Original Article

Prevention of Insulin Resistance by Dietary Intervention among Pregnant Mothers: A Randomized Controlled Trial

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Abstract

Background: Chronic insulin resistance (IR) is a basic part of the pathophysiology of gestational diabetes mellitus. Nutrition significantly impacts IR and weight loss reduces insulin levels, whereas weight gain increases the concentrations. Therefore, we surveyed the effect of nutrition intervention on IR in pregnant women and whether this effect is irrespective of weight gaining in accordance with Institute of Medicine limits. **Methods:** This prospective, randomized clinical trial was carried out among 150 primiparous pregnant mothers in fifteen health centers, five hospitals, and 15 private obstetrical offices in Isfahan. The nutrition intervention included education of healthy diet with emphasize on 50%–55% of total energy intake from carbohydrate (especially complex carbohydrates), 25%–30% from fat (to increase mono unsaturated fatty acids and decrease saturated and trans-fatty acids), and 15%–20% from protein during pregnancy for experimental group. The controls received the usual prenatal care by their health-care providers. **Results:** This trial decreased pregnancy-induced insulin increases (P = 0.01) and IR marginally (P = 0.05). ANCOVA demonstrated that control of gestational weight gaining was more effective to decrease IR (P = 0.02) while insulin values decreased by nutrition intervention and irrespective of weight control (P = 0.06). Fasting plasma glucose (FPG) concentrations did not decrease by intervention (P = 0.56) or weight management (P = 0.15). **Conclusions:** The current intervention was effective to decrease pregnancy-induced insulin increases and IR. Considering study results on FPG levels and incidence of GDM, we suggest repeat of study design in a larger sample.

Keywords: *Diet modification, insulin resistance, intervention studies, Iran, pregnancy*

Introduction

Insulin sensitivity to nutrients decreases during pregnancy to deliver adequate substrate to the fetus. Increased maternal pregravid insulin resistance (IR) accompanied by insufficient insulin response worsens during pregnancy and becomes obvious as gestational diabetes mellitus (GDM).Thus, chronic IR is a basic component of the pathophysiology of GDM.[1] GDM will end to development of type 2 diabetes in the mother and increased risk for obesity and glucose intolerance in the offspring.[2]

Recent studies explained the role of IR in progress of hepatic lipogenesis, nonalcoholic fatty liver disease, and atherogenic dyslipidemia.[3] Furthermore, women with IR were more likely to develop preeclampsia[4] and cardiovascular diseases.[5] On the other hand, alterations in blood glucose levels mediated through enhanced insulin may trigger obstetric complications.

Studies indicate that nutrition significantly impact IR.[6] In nonpregnancy state, weight loss reduces insulin levels, whereas weight gain increases the concentrations. Results of one study showed that restricted gestational weight gain in obese women could prevent pregnancy-induced changes in glucose and insulin levels.[7]

Therefore, in this paper which is part of a study on nutrition education for improving gestational weight gaining (GWG), we examined the effect of nutrition intervention on insulin resistance in pregnant women with varying BMIs and whether this effect is irrespective of weight gaining according to Institute of Medicine (IOM) (In 2009, the Institute of Medicine (IOM) updated guidelines for GWG, formulated as a range of weight gain for each category of prepregnancy BMI) BMI limits.

Methods

This prospective randomized clinical trial was carried out among primiparous

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pregnant mothers in Isfahan, Iran, during May 2015–September 2016. The registration number is IRCT2016012026129N1. Considering a 5% significance level, at least 80% power, assuming a standard deviation of 2.7 for at least 3 μU/ml difference in serum insulin levels[8] between intervention and control groups with an expected attrition rate of 10%, 70 participants were considered for each group. Fifteen Community Health Centers, five hospitals, and fifteen obstetrical offices were selected (stratified sampling). Eligibility criteria included gestational age between 6 and 10 weeks, BMI lesser than 40 kg/m^2, nonsmoking, aged 18 and older, originally Iranian, and a singleton pregnancy.

