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The effect of FT500 Plus® on ovarian stimulation in PCOS women

Carlo Alviggi [a], Federica Cariati [b,c], Alessandro Conforti [a,*], Pasquale De Rosa [a], Roberta Vallone [a], Ida Strina [a], Rosario Pivonello [c], Giuseppe De Placido [a]

[a] Department of Neuroscience, Reproductive Medicine, Odontostomatology—University of Naples "Federico II", via Sergio Pansini 5, 80131 Naples, Italy
[b] CEINGE Biotecnologie Avanzate, via G. Salvatore 486, 80145 Naples, Italy
[c] Department of Clinical Medicine and Surgery, Endocrinology Section, University "Federico II", via Pansini 5, 80131 Naples, Italy

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ABSTRACT

Both oxidative stress and polycystic ovary syndrome have been involved in several aspects of female reproduction. In this retrospective observational study, the outcome of controlled ovarian stimulation and follicular microenvironment of twenty-five women affected by PCOS (Group A) have been explored, evaluating the effects of myo-inositol in association with antioxidant activities (FT500 Plus®). Twenty-five untreated-PCOS women (Group B) with similar characteristics served as control group. Although there was no difference in ovarian volume at time zero, this parameter was significantly smaller at the 5-month follow-up in the Group A (11.1 ± 0.9 *versus* 13.5 ± 1; $P = 0.0001$). Group A showed a significant increase in the number of MII oocytes (6.3 ± 2.5 *versus* 4.5 ± 2; $P = 0.03$) and glutathione peroxidase activity in follicular fluid (15.4 ± 6.2 *versus* 11 ± 2.2; $P = 0.04$). FT500 Plus® may be considered in PCOS patient for improving oocyte quality.

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1. Introduction

Both oxidative stress and polycystic ovary syndrome (PCOS) have been involved in the pathogenesis of some forms of female infertility [1,2]. Oxidative stress occurs when the production of reactive oxygen species (ROS) and other radical species exceeds the scavenging capacity of antioxidants. These factors interfere with several aspects of female reproduction namely, oocyte maturation, steroidogenesis, corpus luteum function and luteolysis [1–3]. On the other hand, PCOS is considered one of the most frequent causes of sub-fertility [4]. A significant decrease in follicle quality in women with PCOS has been reported. In detail, it seems that the hyperandrogenic and hyperinsulinaemic milieu causes premature maturation of granulosa cells, which in turn results in dysregulation of cytoplasmic and nuclear maturation of oocytes [5]. Several lines of evidence indicate an association between oxidative stress and PCOS [6]. Oxidative stress markers are elevated in PCOS patients irrespective of weight [7]. Moreover, hyperinsulinaemia may determine a disequilibrium between free radicals and physiological antioxidant defences thereby increasing oxidative stress [8].

FT500 Plus® (IDI Pharma SRL, Catania, Italy) is a new dietary supplement based on myo-inositol, folic acid and active antioxidants (glutathione, selenium, vitamins C and E and zinc). Each element of this product has been implicated in the optimization of fertility outcome. Myo-inositol has been reported to promote follicular growth and physiological maturation of oocytes [9,10]. Specifically, myo-inositol supplementation significantly improved oocyte quality by reducing both stimulation time and the risk of ovarian hyperstimulation syndrome in patients undergoing controlled ovarian stimulation (COS) [11]. Finally, high concentrations of myo-inositol in follicular fluid (FF) seem to correlate with improved oocyte quality and fertilization rate in patients undergoing intracytoplasmic sperm injection (ICSI) [12].

The intake of folic acid in the preconceptional period significantly reduces the incidence of premature births and pregnancy complications. In addition, folic acid could compensate the negative effect of homocysteine in FF [13–15]. Antioxidant compounds have been shown to protect against oxidative stress systems and

Abbreviations: AFC, antral follicles count; AMH, antimullerian hormone; ASRM, American Society for Reproductive Medicine; BMI, body mass index; COS, controlled ovarian stimulation; ET, embryos transferred; FF, follicular fluid; FSH, follicle stimulating hormone; GnRH, gonadotropin releasing hormone; GPx, glutathione peroxidase; hCG, human chorionic gonadotropin; HOMA, homeostasis model assessment; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; ROS, reactive oxygen species; SOD, superoxide dismutase; TAC, total antioxidant capacity; TG, pregnancy rates; USG-TV, trans-vaginal pelvic ultrasound assessment.

