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Original Article

Effect of estradiol valerate on the pregnancy rate in patients receiving letrozole for induction of ovulation

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ABSTRACT

Background: Letrozole is as effective as clomiphene citrate for induction of ovulation in patients with PCOS. Adequate endometrial development is required for pregnancy to occur, and pregnancy rates were found to be higher when the endometrium reached at least 10 mm thickness.
Objective: To study the effect of estradiol valerate on the endometrial thickness and subsequently the pregnancy rate in PCOS cases receiving letrozole for induction of ovulation as compared to letrozole alone.
Study design: A randomized controlled study. Setting was at the infertility clinic of the Cytogenetic and Endoscopy Unit, Zagazig University Hospital.
Material and methods: The study included 273 patients who underwent ovulation induction and timed intercourse. Patients were divided into 2 groups: controlled ovarian stimulation was done in group 1 by letrozole with addition of estradiol valerate and in group 2 by letrozole alone.
Results: As regard the clinical pregnancy rate, we found a statistically significant difference between the 2 studied groups, with documented clinical pregnancy in 34 patients in group 1 compared to only 16 patients in group 2.
Conclusion: This study showed that the pregnancy rate achieved with letrozole/estradiol valerate combination was significantly higher than with letrozole alone. This was attributed to the improvement of endometrial thickness by estradiol valerate.

1. Introduction

Polycystic ovary syndrome (PCOS) is the commonest endocrinopathy resulting in anovulatory infertility in young women. Infertility due to chronic anovulation is one of the commonest clinical manifestations of this syndrome [1,2]. Letrozole is as effective as clomiphene citrate for induction of ovulation in patients with PCOS [3]. It is considered a suitable alternative for management of clomiphene citrate resistant cases with good ovulation rate [4].

Letrozole is an orally-active aromatase inhibitor, with good potential for ovulation induction. Many researchers have studied this drug as an option for ovulation induction [5]. Inhibition of aromatase enzyme leads to decrease in estrogen levels, resulting in more follicle stimulating hormone (FSH) release, which results in follicular growth [6].

Aromatase enzyme inhibitors also cause a local increase of ovarian androgens which increases the follicular sensitivity to FSH and stimulation of insulin-like growth factor (IGF)-I. FSH and IGF-I are both essential for follicular maturation [7].

Adequate endometrial development is required for pregnancy to occur, and pregnancy rates were found to be higher when the endometrium reached at least 10 mm thickness [8]. Ethinyl estradiol can reverse the deleterious effects of clomiphene citrate on the endometrial thickness, which may contribute to higher pregnancy rates [9].

1.1. The aim of the study

The add value of estradiol valerate to letrozole in achieving a better pregnancy rate has not been established in literature. This study aimed to assess the effect of letrozole/estradiol valerate combination in controlled ovarian stimulation cycle aiming to improve the endometrial thickness and consecutively the pregnancy rate.

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 July 2014 to January 2016.

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After approval of the local ethics committee, a written informed consent was obtained from all patients before starting. The study included 273 patients who underwent ovulation induction and timed intercourse. They fulfilled the following inclusion criteria: female age 18–35 years with primary or secondary infertility due to PCOS, with normal husband semen parameters. Patient's both tubes and uterine cavity were normal as assessed by hysterosalpingography (HSG). Body mass index (BMI) was ranging between 18 and 34.9 kg/m^2. According to the Rotterdam Consensus, 2004 [10], 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. Normal husband semen analysis was well-defined by the WHO 2010 [11].

Exclusion criteria were patients with history of abnormal HSG or laparoscopy suggestive of pelvic adhesions with altered tubo-ovarian relationship (like pelvic endometriosis, chronic PID and postoperative adhesions), Mullerian malformations, primary amenorrhea, hypogonadotropic hypogonadism, premature ovarian failure, cases of failed IUI or IVF, and male factor infertility (abnormal semen profile).

Hyperprolactinemia and thyroid diseases were treated before enrollment. Morbidly obese patients with BMI $\geq$35 kg/m^2 were excluded and advised for weight reduction.

