have a lower overall rise in insulin concentrations from early pregnancy to 28 weeks gestation, $P = .04$. Of the women in the intervention arm, 20% were in the highest quartile for insulin change (28-week insulin – insulin at booking) compared to 29% of controls ($P = .02$). In conclusion, a low GI diet in pregnancy has little effect on leptin and markers of inflammation although an attenuated response to the typical increase in insulin resistance seen in pregnancy with advancing gestation was seen in those who received the low GI advice.

Keywords

pregnancy, diet, glycemic index, insulin resistance, leptin

Introduction

Intrauterine growth and development are subject to a host of maternal, environmental, and genetic factors. Rates of intrauterine growth, particularly if restrictive or excessive, can have profound and lasting implications for later adult health.^{1,2}

In particular, the large for gestational age fetus is predisposed to a variety of adverse obstetric and neonatal outcomes, and delivery of a large infant significantly increases the risk of birth complications for the mother.^{3,4} In the long term, infants who are at the highest end of the distribution for weight or body mass index (BMI) are more likely to be obese in childhood, adolescence, and early adulthood than other infants⁵ and are at risk of cardiovascular and metabolic complications later in life.^{6,7}

The primary maternal environmental factor that regulates fetoplacental growth is substrate delivery to the placental site, and glucose is the main energy substrate for intrauterine growth.⁸ The predominant dietary source of glucose comes from carbohydrates. Different carbohydrate foods produce different glycemic responses, and carbohydrates are classified according to their induced glycemic response as either high or low glycemic index (GI).⁹

We recently reported the results of the ROLO study, a randomized control trial of low GI diet in pregnancy to prevent the

recurrence of macrosomia, in a group of women who had previously given birth to infants weighing greater than 4000 g.¹⁰

The ROLO study established that a low GI diet in pregnancy had no effect on infants' birth weight in a group at risk of fetal macrosomia. It did, however, have a significant positive effect, with less gestational weight gain and less maternal glucose intolerance.

In order to further probe the effects of this intervention on maternal and fetal metabolism, we performed an analysis of maternal and fetal insulin resistance and leptin. Furthermore, due to increasing data linking pro- and anti-inflammatory mediators in the pathogenesis of obesity-related consequences, and, in particular, the development of insulin resistance and overt diabetes mellitus,^{11,12} we also compared concentrations of

¹ UCD Obstetrics & Gynaecology, School of Medicine and Medical Science, University College Dublin, National Maternity Hospital, Dublin, Ireland

Corresponding Author:

Fionnuala M. McAuliffe, UCD Obstetrics & Gynaecology, School of Medicine and Medical Science, University College Dublin, National Maternity Hospital, Dublin, Ireland.

Email: fionnuala.mcauliffe@ucd.ie

Table 1. A Comparison of Leptin, Insulin, HOMA, TNF- α , IL-6, and C-Peptide and the Changes in Insulin and HOMA Throughout Pregnancy Between Those Who Did and Those Who Did Not Receive Low Glycemic Index Dietary Advice.^a

		Intervention Group Median (Interquartile Range)	Control Group Median (Interquartile Range)	Asymptotic Sig (2-sided Test)
Leptin, pg/mL	First trimester	12499 (7265-22107)	13568 (7331-22045)	.76
	28 weeks	17006 (8630-25970)	15616 (8820-26307)	.97
	Cord	19986 (11793-40129)	19817 (12406-34158)	.78
HOMA	First trimester	2.2 (1.09-3.62)	2.08 (1.08-3.30)	.48
	28 weeks	2.82 (1.65-4.56)	2.63 (1.54-4.55)	.79
Cord blood C-peptide, pg/mL		206.6 (65.65-700.56)	206.4 (52.79-731.37)	.96
TNF- α , pg/mL	First trimester	4.82 (3.02-7.50)	4.60 (2.91-7.57)	.81
	28 weeks	5.36 (3.19-7.83)	4.65 (3.09-7.71)	.55
	Cord	5.62 (0.58-9.2)	5.08 (0.88-8.49)	.43
	First trimester	9.70 (4.17-21.1)	9.48 (4.38-26.26)	.96
IL-6, pg/mL	28 weeks	9.98 (5.38-20.8)	9.37 (4.21-22.34)	.78
	Cord	10.95 (3.55-29.0)	9.17 (3.06-23.91)	.53
Insulin change, pg/mL		1.79 (-2.64-4.56)	2.82 (-1.4-8.2)	.04

Abbreviations: HOMA, homeostatic model assessment; IL-6, interleukin 6; TNF- α , tumor necrosis factor α .

