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ORIGINAL ARTICLE

Synbiotic Food Consumption Reduces Levels of Triacylglycerols and VLDL, but not Cholesterol, LDL, or HDL in Plasma from Pregnant Women

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Abstract To our knowledge, no reports are available indicating the effects of synbiotic food consumption on blood lipid profiles and biomarkers of oxidative stress among pregnant women. This study was conducted to evaluate the effects of daily consumption of a synbiotic food on blood lipid profiles and biomarkers of oxidative stress in pregnant women. This randomized, double-blind, controlled clinical trial was performed among 52 primigravida pregnant women, aged 18 to 35-year-old at their third trimester. After a 2-week run-in period, subjects were randomly assigned to consume either a synbiotic ($n = 26$) or control food ($n = 26$) for 9 weeks. The synbiotic food consisted of a probiotic viable and heat-resistant *Lactobacillus sporogenes* (1×10^7 CFU) and 0.04 g inulin (HPX)/g as the prebiotic. Patients were asked to consume the synbiotic and control foods two times a day. Biochemical measurements including blood lipid profiles, plasma total antioxidant capacity (TAC) and total glutathione (GSH) were conducted before and after 9 weeks of intervention. Consumption of a synbiotic food for 9 weeks resulted in a significant reduction in serum TAG ($P = 0.04$), VLDL ($P = 0.04$) and a significant rise in plasma GSH levels ($P = 0.004$) compared to the control food. No significant effects of the synbiotic food consumption on serum TC, LDL, HDL and plasma TAC levels ($P > 0.05$) were observed. Trial registry code: http://www.irct.ir. IRCT201212105623N3.

Keywords Synbiotic · Lipid profiles · Oxidative stress · Pregnant women

Abbreviations

GSH	Total glutathione
HDL	High density lipoprotein
LDL	Low density lipoprotein
MUFA	Monounsaturated fatty acid(s)
PUFA(s)	Polyunsaturated fatty acid
SFA	Saturated fatty acid(s)
TAC	Total antioxidant capacity
TAG	Triacylglycerol(s)
TC	Total cholesterol
VLDL	Very low density lipoprotein

Introduction

Owing to enhanced weight that is general during the mid-pregnancy period [1] and physiological alterations in lipoprotein levels resulting from hormonal changes [2], pregnancy is associated with elevated levels in lipid profiles. Furthermore, the increased oxygen requirement, systemic release of placental factors including inflammatory markers [3] and reduced scavenging power of antioxidants during pregnancy [4], may result in increased susceptibility to oxidative stress. Maternal dyslipidemia and oxidative

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stress are associated with several complications including gestational diabetes mellitus (GDM) [5], pre-eclampsia [6] and intrauterine growth restriction (IUGR) [7].

Diet therapy especially dietary fat restriction, appropriate nutritional supplements, and lifestyle modifications including increased physical activity are the first-line treatments in the management of lipid profiles and oxidative stress during pregnancy [8]. Furthermore, use of lipid lowering agents [9] and drugs to reduce of oxidative stress [10] are suggested to decrease lipid profiles and biomarkers of oxidative stress in pregnant women. Recently, a few studies have assessed the effects of synbiotic-containing products on lipid profiles and biomarkers of oxidative stress among non-pregnant women [11, 12] and animal models [13, 14]. Synbiotics refer to nutritional supplements combining both probiotics and prebiotics in a synergistic form [15]. Our previous study among patients with type 2 diabetes showed a significant increase of plasma total glutathione (GSH) levels following consumption of a synbiotic food after 6 weeks in a cross-over designed trial [16]. Intake of a synbiotic supplement containing *Lactobacillus acidophilus*, fructooligosaccharide, inulin and mannitol for 8 weeks resulted in decreased TAG, TC and LDL levels as well as increased HDL concentrations in hypercholesterolaemic pigs [13].

