Predictors of letrezole success in ovulation induction among women with polycystic ovary syndrome resistant to clomiphene citrate

Fadia Jassim Al-Izzi
CABOG, DOG

Abstract:

Background: Clomiphen citrate is still the traditional therapy used for inducing ovulation in polycystic ovary syndrome. Between 20-25% of patients with this syndrome does not respond to clomiphen citrate and fail to develop follicles of desirable size. Letrozol, an aromatase inhibitor, is increasingly used for induction of ovulation in women in whom clomiphene citrate was unsuccessful.

Methods: In a prospective study, during the period from October 2008 to the end of December 2009, in the infertility clinic in Al-Yarmouk Teaching hospital, fifty one infertile women were diagnosed as having polycystic ovary syndrome according to the Rotterdam criteria; all patients had previously received clomiphene citrate and were diagnosed as having resistance to this drug. Those patients were assigned to receive an aromatase inhibitor, letrezole, in a dose of 2.5 mg, increased to 5 mg in subsequent cycles, given orally from the third day of a spontaneous bleeding or progesterone-induced withdrawal bleeding for 5 days. The primary outcome measures were the number of growing and mature follicles and endometrial thickness. Secondary outcome measures were the occurrence of pregnancy and miscarriage.

Results: With 51 patients and 122 cycles of letrezole therapy, we had 84 (69.2%) ovulatory cycle and 18 pregnancies (15.4%). This study has showed that the body mass index is significantly different between the two groups and the cut off point for it is equal to or more than 26 (sensitivity 60.71% and specificity 78.26%). The mean cycle day of human chorionic gonadotrophine (h CG) administration was 13.4±1.67.The mean number of mature follicles (more than 18 mm in size) on the day of h CG administration was 1.21(range 1-2) and the mean endometrial thickness on the same day was 10.2±1.31mm.Letrezole was well tolerated with no reported side effects

Conclusion: Induction of ovulation with letrezole in clomiphene citrate-resistant polycystic ovary syndrome patients is associated with limited number of mature follicles without adverse effect on endometrial thickness. The rates of ovulation and pregnancy are encouraging. One of notable findings is the association of high body mass index with high response rate to letrezole.

Key word: Aromatase inhibitors (letrezole), polycystic ovary syndrome

Introduction

Anovulation is responsible for about 20% of female infertility of which polycystic ovary syndrome (PCOS) is a major cause.[1] Clomiphen citrate (CC) is still the traditional therapy used for inducing ovulation in PCOS, it is an antiestrogen that results in a 60-85% ovulation rate and 10-20%pregnancy rate per cycle[2], this disparity in outcome may be due to antiestrogen effect of CC, which involves long lasting estrogen receptor (ER) depletion.CC accumulates in the body due to its long half life (2 weeks) [3], thus may have an adverse effect on the quality and quantity of the cervical mucus as well as the endometrial development, causing implantation failure and luteal phase defect. Prolong ER depletion results in significant thinning of the endometrium, which is dose dependant. [4]

On the other hand, 20-25% of patients with PCOS do not respond to CC and fail to develop follicles of desirable size–(clomiphene resistance)[5], for these patients, there are few limited adjuvant therapies that can be tried before moving to gonadotropin therapy or laparoscopic ovarian drilling. However their usefulness is limited to specific abnormalities, because many women with CC failure do not present with any overt signs of a treatable disorder. [6]

Gonadotropin preparations such as pure FSH or pure hMG have been used as a second line treatment for ovulation induction. In women with PCOS, because of the high sensitivity of ovaries to gonadotropin stimulation, treatment with hMG or pure FSH is expensive & difficult to control and characteristically induces several ovulatory follicles, leading to the risk of multiple pregnancies and ovarian hyperstimulation syndrome (OHSS) [7].therefore, a simple oral treatment that could be used without risk of hyperstimulation and with minimal monitoring would be the preferred therapy. [5]

Mitwally and Casper, in 2001, hypothesized that it may be possible to mimic the action of CC without depletion of ER by administration of aromatase inhibitor in the early part of the menstrual cycle. This would result in release of hypothalamic/pituitary axis from estrogenic negative feedback, increasing gonadotropin secretion and resulting in stimulation of ovarian follicle development. In a prospective trial Mitwally and Casper used letrozol, an aromatase inhibitor, for induction of ovulation in women in who

CC was unsuccessful. The ovulation rate in those wih PCOS was 75% and pregnancy rate was 25 %. [5]

For many years, aromatase inhibitors have been used as an adjunct treatment for breast cancer .letrozol and anastrozol are third generation group, they are highly selective, highly potent with reversible action; they are completely absorbed after oral admistration, with a mean half live of 45 hours. Their adverse effects are gastrointestinal disturbances, asthenia, hot flashes, headache, and back pain. [8].

