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Effect of resveratrol administration on ovarian morphology, determined by transvaginal ultrasound for the women with polycystic ovary syndrome (PCOS)

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Abstract

Intake of resveratrol has been associated with improved ovarian morphology under *in vitro* and in the animal models; however, this finding has not been confirmed in trials. The aim of our study was, therefore, to use a placebo-controlled approach with the detailed assessment of the ovarian morphology by applying transvaginal ultrasound to examine the effectiveness of this therapeutic approach in this group of women. The mean age of all participants was 28·61 (SD 4·99) years, with the mean BMI of 28·26 (SD 5·62) kg/m^2. Resveratrol therapy, as compared with placebo, was associated with a significantly higher rate of improvement in the ovarian morphology ($P = 0{\cdot}02$). Women who received resveratrol had a more dominant follicle than those getting placebo, with a significant reduction in the ovarian volume ($P < 0{\cdot}05$). However, the number of follicle count per ovary (FNPO), stromal area (SA), ovarian echogenicity and distribution of follicles were not significantly altered ($P > 0{\cdot}05$). Forty-one women with polycystic ovary syndrome (PCOS) were randomly assigned (1:1) to 3 months of daily 1000 mg resveratrol or placebo. Random assignment was done by blocked randomisation. Our primary endpoints were the change in the ovarian volume, SA and antral FNPO from the baseline to 3 months. Secondary endpoints were improvement in the distribution of follicles and ovarian echogenicity. Differences between the resveratrol and control groups were evaluated by Chi-square, Fisher's exact test and repeated-measures ANOVA. Treatment with resveratrol significantly reduced the ovarian volume and polycystic ovarian morphology, thus suggesting a disease-modifying effect in PCOS.

Key words: **Resveratrol: Ovarian morphology: Transvaginal ultrasound: Polycystic ovary syndrome**

Polycystic ovary syndrome (PCOS) could be regarded as a dilemma for many women at the childbearing age, with a wide range of long-term metabolic derangements, increased risk for cardiovascular events[(1)] and anovulation infertility[(2)]. The latter occurs when there is a lack of the dominant follicle development[(3)]. Furthermore, there are not universally accepted diagnostic criteria; the National Institutes of Health provides criteria for PCOS; these include only oligo- or amenorrhoea

Abbreviations: FNPO, follicle count per ovary; PCOM, polycystic ovarian morphology; PCOS, polycystic ovary syndrome.

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and hyperandrogenism, while Rotterdam consensus criteria considered the sonographic assessment of ovaries as the third diagnosis criterion for PCOS[4].

Theca-interstitial cells play a crucial role in the successful folliculogenesis, controlling follicle maturation and degeneration, providing mechanical support around the follicle and producing androgens[5]. Under pathological conditions such as PCOS, ovaries are significantly enlarged and characterised by prominent theca-interstitial hyperplasia and stromal hypertrophy[6]. The literature indicates that the theca cell overactivity can be associated with ovarian enlargement, which is caused mainly by stromal hypertrophy[7]. Increased ovarian cytochrome P450c17a activity in the theca cells may play a pathogenetic part in the serum androgen concentration in the women with PCOS[8].

Resveratrol (3,4′,5- trihydroxystilbene) is a phytoalexin that has been recognised as a nutraceutical and a potential therapeutic agent for a variety of diseases as well[9]. *In vitro* studies have demonstrated that resveratrol could reduce androgen production and Cyp17a1 mRNA gene expression by the inhibition of Akt/PKB phosphorylation rat theca-interstitial[10]; as another mechanism, it can suppress steroidogenic acute regulatory and cytochrome P450c17 expression[11]. Wong *et al.* have also demonstrated that resveratrol at the concentration 30–100 μM results in the reduction of theca-interstitial proliferation, stimulating apoptosis. These observations are consistent with the concept that resveratrol may function as an apoptotic effector, stimulating caspases 3 and 7, DNA fragmentation and morphologic changes[12]. A study performed in the rodent model of PCOS has revealed that resveratrol could be a promising candidate for the alternative or complementary management of the conditions related to PCOS[13].

