CEOG Clinical and Experimental Obstetrics & Gynecology

Effect of a low glycemic diet in patients with polycystic ovary syndrome and anovulation - a randomized controlled trial

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Summary

Objective: To determine whether a low glycemic index diet is better than a normal glycemic index diet in producing ovulatory cycles in women with polycystic ovary syndrome (PCOS) and anovulation. *Materials and Methods:* A randomized controlled clinical trial involving 37 women with PCOS and anovulation. The authors randomly assigned low glycemic index diets (n = 19) and normal glycemic index (n = 18) diets, and analyzed the number of ovulatory cycles for three months. *Results:* In patients who consumed a low glycemic index diet, 24.6% (14/57) of the cycles were ovulatory. In those who consumed a normal glycemic index diet, only 7.4% (4/54) of the cycles were ovulatory ($p = 0.014$). *Conclusions:* The difference observed in the number of ovulatory cycles could be related to a decrease in the serum levels of circulating androgens, secondary to an improvement in insulin resistance.

Key words: Glycemic index; Ovulatory cycles; Polycystic ovary syndrome; Metabolic syndrome.

Introduction

Polycystic ovary syndrome (PCOS) is considered the most common endocrinopathy in women of reproductive age and can affect 5-10% of all women in this age group [1]. The clinical manifestations of this syndrome include menstrual abnormalities that vary from oligomenorrhea to amenorrhea as a consequence of chronic anovulation that has been associated with an increased serum level of free testosterone [2], which in turn determines a hormonal environment that favors hirsutism and acne [3]. There are also metabolic changes; it is even possible to say that about half of PCOS patients meet diagnostic criteria for metabolic syndrome and the majority present insulin resistance [4]. The association of compensatory hyperinsulinemia has been considered important in the pathogenesis of PCOS [5].

Central obesity is a common finding in patients with PCOS; excess adipose tissue seems to be the main source of insulin resistance in these patients. Furthermore, excess body fat has been associated with an increased risk of anovulation, hyperandrogenism, and anovulatory cycles [6].

In women with menstrual irregularities and insulin resistance, it has been shown that the control of these levels through diet and/or medication, even without a consequent weight loss, can help restore ovulatory function and menstrual cyclicity [7]. Diets based on low glycemic index foods appear to be more effective in reducing weight and body fat [8]. In contrast, high glycemic index diets have been associated with hyperinsulinemia and insulin resistance [9].

The aim of this study is to compare the effect of a low glycemic index and a normal glycemic index diet on ovulation in patients with PCOS and anovulation.

Materials and Methods

This was a controlled clinical trial performed with prior approval by the ethics committee of the present hospital.

Participating patients

The authors included 40 patients with a diagnosis of PCOS, infertility, and anovulation who attended the University Center for Reproductive Medicine (CeUMER) of the Hospital Universitario "Dr. José Eleuterio González", in Monterrey Mexico from January 2 to December 21, 2012.

The diagnosis of PCOS was made according to the Rotterdam criteria of 2003 [10]. Diagnosis of infertility was made according to WHO criteria [11]. Anovulation was diagnosed by vaginal ultrasound monitoring of ovulation. Monitoring included a baseline ultrasound within the first three days of the menstrual cycle and then on days 11, 13, and 15 of the cycle.

After confirming the diagnosis of PCOS, infertility and anovulation, the patients were eligible if they agreed to participate in the study by signing a written informed consent; they also needed to not be under any diet or have received hormone treatment or weight loss drugs at least three months before the study. Patients with a confirmed diagnosis of diabetes mellitus and women with adnexal cystic masses were not included.

Revised manuscript accepted for publication March 26, 2015

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLIII, n. 4, 2016
doi: 10.12891/ceog3037.2016

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Forty patients were recruited and divided randomly, sequentially, into two groups of 20 patients each, group 1 and group 2.

