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The effect of inofolic supplementation on women with polycystic ovarian syndrome (PCOS): a Randomized Clinical Trial study

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ABSTRACT

Objective. Polycystic ovary syndrome is a disorder in women of reproductive age and it is one of the pathological factors that play a role in the failure of laboratory fertilization (IVF). The aim of this study was to determine the effect of inofolic supplementation on women with polycystic ovary syndrome (PCOS).
Material and methods. This clinical trial study was performed on 70 infertile women aged 20 to 40 years with polycystic ovary syndrome referred to the Sanandaj Besat Hospital infertility center in 2019. Patients were randomly divided into intervention and control groups. Patients in the intervention group took Clomiphene and inofolic supplement for 3 months and patients in the control group received only Clomiphene for 3 months. Various parameters such as fasting sugar, LDL, HDL, cholesterol, triglyceride and testosterone level were also measured.
Results. LDL (96.6 ± 19.4 *vs* 105.2 ± 10.1, p = 0.02), cholesterol (158.2 ± 10.4 *vs* 79.8 ± 14.4, p = 0.0001) and triglycerides levels (140.1 ± 30.3 *vs* 160.3 ± 22.0, p = 0.002) was significantly lower in the intervention group than in the control group. The mean HDL level in the intervention group was higher than the control group (47.3 ± 7.5 *vs* 43.2 ± 5.1, p = 0.009). The frequency of follicles (+ 2) in the intervention group (85.7%) was higher than in the control group (37.1%) (p = 0.001). The frequency of clinical pregnancies, pregnancies leading to live births, miscarriages, and preterm births in the two groups did not differ significantly and were almost similar (P > .05).
Conclusions. Inofolic supplementation improved fat profile status, fetal quality and reduced miscarriage and also increased follicles in women with polycystic ovary syndrome.

SOMMARIO

Obiettivo. La sindrome dell'ovaio policistico è un disturbo nelle donne in età riproduttiva ed è uno dei fattori patologici che giocano un ruolo nel fallimento della fecondazione in laboratorio (FIV). Lo scopo di questo studio era di determinare l'effetto dell'integrazione inofolica sulle donne con sindrome dell'ovaio policistico (PCOS).
Materiale e metodi. Questo studio clinico è stato condotto su 70 donne infertili di età compresa tra 20 e 40 anni con sindrome dell'ovaio policistico arrivate al centro per l'infertilità dell'ospedale Sanandaj Besat nel 2019. Le pazienti sono state divise casualmente in gruppi di intervento e di controllo. Le pazienti nel gruppo di intervento hanno assunto Clomifene e integratore inofolico per 3 mesi e le pazienti nel gruppo di controllo hanno ricevuto solo Clomifene per 3 mesi. Sono stati misurati anche vari parametri come glicemia a digiuno, LDL, HDL, colesterolo, trigliceridi e livello di testosterone.
Risultati. LDL (96,6 ± 19,4 *vs* 105,2 ± 10,1, p = 0,02), colesterolo (158,2 ± 10,4 *vs* 79,8 ± 14,4, p = 0,0001) e i livelli di trigliceridi (140,1 ± 30,3 *vs* 160,3 ± 22,0, p = 0,002) erano significativamente più bassi nel gruppo di intervento rispetto al gruppo di controllo. Il livello medio di HDL nel gruppo di intervento era superiore al gruppo di controllo (47,3 ± 7,5 *vs* 43,2 ± 5,1, p = 0,009). La frequenza dei follicoli (+ 2) nel gruppo di intervento (85,7%) era maggiore rispetto al gruppo di controllo (37,1%) (p = 0,001). La frequenza di gravidanze cliniche, gravidanze di nati vivi, aborti spontanei e nascite pretermine nei due gruppi non differivano in modo significativo ed erano quasi simili (P > .05).
Conclusioni. L'integrazione di inofoli ha migliorato lo stato del profilo dei lipidi, la qualità fetale e ha ridotto l'aborto spontaneo ed ha anche aumentato i follicoli nelle donne con sindrome dell'ovaio policistico.

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Key words
Infertility; PCOS; inofolic supplementation; Randomized Clinical Trial; Iran.

