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Research Article

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Clomiphene Citrate Combined with Tamoxifen Citrate versus Letrozole for Inducing Ovulation in Patients with Clomiphene Citrate -Resistant Polycystic Ovary Syndrome

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Abstract

This prospective observational study was conducted on 242 patients with clomiphene citrate (CC) resistant polycystic ovary syndrome (PCOS) who were allocated into two regimens of induction of ovulation, the first group(n=128) received both CC and tamoxifen and the second (n=114) received letrozole. The ovulation rate, endometrial thickness, number of dominant follicles, pregnancy rate, miscarriage rate and live birth rate were found comparable between the two groups. Combined therapy with CC and tamoxifen is beneficial in patients with PCOS who failed to respond to CC alone.

Introduction

Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility that affects 4-7% of women worldwide [1].

Oral agents as clomiphene citrate (CC), letrozole and tamoxifen are the first line drugs for inducing ovulation in patients with anovulatory PCOS [2].

Clomiphene citrate can induce ovulation in 80% of anovulatory patients but only 40% of women get pregnant with pregnancy rate per cycle around 10-20% and as high as 60% after six cycles and 97% after 10 cycles of induction of ovulation. Unfortunately, about 20-25% of patients are resistant to CC and fail to ovulate [2-4].

In a recent systematic review, in the subgroup of case-control studies, tamoxifen was identified to be associated with higher ovulation (RR = 1.28, 95% CI: 1.07, 1.54, I2 = 0.0%) and pregnancy rates (RR = 1.82, 95% CI: 1.09, 3.06, I2 = 0.0%) than CC [5].

For women with PCOS and a body mass index greater than 30, letrozole should be considered first-line therapy for ovulation induction because of the increased live birth rate compared with CC [6].

The aim of this study was to assess whether induction of ovulation using combination of CC and tamoxifen citrate is comparable to letrozole in CC-resistant PCOS or not.

Materials and methods

This was a prospective observational study carried out at the Department of Obstetrics and Gynecology, Faculty of Medicine, Menoufia University, Shibin El-kom city, Menoufia governorate, Egypt during the period between the beginnings of June 2016 and November 2018.

The study protocol has been revised and approved by the medical ethics committee at Menoufia Faculty of Medicine with informed consent form signed by all patients before conducting the study.

The sample size was calculated based on the assumption of a difference of 10% between the two groups regarding the clinical pregnancy rate. The study was designed to have 90% power at the 5% significance level via enrollment of 110 patients in each group.

Criteria of inclusion are CC-resistant PCOS based on the revised Rotterdam criteria with patients failed to respond to CC 150 mg daily for five days after 3-6 cycles of stimulation, normal semen analysis, normal uterine cavity and bilateral tubal patency.

Patients with endocrine disorders affecting ovulation as hyperprolactinemia, thyroid and adrenal gland disorders as well as those with anatomical or structural abnormalities as uterine fibroids, endometriosis, ovarian cyst and pelvic inflammatory disease were excluded from the study.

After enrolment of 302 patients with CC-resistant PCOS, 30 cases dropped out and 242 completed the study (Figure 1)

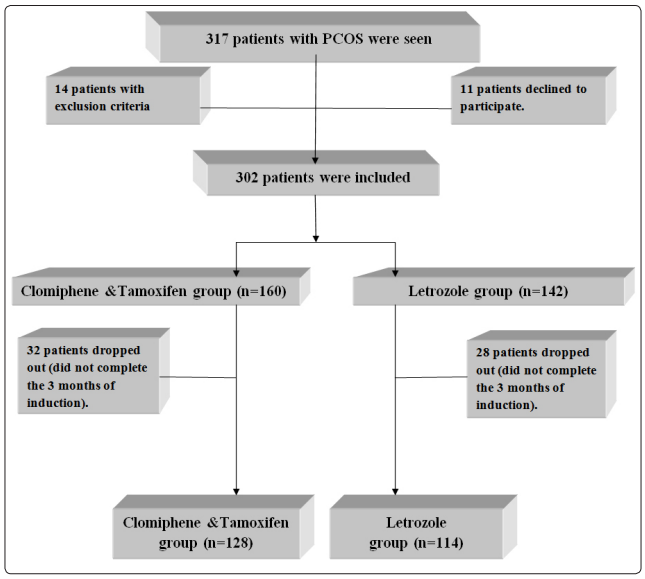

Figure 1: Flow diagram of recruitment and retention of participants in the study

Enrolled patients were allocated into one of the two treatment groups via restricted shuffled approach, as follows:

Group 1(Clomiphene citrate and tamoxifen citrate group): received CC (Clomid, 50 mg tablets, Sanofi-aventis, Egypt) twice daily from the 3rd day of the cycle for 5 days combined with tamoxifen citrate (Tamoxifen 20 mg tablets, Amriya Pharmaceuticlas, Egypt) twice daily from the 3rd day of the cycle for 5 days for 1-3 cycles.