Synbiotics influence the production of short chain fatty acid (SCFA), carbon disulfide and methyl acetate [17], and can result in improved lipid profiles. Synbiotics may affect oxidative stress by effects on caveolin-1 and endothelial NOS [14] as well as down-regulation of genes involved in oxidative stress and toll-like receptor pathways [18]. To our knowledge, no reports are available assessing the effects of synbiotic food consumption on blood lipid profiles and biomarkers of oxidative stress in pregnant women. The aim of the current study was, therefore, to investigate the effects of synbiotic food consumption on blood lipid profiles and biomarkers of oxidative stress among Iranian pregnant women.

Participants

This randomized double-blind placebo-controlled clinical trial was performed in Kashan, Iran, during June 2012 to November 2012. On the basis of the sample size formula suggested for randomized clinical trials, considering the type I error of 5 % ($\alpha = 0.05$) and type II error of 20 % ($\beta = 0.20$; power = 80 %) and plasma GSH concentrations as the key variable [16], we reached the sample size of 26 persons for each group. Pregnant women, primigravida, aged 18 to 35-years-old at 27 weeks of gestation were recruited in this study. Gestational age was assessed from the date of last menstrual period and concurrent clinical assessment [19]. Individuals meeting inclusion criteria were requested to participate in the study selected from those that attended maternity clinics affiliated to Kashan University of Medical Sciences, Kashan, Iran. We did not include those with pre-eclampsia, hypertension, GDM, complete bed rest (CBR), intra-uterine fetal death (IUFD), IUGR, or those with a history of rheumatoid arthritis, thyroid, parathyroid or adrenal diseases, and hepatic or renal failure. Furthermore, smokers and those taking medications including nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin were not included. A total of 85 pregnant women aged 18 to 35-years-old were screened, of these, 56 met inclusion criteria. Participants were randomly assigned to receive synbiotic ($n = 28$) or control food ($n = 28$) for 9 weeks. The study was performed according to the guidelines laid down in the Declaration of Helsinki. The ethical committee of Kashan University of Medical Sciences (KUMS) approved the study and informed written consent was obtained from all participants.

Study Procedure

To obtain detailed information about the dietary intakes of study participants, all women were entered into a 2-week run-in period; during which all subjects had to refrain from taking synbiotic or any other probiotic food. At the end of the run-in period (27 weeks of gestation), subjects were randomly assigned to consume 18 g/day of synbiotic or control food for 9 weeks. Random assignment was done by the use of computer-generated random numbers. A trained midwife at the maternity clinic did the randomized allocation sequence and assigned participants to the groups. Participants were asked not to alter their routine physical activity or usual diets and not to consume any synbiotic or probiotic other than the one provided to them by the investigators. Synbiotic or control foods were provided for participants every week. Compliance was monitored once a week through phone interviews. The compliance was also double-checked by the use of 3-day dietary records completed throughout the study. Dietary intakes of participants were assessed by means of 3-day dietary records (2 week days at weeks 3 and 6 and one weekend day at week 9 of intervention) completed throughout the study. To obtain nutrient intakes of participants based on these 3-day food diaries, we used Nutritionist IV software (First Databank, San Bruno, CA, USA) modified for Iranian foods.

Assessment of Variables

Data on pre-pregnancy weight and height (measured values) were taken from the clinic records. A trained midwife

at the maternity clinic did anthropometric measurements at the study baseline and 9 weeks after intervention. Body weight was measured in an overnight fasting status, without shoes and in a minimal clothing state by the use of a digital scale (Seca, Hamburg, Germany) to the nearest 0.1 kg. Height was measured using a non-stretch tape measure (Seca, Hamburg, Germany) to the nearest 0.1 cm. BMI was calculates as weight in kg divided by height in m^2.

Biochemical Assessment

Fasting blood samples (10 ml) were taken at baseline and after the 9-week intervention at Kashan reference laboratory in an early morning after an overnight fasting. Serum TAG, TC, HDL and LDL concentrations were assayed using the standard enzymatic methods with commercial kits (Pars azmun, Tehran, Iran). Serum VLDL concentration was also assessed by photometric methods in which LDL, HDL and chylomicrons were blocked by antibodies and finally VLDL concentration was evaluated by enzymatic measurement and with available kits (Zist Shimi, Tehran, Iran). All inter- and intra-assay CVs for lipid profile measurements were <5 %. Plasma TAC was assessed by the use of the FRAP method developed by Benzie and Strain [20]. The plasma total GSH was measured by the method of Beutler et al. [21]. CVs for TAC and total GSH were 4.5 and 3.1 %, respectively.

