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Original Article

Effect of oral Tadalafil on endometrial thickness in patients receiving Clomiphene citrate for ovulation induction

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ABSTRACT

Background: Adequate and optimum endometrial development is required for a successful pregnancy to occur. Clomiphene citrate is well known for its negative impact on endometrial thickness. The long-acting phosphodiesterase 5 inhibitor, Tadalafil, was shown to improve endometrial growth in patients under Clomiphene citrate stimulation.

Objective: To study the effect of Tadalafil on the endometrial thickness in Clomiphene citrate stimulated cycles as compared to clomiphene citrate alone and human menopausal gonadotropins.

Study design: A randomized controlled study. Setting was at the infertility clinic of Cytogenetic and Endoscopy Unit, Zagazig University Hospital.

Material and methods: The study included 236 patients who underwent a single cycle of ovulation induction and timed intercourse. Patients were divided into 3 groups: Controlled ovarian stimulation was done in group A by Clomiphene Citrate alone, in group B by Clomiphene Citrate with addition of Tadalafil and in group C by Human Menopausal Gonadotropins.

Results: As regard the number of cases who got pregnant, we found that there was a statistically significant difference ($P < 0.05$) for patients in group B and C when compared with group A.

Conclusion: This study showed that the pregnancy rate achieved with Clomiphene citrate/Tadalafil combination was comparable to that achieved by Human Menopausal Gonadotropins and significantly higher than with Clomiphene citrate alone. This was attributed to the improvement of endometrial thickness by Tadalafil in Clomiphene citrate stimulated patients.

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1. Introduction

Infertility is defined as failure to conceive after one year of practicing sexual intercourse without any contraceptive measures. Primary infertility means that pregnancy has never occurred. While, secondary infertility means that the couple had a previous conception (irrespective of its outcome), but is unable to conceive again after one year of trying [1].

During the menstrual cycle the endometrium undergoes cyclic changes to prepare for implantation. For example, in the follicular phase, the growing follicles produce estradiol that will induce proliferative changes. Following ovulation, the corpus luteum produces progesterone that will induce secretory changes. If implantation did not occur during the window of implantation, the endometrium will shed once the corpus luteum undergoes regres-

sion [2]. Adequate and optimum endometrial development is required for a successful pregnancy to occur [1].

According to Habibzadeh et al. [3], many factors were considered important in affecting the endometrial growth such as woman's age, etiology of infertility, drug protocol, estradiol levels, and previous injuries to the endometrium.

Clomiphene citrate (CC) is a selective estrogen receptor modulator (SERM) that binds to the estrogen receptors at multiple sites throughout the reproductive tract, and can act as an estrogen agonist or as an antagonist. Gonadotrophins are glycoprotein hormones that can be extracted from urine of postmenopausal women or can be manufactured by recombinant technology. They stimulate follicular growth by acting directly on ovarian FSH receptors, and have no anti-estrogenic effect on cervical mucus or endometrium like clomiphene [4].

Short-acting inhibitors of phosphodiesterase 5 (PDE5), such as Sildenafil, have been proposed as useful agents for increasing endometrial development in patients with an endometrium that had previously undergone surgical treatment. The proposed mechanism of these drugs for obtaining a better endometrium

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was the improvement of vascular flow. The use of the longer-acting PDE5 inhibitor, Tadalafil, improved endometrial growth in patients under clomiphene ovarian stimulation [5].

1.1. The aim of the study

As far we know, there is no study in the literature concerning the effect of Clomiphene citrate/Tadalafil combination on endometrial thickness and pregnancy rate compared to Clomiphene citrate alone, and hMG stimulation protocols. Thus, the present study aimed to assess the effect of administering the longer-acting PDE5 inhibitor (Tadalafil) to Clomiphene citrate stimulation protocol aiming to improve the endometrial thickness and consecutively the pregnancy rate and whether this Clomiphene citrate/Tadalafil combination could be used as a safer and cheaper alternative to the conventional hMG stimulation protocol in cases of primary infertility.

2. Patients and methods

The study was conducted in the infertility clinic of the Cytogenetic and Endoscopy Unit, Zagazig University Hospital, as a randomized controlled trial between January 2015 and May 2016. After approval of the local ethics committee, a written informed consent was obtained from all patients before starting. The flowchart of the participants had been shown in Fig. 1.