* Corresponding author: Alessandro Conforti.
E-mail addresses: alviggi@unina.it (C. Alviggi), federicacariati@hotmail.it (F. Cariati), confale@hotmail.it (A. Conforti), derosap85@gmail.com (P. De Rosa), robyvallone@hotmail.it (R. Vallone), ida.strina@unina.it (I. Strina), rosario.pivonello@unina.it (R. Pivonello), gdeplaci@unina.it (G. De Placido).

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have been involved in regeneration of endogenous antioxidants [15]. Impaired levels of glutathione peroxidase in follicular fluid have been associated with reducing fertilization rate [16,17]. Glutathione is the major non-enzymatic antioxidant present in both oocytes and embryos [18]. Mature oocytes have higher levels of glutathione than immature oocytes [13,2]. In addition to its antioxidant action, glutathione contributes to the regeneration of important vitamins, such as vitamins C and E [19,20]. Vitamins C and E reduce the percentage of atresic follicles and help to counteract oxidative stress in oocytes and granulosa cells [21]. Administration of vitamins C and E in women undergoing *in vitro* fertilization (IVF) leads to an increase in their concentration in the follicular fluid, and positively affects pregnancy rates [22–24]. Selenium and zinc enhance a woman's endogenous antioxidant defences and act as co-factors for the enzymatic defensive systems against reactive species [13,17]. In particular, zinc depletion during oocyte maturation, specifically in the initial stages of meiosis, determines the interruption of the cell division process, thereby stopping oocyte maturation [25,26].

The aim of this retrospective study was to investigate the effects of FT500 Plus® supplementation in women with PCOS undergoing controlled ovarian stimulation, and to evaluate antioxidant activity in FF collected during oocyte retrieval.

2. Material and methods

2.1. Study population

The outcome of COS and antioxidant activities in the FF were retrospectively evaluated in 25 PCOS women undergone IVF/ICSI between January and December 2014 and pre-treated with the FT500® supplementation (2 sachets per day) for the 5 months preceding COS (Group A). Control group (Group B) was constituted by 25 age- and BMI-matched women affected by PCOS and undergone IVF/ICSI in the same period. PCOS diagnosis was based on the Rotterdam ESHRE/ASRM criteria (Rotterdam ESHRE/ASRM criteria 2004) when at least two of three major criteria was detected: (1) oligo/anovulation; (2) clinical (Ferriman Gallwey score) or biochemical hyperandrogenism; (3) polycystic ovaries on transvaginal ultrasound (namely, number of follicles > 12 with a diameter between 2 and 9 mm, and ovary volume >0.10 cm^3). Exclusion criteria were: basal FSH >10 IU/L; homeostasis model assessment (HOMA) >2.5; waist-to-hip ratio >0.85; treatment with estrogen–progestin and/or other hormonal therapies in the six months before the study; 21-hydroxylase deficiency; presence of ovarian cysts with a diameter >14 mm observed in two ultrasound examinations conducted within thirty days of each other; stage III-IV pelvic endometriosis assessed according to the criteria of the American Society for Reproductive Medicine (ASRM); genetic and/or autoimmune aberrations; chronic liver disease; chronic systemic inflammatory diseases; hyper- and hypo-adrenal cortical diseases; type 2 diabetes mellitus; intolerance to carbohydrates; presence of a single ovary; and previous ovarian surgery.

This study was conducted according to the Helsinki declaration. All patients enrolled in the study signed a specific consent form. Given the observational nature of the study, ethic approval was not required.