One patient from group 1 and two from group 2 were eliminated from the study; the patient from group 1 for not attending the nutritional assessment, and the two patients from group 2 voluntarily withdrew from the study to seek treatment for ovulation induction. Group 1 had 19 patients and group 2 18 patients.

Nutritional analysis

All patients underwent a nutritional assessment by applying a questionnaire with a 24-hour reminder that asked about food consumed including liquids, both qualitatively and quantitatively, during a period of 24 hours which corresponded specifically to the day before consultation. With this reminder the authors sought to determine the patient's usual intake with the patient being evaluated using the Nutrís system, a computer program developed by the School of Nutrition of the Autonomous University of Nuevo Leon, which provides the composition of the food consumed.

Diet intervention

Patients were subsequently included in a diet program, which was calculated according to the Harris-Benedict formula [12] for determining basal energy expenditure (BEE), adding a physical activity factor to determine the amount of calories for each patient. The diet was calculated individually with a normal percentage distribution of macronutrients: 45% and 50% complex carbohydrates, 30% to 40% fat, 10% to 15% monounsaturated fatty acids, less than 10% of polyunsaturated fatty acids; less than 10% of saturated fatty acids, 15% to 20% protein and 20 to 35 grams/day of fiber, in addition to a source of omega 3 fatty acids. Patients in group 1 received a diet containing foods with a glycemic index lower than 45 and the patients in group 2 received a diet with a glycemic index of 50 to 75 points. Both groups received a diet with between 1,200 and 1,500 kilocalories per day. The glycemic index of foods was calculated using the International table of glycemic index and glycemic load values [13].

Diet adherence monitoring.

As support to confirm good adherence to the diet, the patient was asked to fill out a food diary with all the foods she ate the day before, what time she had her meals, and the amounts ingested. The patients attended once a month for evaluation during three consecutive months at the start of the dietary intervention.

Ultrasound monitoring of ovulation

Ultrasound monitoring of ovulation was performed in all patients included in this study in each of the three cycles after the start of the diet. Monitoring was performed vaginally by the same operator. Baseline ultrasound imaging was performed between days 1 to 3 and then on days 11, 13, and 15 of each cycle. If any follicle was larger than 14 mm on day 15 of the cycle, ovulation was monitored every other day until day 20. The cycle was considered ovulatory, if at least one follicle showed continued growth with subsequent evidence of rupture, which was considered if free fluid was observed in the pouch of Douglas and there was a reduction in follicle diameter.

Serum analysis

All patients underwent baseline determination of serum free testosterone, FSH, LH, prolactin, glucose and insulin; also, the HOMA index was calculated [14].

Evaluation of hirsutism

The presence and degree of hirsutism was assessed with the Ferriman-Gallwey scale [15]. This evaluation was performed in each patient after agreeing to participate in the study.

Table 1. — *Patient demographics.*

	Group 1	Group 2	*p* value
Age (years)	26.05 ± 4.17 (18−31)	26.06 ± 4.68 (18−35)	0.998
Menarche (years)	12.3 ± 1.76 (10−17)	12.9 ± 1.86 (9−17)	0.299
Short cycle (days)	63.2 ± 75.96 (28−365)	36.9 ± 12.73 (30−60)	0.157
Long cycle (days)	123.5 ± 151.91 (28−730)	116.6 ± 94.80 (30−360)	0.870
Days of bleeding	6.0 ± 3.26 (2−15)	4.8 ± 2.74 (3−14)	0.249
SSI* (age)	18.8 ± 3.80 (11−25)	19.6 ± 5.21 (14−30)	0.585
Primary/secondary Infertility	16/3	13/5	0.188
Time of infertility (years)	3.0 ± 2.13 (1−7)	2.78 ± 1.39 (1−6)	0.712
Number of pregnancies	0.16 (0−1 SD ± 0.37)	0.67 (0−3 SD ± 1.02)	0.051
Births	0.05 (0−1 SD ± 0.22)	0.28 (0−2 SD ± 0.57)	0.123
Cesarean section	0.00 (0 SD ± 0.0)	0.22 (0−2 SD ± 0.54)	0.086
Abortions	0.11 (0−1 SD ± 0.31)	0.11 (0−1 SD ± 0.32)	0.956

*SSI: start of sexual intercourse.
Group 1 patients with a low glycemic index diet.
Group 2 patients with a normal glycemic index diet.