The capability of resveratrol in returning the ovarian morphology to the normal limits in the PCOS models is well established[14], as shown by the reduced number of the antral follicle count[4] and atretic follicles[15], as well as the increased number of Graafian follicles[16]. Despite the abundance of *in vitro* and animal research, there are only two clinical trials considering resveratrol as a promising therapeutic agent in PCOS[17,18]. Bahramrezaie *et al.* reported that oral resveratrol with a dose of 800 mg increased the high-quality oocyte rate and total testosterone levels, while it decreased the expression of VEGF and HIF1 genes in the granulosa cells of the PCOS patients[18]; however, this study was performed in the absence of an ultrasonographic evaluation. When resveratrol (1500 mg) was consumed in the patients with PCOS, the ovarian volume was augmented; also, the serum levels of testosterone and Dehydroepiandrosterone sulfate were attenuated, and Insulin Sensitivity Index levels were increased[17]. However, except for the ovarian volume in the latter study, the other polycystic ovarian morphology (PCOM) was not measured in these studies. There is, however, limited information regarding the effect of resveratrol on the ovarian parameters of PCOS and how this may be related to the associated reduction in the testosterone levels. These studies only evaluated the effect of two doses of resveratrol (1500 mg and 800 mg); so, it is not clear whether lower or higher doses may have a similar effect. Moreover, there is no consensus on the optimal dose of resveratrol for PCOS. Therefore, to examine resveratrol's efficacy in PCOS, the present trial was designed to test if the treatment with resveratrol would be effective on the PCOM.

Materials and methods

Subjects

This prospective, randomised, double-blind trial was conducted at Shariati Hospital, affiliated with Tehran University of Medical Sciences, Iran. The subjects for this study were recruited through posters in the hospital lobby from Shariati Hospital, Yas Hospital and Arash Hospital in Tehran, Iran. Based on the results of previous study[17], sample size was calculated using the comparison of two-means formula with $\alpha = 0{\cdot}05$, $\beta = 0{\cdot}2$, mean change and corresponding SD of ovarian volume in resveratrol (mean change = 3·32; SD = 8·73) and placebo (mean change = −2·31; SD = 3·06) groups. The requirement for each group was twenty-one women. The suitability assessments were conducted via telephone. Of the 275 women who responded, forty-one were eligible to participate. Women were eligible for participation if they fulfilled the PCOS criteria, as defined by the Rotterdam consensus, with at least two of the following: (1) clinical or chemical hyperandrogenism (either biochemical or clinical), (2) oligo- or amenorrhoea and/or (3) polycystic ovaries as viewed by transvaginal ultrasound[19]. Oligomenorrhoea was defined as an average cycle length of more than 35 d. PCOM on ultrasonography was defined as follows: either volume >10 cm^3 in diameter per ovary and/or the presence of antral follicle count >25 throughout the entire ovary in the absence of a dominant follicle (>10 mm in diameter)[20]. At the baseline and end of the study, all participants were checked for the PCOM criteria. Women were excluded if they had other disorders mimicking the PCOS (elevated prolactin and thyroid dysfunction), Cushing's disease, acromegaly or diabetes mellitus. Patients with the use of hormonal medication (such as oral contraceptives) or other medications that could modify the metabolism and ovarian function in the past month prior to enrollment were excluded. Also, those whose transvaginal ultrasonography was inappropriate (due to virginity or patient refusal) or who were pregnant or lactating were excluded.

Women who were in the age range of 18–40 years PCOS, as well as meeting the inclusion criteria, were randomly assigned to receive resveratrol (Polygonum cuspidatum) (root), aSquared nutrition, at a dose of 1000 mg; this was done daily for a period of 3 months, or it was matched with the placebo (Maltodextrin), at a dose of 1000 mg, Karen Company. Patients and the researcher, and personnel who assessed the trial outcomes were all unaware of the intervention group's allocation. Participants were contacted by telephone every 2 weeks and queried regarding their adherence to the study agents, illnesses, medication, supplement use and pregnancy. Monthly visits were made to the participants (four times during the study period for each patient) to increase their compliance. Further, the women were asked to return the study supplement bottles on each visit; consuming 90 % or more of resveratrol supplements was considered as compliant.

During the medical examination, the patients were specifically asked about their menstrual history. Clinical assessments included determination of the BMI, waist circumference, hirsutism (using Ferriman and Gallwey score), acne score (using a four-point scale) and transvaginal ultrasonography.