The intention of this study is to evaluate the outcome of letrezole in those with PCOS whom failed to respond to CC.and to compare letrozole responders and nonresponders.

Patients & Methods

During the period from October 2008 to the end of December 2009, fifty one infertile women were included from the patients attending the infertility clinic of Al-Yarmouk teaching hospital-Gynaecology & Obstetric Department, Baghdad. All patients were diagnosed as having PCOS according to the Rotterdam criteria. All patients had previously received CC and were diagnosed as having CC resistance(failure of ovulation after 6-cycles of CC reaching a dosage of 150 mg daily).our inclusion criteria were age 18-39 years, period of infertility more than 2-years,serum level of FSH <12U/L,and serum prolactine within normal in early follicular phase. Exclusion criteria were history of pelvic surgery or infertility factor other than anovulation.letrozole was started after 2-3 months after CC to allow for washout of the CC.Patients underwent physical examination including checking of body mass index(BMI).

A transvaginal ultrasound examination was performed to exclude any pelvic pathology before treatment. The dose of letrezole was 2.5 mg, increased to 5 mg in subsequent cycles, given orally from the third day of a spontaneous bleeding or progesterone-induced withdrawal bleeding for 5 days. The response was monitored using transvaginal ultrasound starting from day ten of the cycle and thereafter according to the growth of follicles. When at least one follicle reached more than18 mm in diameter, 10 000 U hCG (pregnyl) was given intramuscularly, and timed intercourse was advised. Two days after giving hCG, the patients were assessed for ultrasound signs of ovulation. Clinical pregnancy was diagnosed when a gestational sac was detected on transvaginal ultrasound one week after the missed period.

The primary outcome measures were the number of growing and mature follicles and endometrial thickness. Secondary outcome measures were the occurrence of pregnancy and miscarriage.

Data were analyzed using SPSS computer package by Students *t* test. Proportions were analyzed using the chi-square test. Results were expressed as mean and standard error of mean. P<0.5 was considered a statistically significant difference.

Results

With 51 patients and 122 cycles of letrezole therapy, we have 84 (69.2%) ovulatory cycle and 18 pregnancies (15.4%), these pregnancies were singleton. **Table 1** shows the clinical characteristics of the responders and no responders. There were no significant differences between the two groups regarding period of infertility, LH,FSH,or LH/FSH Ratio (**table 2**).

Table (1) the characteristics of the responders and nonresponders

characteristics	Responder group (N=28)	Non responder group (N=23)	P value
Age	25.71+4.29	29.52+4.32	0.0029
Period of infertility	3.65+2.00	3.375+1.1597	0.5404
Body mass index	28.3043+2.5483	25.6786+2.8938	0.0013
FSH levels	6.7870+1.6007	5.8857+1.4478	0.0401
LH levels	17.2391+3.8803	15.5643+4.0248	0.1393
LH/FSH Ratio	2.7956+0.9881	2.6242+0.5972	0.4696

This study has showed that the body mass index is significantly different between the two groups and the cut off point for it is equal to or more than 26 with a sensitivity of 60.71% and specificity of 78.26% **fig 1**.

The mean cycle day of h CG administration was 13.4+/-1.67.The mean number of mature follicles>18 mm on the day of h CG was 1.21(range 1-2) and the mean endometrial thickness on the same day was 10.2±1.31mm. Letrezole was well tolerated with no reported side effect.

Table (2): The Adjusted Odd Ratios for the different variables included in this study

Variable	Odds Ratio	95% CI	P Value
Age	0.8458	0.7064 to 1.0127	0.06829
BMI	0.7264	0.5478 to 0.9632	0.02637
FSH	0.9699	0.1288 to 7.3017	0.9763
LH	0.8514	0.4143 to 1.7499	0.6616
LH_FSH_Ratio	2.2656	0.0355 to 144.4110	0.6996
period_of_infertility	0.9117	0.5112 to 1.6258	0.7540

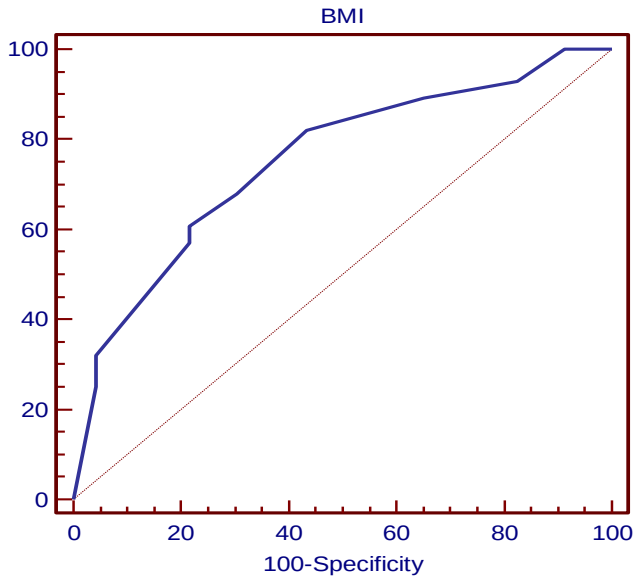

Figure (1): the ROC Curve analysis to predict the cut off value for BMI for the responder group. BMI >= 26(Sensitivity = 60.71 %, specificity = 78.26 %)

