Effect of resveratrol administration on ovarian morphology, determined by transvaginal ultrasound in patients with PCOS

Amir Pejman Hashemi Taheri

Tehran University of Medical Sciences

Behnaz Moradi

Tehran University of Medical Sciences

Amir Reza Radmard

Tehran University of Medical Sciences

Milad Sanginabadi

Tehran University of Medical Sciences

Mostafa Qorbani

Tehran University of Medical Sciences

Mohammad Reza Mohajeri-Tehrani

Tehran University of Medical Sciences

Nooshin Shirzad

Tehran University of Medical Sciences

Saeed Hosseini

Tehran University of Medical Sciences

Azita Hekmatdoost

Shaheed Beheshti University of Medical Sciences

Sedigheh Asadi

Tehran University of Medical Sciences

Majid Samadi

Tehran University of Medical Sciences

Asieh Mansour (✉ asiehmansour@yahoo.com)

tums <https://orcid.org/0000-0002-4543-8757>

Research

Keywords: Resveratrol, Ovarian morphology, Transvaginal Ultrasound, PCOS, Polycystic ovary syndrome

Posted Date: December 19th, 2019

DOI: <https://doi.org/10.21203/rs.2.19190/v1>

Abstract

Background

High rate of anovulation in PCOS is associated with lack of development a dominant follicle. Intake of resveratrol has been associated with improved ovarian morphology in vitro and in animal PCOS model, but this finding has not been confirmed in randomized trials.

Methods

We randomly assigned 41 patients with PCOS, but without evidence of major medical disorders and who was not taking confounding medications including insulin sensitizers and steroids to received 1000 mg capsules containing resveratrol or matching placebo daily for up to 3 months. Transvaginal ultrasound examination was used to evaluate ovarian morphology.

Results

Resveratrol therapy, as compared with placebo, was associated with significantly higher rate of improvement in ovarian morphology (resveratrol group: 5 no polycystic ovarian morphology (PCOM), 8 bilateral and 6 unilateral and placebo group: 10 bilateral and 7 unilateral, ($p = 0.02$)). Women who received resveratrol had more dominant follicle than who received placebo with a significant reduction in ovarian volume ($p < 0.05$). However, the number of antral follicles per ovary (FNPO) and stromal area were not significantly altered ($P > 0.05$).

Conclusions

This study offered the novel therapeutic approach of resveratrol administration for PCOS women.

Introduction

Polycystic ovary syndrome (PCOS) could be a dilemma for many women of 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 dominant follicle development (3). Furthermore, there is not a universally accepted diagnostic criteria; The National Institutes of Health (NIH) provides criteria for PCOS, which include only oligo- or amenorrhea and hyperandrogenism, while Rotterdam consensus criteria considered the sonographic assessment of ovaries as a third diagnosis criteria for PCOS (4).

Theca-interstitial cells play a crucial role for 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 characterized by prominent theca interstitial hyperplasia and stromal hypertrophy (6). Data from the literature indicated that theca cell overactivity can be associated with ovarian enlargement which is caused mainly by stromal

hypertrophy (7). Increased ovarian cytochrome P450c17a activity in theca cells may play a pathogenetic part in the serum androgen concentration in women with the PCOS (8).

Resveratrol (3,4',5- trihydroxystilbene), a phytoalexin have been recognized as a nutraceutical and a potential therapeutic agent for a variety of diseases as well (9). Studies in vitro have demonstrated that resveratrol reduce androgen production and Cyp17a1 mRNA gene expression by inhibition of Akt/PKB phosphorylation rat theca-interstitial (10) and as another mechanism, suppression of StAR (steroidogenic acute regulatory) and cytochrome P450c17 expression (11). Wong et al. have demonstrated that resveratrol at concentration 30–100 μ M results in reduction of theca-interstitial proliferation and stimulated the apoptosis. These observations are consistent with the concept that resveratrol may function as apoptotic effector, stimulating caspases 3 and 7, DNA fragmentation and govern morphologic changes (12). A study performed in rodent model of PCOS revealed that resveratrol represents a promising candidate for the alternative or complementary management of conditions that are related to PCOS (13).