The study included 236 patients who underwent a single cycle of ovulation induction and timed intercourse. They fulfilled the following inclusion criteria: female age 18–35 years with primary infertility due to either unexplained infertility or PCOS. Patient's both tubes and uterine cavity were normal as assessed by

hysterosalpingography (HSG). All patients had neither history of previous endometrial surgery nor history of smoking and were willing to participate in the study. Body mass index (BMI) was ranging between 18 and 25 kg/m². The following criteria were mandatory for diagnosis of unexplained infertility [6]: Acceptable seminal analysis, bilateral patent tubes, no tubal kinking and no peritubal adhesions according to hysterosalpingography and/or laparoscopy and confirmed ovulation as supported by regular cycles and mid luteal serum progesterone levels >10 ng/ml. According to the Rotterdam Consensus, 2004 [7]; diagnosis of PCOS was based on at least 2 of the following 3 criteria: oligo-ovulation or anovulation, clinical or biochemical evidence of hyperandrogenism, and polycystic ovaries on ultrasound assessment (>12 small antral follicles in an ovary), with the exclusion of medical conditions such as congenital adrenal hyperplasia, androgen-secreting tumours, or Cushing's syndrome. All patients had normal husband semen parameters as defined by the WHO, 2010 [8].

Exclusion criteria were patients with endometriosis, a history of ovarian hyper stimulation syndrome (OHSS), abnormal HSG/laparoscopy suggestive of pelvic adhesions with altered tubo-ovarian relationship (like pelvic endometriosis, chronic PID and postoperative adhesions), Mullerian malformations, hypogonadotropic hypogonadism, primary amenorrhea, premature ovarian failure, cases of secondary infertility, cases of failed IUI or IVF, and patients with abnormal husband semen parameters.

2.1. Ovarian stimulation and folliculometry

Basal transvaginal pelvic ultrasonography (TVS) on day 2 of the menstrual cycle was mandatory before starting. Patients were divided randomly by using random number table (computer),

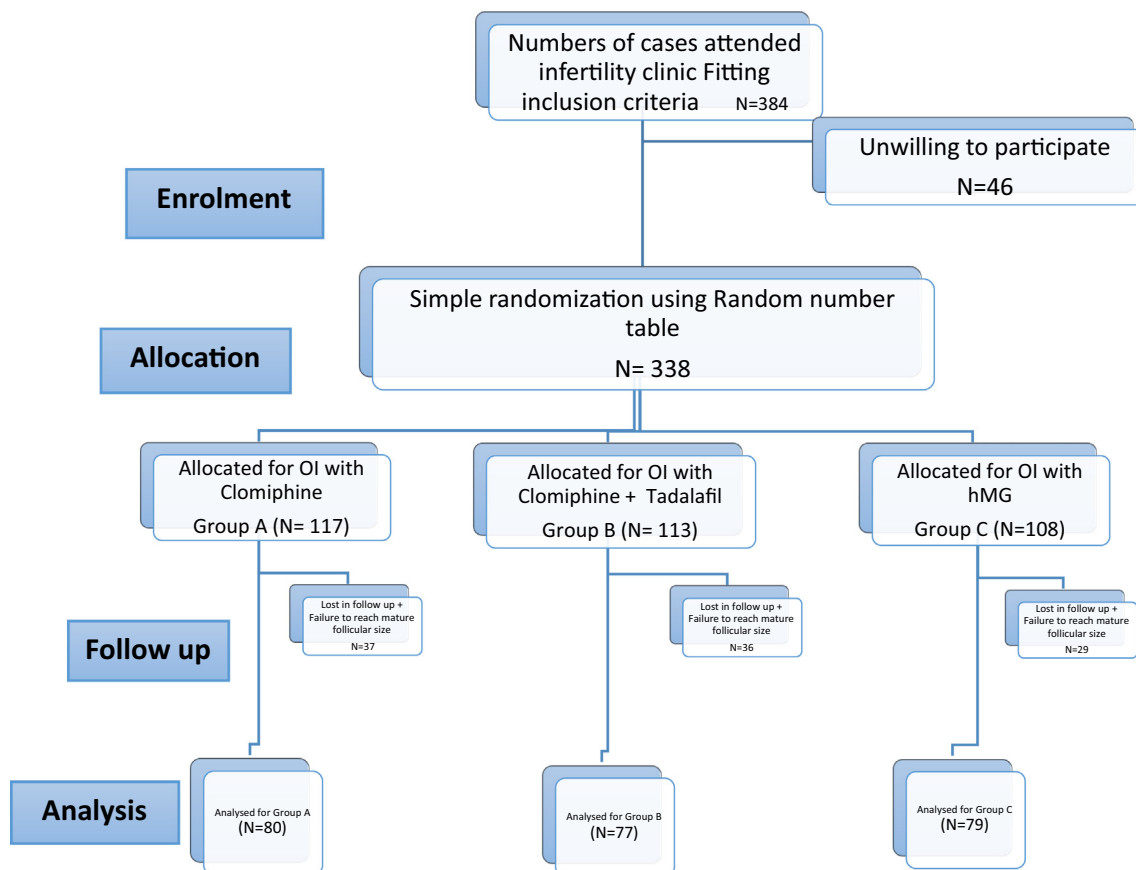


Fig. 1. Flowchart of the study population.

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