Discussion:

Clomiphene citrate (CC) resistance, persistence of anovulation after a standard dose, and the discrepancy between the ovulation and pregnancy rates with CC therapy paved the way for another oral therapy that overcomes the previous gaps. Mitwally and Casper performed the first trial with letrezole in a group of PCOS women who had failed to respond to CC, the ovulation rate was 75% and the pregnancy rate was 25% [5] thereafter, many reports released confirming the efficacy of aromatase inhibitors.

There have been several mechanisms proposed for aromatase inhibitors success .one proposed mechanism was that it would be possible to block estrogenic negative feedback, without depletion of estrogen receptors by administration of aromatase inhibitors in early part of the menstrual cycle. Inhibition of aromatization would block estrogen production from all sources and would release the hypothalamic–pituitary axis from estrogenic negative feedback. The resultant increase in gonadotropin secretion would stimulate growth of ovarian follicles.

Withdrawal of estrogen centrally also increases activins, which are produced by a wide variety of tissues, including the pituitary gland, and stimulate synthesis of FSH [9] .Because aromatase inhibitors do not deplete estrogen receptors, normal central feedback mechanism remains intact. As the dominant follicle grows and estrogen levels rise, normal negative feedback occurs centrally, resulting in suppression of FSH and atresia of the smaller growing follicles [10]. A single dominant follicle, and mono-ovulation, should occur in most cases. This might be of advantage in cases of PCOS, thereby avoiding the risk of ovarian hyperstimulation syndrome. Also, letrezole may act locally on the ovary to increase the follicular sensitivity to FSH by blocking conversion of androgen substrate to estrogen, increasing the local androgen.[11]

The ovulation rate in this study is about 69.2% out of 122 cycles.Mitwally and Casper had 75%[5],Al-Omari etal had ovulation rate of 87.5%[12],and Metawie reported 92.5%[13].this difference may be explained by the small sample size , or repeated cycle where in our study the average number of cycles was 2 per patient .Recent randomized trial by Bayar etal reported 65.5% ovulation induction where 38 patients with 99 cycles all of them have PCOS and they had letrezole as first line therapy[14] ,approximately the same percentage reported by Badawy etal after recruitment of 218 patients with 543 cycles[15]. In the last 2 randomized trials (Bayar etal & Badawy etal) the dose of letrezole was different 2.5mg vs 5mg yet no obvious change in ovulation rates, in our study we were using 5mg in subsequent cycles in

some patients but the smaller sample size makes evaluation not proper.

Pregnancy occurred in 18 cycles i.e. 22%of ovulatory cycles and it was 15% per total number of cycles. This result is comparable with the result of Mitwally and Casper (25%). Al-Omeri etal (27.7%), and Metawie (>17.5%).all pregnancies were singleton in this study, which is consistent with the above studies. This may be due to the limited number of mature follicles compared to other methods of treatment. The multiple pregnancies in CC are 10% .15-25% with gonadotropins and about 2% with ovarian drilling. [16, 17]

Although, we did not report any complications in the gestational group, almost all the studies [5, 16, 17] reported the same rates of abortion, ectopic pregnancy, and cycle cancellation rates as well as pregnancy outcome in letrezole –treated patients. The teratogenic potential of AIs was shown in animal's studies, leterzole has short half- life (two days) and usage for short period of time and in the follicular phase of the menstrual cycle prevents drug exposure during organogenesis. [14]

Comparing the responders and nonresponders with regard to clinical and laboratory characteristics, there was significant difference in BMI, after a search for this finding in other researches, we failed to find such result and we think a larger sample is needed to certify this point, and it will be a predictor of response to leterzole.Aboubaker Elnashar et al, they compared the above parameters between responders and non responders but there were no differences. [18]

At least 4 randomized trials comparing letrezole as 1st line vs CC, the meta-analysis of these trials provides strong evidence that letrezole is at least as effective as CC.[19]

Induction of ovulation with letrezole in CC-resistant PCOS patients is associated with limited number of mature follicles but no adverse effect on endometrial thickness. The rate of ovulation and pregnancy is encouraging. One of notable findings is the association of high BMI with high response rate to letrezole.

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Department of Obstetrics & Gynecology, Collage of Medicine-Mustansiriya University