The capability of resveratrol in returning the ovarian morphology to normal limits in PCOS models are well established (14), as reduced the number of antral follicle count, (4) and also reduced atretic follicles(15), and increased number of Graafian follicle (16). Despite an abundance of in vitro and animal research, there is only two clinical trial that resveratrol could be a promising therapeutic agent in PCOS (17, 18). We have therefore in order to examine resveratrol's efficacy in PCOS, designed the trail to test the hypothesis that treatment with resveratrol would effect on polycystic ovarian morphology.

Materials And Methods

Subjects

This prospective, randomized, double-blind trial was conducted at Shariati hospital affiliated Tehran University of Medical Sciences in the Iran. The Subjects for this study were recruited through posters in hospital lobby from the Shariati hospital, Mohebe Yas hospital and Arash hospital in Tehran, Iran. The suitability assessments were conducted via telephone. OF the 275 women who responded, 41 were eligible to participate. Women were eligible for participation if fulfilled PCOS criteria, which was defined by the Rotterdam consensus and had at least two of the following: 1) clinical or chemical hyperandrogenism (either biochemical or clinical); 2) oligo- or amenorrhea; and/or 3) polycystic ovaries as viewed by transvaginal ultrasound (19). Oligomenorrhoea was defined as an average cycle length of more than 35 days. Polycystic ovarian morphology (PCOM) on ultrasonography was defined as follows: either volume > 10 cm³ 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 baseline and at the end of study, all participants were checked for the PCOM criteria. Women were excluded if they had other disorders that mimic the PCOS (elevated prolactin and thyroid dysfunction), and Cushing's disease, acromegaly, or diabetes mellitus. Patients with 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 excluded were persons who transvaginal ultrasonography was inappropriate (due to virginity or patient refusal) or who were pregnant or lactating.

Women 18 to 40 years of age who presented with PCOS and met inclusion criteria were randomly assigned to receive resveratrol, at a dose of 1000 mg once daily after lunch for 3 months, or matching placebo. Patients and researcher, and personnel who assessed the trial outcomes were unaware of the intervention group's allocation. Participants were contacted by telephone every 2 weeks and queried regarding adherence to study agents, illnesses, medication, supplement use, and pregnancy. Bottles of study tablets were sent to participants every one month. During the medical examination, patients were specifically asked about their menstrual history. Clinical assessments included determination of body mass index (BMI), waist circumference, hirsutism (using ferriman and gallwey score), acne score (using a four-point scale) and transvaginal ultrasonography.

Patients provided 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, USA, Inc.) in the early follicular phase on days 2–7 of the menstrual cycle and women with irregular menses were scanned at an unspecified time by one of two experienced ultrasonographers at Moheb 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 follicle, follicle distribution pattern, stromal area (SA) and mean total echogenicity were evaluated. The volume of each ovary was estimated using the equation: $\pi/6$ (transverse diameter) $\times$ (anteroposterior diameter) $\times$ (longitudinal diameter). For each ovary, the total number of all visible follicles with a diameter of 2–9 mm (antral follicles) were achieved 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 was reported (19). Ovarian stromal area measured by outlining the outer peripheral profile of the stroma with the caliper (22). Subjects were considered to have a peripheral distribution pattern by evaluating the largest cross-sectional plane if of 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., Chicago, IL, USA). The Kolmogorov-Smirnov test and the Shapiro-Wilk's W test were used to verify whether 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 used to compare any

differences between the two groups at the baseline. Repeated-measures of ANOVA were used to test the difference between study groups at the end of study. $P < 0.05$ was considered statistically significant.

Results

The flowchart of this study is summarized in Fig. 1. A total of 275 women were screened, and 41 were randomly allocated to two treatment groups for three months. Three patients in resveratrol group and two patients in placebo group dropped out from the study.