Statistical analysis was performed by calculating the mean, standard deviation, and range for continuous variables, whereas frequencies were calculated for categorical variables. To compare the results, the authors used the chi-square test and Student's *t*-test as appropriate. They considered a p-value < 0.05 as statistically significant. SPSS version 21 was used for data analysis.

Results

A total of 19 patients in group 1 and 18 patients in group 2 participated. Mean age was similar in both groups; in group 1 it was 26.06 years and in group 2 it was 26.05 years. No statistically significant difference was found in relation to age at menarche, duration of menstrual cycles, days of menses, age of first intercourse, number of sexual partners, time and type of infertility, number of previous pregnancies, births, cesarean sections, or abortions (Table 1).

The results of the Ferriman-Gallwey score for the evaluation of hirsutism were: a mean of 11.05 for group 1, ranging from three to 26 with a standard deviation of 6.55. Similarly, the mean score for patients in group 2 was 11.28 with a range of five to 23 and a standard deviation of ± 4.53; the difference between the groups was not statistically significant.

In relation to the evaluation of laboratory tests, no statistically significant differences were found in any of the serum parameters evaluated (Table 2).

Table 2. — *Basal laboratory test results.*

Variable	Group 1	Group 2	*p* value
Testosterone (ng/dL)	1.56 ± 1.91 (0.11−8.30)	2.56 ± 2.48 (0.43−9.0)	0.178
FSH (IU/mL)	5.94 ± 2.13 (3.0−9.8)	7.02 ± 1.78 (4.6−11)	0.106
LH (UI/mL)	7.84 ± 1.62 (4.3−11.0)	8.96 ± 2.11 (6.0−15.0)	0.078
Prolactin (ng/mL)	18.63 ± 6.81 (6.4−34.2)	20.9 ± 14.99 (8−73.1)	0.455
Glucose (mg/dL)	91.4 ± 10.04 (76−111)	84.5 ± 91.9 (63−100)	0.304
Insulin (IU/mL)	26.7 ± 9.77 (11-43)	28.85 ± 20.4 (6.1−100)	0.684
TSH (IU/mL)	2.24 ± 0.80 (0.92−3.88)	1.95 ± 0.50 (1.23-2.22)	0.196
HOMA index	5.66 ± 1.98 (2.21−8.77)	4.95 ± 1.54 (3.1−8.4)	0.234

Values are expressed as means ± standard deviation with ranges in parentheses.

The results of the nutritional assessment of the intake in the previous 24 hours is reported in Table 3. With the exception of cobalt intake, which the authors found was consumed in greater quantity by patients in group 1, there were no differences in the composition of the diet consumed by the patients in both groups prior to the study.

Regarding the weight of the patients, the authors found that women in group 1 weighed at baseline on average 84.136 kg, with a standard deviation of ± 19.468, ranging from 54.6 to 124 kg. The patients in group 2 weighed at baseline, on average, 83.378 kg, with a standard deviation of ± 14.493, ranging from 62.1 to 115.9 kg. The difference was not statistically significant ($p = 0.894$).

The weight of the patients, on average, after the first month was 83.373 in group 1 and 82.216 in group 2 ($p = 0.835$). The decrease in mean weight was 763 grams and 1,161 grams for group 1 and 2, respectively. The difference was not significant ($p = 0.242$).

Body weight after two months of diet averaged 82.542 and 82.427 kg for groups 1 and 2 ($p = 0.983$). The decrease in weight was 1,594 grams and 954 grams, respectively. The difference was not significant ($p = 0.334$).

Body weight after three months of dieting averaged 81.142 and 81.477 kg for groups 1 and 2 ($p = 0.901$). The decrease in weight was 1,994 grams and 1,900 grams, respectively. The difference was not significant ($p = 0.895$) (Table 4).