Patients provided their written informed consent, and the institutional review board at Tehran University of Medical Sciences approved the trial protocol. The study was registered at www.irct.ir with the identifier IRCT2017061917139N2.

Ultrasound image assessment

Participants were evaluated by transvaginal ultrasonography (5–9 MHz) (Sonoline G40; Siemens Medical Solutions, Inc., USA) in the early follicular phase, on days 2–7 of the menstrual cycle; women with irregular menses were scanned at an unspecified time by one of two experienced ultrasonographers at Yas Hospital. Ovarian volume and the number of antral follicles (2–9 mm) per ovary (FNPO), the number of 2–5 and 6–9 mm follicles, follicles distribution pattern, stromal area and mean total echogenicity were evaluated. The volume of each ovary was estimated using the equation: $\pi/6$ (transverse diameter) × (anteroposterior diameter) × (longitudinal diameter). For each ovary, the total number of all visible follicles with a diameter of 2–9 mm (antral follicles) was obtained by continuous scanning of the entire ovary[21]. Ovarian data for each subject are presented as a mean recorded value for the left and right ovaries. When a dominant follicle (≥ 10 mm), corpus luteum or other abnormal ovarian mass was detected, only the data for the other ovary were reported[19]. Ovarian stromal area was measured by outlining the outer peripheral profile of stromal with the caliper[22]. Subjects were considered to have a peripheral distribution pattern by evaluating the largest cross-sectional plane if both ovaries contained ≥ 9 follicles in a clear aggregation around the periphery with ≤ 1 central follicle.

Statistical analysis

Statistical analyses were performed by SPSS, version 16.0, for Windows (SPSS Inc.). The Kolmogorov–Smirnov test and the Shapiro–Wilk's W test were then used to verify whether the study variables were normally distributed. Non-normally distributed variables were transformed (log, inverse square root, square root and inverse). Independent samples *t* test and Chi-square test were also used to compare any differences between the two groups at the baseline. Chi-square, Fisher's exact test and repeated-measures ANOVA were then used to test the difference between study groups at the end of study. $P < 0{\cdot}05$ was considered statistically significant.

Results

The flow chart of this study is summarised in Fig. 1. A total of 275 women were screened; forty-one were randomly allocated to two treatment groups for 3 months. Three patients in the resveratrol group and two in the placebo group were dropped out from the study.

The clinical, endocrine and metabolic features at the baseline for resveratrol and placebo groups are presented in Table 1. The mean age of the patients was resveratrol group = 29·79 (SD 4·61) years: placebo = 27·30 (SD 5·22) years; $P = 0{\cdot}14$ (the range of 19–38 years). Fasting hyperinsulinaemia (>16 μU/ml) was detected in 29·4 and 21·4 % of the subjects in the placebo and resveratrol groups, respectively ($P = 0{\cdot}56$). 21·5 % and 31·6 % were obese (BMI > 30 kg/m^2) in the placebo and resveratrol groups, respectively ($P = 0{\cdot}59$).

Women included in both groups did not differ in terms of BMI, insulin levels and hormone profiles.

All subjects in both groups had a condition of hirsutism. At the baseline, all patients in the resveratrol group had PCOM (ten bilateral and nine unilateral); however, in the placebo group, two had no PCOM and fifteen had PCOM (eight bilateral and seven unilateral) ($P = 0{\cdot}3$). After 3 months of treatment, the ovarian morphology changed in the subjects: resveratrol groups (five no PCOM, eight bilateral and six unilateral) and placebo (ten bilateral and seven unilateral) (PCOM *v.* non PCOM, $P = 0{\cdot}02$, Table 2). At the baseline, no significant difference was observed among groups in the ovarian volume (resveratrol group = 14·88 (SD 3·82): placebo = 12·71 (SD 3·63); $P = 0{\cdot}09$), whereas a significant reduction in the ovarian volume was observed after 3 months in the resveratrol group, as compared with the placebo group (resveratrol group = 12·83 (SD 3·49): placebo = 13·51 (SD 3·79); $P \leq 0{\cdot}001$). No significant difference in the stromal area was observed between placebo and resveratrol groups after 3 months of study (resveratrol group = 2·79 (SD 1·71): placebo = 3·25 (SD 1·54); $P = 0{\cdot}95$) (Table 2).