The clinical, the endocrine and the metabolic features at the baseline for resveratrol and placebo groups are presented in Table 1. The mean age of the patients was years (resveratrol group = 29.79 ± 4.61 : placebo = 27.30 ± 5.22 ; $p = 0.14$) (range 19 to 38 years). Fasting hyperinsulinemia ($> 16 \mu\text{U/ml}$) was detected in 29.4% and 21.4% of subjects in placebo and resveratrol groups, respectively ($p = 0.56$). 21.5% and 31.6% were obese ($\text{BMI} > 30 \text{ kg/m}^2$) in placebo and resveratrol groups, respectively ($p = 0.59$).

Table 1 baseline and characteristics of study participants

	Placebo (n=17)	Resveratrol (n=19)	Pvalue
Age (y)	27.30±5.22	29.79±4.61	0.14
Weight (kg)	70.92±19.96	76.14±10.80	0.32
Body mass index (kg/m ²)	27.10±6.69	29.50±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	5(29.4)	2(10.5)	0.15
Irregular	12(70.6)	17(89.5)	
Disease duration (y)	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

Regular cycle <35 days., irregular cycle >35days. Data are presented as mean± SD and number (%). P value for continuous variables independent samples t- test, categorical variables using chi- square test.

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

All subjects in both groups presented with a condition of hirsutism. At the baseline, all patients in resveratrol group had PCOM (10 bilateral and 9 unilateral) and but in placebo group 2 had no PCOM and

15 had PCOM (8 bilateral and 7 unilateral)) ($p = 0.3$). After three month of treatments, ovarian morphology changed in subjects: resveratrol groups (5 no PCOM, 8 bilateral and 6 unilateral) and placebo (10 bilateral and 7 unilateral) (PCOM vs. non PCOM, $p = 0.02$, Fig. 2). At baseline, no significant difference was observed among groups in ovarian volume (resveratrol group = 14.88 ± 3.82 ; placebo = 12.71 ± 3.63 ; $p = 0.09$), whereas a significant reduction in ovarian volume was observed after 3 months in resveratrol group compared to placebo group (resveratrol group = 12.83 ± 3.49 ; placebo = 13.51 ± 3.79 ; $p = < 0.001$) (Fig. 3). No significant difference in stromal area were observed between placebo and resveratrol groups after 3 months of study (resveratrol group = 2.79 ± 1.71 ; placebo = 3.25 ± 1.54 ; $p = 0.95$) (Fig. 4).

To determine whether the effects of resveratrol on FNPO, we reviewed of the images, the data of ultrasound were unable to be ascertained from both ovaries in two subjects in placebo group before intervention and five subjects in resveratrol group after intervention due to dominant follicles (≥ 10 mm). We observed no significant differences among groups after intervention in mean levels of 2–9 mm FNPO (resveratrol group = 49.28 ± 14.15 ; placebo = 49.15 ± 18.96 ; $p = 0.57$); mean levels of 2–5 mm FNPO (resveratrol group: 43.82 ± 15.68 placebo = 40.96 ± 16.03 ; $p = 0.12$) and mean levels of 6–9 mm FNPO (resveratrol group = 3.35 ± 2.56 ; placebo = 4.61 ± 3.23 ; $p = 0.13$); (Fig. 5). And also there were no differences between groups before and after intervention in distribution of the follicles and echogenicity of ovaries ($p > 0.05$) (Fig. 6–7).