Women with weight-related complications,[9] previous diabetes and diabetes mellitus type 1 and 2,[10] mental disease,[11] anemia, urinary tract complications, usage of an special regimen,[12] chronic disease, addiction,[13] and not participation in all classes because of medical or other reasons were excluded. Randomization occurred in consecutive order at the time of enrollment.

After providing written consent, the willing participants who met the inclusion criteria were randomized to intervention or control group in consecutive order at the time of enrollment. Randomization was performed using computer-generated codes contained in sealed, sequentially numbered envelopes by a responsible person who had no other involvement in the study. Pregnant mothers were randomized by opening the envelopes consecutively until the required sample size was achieved.

Participants took part in the previously planned prenatal visits with physicians and midwives. In addition, women in the intervention group received present intervention while women in control group received routine education by midwives and physicians. Midwives and physicians were blinded to subject randomization and educational content to prevent contamination.

Diagnosis of GDM was carried out based on the criteria of American Diabetes Association.[14] Fasting blood samples (5 mL) were taken in the early morning at Al-Zahra Clinical Laboratory. Fasting plasma glucose (FPG) levels were quantified by the use of Mindray bs-800 automatic biochemical analyzer with Bionik kits. Fasting insulin concentrations were measured by electrochemiluminescence immunoassay with commercially available kits (COBAS 311, Roche Diagnostics GmbH, Mannheim, Germany). IR was assessed using the homeostasis model assessment (HOMA) calculator software.[15]

Ethics approval was obtained from the Human Research Ethics Board for Health Sciences at the Public Health College of Shahid Sadoughi Of Medical Sciences (4326) and Vice of Research and Technology of Isfahan University of Medical Sciences [294048].

Study instrument

Data were collected by a self-administered questionnaire which was completed through interviews with pregnant women and prenatal care-related records considering demographic and reproductive characteristics. Pregnancy records were completed by experts who guaranteed their reliability. In addition, since the records are prepared in fixed and standardized forms, their reliability confidence has already been proven.

The food records were analyzed for nutrients using the N4 software (version 3.5.2), and responsible person was not aware of study goals. Physical activity scores were determined by pregnancy physical activity scale[16] at 6–10 and 34–36 weeks of gestation. Furthermore, FPG and fasting insulin were measured at the 12th week and 34–36 weeks of pregnancy.[15]

Nutrition education intervention

The nutrition intervention was designed based on macronutrients and micronutrients intake for the experimental group included three 45–60 min training sessions in 6–10, 18, and 26 weeks of pregnancy. Assessment of each woman's usual food intake using a 3-d food diary included one weekend day[17] occurred at 6–10 of pregnancy for two groups. Each woman met with the study nutritionist at the time of enrollment for baseline assessment and counseling. FPG and fasting insulin were measured at the 12th week of pregnancy.

The first session was about the importance of healthy nutrition for pregnant mothers and the benefits of instructed points. One booklet,[18] which included the recommended points and the benefits of them, the barriers to implementation, and the ways to overcome these barriers during pregnancy, was given to each of the participants in the experimental group. Instructed points included following components: (i) varied and balanced dietary pattern based on food groups containing grains, vegetables, fruit, milk, and meat expressed as servings/day; (ii) weight gaining according IOM recommendations;[18] and (iii) healthy eating including as low as consumption of fried foods, junk foods, and unhealthy snacks as the most competing preferences to healthy nutrition.

Our intervention goals to prevent excessive gestational weight gain were (i) to determine the total energy intake based on primitive dietary assessment in accordance to 72-h dietary recall; (ii) to provide 50%–55% of total energy intake from total carbohydrate intake. We emphasized on complex carbohydrate intake which should be divided into main meals and snacks (three to four) during the day; (iii) to allocate the total fat intake to 25%–30% of total energy intake.

On a monthly basis, each participant was requested to record her daily dietary food portions on a form and

keep this record with herself for use in future sessions. These data and responses to questions about the leaflet's points were used to examine the participants' obedience and necessary adjustments as needed. Except the first session, pregnant mothers were divided into small groups (3–4 persons) to discuss with each other about educated points.