To determine the effects of resveratrol on FNPO, we reviewed the images; the ultrasound data could not be ascertained from both ovaries in two subjects in the placebo group before intervention and five subjects in the resveratrol group after intervention due to dominant follicles (≥ 10 mm). No significant differences were observed among groups after the intervention in the mean levels of 2–9 mm FNPO (resveratrol group = 49·28 (SD 14·15): placebo = 49·15 (SD 18·96); $P = 0{\cdot}57$), the mean levels of 2–5 mm FNPO (resveratrol group: 43·82 (SD 15·68) placebo = 40·96 (SD 16·03); $P = 0{\cdot}12$) and the mean levels of 6–9 mm FNPO (resveratrol group = 3·35 (SD 2·56): placebo = 4·61 (SD 3·23); $P = 0{\cdot}13$) (Table 2). Also, there were no differences between groups before and after intervention in the distribution of the follicles and echogenicity of ovaries ($P > 0{\cdot}05$) (Table 2).

Discussion

The effects of resveratrol on the metabolic and endocrine parameters have been previously evaluated[17,18]. However, the protective effects of this antioxidant on the reproductive system, particularly ovaries, are still unclear; the data indicate that resveratrol exerts anti-insulin effects[17,23]. The present study pointed the effect of 1000 mg/d resveratrol, when given for 3 months, on the regulation of ovarian. The results seem to suggest an interesting possible new mode of action for a new therapy. In this regard, our results show that resveratrol supplementation causes the significantly higher incidence of dominant follicles rather

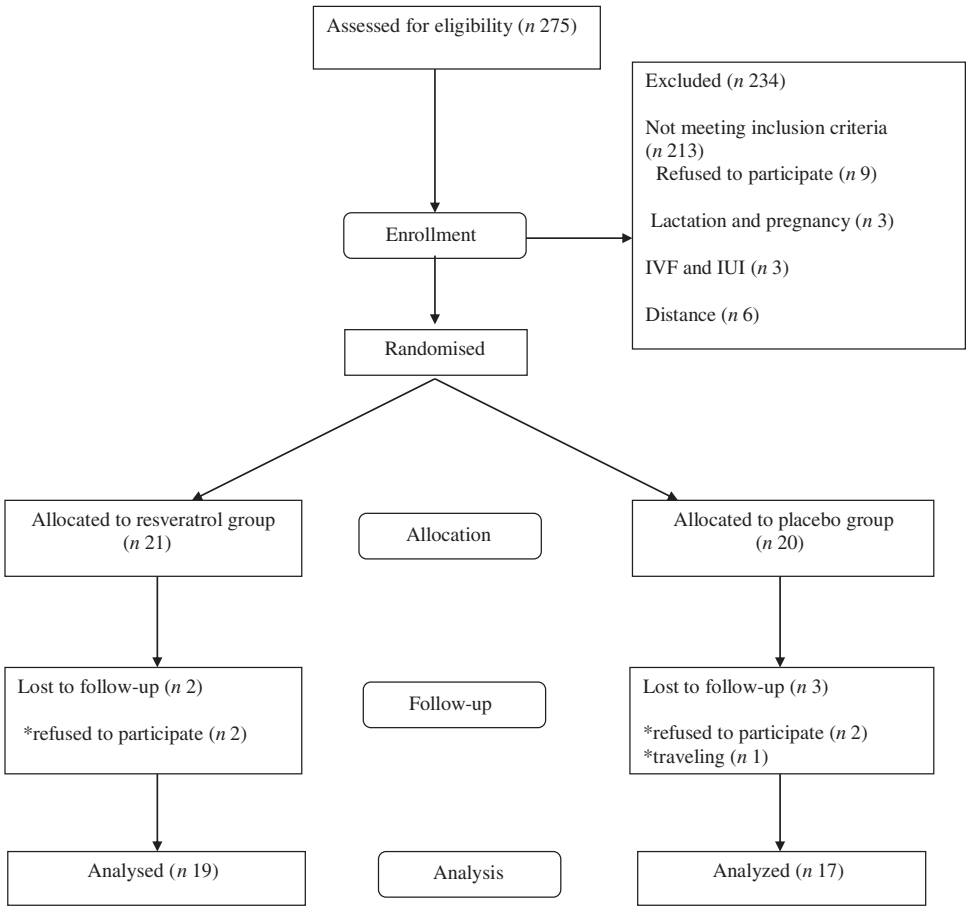

Fig. 1. Flow chart of participants' progress through the intervention.