INTRODUCTION

Polycystic ovary syndrome is one of the most common causes of infertility in the world, affecting 5-10% of women of reproductive age. This syndrome prevents ovulation and increases the level of androgens in the blood (1). Polycystic ovaries cause irregular menstrual cycles and hyper-androgenism, which can lead to acne, alopecia, hirsutism, insulin resistance, male obesity, dyslipidemia, infertility, and fetal loss in early pregnancy (2). More than 50 percent of women with PCOS suffer from insulin resistance, which can lead to conditions such as metabolic disease, obesity, gestational diabetes, type 2diabetes, and cardiovascular disease (3).
Glucose intolerance affects 30 to 40 percent of PCOS patients, and insulin-sensitizers such as inositol are effective on spontaneous ovulation in patients with PCOS. The inositol phosphoglycan molecule plays a direct role in glucose metabolism. Myo-inositol is a type of inositol isoform in nature and also the human body (ovarian follicular environment) that is obtained from the epimerization of inositol. Epimerization is reduced in type 2 diabetes and PCO patients and is a common cause of endocrine disorders and infertility due to chronic ovulation failure in women of reproductive age (4, 5).
Myo-inositol regulates insulin, FSH, LH and TSH. By reducing insulin resistance, triglycerides, testosterone, and blood pressure, and increasing the sensitivity of insulin receptors, myo-inositol can be effective in inducing ovulation and treatment of patients with PCOS (6). Inofolic supplement contains 2000 mg of myo-inositol and 200 micrograms of folic acid, which is useful in the treatment of insulin-resistant polycystic ovary syndrome and type 2 diabetes (7).
The results of a study by Constantino *et al*. showed that consuming myo-inositol with folic acid for 12 to 16 weeks improved ovulation, metabolic factors, and also hormonal factors in women with PCOS (8). In another study, the use of myo-inositol in patients with PCOS showed an improvement in the number of follicles and a decrease in the number of immature oocytes in the control group (9). It has been suggested that there is a link between reduced levels of myo-inositol and insulin resistance. Several studies have suggested that myo-inositol improves ovarian function in patients with PCOS (8-10).
The present study evaluates the role of myo-inositol in the treatment of infertility in patients with PCOS; also, it examines biochemical parameters and evaluates the effects of myo-inositol on pregnancy rate. The main hypothesis is that treatment with myo-inositol reduces germinal vesicles and oocytes degeneration without compromising total numbers of oocytes.
Regarding that patients with PCOS suffer from infertility due to impaired follicogenesis and oocyte immaturity, the aim of this study was to evaluate the effect of myo-inositol on follicogenesis and oocyte maturation on women with polycystic ovary syndrome (PCOS).

MATERIALS AND METHODS

Patients and gathering their demographic and clinical records

This clinical trial study was performed on 70 infertile women aged 20 to 40 years with polycystic ovary syndrome referred to the Sanandaj Besat Hospital infertility center in 2019. Exclusion criteria were: history of ovarian surgery in the past three months, use of antiepileptic drugs and glucocorticoids, congenital adrenal hyperplasia, hypothyroidism, hyperthyroidism, hyperprolactinemia, androgen-secreting tumors, other causes of infertility and metabolic diseases.
Patients were randomly divided into intervention and control groups. Simple random sampling was used. From a package containing 70 cards, includ-

ing 35 cards labeled "A" for intervention group and 35 cards labeled "B" for control group, patients randomly selected a card and according to the label (A or B) they allocated into intervention or control groups. Sampling was continued in parallel until the number of samples was completed in two groups. Finally total of 70 women with PCOS were enrolled in the study and randomly allocated into intervention group (n = 35) and control group (n = 35). No patient was lost for follow up (**figure 1**).
The data collection tool was a questionnaire that was designed based on the objectives of the study. The questionnaire included two sections: the first