2.2. Ovarian stimulation protocol

Starting from the second day of a spontaneous menstrual cycle, the patients of both group received a daily dose of recombinant FSH (75-150 IU). All were treated with gonadotropin releasing hormone (GnRH) antagonists (Cetrorelix, Merck Serono S.p.A., Rome, Italy) at the dose of 0.25 mg/day in case of a dominant follicle at least 14 mm in average diameter. In women with at least three follicles >17 mm mean diameter, 10,000 IU of human chorionic gonadotropin (hCG) was administered intramuscularly (Gonasi HP 5000, IBSA Farmaceutici Italia SRL, Italy). Women at risk of ovarian hyperstimulation syndrome were managed according to the latest American Society for Reproductive Medicine (ASRM) guidelines [27]. Oocyte retrieval was performed by ultrasound-guided transvaginal aspiration 34–36 h after hCG administration. Embryos were transferred 48–72 h after fertilization. Luteal phase was supported using micronized progesterone at the dosage of 200 mg per day. Patients with positive beta human chorionic gonadotrophin (βhCG) were monitored up to the end of the 8th week of gestation. Before ovarian stimulation, all patients underwent trans-vaginal pelvic ultrasound assessment [USG-TV (multi-frequency vaginal probe 5.0–7.5 MHz)], in the early follicular phase of spontaneous menstrual or progestin-induced cycles. In the case of a negative medroxyprogesterone acetate test, USG-TV was carried out in amenorrhea in the absence of dominant follicles (diameter >12 mm).

2.3. Analysis of oxidative stress in follicular fluid

At the time of oocyte sampling, after the removal of the oocytes, the FF was centrifuged at 3000 g for 10 min to remove detritus, blood and granulosa cells as reported elsewhere [28]. The supernatant was transferred into sterile polypropylene tubes and stored at −80 °C until required. To determine oxidative stress we measured the total antioxidant capacity (TAC), the enzymatic activity of the endogenous antioxidants superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and the quantity of 8-Isoprostane. The TAC in the FF was measured with an antioxidant assay Kit (Cayman Chemical, Michigan, USA, intra-assay CV 3.4%, inter-assay CV 3% detection limit: 0.044 mM). Superoxide dismutase was measured with tetrazolium salt for detection of superoxide radicals generated by xanthine oxidase and hypoxanthine (Superoxide Dismutase Assay Kit, Cayman Chemical; intra-assay CV 3.2%, inter-assay CV 3.7% detection limit: 0.025 U/mL). This kit measures the three types of SOD (Cu / Zn, Mn, and FeSOD). A catalase assay kit (Cayman Chemical, Michigan, USA) was used to determine catalase activity (intra-assay CV 3.9%, inter-assay CV 9.9%, detection limit: 2 nmol/min/mL). GPx activity was evaluated with a kit (Cayman Chemical, Michigan, USA) that indirectly determines the enzymatic activity by a coupled reaction with glutathione reductase (intra-assay CV 5.7%, inter-assay CV 7 2% detection limit: 50 nmol/min/mL). In addition, we used Cayman Chemical's 8-Isoprostane EIA kit (intra-assay CV between 6.4% and 20%, inter-assay CV between 9.6 and 24.3%, detection limit: 2.7 pg/mL) to quantify 8-Isoprostane in FF. The analytes were determined using a spectrophotometer (VICTOR, Perkin-Elmer, Milan, Italy), according to the manufacturer's instructions. The final levels of enzyme activities were expressed in units of enzyme activity per μg of protein in the samples.

2.4. Statistical analysis

Statistical analysis was performed with the Statistics Package for Social Sciences software version 12.0 (SPSS Inc., USA). Data are expressed as means ± standard deviations or as percentage. The Student *t* test or Mann Whitney U test was used to compare data between groups according to variables distribution evaluated with the D'Agostino & Pearson omnibus normality test. Categorical variables were evaluated using Fisher's test. *P* values < 0.05 were considered statistically significant. Given the small sample size and the preliminary nature of the study, neither a single end-point nor a relative power analysis are provided. The main end-points are: (1) number of MII oocytes retrieved; (2) percentage of MII oocytes;

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