With regards to ovulatory cycles, it was found that 24.6% (14/57) of patients' cycles in group 1 were ovulatory. In contrast, in the patients in group 2 only 7.4% (4/54) of the cycles were ovulatory. The difference was significant ($p = 0.014$) (Table 5).

In the first cycle after dietary intervention, only one ovulatory cycle was observed in patients in group 1, six in the second month, and seven in the third. In patients in group 2, no ovulatory cycle was observed in the first cycle; however, one and three ovulatory cycles were observed in the second and third cycles, respectively. Cumulative ovulatory cycles, after two cycles, showed a statistical significant difference between groups; this difference was also observed after three cycles. These results are shown in Table 5.

Table 3. — *Basal nutritional analysis. According to the questionnaire of intake in the previous 24 hours.*

	Group 1	Group 2	*p* value
Fiber (g)	12.5 ± 4.58	12.42 ± 9.4	0.978
Energy (Kcal)	2318 ± 736	2411 ± 1105	0.810
Carbohydrates (g)	285.42 ± 112	307.58 ± 121	0.647
Protein (g)	81.25 ± 29.2	82.0 ± 53.4	0.966
Cholesterol (mg)	279 ± 116.5	308 ± 258.1	0.724
Total Fat (g)	95.2 ± 34.9	97.92 ± 65.4	0.926
Monounsaturated fat (g)	31.1 ± 13.8	34.08 ± 25.3	0.730
Polyunsaturated fat (g)	14.1 ± 12.1	19.2 ± 17.1	0.409
Saturated Fat (g)	30.0 ± 13.5	29.5 ± 17.3	0.417
Calcium (mg)	824 ± 435.4	784 ± 411	0.816
Phosphorus (mg)	895 ± 474.4	941 ± 615	0.839
Iron (mg)	14.5 ± 6.1	17.1 ± 13.1	0.545
Magnesium (mg)	157.2 ± 100.0	224 ± 211.0	0.332
Sodium (mg)	1407.3 ± 1125	1828 ± 1748	0.490
Potassium (mg)	1564 ± 1007	1805 ± 1508	0.649
Zinc (mg)	7.25 ± 3.5	8.25 ± 7.0	0.666
Retinol (mcg)	448.1 ± 296.8	375.8 ± 247.8	0.524
Thiamine (mg)	1.33 ± 0.49	1.42 ± 0.79	.0760
Riboflavin (mg)	1.33 ± 0.77	1.25 ± 0.75	0.792
Niacin (mg)	14.1 ± 5.7	15.5 ± 9.6	0.684
Pyridoxine (mg)	0.83 ± 0.57	1.00 ± 0.73	0.544
Folic acid (mcg)	173.1 ± 245.9	179.5 ± 285.7	0.954
Cobalt (mg)	26.9 ± 19.5	12.8 ± 12.4	0.037

Values are expressed as means ± standard deviation.

Table 4. — *Mean weight.*

	Group 1	Group 2	*p* value
Baseline	84.136	83.378	0.894
One month	83.373	82.216	0.835
Two months	82.524	82.427	0.983
Three months	81.142	81.447	0.901

Table 5. — *Ovulatory cycles.*

	Group One	Group Two	*p* value
Cycle 1	1/19 (5.2%)	0/18 (0%)	1.0
Cycle 2	6/19 (31.5%)	1/18 (5.5%)	0.08
Cycle 3	7/19 (38.8%)	3/18 (16.6%)	0.26
Cycle 1 + 2	7/38 /18.4%)	1/36 (2.7%)	0.05 *
Cycle 1 + 2 + 3	14/57 (24.6%)	4/54 (7.4%)	0.01 *

*Statistically significant.