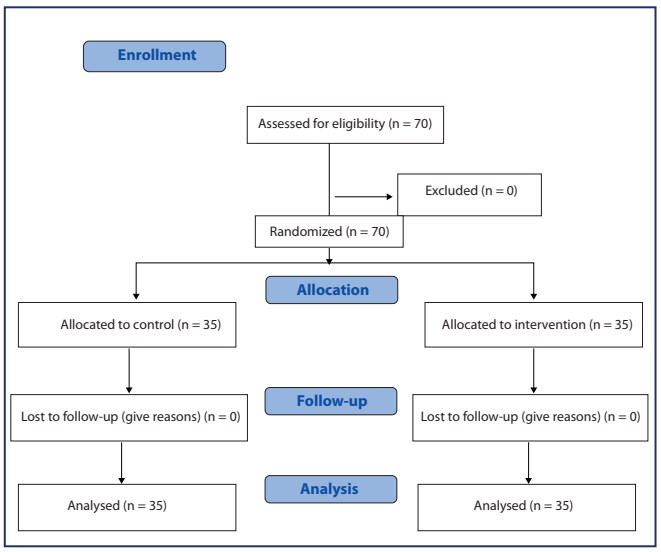

Figure 1. *Flowchart of the study.*

section for demographic information and the second for information on the condition of the follicles, ovaries, pregnancy and its consequences in the patients. Women's demographic information was recorded in the questionnaire and then their body mass index was determined. To determine the fat profile and testosterone levels, 5 cc blood samples was taken. Fasting blood sugar was also taken and recorded.
Patients in the intervention group received Clomiphene and inofolic supplement for 3 months. In the first month of the intervention, 50 mg Clomiphene was administered to the patients for 5 days from the third day of menstruation, inofolic sachets containing 2000 g myo-inositol and 200 µg folic acid was administered daily until the end of the month. In the second month of the intervention, 100 mg Clomiphene was administered to the patients for 5 days from the third day of menstruation, an inofolic sachet containing 2000 g myo-inositol and 200 µg folic acid was administered daily until the end of the month. In the third month of the intervention, 150 mg Clomiphene was administered to the patients for 5 days from the third day of menstruation, an inofolic sachet containing 2000 g myo-inositol and 200 µg folic acid was administered daily until the end of the month.
Patients in the control group received only Clomiphene for 3 months. In the first month 50 mg Clomiphene was administered to the patients for 5 days from the third day of menstruation. In the second month 100 mg Clomiphene was administered to the patients for 5 days from the third day of menstruation. In the third month 150 mg Clomiphene was administered to the patients for 5 days from the third day of menstruation.
After intervention, various parameters such as fasting sugar, LDL, HDL, cholesterol, triglyceride and testosterone were measured. Also, the number of developed follicles, the number of clinical pregnancies, the number of pregnancies leading to live birth and the number of abortions in each group were followed by the researcher and recorded in the questionnaire.
This study was approved by Ethics Committee of Kurdistan University of Medical sciences (IR.MUK.REC.1397.228) and also registered in Iranian Registry of Clinical Trials (IRCT20190825044605N1). Informed consent was taken from all participants of the study.

Statistical analyses

The data were analyzed using SPSS Ver.22 software. The data were summarized using descriptive indicators such as mean, standard deviation, frequency and relative frequency. The normality of quantitatively dependent variables was assessed using Kolmogorov-Smirnov test. To test the relationships between the variables, Kai-Square test, Fisher's exact test and independent t-test were used.

RESULTS

In terms of job, spouse's job, family marriage, medical history, marriage duration, infertility duration, and body mass index, there were no significant statistical differences between the intervention and control groups ($p > .05$), but in terms of average age and age of spouses there was a significant statistical difference between the intervention and control groups ($p < .05$) (**table I**).

Table I. *Comparison of variables in the intervention and control groups.*

Variables		Intervention group N (%)	Control group N (%)	P Value
Women's jobs	Housekeeper	33 (94.3)	27 (77.1)	0.05
	Employed	2 (5.7)	8 (22.9)	
Husband's job	Self-employed	28 (80.0)	23 (65.7)	0.51
	Employed	5 (14.3)	9 (25.7)	
	Army	2 (5.7)	3 (8.6)	
Family marriage	Yes	5 (14.3)	4 (11.4)	0.99
	No	30 (85.7)	31 (88.6)	
Clinical history	Yes	7 (20.0)	4 (11.4)	0.51
	No	28 (80.0)	31 (88.6)	
Women's age		25.9 ± 4.3	31.2 ± 5.6	< 0.001
Husband's age		31.6 ± 4.7	36.2 ± 7.4	0.003
BMI		26.8 ± 3.8	26.9 ± 3.9	0.87
Marriage duration		6.7 ± 3.0	8.0 ± 4.8	0.19
Infertility duration		4.0 ± 3.1	4.6 ± 3.9	0.39

Table II. *Comparison of the frequency of fat profile levels after intervention in the intervention and control groups.*

Variables	Level	Intervention Group N (%)	Control Group N (%)	P Value
LDL	Normal	32 (91.4)	33 (94.3)	0.99
	Abnormal	3 (8.6)	2 (5.7)	
HDL	Normal	6 (17.1)	2 (5.7)	0.15
	Abnormal	29 (82.9)	33 (94.3)	
Cholesterol	Normal	34 (97.1)	31 (88.6)	0.36
	Abnormal	1 (2.9)	4 (11.4)	
Triglycerides	Normal	27 (77.1)	6 (17.1)	< 0.001
	Abnormal	8 (22.9)	29 (82.9)	
FBS	Normal	34 (97.1)	35 (100.0)	0.99
	Abnormal	1 (2.9)	0	
Testosterone	Normal	30 (85.7)	29 (82.9)	0.74
	Abnormal	5 (14.3)	6 (17.1)	