Again at 34–36 weeks of gestation, a consecutive 3-d food intake record was collected and analyzed to assess the effect of intervention. Physical activity, FPG, and fasting insulin values were measured, too [Figure 1].

At each educational session, the participants' weight was measured using a balanced beam and charted on an IOM gestational weight gain grid in front of the participants. We calculated the total gestational weight by deducting the prepregnancy weight from the last gained weight before delivery. All of the above-mentioned tasks were done by first author.

Statistical analysis

The data were analyzed using the SPSS statistical software package (version 18, IBM Company, The United States) and $P < 0.05$ was considered significant. The homogeneity of baseline data was analyzed by χ^2 and independent samples *t*-tests [Table 1]. Normality of the data was also examined through the Kolmogorov–Smirnov test. For not normal distributed variable (insulin), log-transformed value was used for analysis. Paired samples *t*-tests compared baseline and follow-up values within study groups [Table 2]. ANCOVA compared clinical blood parameters after adjustment for baseline values according to study groups [Table 2].

Because IR would be impressed by weight gain, we used ANCOVA to analyze the mean of blood parameters in study groups and gained weight groups (considering adherence to IOM limits and not adherence). Therefore, the study groups and gained weight groups entered the model as fixed factors. Baseline and follow-up values of blood parameters entered as covariate and dependent variables [Table 2].

Nutrients intake was analyzed by paired *t*-test and ANCOVA to compare received amounts in each group and between groups, respectively [Table 3].

Results

Before intervention, no significant differences were found between the two groups for any of the demographic characteristics, the mean of blood parameters, pregravid weight and BMI, and the mean of physical activity scores [Table 1]. We did not exclude women with GDM because results did not change after exclusion. Paired *t*-tests showed that insulin secretion and consequently IR in control group were significantly increased. Insulin increased as it happens during pregnancy in experimental group, but IR did not enhance [Table 2].

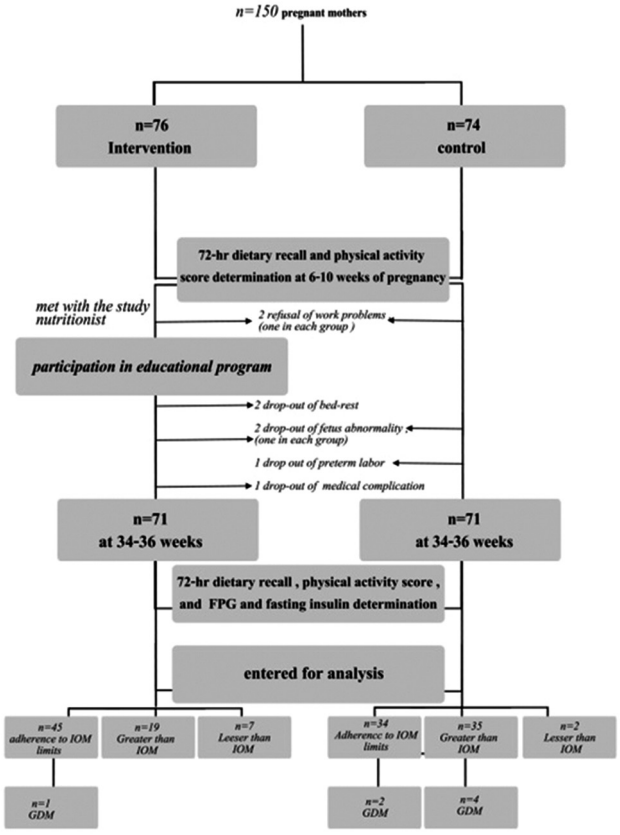

Figure 1: CONSORT trial flow diagram for recruited pregnant mothers

Table 1: Comparison of participants' characteristics and baseline values of blood parameters at the inclusion visit