Discussion

The effects of resveratrol on the metabolic and endocrine parameters have been previously evaluated (17, 18). On the other hand, to date, the protective effects of this antioxidant on the reproductive system, particularly the ovaries are still unclear, with data indicating that resveratrol exerts anti-insulin effects (17, 23). The present study pointed the attention properly on the effect of 1000 mg/d resveratrol given for 3 month on regulation of ovarian. The results seem to suggest an interesting possible new mode of action for a new therapy. In this regard, we present evidence that resveratrol supplementation causes a significantly higher incidence of dominant follicles than placebo. Clearly support the efficacy of resveratrol in modulating the ovarian activity, in particular follicular development. Specifically in five out of nineteen patients PCO morphology disappeared in both ovaries (as showed two or more than two dominant follicles, at least one in each ovary). These results suggest that resveratrol enhances follicular growth and favors to promote proper follicular development, leading to an increase in ovulation susceptibility in the women with PCOS. Decreased in PCOM occurred in parallel with significant decrease in ovarian volume. However, we found no significant differences in the FNPO between resveratrol and placebo groups, which may mainly attribute to the small sample size included and/ or due to exclusion of five people from final analysis who were not PCOM at the end of the study in resveratrol group and two people from placebo who were not PCOM at the beginning of study. Kong et al. suggested that resveratrol significantly increases the total number of oocytes, significantly decreases the atretic follicles and inhibits both the 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 a modulation the insulin signaling pathway on theca-interstitial cell proliferation (14) and/or

through a direct effect in the ovary as well. Resveratrol has distinctly different effects on proliferation of cells in theca and granulosa; antiproliferative effects on theca interstitial cells and proliferative effects on granulosa cell (10). In PCOS, an increase in ovarian size has been reported, and this may be due to thecal and stromal hyperplasia (25). In this study, treatment with resveratrol had decreased effect on ovarian volume and this finding in contrast with previous clinical trial (17) with no significant effect on stromal. In animal models, Ergenoglu et al, showed beneficial effects of resveratrol on antral follicle count (4). However ozcan et al. Showed that treatment with resveratrol significantly increase antral follicle counts and decrease atretic follicle number (26). Nevertheless, the presently observed effects of resveratrol on follicular development are likely due to a reduced proliferation of theca cells because it is likely that a decrease of ovarian volume occurs 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 animal models (16). A key finding from these studies was that low concentration (5–10 μM) of resveratrol potentially induced DNA synthesis. Interestingly decrease in DNA synthesis was observed at high concentration (15–30 μM) of resveratrol (27). Decreased in ovarian volume in polycystic ovary might be due to decreased in the number of antral follicles (1), but this outcome was not statistically significant in this study. Although controversial, it is tempting to speculate that the effects of resveratrol observed in the present study may be, at least in part, due to its effect on the ratio of theca to granulosa cells (27).

Conclusions

This is the first study documenting a modification in the ovarian structure in relation to resveratrol administration. This finding may have fundamental clinical application for the development of alternative therapy for gynecological conditions because a decrease in maturation to a dominant follicle has been linked with decrease in ovulation, leading to an increase susceptibility to infertility in PCOS. Moreover, that there is no consensus on the optimal dose of resveratrol for PCOS. Further large trials evaluating different dose of resveratrol in various population of PCOS are needed.

Declarations

Acknowledgements

This study was supported by Radiology department, Shariati hospital, Tehran University of Medical Sciences, Tehran, Iran.

A.P.H.T. Study conception and design, B.M. Study conception and design, Acquisition of data, Critical revision, M.S. Acquisition of data, M. Q. Analysis and interpretation of data, M.R.M.T. Critical revision, N.S.H. Critical revision, S.H. Critical revision, A.H. Critical revision, S.A. Acquisition of data, M.S. Study conception and design, Acquisition of data, A.M. Study conception and design, Acquisition of data, Analysis and interpretation of data, Drafting of manuscript, Critical revision.

Conflict of interest: *None* of the authors have any conflicts of interest or financial ties to disclose.

Consent for publication: Not applicable.

Availability of data and material: All data generated or analysed during this study are included in this published article.

