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ORIGINAL ARTICLE

Adjuvant sildenafil therapy in poor responders undergoing in vitro fertilization: A prospective, randomized, double-blind, placebo-controlled trial

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KEYWORDS

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Abstract *Objective:* To evaluate the effect of adjuvant sildenafil on ovarian responsiveness in low responders undergoing IVF. *Patient(s) and methods:* Prospective randomized, double-blind, placebo controlled study was conducted at Obstetrics and Gynecology department, Tanta university hospital and Center of Assisted Reproduction, Om El-kora Hospital, Tanta, Egypt. Sixty patients were classified as low responders undergoing IVF. Supplementation with sildenafil (50 mg daily) or placebo to a gonadotropin releasing hormone antagonist protocol was provided. *Result(s):* There were no significant differences in total number of 75 IU FSH ampoules used (60.025 ± 5.52) versus (66.025 ± 4.51), the number of mature follicles recruited (3.35 ± 1.137) versus (2.95 ± .826), and the number of oocytes retrieved (3.95 ± 1.395) versus (3.65 ± 1.137) or cycle cancelation rates (26.7% in the treatment group versus 23.3% in placebo group). *Conclusion:* Adjuvant sildenafil does not enhance ovarian responsiveness in cases of previous low ovarian response to controlled ovarian hyperstimulation.

1. Introduction

Unfortunately, the criteria used for the definition of poor responders to ovarian stimulation varied between different studies. Among the criteria used, the number of dominant follicles and/or number of oocytes retrieved after a standard ovarian stimulation protocol were two of the most important criteria. The number of dominant follicles varied among different studies from less than 3 to less than 6 (1–3), while the number of retrieved oocytes varied from less than 3 to less than 5 (4–6). Other criteria such as at least one canceled IVF cycle because of poor response (7), increased number of hMG or FSH ampoules used (>44) (8), increased dose of gonadotrophin used (>300 IU/day) (9) and prolonged duration of gonadotrophin stimulation (10) have been suggested. These criteria have been used either alone or in combination reflecting the lack of uniformity in the definition.

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More recently, the ESHRE working group on poor ovarian response (POR) definition published the Bologna criteria for low ovarian response and a consensus was reached on the minimal criteria needed to define POR. At least two of the following three features must be present: (i) Advanced maternal age ($\geqslant$40 years) or any other risk factor for POR; (ii) A previous POR ($\leqslant$3 oocytes with a conventional stimulation protocol); and (iii) An abnormal ovarian reserve test (i.e. AFC < 5–7 follicles or AMH < 0.5–1.1 ng/ml) (11).

Although the exact mechanism or mechanisms for ovarian aging is still under investigation, several risk factors for its early development have been identified, some are controversial and yet several others are still being revealed. Currently they are classified into medical, lifestyle, genetic, autoimmune and idiopathic factors (12).

During controlled ovarian hyperstimulation, there is expected increase in ovarian blood flow secondary to the E2 mediated decreased impedance to blood flow. Previous studies observed little or no change in ovarian blood flow in low responders. It has also been shown that pulsatility index (PI) of the ovarian arteries is negatively correlated with the number of preovulatory follicles during stimulation (13).

Sildenafil is a specific inhibitor of type 5 phosphodiesterase so it prevents the breakdown of (cGMP) and potentiates the effects of NO on vascular smooth muscle. It has been approved for the treatment of erectile dysfunction in humans (14,15). The effect of type 5 phosphodiesterase inhibition with sildenafil on endothelium-dependent vasodilation in patients with poor ovarian response to stimulation is unknown.

The rationale of our study was to use the vasodilator effect of sildenafil to enhance the ovarian blood flow and consequently improve ovarian response to stimulation in low responders.

Several studies used sildenafil to improve uterine artery blood flow and sonographic endometrial appearance in patients with prior failed assisted reproductive cycles due to low endometrial response. Some of these studies showed a beneficial effect of sildenafil (16,17). Others did not support these findings (18).

2. Materials and methods

This was a randomized, double-blind, placebo-controlled trial. It was carried out in Obstetrics and Gynecology department, Tanta university hospital and Center of Assisted Reproduction, Om El-kora Hospital, Tanta, Egypt. Approval for the study was obtained from the Clinical Research Ethics Committee of Tanta University. All participating patients provided informed consent before taking part in the study.

In this study we only included patients with previous low response to controlled ovarian hyperstimulation using antagonist protocol. The low responders were defined as those who had $\leqslant$3 dominant follicles on the day of hCG administration or $\leqslant$3 retrieved oocytes. We also included those who had previous cycle cancelation due to poor follicular development.

2.1. Exclusion criteria

We excluded patients older than 35 years of age, those with previous ovarian surgery, ovarian endometrioma, heavy smokers, patients with cardiovascular disorders and those taking medications that could affect the circulation or interact with sildenafil.

The study was performed over a period of 2 years starting from January 2012 to January 2014. Randomization was carried out by asking each patient to choose a number from 1 to 60. One of our nursing staff then put the even numbers in group I and the odd numbers in group II. After informed consent, patients in group I were allocated to receive sildenafil 50 mg/day orally and those in group II were allocated to receive placebo. All patients received the drug from the first day of menstruation of the stimulation cycle. Randomization was done with both the physicians and the patients blinded. We chose not to use vaginal sildenafil suppositories because it is not readily available in our area.

2.2. IVF protocol

All patients received antagonist stimulation protocol. All patients in each group received 300 IU of recombinant FSH, Gonal-F (Serono, Switzerland) and 150 IU of highly purified human menopausal gonadotropin (Merional; IBSA, Lugano, Switzerland) daily for 4 days starting from the second day of menstruation. The dose of gonadotropins was adjusted according to the ovarian response on transvaginal ultrasound and serum oestradiol concentration starting from day 5 of stimulation. The GnRH antagonist cetrorelix 0.25 mg (Cetrotide, Serono Laboratories, Aubonne, Switzerland) was started in all patients on a fixed day which is day 5 of stimulation and continued until day of HCG administration or cycle cancelation. 10,000 units of HCG were administered i.m. when the leading follicle (s) reached $\geqslant$17 mm in diameter. Ultrasound guided transvaginal oocyte retrieval was performed 34–36 h later. Embryo transfer was performed on day 3 after oocyte retrieval. Luteal support was started on day of oocyte retrieval throughout the luteal phase using progesterone in oil 150 mg per day i.m. Serum pregnancy test was done 14 days after embryo transfer. Cycle was canceled when the ovaries failed to respond after 10 days of stimulation or when oestradiol concentration showed a decline or plateau. Stimulation was continued if at least one follicle of 14 mm or more was found after 10 days of stimulation. OOcyte retrieval was canceled and the patient converted to IUI when < 3 follicles of $\geqslant$17 mm were achieved on day of HCG together with the presence of at least one patent tube by HSG and the total motile sperm count $\geqslant$5 millions. Transvaginal ultrasound was used to monitor ovarian response and endometrial thickness. Number of mature follicles $\geqslant$17 mm on day of HCG, endometrial thickness before stimulation and on the day of hCG administration or cancelation were reported. The number of oocytes retrieved, eggs fertilized and embryos transferred were also reported for each case. Biochemical pregnancy (positive serum pregnancy test 14 days after embryo transfer) and clinical pregnancy (detection of gestational sac on ultrasonography) were also reported.

2.3. Hormone assay

In the cycle preceding the stimulation cycle, FSH (iu/l) was measured on the second day of menstruation and AMH (ng/ml) was measured on any day of the cycle. Serum E2 (pg/ml), LH (iu/l) and progesterone (ng/ml) were measured