Table III. *Comparison of mean fat profiles, FBS and testosterone level after intervention in the intervention and control groups.*

Variables	Intervention Group	Control Group	P Value
LDL	96.6 ± 19.4	105.2 ± 10.1	0.02
HDL	47.3 ± 7.5	43.2 ± 5.1	0.009
Cholesterol	158.2 ± 10.4	179.8 ± 14.4	< 0.001
Triglycerides	140.1 ± 30.3	160.2 ± 22.0	0.002
FBS	91.0 ± 2.2	89.5 ± .8	< 0.001
Testosterone	4.0 ± 2.5	4.6 ± 2.6	0.36

Table IV. *Comparison of the frequency of follicles in the intervention and control groups.*

Number of follicles	Intervention Group N (%)	Control Group N (%)	P Value
0	1 (2.9)	3 (8.6)	< 0.001
1	4 (11.4)	19 (54.3)	
2	24 (68.6)	9 (25.7)	
More than three	6 (17.1)	4 (11.4)	
Total	35 (100)	35 (100)	

Table V. *Comparison of the frequency of outcomes in the intervention and control groups.*

Outcomes		Intervention Group N (%)	Control Group N (%)	P Value
Clinical pregnancy	Yes	6 (17.1)	5 (14.3)	0.74
	No	29 (82.9)	30 (85.7)	
Pregnancy leads to a live birth	Yes	5 (14.3)	3 (8.6)	0.71
	No	30 (85.7)	32 (91.4)	
Spontaneous abortion	Yes	1 (2.9)	2 (5.7)	0.99
	No	34 (97.1)	33 (94.3)	
Preterm birth	Yes	0	0	-
	No	35 (100)	35 (100)	

The levels of fat profiles did not differ significantly in terms of LDL, HDL and cholesterol after the intervention, but it was significantly different in terms of triglycerides (22.9% in the intervention group and 82.9% in the control group) ($p = 0.0001$). There was no significantly difference between the two groups in terms of fasting blood sugar and testosterone levels ($p > .05$) (**table II**).

When calculating the fat profile average, the findings showed that LDL levels (96.6 ± 19.4 *vs* 105.2 ± 10.1, $p = 0.02$), cholesterol levels (158.2 ± 10.4 *vs* 79.8 ± 14.4, $p = 0.0001$) and triglycerides levels (140.1 ± 30.3 *vs* 160.2 ± 22.0, $p = 0.002$) were significantly lower in the intervention group than in the control group. The mean HDL level in the intervention group was higher than the control group (47.3 ± 7.5 *vs* 43.2 ± 5.1, $p = 0.009$) (**table III**).

The prevalence of 2 follicles and more in women of the intervention group (85.7%) was higher than in the control group (37.1%). This difference was also statistically significant ($p = 0.001$) (**table IV**).

In terms of the frequency of clinical pregnancies, pregnancies leading to live births, spontaneous abortion and preterm births there were no significant difference between intervention and control groups and were almost similar ($p > 0.05$) (**table V**).

DISCUSSION

In our study, the mean LDL, cholesterol, and triglycerides in the intervention (the myo-inositol) group were significantly lower than in the control

group. In the study by Constantino *et al*. triglyceride and cholesterol levels in the myo-inositol group were significantly reduced compared to the control group (8). Monstra *et al*. reported that myo-inositol, alone or in combination with its isomer D-Chiro-Inositol is able to improve the symptoms and outcomes of PCOS patients significantly (11). In a study by Greli *et al*. significant weight loss as well as a significant reduction in LDL was observed in patients treated with myo-inositol (6). In this study, the mean HDL level in the myo-inositol group was higher than the control group. An increase in HDL levels was observed in Greli's study. These data on fat profiles and HDL suggest that treatment with myo-inositol may be helpful in reducing the risk of cardiovascular disease in PCOS women. In a study by Hernandez Marin *et al*. the metabolic profiles of PCOS patients were improved by administrating myo-inositol and alpha-lactalbumin (12). In general, the findings of the mentioned studies were consistent with our study.