References

1. Banaszewska B, Pawelczyk L, Spaczynski RZ, Duleba AJ. Effects of simvastatin and metformin on polycystic ovary syndrome after six months of treatment. *The Journal of Clinical Endocrinology & Metabolism*. 2011;96(11):3493-501.
2. Barthelmess EK, Naz RK. Polycystic ovary syndrome: current status and future perspective. *Frontiers in bioscience (Elite edition)*. 2014;6:104.
3. Sandhu H, Kuburas R. Insulin Resistance in Women with Polycystic Ovary Syndrome: Optimising treatment by Implementing. 2015.
4. Ergenoglu M, Yildirim N, Yildirim AGS, Yeniel O, Erbas O, Yavasoglu A, et al. Effects of resveratrol on ovarian morphology, plasma anti-mullerian hormone, IGF-1 levels, and oxidative stress parameters in a rat model of polycystic ovary syndrome. *Reproductive Sciences*. 2015;22(8):942-7.
5. Ortega I, Villanueva JA, Wong DH, Cress AB, Sokalska A, Stanley SD, et al. Resveratrol potentiates effects of simvastatin on inhibition of rat ovarian theca-interstitial cells steroidogenesis. *Journal of ovarian research*. 2014;7(1):21.
6. Verit FF, Erel O, Kocyigit A. Association of increased total antioxidant capacity and anovulation in nonobese infertile patients with clomiphene citrate-resistant polycystic ovary syndrome. *Fertility and sterility*. 2007;88(2):418-24.
7. Kyei-Mensah AA, LinTan S, Zaidi J, Jacobs HS. Relationship of ovarian stromal volume to serum androgen concentrations in patients with polycystic ovary syndrome. *Human reproduction (Oxford, England)*. 1998;13(6):1437-41.
8. Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome P450c17 α activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. *New England journal of medicine*. 1996;335(9):617-23.
9. Berman AY, Motechin RA, Wiesenfeld MY, Holz MK. The therapeutic potential of resveratrol: a review of clinical trials. *NPJ precision oncology*. 2017;1(1):35.
10. Ortega I, Villanueva JA, Wong DH, Cress AB, Sokalska A, Stanley SD, et al. Resveratrol reduces steroidogenesis in rat ovarian theca-interstitial cells: the role of inhibition of Akt/PKB signaling pathway. *Endocrinology*. 2012;153(8):4019-29.
11. Svechnikov K, Spatafora C, Svechnikova I, Tringali C, Söder O. Effects of resveratrol analogs on steroidogenesis and mitochondrial function in rat Leydig cells in vitro. *Journal of Applied Toxicology: An International Journal*. 2009;29(8):673-80.
12. Wong DH, Villanueva JA, Cress AB, Duleba AJ. Effects of resveratrol on proliferation and apoptosis in rat ovarian theca-interstitial cells. *Molecular human reproduction*. 2010;16(4):251-9.