than placebo. This clearly supports the efficacy of resveratrol in modulating the ovarian activity, in particular follicular development. Specifically, in five out of nineteen patients, PCOM disappeared in both ovaries (as two or more dominant follicles were shown, at least one in each ovary). These results, thus, suggest that resveratrol enhances the follicular growth and promotes the proper follicular development, thus leading to an increase in the ovulation susceptibility in the women with PCOS. The decrease in PCOM was parallel with a significant decrease in the ovarian volume. No significant differences in the FNPO were found between resveratrol and placebo groups, which could be mainly attributed to the small sample size included and/or the exclusion of five people from final analysis who were not diagnosed with PCOM at the end of the study in resveratrol group; further, two from the placebo were not found to have PCOM at the beginning of study. Kong *et al.* also suggested that resveratrol significantly increased the total number of oocytes; it remarkably decreased the atretic follicles and inhibited both primordial-to-developing-follicle transition and apoptosis in different age groups of rats[24]. The mechanisms by which resveratrol exerts this regulatory action on follicular development can be through the modulation of the insulin signalling direct effect in the ovary as well. Resveratrol has distinctly different effects on the proliferation of cells in theca and granulosa; these include antiproliferative effects on theca-interstitial cells and proliferative effects on granulosa cell[10]. In PCOS, an increase in the ovarian size has been reported; this may be due to thecal and stromal hyperplasia[25]. In this study, treatment with resveratrol had decreased effect on the ovarian volume; this finding was in contrast with a previous clinical trial[17] and showed no significant effect on stromal. In animal models, Ergenoglu *et al.* showed the beneficial effects of resveratrol on the antral follicle count[4]. However, ozcan *et al.* revealed that the treatment with resveratrol significantly increased antral follicle counts and decreased the atretic follicle number[26]. Nevertheless, the observed effects of resveratrol on the follicular development could be due to the reduced proliferation of theca cells; this is because a decrease in the ovarian volume may occur in parallel with a reduction in the number of theca cells[1]; the effects of resveratrol on theca cells are well documented when studied *in vitro*[12] and in the animal models[16]. A key finding from these studies is that low concentration (5–10 μM) of resveratrol could potently induce the DNA synthesis. Interestingly decrease in the DNA synthesis was observed at the high concentration (15–30 μM) of resveratrol[27]. The decrease in the ovarian volume in the polycystic ovary might be due to the reduced number of antral follicles[1]; however, this was not statistically significant in this study. Although controversial, it is tempting to speculate that the effects of resveratrol observed in the present study could be, at least partly, due to its effect on the ratio of theca to granulosa cells[27].

Table 1. Baseline and characteristics of study participants*
(Mean values and standard deviations; numbers and percentages)

	Placebo (*n* 17)		Resveratrol (*n* 19)		
	Mean	SD	Mean	SD	*P*
Age (years)	27·30	5·22	29·79	4·61	0·14
Weight (kg)	70·92	19·96	76·14	10·80	0·32
BMI (kg/m^2)	27·10	6·69	29·30	4·37	0·24
Waist circumference (cm)	94·79	17·26	95·23	10	0·92
Systolic blood pressure (mmHg)	110·41	20·06	103·97	25·79	0·41
Diastolic blood pressure (mmHg)	75	11·59	73·97	9·79	0·77
Menstrual cycle					
Regular					
n	5		2		
%	29·4		10·5		
Irregular					
n	12		17		
%	70·6		89·5		0.15
Disease duration (years)	3·70	4·6	9·63	5·67	0·002
Acne score	1·29	1·72	1·26	1·36	0·95
Hirsutism	19·18	6·32	19·16	5·09	0·98
Testosterone (ng/ml)	0·46	0·15	0·5	0·2	0·44
DHEA (ng/dl)	151·19	64·82	165·2	83·09	0·58
SHBG (nmol/l)	48·97	3·23	45·49	2·18	0·81
LH (mIU/ml)	10·37	3·45	9·02	2·55	0·7
FSH (mIU/ml)	4·95	0·34	6·2	0·3	0·17
LH/FSH	2·26	2·36	1·52	2·55	0·19
Prolactin (ng/ml)	15·13	1·34	13·18	1·94	0·48
TSH (mIU/ml)	2·51	1·32	3·01	1·81	0·32
Insulin (μIU/ml)	14·07	4·22	11·7	3·45	0·07
HOMA-IR	3·03	0·97	2·53	1·03	0·14
Fasting blood sugar (mg/dl)	87·32	9·51	86·26	15·86	0·82
HbA1C	5·24	0·42	5·39	0·35	0·26

