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

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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 µM 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 anteral 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 $> 10 \text{ cm}^3$ 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 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 months. 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 gallweyy 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: \( \pi/6 \times (\text{transverse diameter}) \times (\text{anteroposterior diameter}) \times (\text{longitudinal diameter}) \). 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 stromal 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 µU/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 (BMI > 30 kg/m²) in placebo and resveratrol groups, respectively (p = 0.59).

Table 1 baseline and characteristics of study participants
|                                | Placebo (n=17)       | Resveratrol (n=19) |
|--------------------------------|----------------------|--------------------|
| Age (y)                        | 27.30±5.22           | 29.79±4.61         |
| Weight (kg)                    | 70.92±19.96          | 76.14±10.80        |
| Body mass index (kg/m²)        | 27.10±6.69           | 29.50±4.37         |
| Waist circumference (cm)       | 94.79±17.26          | 95.23±10           |
| Systolic blood pressure (mmHg) | 110.41±20.06         | 103.97±25.79       |
| Diastolic blood pressure (mmHg)| 75±11.59             | 73.97±9.79         |
| Menstrual cycle                |                      |                    |
| Regular                        | 5(29.4)              | 2(10.5)            |
| Irregular                      | 12(70.6)             | 17(89.5)           |
| Disease duration (y)           | 3.70±4.6             | 9.63±5.67          |
| Acne score                     | 1.29±1.72            | 1.26±1.36          |
| Hirsutism                      | 19.18±6.32           | 19.16±5.09         |
| Testosterone (ng/ml)           | 0.46±0.15            | 0.5±0.2            |
| DHEA (ng/dl)                   | 151.19±64.82         | 165.2±83.09        |
| SHBG (nmol/l)                  | 48.97±3.23           | 45.49±2.18         |
| LH (mIU/mL)                    | 10.37±3.45           | 9.02±2.55          |
| FSH (mIU/mL)                   | 4.95±0.34            | 6.2±0.3            |
| LH/FSH                         | 2.26±2.36            | 1.52±2.55          |
| Prolactin (ng/ml)              | 15.13±1.34           | 13.18±1.94         |
| TSH (mIU/mL)                   | 2.51±1.32            | 3.01±1.81          |
| Insulin (µIU/mL)               | 14.07±4.22           | 11.7±3.45          |
| HOMA-IR                        | 3.03±0.97            | 2.53±1.03          |
| Fasting blood sugar (mg/dl)    | 87.32±9.51           | 86.26±15.86        |
| HbA1C                          | 5.24±0.42            | 5.39±0.35          |

Regular cycle <35 days., irregular cycle >35 days. 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 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 potently 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

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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

Figure 3

Ovarian volume (cm³) as mean ±SD at baseline and after 3 months of treatment
Stromal area (cm²) as mean ±SD at baseline and after 3 months of treatment with...
Figure 5

Follicle number as mean ±SD per ovary (FNPO) at baseline and after 3 months of
Figure 6

Distribution of follicles at baseline and after 3 months of treatment with resveratrol.

Figure 7

Ovarian echogenicity at baseline and after 3 months of treatment with resveratrol.