Synbiotic and Control Foods

The synbiotic food consisted of a probiotic viable and heat-resistant *L. sporogenes* (1×10^7 CFU), 0.04 g inulin (HPX) as prebiotic with 0.38 g isomalt, 0.36 g sorbitol and 0.05 g stevia as sweetener per 1 g. The pregnant women were asked to consume the synbiotic food two times a day in 9 g portions. Therefore, they received 18×10^7 CFU *L. sporogenes* and 0.72 g inulin each day. Control food (the same substance without probiotic bacteria and prebiotic inulin) was packed in identical packages and coded by the producer to guarantee blinding. Due to its viability against the high temperature, acidity of the stomach, bile acids and growth at physiological conditions as well as beneficial effects on the intestinal environment, stool frequency and characteristics [22], we selected *L. sporogenes* rather than other *Lactobacillus* species. The synbiotic and control foods were provided by Sekkeh Gaz Company, Isfahan, Iran.

Statistical Analysis

To assess the normal distribution of variables, Kolmogorov–Smirnov test were applied. Data on dietary intake were compared by the paired *t* test. Paired-sample *t* tests were used to detect within-group differences. To determine the effect of the synbiotic food on lipid profiles and biomarkers of oxidative stress, we applied repeated measures analysis of variance. In these analyses, the treatments (synbiotic and control foods) were regarded as between-subject factors and time was considered as within-subject factor. To assess if the magnitude of the change depended on the starting value, we conditioned all analyses on baseline values to avoid the potential bias that might have resulted. These adjustments were done using analysis of covariance (ANCOVA). All statistical analyses were done using the Statistical Package for Social Science version 17 (SPSS Inc., Chicago, IL, USA).

Results

Among individuals in the synbiotic group, two persons [CBR ($n = 1$) and IUGR ($n = 1$)] were excluded. The exclusions in the control group were also two women [hospitalization ($n = 1$) and GDM ($n = 1$)]. The remaining, 52 participants [synbiotic ($n = 26$) and control food ($n = 26$)] completed the trial (Fig. 1).

No serious adverse events were reported following consumption of the synbiotic food in the pregnant women throughout the study. We found no significant differences in the mean values of age, pre-pregnancy weight, or BMI between the two groups (Table 1). Baseline and post intervention weight and BMI were not significantly different between control and synbiotic groups.

Based on the 3-day dietary records, no statistically significant differences were seen between the two groups in terms of dietary intakes of energy, carbohydrates, protein, fat, saturated fatty acids (SFA), polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA), cholesterol, dietary fiber, magnesium, manganese and vitamin C (Table 2).

Consumption of a synbiotic food for 9 weeks resulted in a significant reduction in serum TAG ($P = 0.04$), VLDL ($P = 0.04$) and a significant rise in plasma GSH levels ($P = 0.004$) compared to the control food (Table 3). No change was observed on serum TC, LDL, HDL and plasma TAC levels ($P > 0.05$). Within-group differences in the control group revealed a significant increase in serum TAG ($P = 0.008$), VLDL ($P = 0.008$), a significant decrease in serum HDL ($P = 0.02$) or plasma GSH ($P < 0.0001$). When we adjusted the analyses for baseline values, no significant changes in our findings were evident (data not shown).