Discussion

PCOS is a complex condition that affects women of reproductive age. It not only produces changes related to menstrual cycles, such as oligomenorrea and amenorrhea secondary to anovulatory cycles with a consequent increase in infertility rates, but also metabolic changes. Insulin resistance that predisposes the development of diabetes mellitus and cardiovascular disease has been documented [4, 16].

Most patients that present PCOS have central obesity, which is usually associated with insulin resistance [6]. For this reason, strategies that reduce obesity have been previously recognized as the first measure in the treatment of these women, which include changes in lifestyle, increased physical activity, and dietetic changes [17].

Despite having used a variety of food schemes for the prevention and treatment of PCOS, the best diet for this purpose has not been clearly determined. Diets high in monounsaturated fat, high-carbohydrate diets, low glycemic diets, as well as high protein and low carbohydrate diets have been previously used with variable results [7, 18, 19].

It is also known that not all patients with PCOS are overweight or obese; therefore the effect of a diet to decrease body weight alone could be inadequate. In this manner, an intervention that includes lowering glycemic load may favorably improve insulin resistance in these patients. An intrinsic mechanism independent from the obesity related mechanism has been suggested in patients with PCOS to explain the pathogenesis of insulin resistance in these patients [20].

In the present study the authors found a higher number of ovulatory cycles in patients who underwent a diet with a low glycemic index. In this group of patients there were three times more ovulatory cycles in comparison with those who followed the glycemic index diet normally. The low glycemic index diets have been proven effective in improving insulin resistance. This is particularly true in studies conducted in patients with chronic diseases [21]; however, to date, reports on its effects in patients with PCOS are limited.

In patients with PCOS and insulin resistance, an elevated ovarian production of androgens is found, which causes anovulatory menstrual disorders related to this syndrome [22]. Marsh *et al.* [23] demonstrated an improvement in the regularity of menstrual cycles in a group of patients subjected to a low glycemic index diet when compared with a group of patients undergoing a diet for weight reduction, however their study was limited to reviewing menstrual cyclicity. In contrast, the present authors documented a higher number of ovulatory cycles, demonstrated by ultrasound monitoring of ovulation performed vaginally, in patients who consumed a low glycemic index diet. These findings seem to be independent of weight loss. This could suggest that weight reduction per se did not influence the differences found in relation to the number of ovulatory cycles seen in both groups.

The present authors consider the increase in the number of ovulatory cycles in patients consuming a low glycemic index diet may be related to a decrease in the serum levels of circulating androgens, secondary to an improvement in insulin resistance. There are reports that document a minor decrease in androgen binding globulin and a further reduction in the free androgen index in a group of patients with acne who consumed a low glycemic index diet when compared with patients who consumed a high glycemic index diet [24].

In the present study, the authors found that the amount of cobalt consumed by the patients in group 1 was the only nutrient that showed a significant difference in the diets consumed in both groups before entering the study; however, the authors have no explanation for this finding and do not know if this could have a relationship with the results.

The strength of this study is that it is a controlled clinical trial, conducted jointly by the Departments of Gynecology and Nutrition at a university medical center. Its weaknesses could be the number of patients included in the study and the follow-up time; however, the present authors feel that with the data obtained, they can suggest that future studies be conducted that include hormonal evaluation at the end of the follow-up period. There is no doubt that this will assist to more accurately explain the increase in ovulatory cycles found in this clinical trial.

Conclusions

With the results of this study it can be concluded that a low glycemic index diet could be a strategy available to a large number of women with PCOS, particularly those looking to achieve pregnancy. The recovery of ovulatory cycles through a dietary intervention is an affordable and accessible strategy for any patient, regardless of their socioeconomic status. Cumulative ovulatory cycles show the need of commitment from patients to achieve these results. This strategy could be the first therapeutic intervention in the complex treatment of patients with PCOS. These findings should be confirmed in future studies.

Acknowledgments

The authors thank Sergio Lozano-Rodriguez, M.D., Scientific Publications Support Coordinator, Office of the Vice Dean of Research and Dr. Jose E. Gonzalez University Hospital, for his help in reviewing the manuscript.

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