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CASE REPORT
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Successful Mestrual Regularity and Spontaneous Pregnancies with a Resveratrol-Based Multivitamin Supplement in Women with Idiopathic Premature Ovarian Insufficiency

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Abstract

Premature ovarian insufficiency (POI) is a clinical syndrome defined by loss of ovarian activity before the age of 40 years and is characterized by menstrual disturbance, follicle stimulating hormone (FSH) concentration above 40 IU/l and infertility. In some patients the best option is to conceive spontaneously since many treatment strategies remain unsuccessful or involve eggs donation. In this case report series, we describe the effects of a resveratrol-based multivitamin supplement containing trans-resveratrol, folic acid, vitamin B6, B12 and D, in six women with poor prognosis of pregnancy due to POI and evaluate the achievement of desired conception.

These women, aged less then 40 years, suffered from menstrual irregularities, anovulation and infertility. They all had normal karyotype, and no history of ovarian surgery, radiation exposure or chemotherapy. Blood test showed at least two values of FSH above 40 IU/l.

Four out of six patients with POI conceived after 3-6 months of a resveratrol-based multivitamin supplement, ultimately giving birth to a full-term baby. Regular menstrual cycle was restored in all patients after two to four months the start of treatment. In conclusion the treatment with a resveratrol-based supplement improved menstrual regularity and suggest a useful potential of this supplementation in some cases of POI.

Keywords: infertility, resveratrol, menstrual irregularity, POI

Introduction

Premature Ovarian Insufficiency, also known as primary ovarian insufficiency, is characterized by premature depletion or dysfunction of ovarian follicle (1), with irregular menses (intermittent or unpredictable) before the age of 40. There is no unanimous consensus on what the correct criteria are for identifying POI in adolescent, and delay in diagnosis is common (1). Despite the description of different genetic, immune and iatrogenic factors of POI, the etiology in most cases of this disease are unexplained. POI is characterized by the presence of oligo/amenorrhea in association with menopausal serum level of FSH above 40 IU/l and must be distinguished from natural premature menopause characterized by serum level of FSH very high (between 16 and 134 IU/L), estradiol very low (less than 20 pg/ml), permanent amenorrhea and absence of ovulatory cycles. POI occurs in approximately 1-2% of women aged under 40 years and in 0.1% of women aged under 30 years that present abnormal bleeding pattern (3). Clinical symptoms are similar to premature menopause, including hot flashes, night sweats, vaginal dryness, irritability, difficult on concentration (3). Five to ten percent of women with POI manage to conceive spontaneously while no women affected by premature menopause can conceive naturally.

The diagnosis of POI is psychologically devastating in reproductive-aged women because of deleterious impact on fertility. As long as ovulation is extremely rare and unpredictable in women with POI and none of the ovulation induction regimens have been shown to be effective, treatment strategies are lacking. Successful pregnancy with assisted reproductive technology (ART) rarely occurs in POI patients and the most successful

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method remains eggs donation, with important ethical limitations (3,4).

Recent studies have demonstrated the beneficial effects of resveratrol in humans. Resveratrol has been reported to decrease oxidative stress and attenuate inflammation, and these mechanisms may account for many of its health benefits. Important evidence is also emerging in the field of human reproduction indicating that resveratrol has potential positive effects in older women, PCOS, endometriosis, uterine fibroids and menopause (5). Concerning the oocyte aging, recent research have demonstrated that resveratrol is effective on granulosa cells and impacts positively on the ovarian physiology. Specifically, resveratrol induces granulosa cells proliferation through activation of the PI3K pathway and promotes primordial follicle activation (6). Compared to untreated tissues, a higher proportion of growing follicles in human ovarian tissue culture in the presence of resveratrol has been reported (6,7). However, recently conflicting findings on the actions of resveratrol on decidualization of human endometrial stromal cells (HESCs) have been published. Ochiai et al. demonstrated that resveratrol inhibits decidual transformation of primary cultured HESCs (8) while Mestre Citrinovitz et al. showed that resveratrol enhances decidualization of HESCs in culture (9). Nevertheless, because of the lack of robust data, more studies are required to verify these effects.

Furthermore in premature ovarian failure (POF) animal models, resveratrol effectively improved the ovarian function and the productive capacity of FGSCs via relieving oxidative stress and inflammation and a mechanism involving the hh signaling pathway, suggesting that resveratrol is a potential agent against POF (10).

Case Report Series

In this case report series, we describe the effects of a resveratrol-based multivitamin supplement containing trans-resveratrol (150mg /day in two administrations), folic acid, vitamin B6, B12 and D for at least 60 days, in 6 infertile women, with poor prognosis of pregnancy due to POI, with particular attention to the resumption of regular menstrual flow and/or the achievement of spontaneous conception, during an observation period of 12 months. None of the patients observed could access ART procedures because of an insufficient ovarian reserve whereas every partner has normal seminal test. When POI was diagnosed, all six patients had FSH level above 40 UI/L, irregular menses, normal karyotype, no history of ovarian surgery, radiation exposure or chemotherapy, and a BMI < 30 kg/m2.

Hereafter the description of the individual 6 cases.

Case 1

A 35-year-old female who was diagnosed with POI when she was 34, at the time of the first visit reported vasomotor symptoms, night sweats and being in amenorrhea for six months. The FSH serum level was 39,5UI/L.