Discussion

This study investigated the effect of a synbiotic food on lipid profiles and biomarkers of oxidative stress among

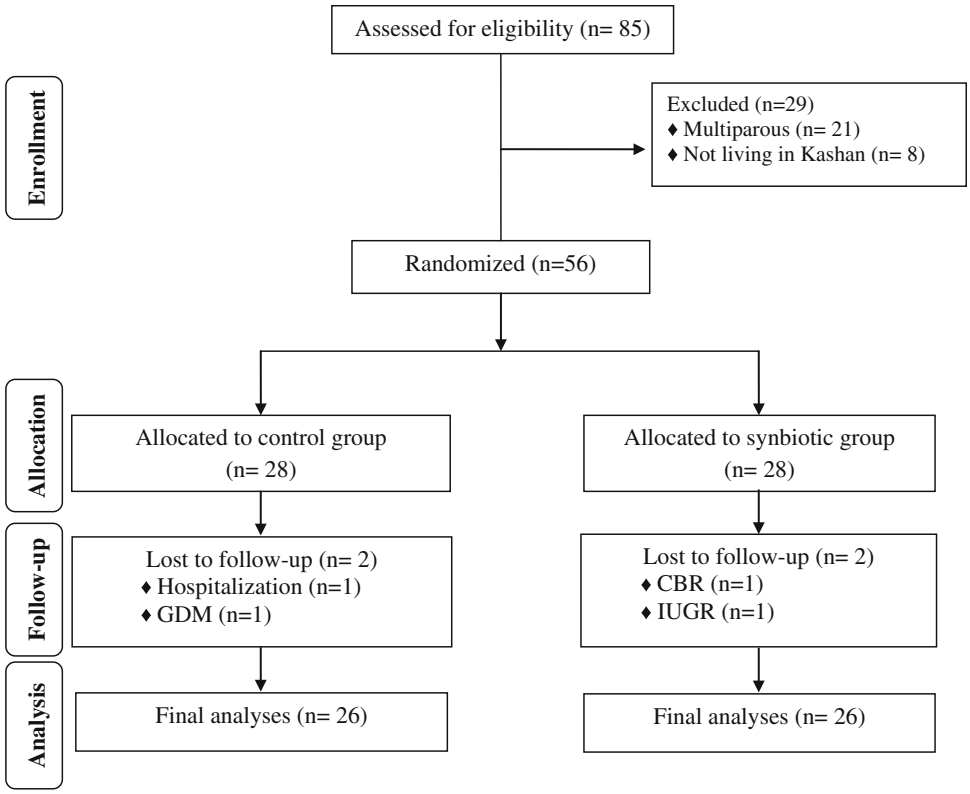

Fig. 1 Summary of study participant flow: *GDM* gestational diabetes mellitus, *CBR* complete bed rest, *IUGR* intrauterine growth retardation

Table 1 General characteristics of the study participants

	Control food ($n = 26$)	Synbiotic food ($n = 26$)	P value[a]
Maternal age (years)	29.0 ± 4.6[b]	26.9 ± 6.0	0.16
Height (cm)	160.4 ± 6.0	160.0 ± 7.2	0.85
Pre-pregnancy weight (kg)[c]	66.5 ± 10.9	65.0 ± 12.9	0.64
Weight at study baseline (kg)	71.8 ± 11.7	71.9 ± 14.0	0.98
Weight at end-of-trial (kg)	75.2 ± 11.7	75.5 ± 13.5	0.94
Pre-pregnancy BMI (kg/m^2)[c]	25.8 ± 3.8	25.3 ± 4.5	0.67
BMI at study baseline (kg/m^2)	28.0 ± 4.2	28.0 ± 4.9	0.99
BMI at end-of-trial (kg/m^2)	29.4 ± 4.2	29.5 ± 4.7	0.93

[a] P values were computed by an independent t test

[b] Values are presented as means ± SD

[c] Based on participants' measured weight and height in their records in the maternity clinics