^a HOMA = (Fasting insulin μ U/mL $\times$ fasting glucose mmol/L)/22.5. Insulin change = Insulin at 28 weeks gestation minus — in early pregnancy. A 2-tailed *P* value of <.05 considered statistically significant.

tumor necrosis factor α (TNF- α) and interleukin 6 (IL-6) between the 2 groups.

Our hypothesis was that a low GI diet in pregnancy would result in less maternal insulin resistance, lower leptin concentrations, and lower levels of inflammatory markers in both mother and fetus.

Methods

This is a nested cohort study of 621 mother and infant pairs recruited to the ROLO study with institutional ethical approval and written informed maternal consent.¹³ Women were excluded if they had any underlying medical conditions, if they were less than 18 years of age, if they had previous gestational or preexisting type 1 or type 2 diabetes, or if they were unable to give full informed consent. For the purposes of this secondary analysis, those with incomplete blood results were also excluded (*n* = 138). At recruitment and at 28 weeks, all women had measurement of weight, height, and upper arm circumference, and fasting serum glucose, fasting serum was analyzed for glucose, insulin, leptin, TNF- α , and IL-6.

At delivery, infant birth weight, infant length, and head circumference were recorded, and a cord blood sample was taken for the measurement of concentrations of fetal glucose, leptin, C-peptide, TNF- α , and IL-6.

Multianalyte profiling was performed on the Luminex Magpix system (Luminex Corporation, Austin, Texas.). The Human Endocrine Panel determined plasma concentrations of leptin, insulin, and C-peptide. Maternal insulin resistance was calculated using the homeostatic model assessment (HOMA) index: HOMA score = (fasting insulin μ U/mL $\times$ fasting glucose mmol/L)/22.5. Fetal insulin resistance was assessed with cord blood C-peptide estimation.¹⁴

Data were assessed for normality using Shapiro-Wilk and P-P plot. None of the analytes were normally distributed. A

comparison of medians between the groups was accomplished using the Mann-Whitney *U* test. Further analysis was performed by calculating the interquartile range for each analyte overall and comparing the proportion of patients in the lowest and the highest quartiles between the intervention and the control arms of the study using chi-square test.

To assess adherence to the low GI diet, we gave patients in the intervention group a questionnaire at their 34-week antenatal visit. This was based on a 5-point Likert-type scale (1 = *I followed the recommended diet all of the time*; 5 = *I followed the recommended diet none of the time*).

As pregnancy is a state of physiologically increased insulin resistance, particularly in the third trimester, a final analysis was performed comparing the change in insulin from early pregnancy to 28 weeks between the 2 groups. Statistical significance was set at *P* < .05. Statistical analysis was performed using SPSS Windows's version 18.0 (SPSS, Chicago, Illinois).

Results

Patients were recruited at first antenatal consultation at 13.8 ± 2.4 weeks. There was no difference between the 2 groups in either fasting insulin or the HOMA index at 28 weeks gestation following the intervention (Table 1). Similarly, no difference was noted in cord blood C-peptide between those who did and those who did not receive low GI dietary advice in early pregnancy.

Women in the intervention arm of the study did have a lower overall rise in insulin concentrations from early pregnancy to 28 weeks gestation (Table 1). When the proportion of women within the highest versus the lowest quartile for the cohort was compared, 20% of women in the intervention arm were in the highest quartile for insulin change (28-week insulin — insulin at booking) compared to 29% of the controls (*P* = .02; Table 2).

Table 2. A Comparison of the Proportion of Women in the Lowest and in the Highest Quartiles for Each Test in Each Group.^a

			Lowest Quartile	Highest Quartile
Leptin	First trimester	Intervention	71/286	71/286
		Control	76/286	74/286
		P value	.7	.8
	28 weeks	Intervention	70/275	67/275
		Control	71/283	72/283
		P value	.9	.7
	Cord	Intervention	60/234	65/234
		Control	59/242	54/242
		P value	.7	.17
Insulin	First trimester	Intervention	67/275	77/275
		Control	78/296	62/296
		P value	.6	.0508
	28 weeks	Intervention	62/270	65/270
		Control	80/290	72/290
		P value	.24	.84
	Cord c-peptide	Intervention	55/235	59/235
		Control	66/250	62/250
		P value	.46	1.0
HOMA	First trimester	Intervention	48/266	78/266
		Control	56/285	69/285
		P value	.66	.17
	28 weeks	Intervention	27/259	63/259
		Control	36/277	74/277
		P value	.43	.55
TNF- α	First trimester	Intervention	74/285	68/285
		Control	76/302	77/302
		P value	.8	.7
	28 weeks	Intervention	69/274	67/274
		Control	74/294	73/294
		P value	1.0	.9
	Cord	Intervention	10/138	49/138
		Control	9/150	40/150
		P value	.8	.1
IL-6	First trimester	Intervention	54/205	49/205
		Control	52/215	54/215
		P value	.6	.8
	28 weeks	Intervention	44/197	46/197
		Control	62/225	58/225
		P value	.2	.5
	Cord	Intervention	23/98	26/98
		Control	28/111	26/111
		P value	.8	.6
Insulin change		Intervention	67/234	47/234
		Control	55/253	74/253
		P value	.09	.02^b
HOMA change		Intervention	66/246	56/246
		Control	61/259	71/259
		P value	.4	.2