Variable	Intervention (*n*=71)	Control (*n*=71)	*P**
Age (years)	26.58±3.80	26.71±4.04	0.83
Pregravid weight (kg)	63.29±11.85	61.14±10.04	0.17
Pregravid BMI (kg/m^2)	23.70±4.07	22.32±3.91	0.99
Education (years)	14.62	14.15	0.66
Family income (rials) (%)			
<6,000,000	17 (23.95)	11 (15.49)	0.66**
6,000,000-12,000,000	33 (46.47)	47 (66.20)	
>12,000,000	21 (29.58)	13 (18.31)	
FBG (mg/dl)	83.71±6.12	81.50±8.68	0.19
Insulin (μU/ml)	8.82±4.21	8.40±3.43	0.55
HOMA-IR (μIU/ml)	1.17±0.70	1.11±0.58	0.61
First trimester physical activity (met/h)	31.02±11.55	30.01±11.02	0.61
Third trimester physical activity (met/h)	29.92±10.78	27.89±10.50	0.548

**P* values using independent samples *t*-tests, ***P* values using Chi-square analysis. BMI=Body mass index, FBS=Fasting blood glucose, HOMA-IR=Homeostasis model assessment of insulin resistance

ANCOVA [Table 2] showed that intervention reduced insulin increases in experimental group compared with

Table 2: Comparison of baseline and follow-up values within and between study groups and gained weight groups

Variable	Intervention (*n*=71)		*P**	Control (*n*=71)		*P**	*P***	*P****
	Baseline values	Follow-up values		Baseline values	Follow-up values			
FPG (mg/dl)	83.16±6.02	81.41±8.50	0.84	82.21±8.46	81.98±10.19	0.89	0.56	0.70
Fasting insulin (μU/ml)	8.44±4.00	10.11±5.22	0.006	8.43±3.45	12.27±5.64	<0.001	0.01	0.06
HOMA-IR (μIU/ml)	1.12±0.70	1.29±0.61	0.13	1.12±0.61	1.54±0.72	0.002	0.05	0.19
Variable	**Adherence to IOM**		***P****	**None adherence to IOM**		***P****	***P*** **	***P*** **
	Baseline values	**Follow-up values**		**Baseline values**	**Follow-up values**			
FPG (mg/dl)	83.17±7.03	81.78±8.74	0.24	82.31±7.86	81.44±0.30	0.55	0.15	0.11
Fasting insulin (μU/ml)	8.06±3.12	9.98±4.75	0.001	9.32±3.58	13.21±6.17	<0.001	0.02	0.21
HOMA-IR (μIU/ml)	1.09±0.74	1.26±0.56	0.13	1.21±0.45	1.69±0.77	<0.001	0.002	0.02

*Paired *t*-tests to compare baseline and follow-up values for the intervention and control groups and weight gaining groups (according with IOM limits), **Compare of clinical mean values in study groups and gained weight groups separately after adjustment for baseline values using analysis of covariance, ***ANCOVA to analyze the mean values in study groups and gained weight groups synchronously to adjust the effect of weight gaining on blood parameters. IOM=Institute of medicine, FBS=Fasting blood glucose, HOMA-IR=Homeostasis model assessment of insulin resistance

Table 3: Comparison of macronutrient and micronutrient intakes before and after intervention within and between study groups

