AROMATASE INHIBITOR FOR OVULATION INDUCTION: A COMPARATIVE STUDY BETWEEN LETROZOLE AND CLOMIPHEN CITRATE IN ANOVULATORY INFERTILE WOMEN

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ABSTRACT

The study was designed to compare the effectiveness of Letrozole and clomiphen citrate in the treatment of anovulatorv infertility. Thirty patients were selected randomly who had anovulatorv infertility. In letrozole group, fifteen patients got 5-7.5 mg of letrozole orally and in clomiphen citrate group, 100-150 mg of clomiphen citrate was given orally for maximum of six cycles and in both the groups the drugs were started from day 3 -7 of the menstrual cycle. There were no significant differences between the age, duration and type of fertility. But statistically significant increase of follicular development in letrozole group (ñ=0.020). Mean endometrial thickness was 8.33±1.54 and 5.36±1.84 respectively in letrozole and in clomiphen citrate group (ñ =0.048). There was no significant difference in ovulation in both the groups but pregnancy was more (33.3%) with the letrozole group. Letrozole is an effective agent for ovulation induction. It can be used as an alternative to CC as a first-line of treatment for ovulation induction.

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INTRODUCTION

Impaired fertility is thought to affect 10 to 15% of couples[1]. Ovulation is the prerequisite for pregnancy in female[2]. Clomiphen citrate (CC) has been the first-line method of ovulation induction in couples with anovulatory infertility since its introduction in 1956[3]. Clomiphen citrate is a non-steroidal selective estrogen receptor modulator, which acts primarily by binding with estrogen receptors at the hypothalamus[4]. This competitive inhibition results in a perceived drop in drop of circulating estrogen to the hypothalamus, leading to increased gonadotrophin secretion and subsequent induction of ovulation[5]. Approximately 80% of women ovulate while using clomiphen[6]. But only 40% of women will achieve pregnancy[7]. This reduced pregnancy rate is disappointingand due to its peripheral antiestrogenic effects, mainly on the quality or quantity of cervical mucus, and endometrial growth and maturation[8]. Long lasting estrogen receptor depletion has been involved in the antiestrogenic mechanism of action of CC. Prolonged estrogen receptor depletion results in the significant thinning of the endometrium, which is dose dependent[9]. It also appears that CC accumulates in the body because of its long half-life (2 weeks)[10].

Because of these problems, the concept of aromatase inhibition was proposed as a new method of ovulation induction that could avoid many of the adverse effects of CC[11]. Aromatase is a microsomal member of the cytochrome P450 hemoprotein-containing enzyme complex superfamily that catalyzes the rate limiting in the production of estrogen. Aromatase converts androstenedion to estrone and testosterone to estradiol[12]. Aromatase activity is present in many tissues, such as the ovaries, the brain, adipose tissue, muscle, liver, and breast, and in malignant breast tumors. The main sources of circulating estrogens are the ovaries in premenopausal women and adipose tissue in post menopausal women[13].

Letrozole is a third generation selective aromatase inhibitor[14]. It is an aromatase inhibitor that has been used in women with breast cancer[15]. In the late 1990s, Letrozole began to be used to induce ovulation by being administered in the early part of the menstrual cycle[16]. In this study, ovulation was induced in the infertile

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anovulatory women due to polycystic ovarian syndrome by letrozole and clomiphen citrate.

MATERIALS AND METHODS

The study was conducted in Bangladesh Infertility Management Center, Dhaka, a private infertility care center. The study period was from February 2008 to January 2009. Thirty infertile women of anovulatory polycystic ovarian syndrome (PCOS) were included in the study. The exclusion criteria were the tubal factor infertility, male factor infertility, endometriosis, hyperprolactinaemia and thyroid disorder. Once inclusion and exclusion criteria were met, alternate woman was selected either for letrozole group or for clomiphen citrate group. Before the study informed verbal consent was taken from all women. In letrozole group, 5-7.5 mg of letrozole and in clomiphen citrate group 100-150 mg of clomiphen citrate were given orally for maximum of six cycles and in both the groups the drugs were started from day 3-7 of the menstrual cycle. The main outcome measures were the follicular growth, endometrial thickness, occurrence of ovulation and pregnancy rate.