Abbreviations: HOMA, homeostatic model assessment; IL-6, interleukin 6; TNF- α , tumor necrosis factor α .

^a HOMA = (Fasting insulin $\mu\text{U/mL} \times \text{fasting glucose mmol/L})/22.5$. Insulin change = Insulin at 28 weeks gestation – insulin in early pregnancy.

^b A 2-tailed P value of $< .05$ was considered statistically significant. Italics indicate P values only and bold values are significant.

There was no difference between the 2 groups in serum leptin concentrations in early pregnancy prior to intervention, at 28 weeks gestation, or in cord blood at delivery when compared using Mann-Whitney *U* test. Similarly, no difference existed between the 2 groups in terms of the proportion of women in the highest compared to the lowest quartile of leptin concentrations for the cohort using chi-square test (Tables 1 and 2).

There was no difference between those who did and those who did not receive low GI dietary advice with respect to the concentrations of either TNF- α or IL-6 in early pregnancy prior to intervention, at 28 weeks gestation, or in cord blood at delivery when compared using Mann-Whitney *U* test. Similarly, no difference existed between the 2 groups in terms of the proportion of women in the highest compared to the lowest quartile of TNF- α or IL-6 concentrations for the cohort using chi-square test (Tables 1 and 2). Almost 80% ($n = 294$) of the intervention arm reported following the low GI dietary advice either all or most of the time on the adherence questionnaire.

Discussion

In summary, we have found that a low GI diet in pregnancy has little effect on markers of maternal insulin resistance or inflammation in a cohort of euglycemic women at risk of macrosomia. We did note an attenuated response to the typical increase in insulin resistance, seen in pregnancies in Westernized countries, with advancing gestation in those who received the low glycemic dietary advice although the overall effect was limited.

The ROLO study did identify a lower rate of glucose intolerance in the intervention arm overall, with significantly less women on the low GI diet having either a fasting glucose concentration of greater than 5.1 mmol/L or a glucose challenge test of greater than 7.8 mmol/L following a 50 g glucose load (21% vs 28%, $P < .05$).¹³ The rate of gestational diabetes in the study cohort overall, however, was low, with just 7 in the intervention and 9 in the control arm according to Carpenter and Coustan criteria (or 12 vs 18 according to the American Diabetes Association criteria).^{15,16} This low rate may account for the lack of difference seen in the current analysis.

Data in the literature pertaining to leptin and markers of inflammation and pregnancy relate predominantly to obese and diabetic populations. Leptin is an adipokine that is secreted from adipose tissue and concentrations rise significantly with increasing percentage of body fat.¹⁷ Inflammatory markers are equally produced by adipose tissue and are known to regulate fat deposition and appetite.¹⁸ Although the ROLO trial did result in less gestational weight gain in women who received the low GI dietary advice, it was not a trial of obese and overweight women. The mean BMI of our study participants was $26.8 \pm 5.1 \text{ kg/m}^2$ in early pregnancy.

The strict inclusion criteria of the ROLO study, which excluded those with previous gestational or preexisting diabetes mellitus, those with any underlying medical conditions, and those with a previous poor obstetric outcome, are likely to have excluded women with underlying metabolic derangements which may predispose them to insulin resistance.

Equally, the trial was powered for the primary outcome, birth weight, and not for the secondary analysis of maternal and fetal metabolic factors, and the use of multiple comparisons may have resulted in a type 1 statistical error.

Our study group likely represents a heterogeneous population, comprising healthy women giving birth to genetically healthy large infants; women with subthreshold gestational diabetes who are giving birth to infants that are large due to a relative maternal hyperglycemia and perhaps a third cohort of women who are giving birth to infant that are large due to a pathological process other than maternal hyperglycemia /fetal hyperinsulinemia.