2.1. Ovarian stimulation and folliculometry

Basal transvaginal ultrasonography (TVS) on day 2 of the menstrual cycle was done for all patients before starting. Patients were then divided by using random number table (computer), software Open Epi version 3.21 into two groups (1 and 2). Patients were assigned to either group by the randomization known while allocation concealment concentrated on preventing selection and confusing biases. In group 1, controlled ovarian stimulation (COS) was done by letrozole (Femara 2.5 mg tablets, NOVARTIS) 2 tablets daily for 5 days (from 3rd day till 7th day of the cycle) followed by estradiol valerate 2 mg (The white tablets of Cyclo-Progynova, BAYER) 2 tablets daily for 5 days (from 8th day till 12th day of the cycle). In group 2, controlled ovarian stimulation (COS) was done by letrozole (Femara 2.5 mg tablets, NOVARTIS) 2 tablets daily for 5 days (from 3rd day till 7th day of the cycle).

Serial TVS started at cycle day 8 for assessment of follicular growth (number and diameter of follicles) and endometrial thickness and was continued at 1–3 day interval till a mean follicular diameter (mean of two orthogonal diameter measurements) reaching $\geq$18 mm. Then 5000–10,000 units of human Chorionic Gonadotropin (Choriomon, IBSA, Institut Biochimique SA) was given IM. Endometrial thickness measurements were conducted in the mid sagittal plane, from the outer edge of the endometrial-myometrial interface to the outer edge of the widest part of the endometrium [12].

Monitoring of the follicular growth and endometrial thickness was done with B-mode imaging using wide band micro-convex endocavity probe with 4.5–8.5/D6 MHz frequency specially used for obstetrics and gynecological purpose, Sonoace_8800 digital Gaia system. All measurements were performed by one blind single operator. All data were digitally stored and were not analysed until the end of the study. All patients were advised for a timed intercourse (TI) 36 h after human Chorionic Gonadotropin (hCG) triggering.

All cases with a positive serum pregnancy test, defined as a finding of plasma β-hCG concentration >10 mU/ml using immunoassay two weeks after timed intercourse, were followed up by abdominal ultrasound scan at 6 weeks from the first day of their last menstrual period (Transabdominal 2D probe of Voluson 730 pro V machine, GE healthcare, Austria, with 3.5 MHz sector transducer was used) for detection of intrauterine gestational sac (Clinical pregnancy). If pregnancy did not occur, the patient was followed up for 2 successive cycles with the same procedure.

The outcomes measured were, the number of cases reaching mature ovarian follicle ($\geq$18 mm), the number of stimulated cycles, the endometrial thickness on the day of hCG triggering, the number of cases with positive serum pregnancy test and the clinical pregnancy rate in the two studied groups along the three cycles of treatment. The sample size was calculated through Epi-Info (Epidemiological Information Package) software version 6.1.

2.2. Statistical analysis

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analysed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance; Differences between frequencies (qualitative variables) and percentages in groups were compared by Chi-square test. Differences between parametric quantitative independent groups by *t*-test in non-parametric by Man Whitney, P value was set at <0.05 for significant results & <0.001 for high significant result.

3. Results

Total of 398 new cases attended the infertility clinic during the study period and were assessed for eligibility and 312 Patients were fitting to the inclusion criteria. The study protocol, the intervention involved, possible early and long term side effects of interventions were explained to the patients. Out of which, 299 patients were willing to participate in the study and consented for participation. Simple randomization of those 299 patients was done and 150 cases were allocated in group 1 (letrozole + estradiol valerate) and 149 cases in group 2 (letrozole alone). 26 patients were dropped from follow up (11 and 15 from group 1 and 2 respectively). So, finally 273 patients were analysed (139 and 134 patients from group 1 and 2 respectively). Study flowchart is shown in Fig. 1.

There were no statistically significant differences (P > 0.05) between the 2 studied groups regarding the demographic and clinical parameters (i.e. age, BMI, type of infertility and duration of infertility) as shown in (Table 1 and Fig. 2).

Regarding the basal hormonal profile (serum FSH and LH), there was no statistically significant difference (P > 0.05) between the 2 studied groups. The mean value for basal serum FSH levels for group 1 was 5.64 ± 2.33 IU/mL compared to 5.59 ± 2.24 IU/mL for group 2. The mean value for basal serum LH levels for group 1 was 5.21 ± 1.79 IU/mL compared to 4.98 ± 1.83 IU/mL for group 2 (Table 1).

As regard the number of Cases reaching mature follicular size during the study period, there was no statistically significant differences (P > 0.05) between the 2 studied groups (61.1% compared to 60.4% in the first cycle, 59.5% compared to 61.2% in the second cycle, and 60.1% compared to 58.8% in the third cycle) (Table 2).

As regard the number of stimulated cycles during the study period (till pregnancy occurs or completing the 3 cycles of the study, whichever is earlier), there was no statistically significant differences (P > 0.05) between the 2 studied groups (139 compared to

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