Variable	Interventional group (*n*=71)		*P**	Control group (*n*=71)		*P**	*P***
	Baseline values	Follow-up values		Baseline values	Follow-up values		
Energy (kcal/day)	1682.19±421.35	1863.42±498.26	0.02	1931.59±621.45	1970.74±519.93	0.68	0.70
Percentage of energy from carbohydrate	54.22±18.02	60.18±7.80	0.02	55.95±13.79	57.26±11.20	0.32	0.27
Percentage of energy from protein	13.57±4.87	15.52±3.13	0.006	12.53±3.43	14.09±3.53	0.008	0.03
Percentage of energy from fat	23.36±9.99	24.21±7.52	0.51	28.66±11.52	27.99±10.74	0.40	0.03
Total carbohydrate (g)	248.79±74.45	284.10±86.25	0.007	283.72±104.74	288.35±102.66	0.81	0.64
Total protein (g)	63.11±22.67	75.64±27.20	0.003	63.60±23.35	71.07±19.66	0.08	0.47
Total fat (g)	48.67±23.74	52.25±20.80	0.35	64.97±31.16	60.40±25.21	0.34	0.03
Monounsaturated fat (g)	13.05±7.42	14.14±7.83	0.37	21.28±12.63	20.05±11.16	0.55	0.05
Polyunsaturated fatty acids (g)	10.91±7.48	11.33±6.62	0.56	17.07±11.12	14.50±9.49	0.18	0.01
w6 fatty acids (g)	10.81±7.53	10.25±6.64	0.64	17.52±11.27	14.66±9.65	0.15	0.07
w3 fatty acids (g)	0.21±0.40	0.35±0.43	0.01	0.14±0.13	0.27±0.33	0.02	0.27
Saturated fat (g)	12.94±7.99	13.13±5.73	0.36	14.85±6.89	15.80±6.26	0.49	0.07
Cholesterol (mg)	169.01±112.56	188.35±98.47	0.27	129.86±121.85	196.87±118.22	0.01	0.62
Dietary fiber (g)	16.97±7.75	21.78±10.73	0.003	17.09±10.78	15.13±7.97	0.27	0.001

*Paired *t*-tests to compare baseline and follow-up values separately for the interventional and control groups, **Analysis of covariance was used to compare clinical nutrients intake in two groups after adjustment for baseline values

control (P = 0.01) and HOMA-IR scores decreased marginally (P = 0.05).

Because our nutrition education was effective on GWG in addition to insulin values, we used ANCOVA to adjust the effect of weight gaining on blood parameters [Table 2] in study groups. This trial decreased pregnancy-induced insulin increases (P = 0.01) and IR marginally (P = 0.05). ANCOVA demonstrated that control of GWG was more effective to decrease IR (P = 0.02) while insulin values decreased by the nutrition intervention and irrespective of weight control (P = 0.06). FPG concentrations did not decrease by intervention (P = 0.56) or weight management (P = 0.15).

This test demonstrated that control of GWG was more effective to decrease IR (P = 0.02) while insulin values decreased by nutrition intervention and irrespective of weight control (P = 0.06). FPG concentrations did not decrease by intervention (P = 0.56) or weight management (P = 0.15). ANCOVA did not show any interaction between intervention and weight control effects for blood parameters (P > 0.05).

FPG concentrations did not change in study groups (P = 0.56), but the frequency of GDM was marginally lower in experimental group by Fisher's exact test (P = 0.07). Chi-square analysis indicated that 3% of women who gained weight according with IOM limits met with GDM while it was 7.8% in opposite group (P = 0.26) and intervention was more effective than weight management on the incidence of GDM.

Paired *t*-test showed that energy, carbohydrate, protein, and fiber intake increased in intervention group while cholesterol intake increased in control group. Protein and n-3 polyunsaturated fatty acid (PUFA) increased in two groups [Table 3]. ANCOVA indicated that protein

percentage of energy was higher in experimental group while fat percentage of energy was lower. Fiber intake increased while fat and polyunsaturated fat intake were lower after intervention. Saturated and n-6 PUFA in the intervention group were lower marginally [Table 3].

Discussion

The current nutrition education intervention decreased gestational insulin increases irrespective of weight control. Furthermore, our trial decreased IR which was more affected by maintaining gestational weight within the IOM limits and has not been widely studied.

Wolff *et al*.' intervention reduced total gestational weight gain to half that of the control group, and consequently, this restriction decreased pregnancy-induced insulin and glucose increases.[7] Fraser *et al*. reported that dietary intervention may be effective on insulin sensitivity which decreases during pregnancy physiologically.[19] Another trial decreased insulin concentrations by a regimen of low-glycemic diet combined with a low-volume exercise among pregnant mothers. The proportion of carbohydrate/fat in their diet was low, too. However, the maternal weight gain and birth size attenuated noticeably.[20] In one study, the dietary approaches to stop hypertension (DASH) diet decreased plasma glucose concentrations, serum insulin levels, and HOMA-IR score in pregnant mothers with GDM.[21] Furthermore, the effect of diets or nutrient intakes on IR in nonpregnancy state was mediated by weight control[22,23] or irrespective of weight management.[24]

Thus, prevention of IR by nutrition education could be regarded for pregnant mothers.