Our findings showed that fasting blood sugar and testosterone levels were not significant between the two groups, although testosterone was reduced in the myo-inositol group, but this decrease was not significant. In a study by Constantino *et al*., the results showed that in myo-inositol group the serum level of testosterone was reduced compared with the control group (8). In Regidor's study, the mean testosterone level was reduced from 96.6 to 43.3 ng/dL after administration of myo-inositol (13). The reason may be due to differences in the statistical population of the studies, the prescribed dose of myo-inositol and the duration of the intervention.

In our study the frequency of follicles (+ 2) in the intervention group (85.7%) was higher than in the control group (37.1%). Constantino *et al*. showed that myo-inositol improved ovulation (8). In a clinical trial by Ciotta *et al*., greater numbers of follicles with a diameter greater than 15 mm, higher mean of the transferred embryos, as well as a decrease in the number of immature oocytes were observed in the intervention group compared to the control group (9). Kane and Chiu stated in their studies that high concentrations of myo-inositol in human follicular fluid play a role in follicle maturation and cause the development of oocytes with good quality (14, 15). Goud also showed that myo-inositol had a positive effect on the growth of mature oocytes (16). In a clinical trial aimed to compare the effect of myo-inositol supplementation and D-chiroinositol on the oocytes quality of patients with PCOS the results showed that myo-inositol was able to improve oocytes quality instead of D-chiroinositol (17).

In fact, higher concentrations of myoinositol indicate high quality oocytes. A direct relationship between the concentration of myoinositol and melatonin has been reported by two independent research laboratories (15, 18).

Although in our study, the frequency of clinical pregnancies and pregnancies leading to live births in the intervention group was higher than in the control group, but the differences were not statistically significant. In a study by Abdollahi *et al*., although the frequency of successful pregnancies in the two groups with and without the administration of inofluate was 31% and 40.1%, respectively, but it was not statistically significant (19). A laboratory study has shown that myo-inositol is effective in stimulating the ovaries in women with PCOS (20). In addition, Raffone *et al*. indicated that myo-inositol slightly improved pregnancy rates compared to Metformin (21). These findings confirm the hypothesis that a decrease in insulin levels due to an oral supplement of myo-inositol depends on an increase in IPG which stimulates ovarian, reduces FSH and increases the chance of pregnancy (22). Myo-inositol can affect LH and FSH signaling. These gonadotropins bind to receptors in the ovaries, leading to their effects on steroidogenesis and gametogenesis (23). The effects of gonadotropins on follicle growth, ovulation, and luteinization are associated with differences in FSH and LH receptor concentrations (24). The results of a study by Amjadi *et al*. that evaluated the changes in the genomic profile of comulosa cells in women with PCOS under the influence of inofolic supplementation in assisted reproductive cycles showed that the quality of the oocytes, the quality of the embryos and the fertility rate were improved (25). In areview article, Unfer *et al*. concluded that myo-inositol improves hormonal and metabolic parameters, as well as improves ovarian activity and subsequently increases the risk of fertility in women with PCOS (26).

In our study, the pregnancy rate in intervention group was 17.1% and in a study by Ragidor *et al*., the pregnancy rate was 15.1% (11). The pregnancy rate in a study by Karimzadeh and Javedani was 14.4% (27) and in Legro *et al*. study the pregnancy rate was 12.3% (26) which were consistent with our study.

In our study 97.1% in intervention group and 94.3% in the control group had no spontaneous

abortion, but in a study by Abdollahi *et al*. spontaneous abortion in intervention group was 64.5% and in control group was 77.4% (19). The frequency of spontaneous abortions in our study was lower than Abdollahi *et al*. study.

Notably, in our study, one inofolic powder chassis was prescribed, while in most studies two chassis were used. Also, in our study and other studies, no side effects have been reported for doses of 2 and 4 grams per day, consequently it leads to high patient compliance. We suggest a 4-gram per day dose.

It is better to mention that several therapeutic strategies including fasting have been proposed for the treatment of PCOS, claiming to improve symptoms and signs. Three or more days fasting reduces circulating insulin, glucose levels and IGF-1 (29). Different fasting regimens may have beneficial effects on ovarian function (30). Considering the importance of InsR and compensatory hyperinsulinemia in inducing androgen excess in PCOS women, fasting may improve hyperandrogenism-related symptoms and signs. Although several studies evaluated the correlation between insulin signaling pathways and fasting, there is no adequate data to suggest a clear fasting regime for PCOS patients (31). It seems that more studies should be conducted to prove the above claim.

CONCLUSIONS

The results of our study showed that inofolic supplementation improved fat profile status, fetal quality and reduced miscarriage and also increased follicles in women with polycystic ovary syndrome.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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