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ORIGINAL ARTICLE

Impact of letrozole on ultrasonographic markers of endometrial receptivity in polycystic ovary syndrome women with poor endometrial response to clomiphene citrate despite adequate ovulation

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KEYWORDS

PCOS;
Clomiphene citrate;
Letrozole;
Thin endometrium;
Receptivity;
Doppler

Abstract *Objectives:* To investigate the endometrial effects of letrozole in PCOS women with poor endometrial response (endometrium thickness ⩽7 mm) to clomiphene citrate (CC) despite adequate ovulation, using the ultrasonographic markers of endometrial receptivity.

Study design: Ambidirectional cohort study.

Patients and methods: Sixty women with anovulatory PCOS having endometrial thickness less than 7 mm despite adequate ovulation with CC underwent ovulation induction with Letrozole (5 mg/day from cycle day 3 to 7) for one treatment cycle. Main outcome measures: Comparison of the endometrial thickness (ET) and pattern, uterine artery and spiral artery, resistance index (RI) and pulsatility index (PI) between the current letrozole and previous CC stimulated cycles.

Results: In the current letrozole cycle compared with the previous CC cycles, there were significantly greater midcycle endometrial thickness (8.97 ± 1.32 vs. 5.7 ± 1.2, respectively; $P < 0.05$), multilayered endometrial pattern (93.33% vs. 50%, respectively; $P < 0.05$) and rate of detection of subendometrial blood flow. Both RI and PI of spiral arteries in the letrozole cycle (0.63 ± 0.05 and 1.12 ± 0.06, respectively) showed significantly lower impedance compared to the previous CC cycle (0.75 ± 0.09 and 1.42 ± 0.13, respectively) ($P < 0.05$). Pregnancy rate per cycle was 20% (12/60) in the letrozole cycle, all in women with endometrial thickness ⩾7 mm.

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Conclusion: Letrozole is an effective second-line treatment in women with inadequate endometrial response to CC, as letrozole increased endometrial thickness trilaminar pattern and improved endometrial perfusion.

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1. Introduction

Polycystic ovary syndrome (PCOS) is a complex, heterogeneous endocrine disorder in the reproductive-age women, with an incidence of 5–10% (1). Infertility due to anovulation affects 75% of women with PCOS (2). Since the 1960s, clomiphene citrate (CC) has been the first-choice ovulation inducer in PCOS anovulatory infertility. Clomiphene citrate is an orally active nonsteroidal drug with mixed estrogen agonist/antagonist properties. Clomiphene citrate stimulates ovulation by competitively inhibiting the estrogen (E) binding to the hypothalamic estrogen receptors (ER), thereby releasing the hypothalamus from the negative inhibition of endogenous (E), leading to increase in gonadotropin pulse frequency, which consecutively induces ovulation (3). Clomiphene citrate has the advantages of being highly effective in inducing ovulation, while relatively safe, low-priced and orally administered. The lower pregnancy rate (30–40%) in relation to the ovulation rate (60–85%), and the reported miscarriage rate (13–25%), in the CC-stimulated cycles, may be attributed to the antiestrogenic effects of CC on cervical mucus and endometrium (4). Several studies revealed that CC reduces endometrial receptivity, as it impaired endometrial development and uterine blood flow resulting in endometrial thinning in 15–50% of patients with subsequent implantation failure and induces early pregnancy loss due to luteal phase defect (3,5).

Letrozole, a selective reversible third-generation aromatase inhibitor, has the potential to be used for ovulation induction with demonstrable endometrial sparing effect. Letrozole induces ovulation by inhibiting the conversion of androgens to estrogen, creating an estrogen-deficient environment; mimic the central reduction of negative feedback through which CC works (6). Several studies revealed that letrozole may be superior or at least equal to CC in ovulation and pregnancy rates in women with anovulatory PCOS and inadequate clomiphene response. Compared to CC, letrozole is cleared from circulation more rapidly due to shorter half-life; associated with monofollicular growth, lower preovulatory estradiol (E2) levels, and thicker endometrium. Letrozole does not deplete estrogen receptors and is devoid of any antiestrogenic peripheral actions; therefore, it has no adverse effect upon the endometrial receptivity and cervical mucous quality (7).

Receptive endometrium is fundamental for the successful implantation of an embryo. Receptive endometrium is endometrium adequately primed for implantation and its growth is regulated by steroid hormones, various growth factors and cytokines. A good blood supply toward the endometrium is essential for these factors to reach the endometrium. Ultrasonography evaluation of the endometrial morphology (thickness and pattern) and Doppler assessment of blood flow toward the endometrium and the subendometrial region, measured during the preovulatory period provide non invasive tool for the evaluation of endometrial receptivity (8,9). Moreover, conventional 2D and 3D power Doppler sonography had comparable efficacy for the prediction of endometrial receptivity and pregnancy outcome (8).

Based upon these considerations, this study was designed to investigate the endometrial effects of letrozole in PCOS women with poor endometrial response (i.e., endometrium thickness $\leqslant$7 mm) to CC despite adequate ovulation, using the ultrasonographic markers of endometrial receptivity.

2. Patients and methods

This ambidirectional cohort study was conducted at the Department of Obstetrics and Gynecology, Benha University Hospitals, and private practice settings, Alkalubia, Egypt from September 2012 to January 2014. The study protocol was approved by the Local Ethics Committee. All participants gave their written informed consent before their inclusion in the study. The study included 60 women with anovulatory PCOS, who had endometrial thickness less than 7 mm measured on the day of hCG injection, despite adequate ovulation (i.e. mid-luteal serum progesterone $\geqslant$5 ng/ml) with CC. Diagnosis of PCOS was based on the Rotterdam criteria (2003 ESHRE/ASRM consensus), (10) whereby the diagnosis of PCOS requires the presence of two of three criteria, i.e., oligomenorrhea and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and/or polycystic ovaries on ultrasound. Other inclusion criteria were: (i) age of women between 18 and 35 years at the time of screening; (ii) period of infertility $>$2 years; (iii) basal serum follicle stimulating hormone level (FSH) $<$10 mIU/mL in the early follicular phase; (iv) all women had bilateral tubal patency proved by hysterosalpingography or laparoscopy and their partners satisfied the normal parameters of semen analysis according to the modified WHO criteria (11); and (v) good physical and mental health. Those with (i) history of laparoscopic ovarian drilling or ovarian cystectomy; (ii) endocrinopathies such as hyperprolactinemia, congenital adrenal hyperplasia, thyroid disease and clinically suspected Cushing's syndrome; (iii) uterine pathology such as leiomyoma, adenomyosis, or congenital uterine anomalies; (iv) androgen-secreting neoplasm;(v) chronic cardiovascular, hepatic, renal or pulmonary disease; (vi) hypersensitivity or contraindications to Letrozole; and (vii) users of metformin, gonadotropins, hormonal contraception or diet regimen within the last 6 months were excluded from the study. Letrozole cycle was started two months after last CC treatment cycle to eliminate any post-treatment effect of CC.

The patients received Letrozole oral tablets (Femara 2.5 mg tablet; Novartis Pharma Services, Switzerland) 5 mg daily from cycle day 3 to 7 of the spontaneous or progestin induced cycle. Only one complete treatment cycle was offered to each woman. Starting from cycle day 9, follicular growth monitoring (number and mean diameter) by transvaginal sonography

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