Transvaginal ultrasounds were performed to document the follicular growth and the endometrial thickness on day 10 of the cycle and whenever necessary. Follicles were considered as mature when they attained the size of 18 mm or more. Endometrial thickness was measured as the maximal thickness of the endometrial lining in the plane through the central longitudinal axis of the uterine body. The tri-laminar endometrial pattern and the thickness of endometrium, 8 mm or more were considered satisfactory. When both the follicular growth and the endometrial thickness were satisfactory, 5000 IU HCG injection was given intramuscularly and advised for timed coitus. Ovulation was observed by transvaginal ultrasounds at 48 hours after the HCG injection and by day 21 progesterone. Pregnancy was confirmed by ultrasonography. The results were analyzed statistically by Statistical Program of Social Science (SPSS) version 11.5.

RESULTS

The age, duration of infertility and the type of infertility, i.e., primary and secondary were similar in both the groups. The follicular diameter was 19.33± 2.55 and 16.67± 3.33 in letrozole and in clomiphen groups respectively. The follicular growth was significantly more in letrozole (p=0.020). Endometrial thickness was significantly higher in letrozole group (p=0.048). Ovulation rate was 80% and 73.3% in letrozole and in clomiphen groups respectively and showing no significant differences. Pregnancy rate was higher in letrozole group (p=0.025).During the study period, no miscarriage was reported.

Table I

Response to Letrozole and Clomiphen Citrate (c.c)

Response	Letrozole n=15	CC n=15	p
Follicular diameter in mm at day 12	19.33±2.55	16.67±3.33	0.020
Endometrial thickness	8.33±1.54	5.36±1.84	0.048
Ovulation	12(80%)	11(73.3%)	0.666
Pregnancy	5(33.3%)	1(6.66%)	0.025

DISCUSSION

Many women suffering from infertility, who failed to release an egg each month. This state of chronic anovulation is characterterized by irregular menstrual cycles and may be accompanied by obesity or hirsutism. The condition is known as polycystic ovarian syndrome. The 20-25% of patients with PCOS patients are "clomiphen resistant"[17,18].

Clomiphen citrate is the most commonly prescribed agent for induction of ovulation. Despite high rate of ovulation, pregnancy rate per cycle remain relatively low. Regardless of normal ovulation, 15%-50% of women on clomiphen citrate will develop a thin endometrium[19] and it is not improved by addition of supplemental estrogen, suggesting that it is a result of estrogen receptor depletion. Both thin endometrium and non-trilaminar pattern of the endometrium at midcycle have been associated with low pregnancy rates and early pregnancy loss. Letrozole induced accumulation of ovarian androstenidion may result in increased expression of FSH receptors. This would result in enhanced sensitivity of the developing follicles to existing FSH.

In this study, the follicular development was significantly more in letrozole group. Stephanie et al [19] in their study showed no significant difference (p =0.11) in follicular growth between two groups. This may be due to the selection criteria of taking normal ovulating volunteers in their study. However Begum et al[2] in their study showed significant increase in follicular development (ñ <0.005) in letrozole group. In their study, perhaps the population was poor responder to clomiphen citrate. The endometrial thickness in letrozole group is significantly higher (p=0.048). Other studies also showed the similar results. This may be the antiestrogenic effect of clomiphen citrate on the endomertium. There was no significant difference in ovulation in both the groups but pregnancy was more (33.3%) with the letrozole group. However, one study showed 25.93% pregnancy with letrozole group and no pregnancy with clomiphen citrate group[2]. No miscarriage found during the study period. In

another couple of studies letrozle was proven to be safe for women and was not a human teratogen, nevertheless clomiphen citrate may result small for gestational age infants[14,20].

Letrozole is an effective agent for ovulation induction. In clomiphen citrate resistant cases, letrozole should be the drug of choice before proceeding to injectable drugs, which are far more expensive and carry higher risks of multiple pregnancies. It can be used as an alternative to clomiphen citrate as a first-line of treatment for ovulation induction.

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