Moreover, it has been suggested that the proportion of infants weighing greater than 4000 g who are larger than expected due to excess glucose transfer across the placenta as detected by fetal cord hyperinsulinemia may be as low as 15% to 20%.¹⁹ A major difficulty therefore lies in the identification of pregnancies that are going to result in pathological growth secondary to maternal metabolic derangements and that may therefore benefit from any dietary or lifestyle intervention prenatally.

The pathogenesis underlying the fetal programming of later metabolic health and obesity is complex and multifactorial but is likely to relate to the metabolic milieu of the intrauterine environment.

Further studies are now needed to clarify whether pregnancy interventions, such as dietary and lifestyle modifications, can result in improvements in maternal and fetal insulin resistance and metabolism. It would appear from these results that such studies would be best suited to women specifically at risk of metabolic dysfunction, such as the overweight, obese, and diabetic populations.

Authors' Note

Ethical approval was granted by the National Maternity Hospital Ethics Committee (June 2007). All participants provided written informed consent. None of the funding sources had a role in the trial design or manuscript preparation.

Acknowledgments

The authors would like to thank the staff at National Maternity Hospital and the mothers who participated in the study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The Health Research Board of Ireland funded this trial, with additional financial support from the National Maternity Hospital Medical Fund. Trial registration Current Controlled Trials ISRCTN54392969.

References

1. Barker DJP, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. *Lancet*. 1993;341(8850):938-941.
2. Barker DJP, Osmond C, Simmonds SJ, Wield GA. The relation of small head circumference and thinness at birth to death from cardiovascular disease in adult life. *Br Med J*. 1993;306(6875):422-426.
3. Boulet SL, Alexander GR, Salihu HM, Pass M. Macrosomic births in the United States: determinants, outcomes, and proposed grades of risk. *Am J Obstet Gynecol*. 2003;188(5):1372-1378.
4. Gregory KD, Henry OA, Ramicone E, Chan LS, Platt LD. Maternal and infant complications in high and normal weight infants by method of delivery. *Obstet Gynecol*. 1998;92(4 pt 1):507-513.
5. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics*. 2005;115(3):e290-e296.
6. Hermann GM, Dallas LM, Haskell SE, Roghair RD. Neonatal macrosomia is an independent risk factor for adult metabolic syndrome. *Neonatology*. 2010;98(3):238-234.
7. Ornoy A. Prenatal origin of obesity and their complications: gestational diabetes, maternal overweight and the paradoxical effects of fetal growth restriction and macrosomia. *Reprod Toxicol*. 2011;32(2):205-212.
8. Clapp JF 3rd. Maternal carbohydrate intake and pregnancy outcome. *Proc Nutr Soc*. 2002;61(1):45-50.
9. Jenkins DJ, Wolever TM, Taylor RH, et al. Glycaemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr*. 1981;34(3):362-366.
10. Walsh JM, McGowan CA, Mahony R, Foley ME, McAuliffe FM. Low glycaemic index diet in pregnancy to prevent macrosomia (ROLO study): randomised control trial. *BMJ*. 2012;345:e5605.
11. Neeland IJ, Turer AT, Ayers CR, et al. Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. *JAMA*. 2012;308(11):1150-1159.
12. Ramsay JE, Ferrell WR, Crawford L, Wallace M, Greer IA, Sattar N. Maternal obesity is associated with dysregulation of metabolic, vascular, and inflammatory pathways. *J Clin Endocrinol Metab*. 2002;87(9):4231-4237.
13. Walsh J, Mahony R, Foley M, Mc Auliffe F. A randomised control trial of low glycaemic index carbohydrate diet versus no dietary intervention in the prevention of recurrence of macrosomia. *BMC Pregnancy Childbirth*. 2010;10:16.
14. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412-418.
15. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol*. 1982;144(7):768-773.
16. American Diabetes Association. Standards of medical care in diabetes—2011. *Diabetes Care*. 2011;34(suppl 1):S11-S61.
17. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive leptin concentrations in normal-weight and obese humans. *N Engl J Med*. 1996;334(5):292-295.
18. Kim C, Cheng YJ, Beckles GL. Inflammation among women with a history of gestational diabetes mellitus and diagnosed diabetes in the third national health and nutrition examination survey. *Diabetes Care*. 2008;31(7):1386-1388.
19. Stanley KP, Fraser RB, Milner M, Bruce C. Cord insulin and C-peptide—distribution in an unselected population. *Br J Obstet Gynaecol*. 1992;99(6):512-515.