pregnant women in the third trimester. Overall, pregnant women are very susceptible to increased lipid concentrations and oxidative stress. Elevated lipid profiles and biomarkers of oxidative stress may result in several aberrations in the mother and fetus [23, 24]. We found out that intake of the synbiotic food significantly decreased serum TAG and VLDL levels, but did not affect serum TC, LDL and HDL levels compared with the control food. In a study by Liong et al. [13] decreased serum TAG, TC and LDL levels as well as an increased concentrations of HDL was seen with consumption of a synbiotic food containing *L. acidophilus*, fructooligosaccharide, inulin and mannitol in hypercholesterolemic pigs after 8 weeks. Similar findings have also been shown the following consumption of *L. rhamnosus* KY-3 and cellobiose as synbiotics [25] and a synbiotic product containing soybean and yacon extract, *Enterococcus faecium* and *L. helveticus* in animal models [26]. Inconsistent with our study, a significant reduction in serum TC and LDL levels was seen with intake of a synbiotic containing *L. gasseri* and inulin among hypercholesterolemic patients after 12 weeks, although serum TAG levels were unaffected [27]. The underlying mechanisms of decreased serum TAG and VLDL levels by synbiotics have remained largely obscure. Study results suggest that TAG and VLDL decreasing in response to synbiotic food is largely due to SCFA production, especially propionate, which may inhibit the synthesis of fatty acids in the liver, thereby decreasing the TAG secretion rate and serum TAG levels [28]. Another point worth mentioning is that inulin has been extensively investigated as a determinant factor in decreasing the expression of enzymes involved in fatty acid synthesis [29] and suppression of gene expression of

Table 2 Reported nutrient intake of participants on control and synbiotic foods at baseline and throughout the study

Variables	Baseline			Throughout the study[a]		
	Control food ($n = 26$)	Synbiotic food ($n = 26$)	P value[b]	Control food ($n = 26$)	Synbiotic food ($n = 26$)	P value[b]
Energy (kcal)	2363 ± 153[c]	2350 ± 205	0.80	2406 ± 226	2357 ± 292	0.49
Carbohydrates (g)	324.2 ± 36.3	323.8 ± 48.2	0.97	330.9 ± 40.5	330.1 ± 56.9	0.95
Protein (g)	87.4 ± 9.9	85.3 ± 19.4	0.61	88.5 ± 14.5	89.9 ± 19.9	0.72
Fat (g)	83.0 ± 12.8	82.8 ± 17.0	0.95	86.4 ± 11.2	80.2 ± 15.7	0.10
SFA (g)	23.6 ± 5.6	24.3 ± 7.4	0.72	26.1 ± 5.5	24.5 ± 6.0	0.33
PUFA (g)	28.2 ± 6.8	26.9 ± 5.8	0.45	26.2 ± 6.7	23.8 ± 6.5	0.18
MUFA (g)	21.8 ± 5.2	22.2 ± 7.5	0.81	24.6 ± 6.3	22.5 ± 6.9	0.27
Cholesterol (mg)	219.6 ± 124.1	205.8 ± 147.8	0.71	211.9 ± 106.3	197.3 ± 108.2	0.62
Dietary fiber (g)	18.1 ± 4.2	18.2 ± 5.0	0.90	19.8 ± 4.0	19.8 ± 4.3	0.99
Magnesium (mg)	272.1 ± 44.5	273.9 ± 79.2	0.91	291.2 ± 67.1	282.3 ± 67.7	0.63
Manganese (mg)	2.1 ± 0.6	2.3 ± 0.8	0.41	2.3 ± 0.8	2.3 ± 0.9	0.95
Vitamin C (mg)	180.4 ± 96.0	166.7 ± 70.7	0.56	195.7 ± 85.6	186.0 ± 99.6	0.70

SFA saturated fatty acids, *PUFA* poly unsaturated fatty acids, *MUFA* mono unsaturated fatty acids

[a] Two week days at weeks 3 and 6 and one weekend day at week 9 of intervention

[b] P values were computed by independent t test

[c] Values are presented as means ± SD

Table 3 Lipid profiles and biomarkers of oxidative stress at baseline and after 9 weeks of study