13. Rackow BW, Brink HV, Hammers L, Flannery CA, Lujan ME, Burgert TS. Ovarian Morphology by Transabdominal Ultrasound Correlates With Reproductive and Metabolic Disturbance in Adolescents With PCOS. *Journal of Adolescent Health*. 2018;62(3):288-93.
14. Ortega I, Duleba AJ. Ovarian actions of resveratrol. *Annals of the New York Academy of Sciences*. 2015;1348(1):86-96.
15. Cabello E, Garrido P, Morán J, del Rey CG, Llaneza P, Llaneza-Suárez D, et al. Effects of resveratrol on ovarian response to controlled ovarian hyperstimulation in ob/ob mice. *Fertility and sterility*. 2015;103(2):570-9. e1.
16. Rencber SF, Ozbek SK, Eraldemir C, Sezer Z, Kum T, Ceylan S, et al. Effect of resveratrol and metformin on ovarian reserve and ultrastructure in PCOS: an experimental study. *Journal of ovarian research*. 2018;11(1):55.
17. Banaszewska B, Wrotyńska-Barczyńska J, Spaczynski RZ, Pawelczyk L, Duleba AJ. Effects of resveratrol on polycystic ovary syndrome: a double-blind, randomized, placebo-controlled trial. *The Journal of Clinical Endocrinology & Metabolism*. 2016;101(11):4322-8.
18. Bahramrezaie M, Amidi F, Aleyasin A, Saremi A, Aghahoseini M, Brenjian S, et al. Effects of resveratrol on VEGF & HIF1 genes expression in granulosa cells in the angiogenesis pathway and laboratory parameters of polycystic ovary syndrome: a triple-blind randomized clinical trial. *Journal of assisted reproduction and genetics*. 2019:1-12.
19. Group REASPCW. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Human reproduction*. 2004;19(1):41-7.
20. Lujan ME, Jarrett BY, Brooks ED, Reines JK, Peppin AK, Muhn N, et al. Updated ultrasound criteria for polycystic ovary syndrome: reliable thresholds for elevated follicle population and ovarian volume. *Human Reproduction*. 2013;28(5):1361-8.
21. Lujan ME, Brooks ED, Kepley AL, Chizen DR, Pierson RA, Peppin AK. Grid analysis improves reliability in follicle counts made by ultrasonography in women with polycystic ovary syndrome. *Ultrasound in medicine & biology*. 2010;36(5):712-8.
22. Christ JP, Brink HV, Brooks ED, Pierson RA, Chizen DR, Lujan ME. Ultrasound features of polycystic ovaries relate to degree of reproductive and metabolic disturbance in polycystic ovary syndrome. *Fertility and sterility*. 2015;103(3):787-94.
23. Zhu X, Wu C, Qiu S, Yuan X, Li L. Effects of resveratrol on glucose control and insulin sensitivity in subjects with type 2 diabetes: Systematic review and meta-analysis. *Nutrition & metabolism*. 2017;14(1):60.
24. Kong X-X, Fu Y-C, Xu J-J, Zhuang X-L, Chen Z-G, Luo L-L. Resveratrol, an effective regulator of ovarian development and oocyte apoptosis. *Journal of endocrinological investigation*. 2011;34(11):e374-e81.
25. Uberti F, Morsanuto V, Aprile S, Ghirlanda S, Stoppa I, Cochis A, et al. Biological effects of combined resveratrol and vitamin D3 on ovarian tissue. *Journal of ovarian research*. 2017;10(1):61.

26. Özcan P, Fıçıcıoğlu C, Yıldırım ÖK, Özkan F, Akkaya H, Aslan İ. Protective effect of resveratrol against oxidative damage to ovarian reserve in female Sprague–Dawley rats. Reproductive biomedicine online. 2015;31(3):404-10.

27. Ortega I, Wong DH, Villanueva JA, Cress AB, Sokalska A, Stanley SD, et al. Effects of resveratrol on growth and function of rat ovarian granulosa cells. Fertility and sterility. 2012;98(6):1563-73.

Figures

Figure 1

Flowchart of participants' progress through the intervention

Figure 2

Effect of resveratrol 1000 mg/d on polycystic ovary morphology (PCOM). Each bar presented as percent of patients with PCOM from two independent treatment groups, PCOM vs. No PCOM ($P=0.02$). PCOM: polycystic ovarian morphology

Figure 3

Ovarian volume (cm³) as mean $\pm$ SD at baseline and after 3 months of treatment with resveratrol and placebo $P<0.0001$, treatment effect (resveratrol vs. placebo).

Figure 4

Stromal area (cm²) as mean $\pm$ SD at baseline and after 3 months of treatment with resveratrol and placebo P=0.95, treatment effect (resveratrol vs. placebo).

Figure 5

Follicle number as mean $\pm$ SD per ovary (FNPO) at baseline and after 3 months of treatment with resveratrol and placebo (only patients who had PCOM are included). (A) FNPO (2-9 mm); $P=0.57$ treatment effect (resveratrol vs. placebo), (B) FNPO(2-5 mm) ; $p=0.12$ treatment effect (resveratrol vs. placebo), (C) FNPO(6-9 mm); $p=0.13$ treatment effect (resveratrol vs. placebo).

Figure 6

Distribution of follicles at baseline and after 3 months of treatment with resveratrol and placebo $P=0.12$, treatment effect (resveratrol vs. placebo).

Figure 7

Ovarian echogenicity at baseline and after 3 months of treatment with resveratrol and placebo $P=0.08$, treatment effect (resveratrol vs. placebo).