DHEA, dehydroepiandrosterone; SHBG, sex hormone-binding globulin; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid stimulating hormone; HOMA-IR, homeostasis model assessment insulin resistance.
* Regular cycle <35 d, irregular cycle >35 d. *P* value for continuous variables independent samples *t* test, categorical variables using Chi-square test.

Table 2. Parameters of PCOM at baseline and after 3 months of treatment with resveratrol and placebo
(Mean values and standard deviations; numbers and percentages)

	Placebo (*n* 17)		Resveratrol (*n* 19)		
	Mean/n	SD/%	Mean/n	SD/%	*P*
Ovarian volume (cm^3)					
Before	12·72	3·63	14·88	3·83	
After	13·51	3·79	12·83	3·50	<0·0001†
Stroma (cm^2)					
Before	2·44	1·24	1·93	0·99	
After	3·25	1·55	2·79	1·71	0·95†
FNPO (2–9 mm)					
Before	43·00	20·92	39·28	8·14	
After	49·15	18·96	49·28	14·15	0·57†
FNPO (2–5 mm)					
Before	35·61	22·52	28·11	11·19	
After	40·96	16·03	43·82	15·69	0·12†
FNPO (6–9 mm)					
Before	5·85	5·12	8·11	7·18	
After	4·61	3·23	3·36	2·57	0·13†
Distribution of follicles					
Before					
Peripheral	12	70·6	18	94·7	
Diffused	5	29·4	1	5·3	0·08*
After					
Peripheral	11	68·80	17	89·50	
Diffused	5	31·30	2	10·50	0·20*
Ovarian echogenicity					
Before					
Mild	5	29·40	8	42·10	
Moderate	9	52·90	10	52·60	
Severe	3	17·60	1	5·30	0.44‡
After					
Mild	5	31·30	11	57·90	
Moderate	8	50·00	8	42·10	
Severe	3	18·80	0		0.08‡
PCOM					
Before					
No PCOM	2	11·8	0		
Unilateral PCOM	7	41·2	9	47·4	
Bilateral PCOM	8	47·1	10	52·6	0·3‡
After					
No PCOM	0		5	26·3	
Unilateral PCOM	7	37·5	6	31·6	
Bilateral PCOM	10	62·5	8	42·1	0·02‡

FNPO, follicle number per ovary; PCOM, polycystic ovarian morphology.
Each value represents mean and standard deviations except for distribution of follicles and ovarian echogenicity and PCOM *n* (%).
* Fisher's exact test.
† Repeated-measures ANOVA.
‡ Chi-square.

MicroRNA could play a key role in the PCOS pathology, as shown by the microRNA expression, which were different in the women with PCOS patients and in the healthy ones[28]. MicroRNA are untranslated small RNA acting as epigenetic modifiers. Several studies have described the roles of resveratrol in various metabolic markers via microRNA mechanism[29,30]. For instance, in high fat diet-fed model mice, resveratrol treatment lowered the insulin resistance by acting via the up-regulation of mmu-miR-363–3p[31], thus providing new insights into the effect of resveratrol on improving the metabolic factors in PCOS.

This study had several strengths. This was the first research documenting a modification in the ovarian structure in relation to the resveratrol administration. This finding may have fundamental clinical applications for the development of an alternative therapy for gynaecological conditions because a decline of maturation to a dominant follicle has been linked to a decrease in ovulation, thus enhancing the susceptibility to infertility in PCOS. In addition, this study was double blinded. However, interpretation of our study is limited due to the small sample size. Furthermore, some variables which can affect the results for example, dietary intake and physical activity were not measured.

Conclusions

In the PCOS patients, resveratrol improved PCOM and decreased the ovarian volume. These findings support the use of therapeutic resveratrol supplementation to improve the ovarian morphology in the patients with PCOS. Further, large trials with longer intervention periods are needed for to explore the effect of long-time exposure to resveratrol.

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