After starting resveratrol supplementation, at the second visit two months later, she reported that her period has resumed about six weeks after starting treatment and that vasomotor symptoms and night sweats have disappeared. The FSH serum level in early follicle fase was 13UI/L.. She continued the treatment and returned for a check-up visit after 10 months in which she reported that she was back in amenorrhea. A transvaginal ultrasound was performed and a gestational sac with a viable embryo was recognized. She delivered a healthy full-term baby.

Case 2

A 29-year-old woman presented to our clinic with a 6-month history of oligo-amenorrhea and no vasomotor symptoms or night sweats. Laboratory blood tests performed while the patient was in amenorrhea revealed an elevated serum FSH level (38 IU/l) and AMH 0.01 ng/ml. She was given a diagnosis of POI. Since the patient wished to become pregnant it was suggested to her that egg donation or IVF were her best option to have a child. She chose to attempt conception with her own rather than using donor eggs. She started resveratrol-based multivitamin supplementation and her period was restored after 40 days of treatment. Three months later she conceived a baby naturally, without the need for assisted reproductive technology. This was confirmed by serial serum beta HCG measurements. The pregnancy proceeded uneventfully until the 35th week of gestation when she developed gestational hypertension. The baby was born at 39 weeks and 4 days of gestation, without any serious complications.

Case 3

A 38-years-old patient presented to our clinic reporting that she had been in amenorrhea for 8 months, with vasomotor symptoms and night sweats, and that she wished to become pregnant. She was diagnosed with POI and treated with various hormonal regimens coupled with close ultrasound follicle monitoring. She referred that she had very few ovulatory cycles over the last 2 years. Her serum FSH value at the moment of diagnosis was 55 IU/L. After about 4-months of treatment with resveratrol-based supplement her period resumed. The serum FSH level decreased to 18 IU/L. She continued to have menstrual bleeding every 60 days, but unfortunately, she was unable to get pregnant.

Case 4

A 39-years-old patient presented to our clinic reporting oligo-amenorrhea over the last 2 years and 4 years of infertility. Laboratory blood tests performed at the age of 37, revealed FSH serum level of 45 IU/L and AMH 0.02 ng/ml. The patient reported to have undergone several hormone replacement cycles and ovulation induction cycles and even an unsuccessful trial of intrauterine insemination (IUI) over the last 3 years. She said she was on the waiting list for eggs donation, thus we decided to start a resveratrol-based multivitamin supplementation. Four months after starting the treatment she began to menstruate regularly (every 40days), the serum FSH level decreased to 12,2 IU/L and she was able to conceive after eight

months of treatment with resveratrol-based multivitamin supplementation and delivered a healthy baby after 38 weeks of gestation.

Case 5

A 34-year-old patient came to our observation reporting that she had not menstruated for three months. Her female hormone panel showed serum FSH level of 49IU/mL and AMH of 0,01 ng/ml. Seven-weeks after starting the treatment with resveratrol-based supplement she reported having started menstruating again and a FSH serum level that was decreased to 16 IU/L. She was monitored for one year and her menstrual cycle appeared regularly every 32.4 +4 days, but unfortunately, she was unable to get pregnant.

Case 6

A 30-year-old patient with an 8-month history of amenorrhea and a previous diagnosis of POI at age of 28 presented to our clinic, manifesting her maternity desire. We confirmed diagnosis of POI (FSH value 40,8IU/L) and treated her with a resveratrol-based multivitamin supplement. After about 6 months of treatment her menstrual cycle appeared regularly every 30.4+3.8 days and the FSH value decreased to 11IU/L. This patient underwent to close ultrasound follicle monitoring; spontaneous ovulation occurred and the resulting pregnancy was confirmed by serum HCG and ultrasonography performed 28 days after ovulation. She delivered a healthy baby after 38 weeks of gestation.

Discussion

Several regimens have been employed in the setting of POI to restore menses and to achieve pregnancy however none have been proven to be effective (11,12). Oocyte donation is the most frequent suggested route of treatment in order to get pregnant, nevertheless this practice is not yet available in many countries. There is also no evidence that assisted reproductive technology (ART) without oocyte/embryo donation may improve pregnancy rate of POI patients without any other infertility factors within a spontaneous ovulatory cycle (11,12). Analysis of the six cases presented herein revealed restoration of menstrual cycle flow in all the patients after supplementation with resveratrol for at least 2 months Moreover four out of six patients with a diagnosis of POI successfully conceived spontaneously without the need of assisted reproductive technologies. Only one preclinical study, conducted on animal models, discussed the opportunity of resveratrol supplementation for women with premature ovarian insufficiency (10). The potential pitfall of this present case report is the lack of homogenous classifications of the POI population and the little number of cases. We are aware that case reports cannot decide a therapeutic management but certainly these findings can be useful to pave the way for new treatment hypotheses especially in this selected population (POI) whose treatment is not yet universally defined. Further studies are required to verify these possible beneficial effects of resveratrol observed in this limited case series.

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Table 1. Summary of POI women

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age of POI diagnosis	34	29	38	37	34	28
Age at menarche	12	11	13	13	11	12
Age at initial visit to our clinic	35	29	38	39	34	30
FSH UI/L at diagnosis (medium value)	39,8	38	55	45	49	40,8
FSH UI/L early follicular fase	13	15	18	12,2	16	11
Menses /DAYS (medium value)	55	39	62	43	80	38
Treatments: Resveratrol-based multi supplement	+	+	+	+	+	+
Method for pregnancy	Spontaneous	Spontaneous	-	Spontaneous	-	Spontaneous
Pregnancy outcome	40 wks, female 3900g	39 wks, female 3455g	-	38 wks, female 3100g	-	38 wks, male 3840g

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