	Control food ($n = 26$)			Synbiotic food ($n = 26$)			P value[a]
	Week 0	Week 9	Change	Week 0	Week 9	Change	
TAG (mg/dl)	166.3 ± 68.0[b]	202.7 ± 83.4[c]	36.4 ± 64.9	162.5 ± 54.0	161.0 ± 55.2	−1.5 ± 70.7	0.04
TC (mg/dl)	214.3 ± 42.2	214.0 ± 58.6	−0.3 ± 47.8	209.1 ± 41.4	203.7 ± 32.3	−5.4 ± 47.8	0.69
HDL (mg/dl)	60.0 ± 11.0	54.9 ± 12.6[c]	−5.1 ± 10.7	63.0 ± 12.9	63.3 ± 12.2	0.3 ± 17.5	0.18
VLDL (mg/dl)	33.3 ± 13.6	40.5 ± 16.7[c]	7.2 ± 12.9	32.5 ± 10.8	32.2 ± 11.1	−0.3 ± 14.1	0.04
LDL (mg/dl)	121.0 ± 41.5	118.6 ± 56.0	−2.4 ± 41.0	113.8 ± 34.9	108.2 ± 32.3	−5.6 ± 45.6	0.78
TC/HDL	3.6 ± 0.8	4.0 ± 1.6	0.4 ± 1.4	3.4 ± 0.7	3.3 ± 0.7	−0.1 ± 0.9	0.10
TAC (mmol/l)	606.6 ± 247.8	638.5 ± 147.4	31.9 ± 218.8	678.8 ± 316.7	670.5 ± 204.8	−8.3 ± 305.0	0.58
GSH (μmol/l)	942.7 ± 425.0	661.4 ± 239.6[c]	−281.3 ± 330.7	715.7 ± 353.3	735.4 ± 372.0	19.7 ± 393.7	0.004

TAG triacylglycerol, *TC* total cholesterol, *HDL* high density lipoprotein, *VLDL* very low density lipoprotein, *LDL* low density lipoprotein, *TAC* total antioxidant capacity, *GSH* total glutathione

[a] P values represent the time × group interaction (computed by analysis of the repeated measurements ANOVA)

[b] Values are presented as means ± SD

[c] P values were computed by the paired t test

lipogenic enzymes [30]. Furthermore, a series of human studies demonstrated that inulin affects the metabolism of lipids primarily by decreasing TAG due to a reduction in the number of VLDL particles with the same composition in lipids and the same size [31]. Inulin and probiotics, when administered as a synbiotic, have a synergistic effect which may modulate lipid profiles [32]. The difference in observed lipid profiles in the current study may result from differences in study design, the dosage and duration of synbiotic used, and the patients under investigation.

We demonstrated that supplementation with a synbiotic food significantly increased plasma total GSH levels, but did not affect plasma TAC levels. We previously showed that consumption of a synbiotic food containing *L. sporogenes* and inulin among T2D led to elevated plasma GSH after 6 weeks, but did not affect plasma TAC levels [16]. Increased levels of GSH and superoxide dismutase, along with reduced levels of nitric oxide were also seen with intake of a synbiotic containing *L. acidophilus* and inulin in a murine model [33]. The same as findings in biomarkers of

oxidative stress have been reported after intake of synbiotics in neonatal rats [18], human breast milk [34] and after intake of probiotics in diabetic patients [35]. GSH is a prominent regulator of intracellular redox homeostasis. Increased GSH concentration in the synbiotic group is in line with others, since SCFA production, in particular butyrate, is known to provide NADPH for synthesis of GSH [36]. Another factor is that GSH synthesis increase following the consumption of probiotics may be due to enhanced glutamate cysteine ligase (GCL) activity and increased mRNA expression of both of the GCL subunits [37]. Furthermore, the effect of synbiotics on suppression of pro-inflammatory cytokines as well as on down-regulation of genes involved in oxidative stress and toll-like receptor pathways [18] may explain their effect on circulating GSH levels. The lack of effect on TAC in our study may be attributed to the strain and dosage of probiotics and inulin.

Limitations

Several limitations must be considered in the interpretation of our findings. First of all, we did not assess effects of the synbiotic food on fecal SCFA, other biomarkers of oxidative stress. Additionally we were unable to make more accurate determination of serum HDL levels with HPLC or GC methods. Secondly, we did not assess the effects of synbiotic-containing food on the biochemical indicators of the newborn infants of the pregnant women evaluated.

In summary, the results of our study showed that consumption of a synbiotic food for 9 weeks among pregnant women resulted in decreased serum TAG and VLDL, and increased plasma total GSH levels compared with the control food.

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Conflict of interest None of the authors had any personal or financial conflict of interest.

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