Our results showed that mean values of FPG after intervention did not decrease while the incidence of GDM was 1.3% compared to 7.7% in control group (P = 0.07). Wolff *et al*.' trial on obese women with calorie restriction reduced the fasting glucose amounts at 36.[7] The DASH eating pattern in pregnant women with GDM had beneficial effects on FPG levels.[24] Similar to our results, a systematic review showed that dietary interventions did not decrease fasting blood glucose but reduced GDM incidence.[25] The impact of the present intervention on fasting blood glucose levels is interesting because hypoglycemia-induced complications were not reported by participants and neonates' anthropometric indexes did not lessen while the incidence of GDM decreased marginally.

In the current study, the percent of energy intake from protein increased significantly while the percentage of energy from fat decreased, and carbohydrate energy percentage did not change between two groups. This finding is consistent with Wolff *et al*. who reported that the fat energy decreased in the intervention group while the protein energy percent of the diet increased and insulin secretions decreased consequently.[7] They restricted percentage of energy intake from carbohydrate in obese women, but we individualized energy intake in women with varying BMIs. Hence, we did not observe significantly different in carbohydrate intake between two groups.

Our result showed that fiber intake increased significantly in interventional group while carbohydrate intake did not change between two groups. Coherently, Fraser *et al*. demonstrated that insulin sensitivity decreased on a diet contained 40% of energy from carbohydrate and 10 g dietary fiber. Insulin sensitivity in their survey did not decrease in diets with 40% of energy as carbohydrate and 52 g dietary fiber or 60% of energy from carbohydrate and 84 g dietary fiber.[19] Carbohydrate intake in our intervention group increased compared with baseline values while in control group, there was not any significant change in carbohydrate intake. However, HOMA-IR score in intervention group was lesser compared to control. Of course, our participants' energy intake was near pregnancy goals. Similarly, one study suggests that pregnant mothers who consume a diet with lesser than 30% fat and further than 50% carbohydrate as they increase their energy intake will reduce the risk of GDM.[26] However, further studies are needed about this result. Furthermore, higher intake of carbohydrate in our trial is because of higher intake of complex carbohydrates which have been shown with higher fiber intakes in the intervention group. McAuley *et al*. concluded that a diet which provide requisite amounts of received carbohydrate and fiber would probably decrease IR similar to high protein diet.[27]

According to our findings, lower fat and PUFA intake were associated with lesser HOMA-IR scores. Significant increases in Glutathione Peroxidase Activity and HOMA-IR consequently were correlated positively with dietary fat and PUFA intake in another study.[28] Harding *et al*. reported that there was no evidence that the association between dietary fat intake and insulin resistance was modified by physical activity.[29]

We found that n-6 PUFAs and saturated fat intake were marginally higher in control group. Similarly, researcher stated that high dietary n-6 PUFA and SFA intake are significant independent forecasters of fasting hyperinsulinemia in adolescents.[6] Stefan *et al*. showed that high α2-heremans-schmid glycoprotein plasma levels are associated with IR in humans which could be decreased significantly by lower intake of energy and saturated fat particularly.[30]

Fedor and Kelley mentioned to lesser intake of n-6 PUFA and saturated fatty acids and greater intake of n-3 PUFA to the prevention of insulin resistance.[31]

Strengths and limitations

This randomized, controlled, single blind trial was performed on a sample of community instead of one or two groups of BMI. Individuals followed from early in pregnancy through delivery with an intervention which had practical relevance during prenatal care in the clinical settings. Adverse pregnancy

outcomes were not observed, too. To keep the number of words, we did not show the effect of the intervention on micronutrients and their association with IR. Furthermore, the effect of the intervention on mean birth sizes did not discuss.

Conclusions

The current intervention was effective to decrease pregnancy-induced insulin increases and IR. We suggest restating of trial in a larger sample considering study results on FPG concentrations and incidence of GDM.

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Conflicts of interest

There are no conflicts of interest.

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