Group 2 (Letrozole group): received letrozole 2.5 mg (Letrozole 2.5 mg, Acdima International, Egypt) twice daily from the 3rd day of the cycle for 5 days for 1-3 cycles.

In both groups, folliculometry was started on day 8 till confirmation of ovulation and administration of human chorionic gonadotrophins (Epifasi 5000 IU, ampoule, EIPICO pharmaceuticals, Egypt).

Outcome measures

- Ovulation rate, number of mature follicles and endometrial thickness on the day of hCG administration.
- Clinical pregnancy rate during every cycle of stimulation. Pregnancy was diagnosed by positive pregnancy test in the serum to be confirmed by transvaginal ultrasound for the confirmation of fetal cardiac activity.
- Miscarriage rate: number of spontaneous or induced pregnancy terminations before 20 weeks' gestation.
- Live birth rate: the number of deliveries that resulted in a live born neonate.

Statistical analysis

Data was analyzed with an IBM computer using the SPSS 22 statistical software package (SPSS Inc., Chicago, IL). Student's t test and Chi square tests were used when appropriate. P-value ≤ 0.05 was statistically significant and < 0.001 was highly significant.

Results

There was no significant difference between the two groups regarding patients' characteristics in terms of age, duration of infertility, body mass index and basal FSH and LH levels (p>0.05) as depicted in (Table 1).

Table 1: Patients characteristics

	Clomiphene and Tamoxifen (n=128)	Letrozole (n=114)	Student's t-test	P-value
Age (years)	25.6±3.1	25.3±3.5	0.71	>0.05
Duration of infertility (months)	23.9±3.3	24.2±3.1	0.73	>0.05
Body mass index (Kg/m²):	25.2±4.8	25.8±4.1	1.04	>0.05
<25	60(46.87%)	54(47.36%)	0.001†	>0.05
≥25	68(53.13%)	60(52.64%)		
Basal hormones:				
FSH(IU/L)	6.2±1.4	6.5±1.1	1.84	>0.05
LH (IU/L)	12.7±3.3	12.3±3.8	0.88	>0.05

†Chi square test, FSH=Follicle stimulating hormone, LH=Leutinizing hormone.

The ovulation rate, endometrial thickness, number of dominant follicles, pregnancy rate, miscarriage rate and live birth rate were comparable between the two groups (p>0.05) as revealed in (Table 2).

Table 2: Outcome of treatment

	Clomiphene and Tamoxifen (n=128)	Letrozole (n=114)	Student's t-test	P-value	Odd's ratio at 95%CI
Ovulation rate					
First cycle	78 (60.9%)	72	0.05	>0.05	0.91(0.54-1.53)
Second cycle	84 (65.6%)	74	0.001	>0.05	1.03(0.61-1.75)
Third cycle	82 (64.1%)	72	0.001	>0.05	1.04(0.62-1.76)
Endometrial thickness (mm)					
First cycle	8.7±2.5	8.5±2.6	0.61	>0.05	
Second cycle	8.6±2.8	8.7±2.5	0.29	>0.05	
Third cycle	8.5±2.6	8.6±2.6	0.3	>0.05	
Number of dominant follicles					
First cycle	1.7±1.7	1.8±1.6	0.47	>0.05	

Second cycle	1.8±1.7	1.9±1.7	0.46	>0.05	
Third cycle	1.8±1.5	1.7±1.6	0.5	>0.05	
Clinical pregnancy rate	41(32%)	36 (31.57%)			
First cycle	12	10	0.001	>0.05	1.08(0.45-2.59)
Second cycle	14	12	0.01	>0.05	1.04(0.46-2.36)
Third cycle	15	14	0.001	>0.05	0.95(0.44-2.06)
Miscarriage rate	8 (19.5%)	6 (16.6%)	0.001	>0.05	1.2(0.4-3.57)
Live birth rate	33 (25.78%)	30 (26.3%)	0.001	>0.05	0.97(0.55-1.73)

†Chi square test.

Discussion

The current study revealed that combination of CC and tamoxifen citrate was comparable to letrozole in patients with CC-resistant PCOS in terms of achieving ovulation, pregnancy as well as both miscarriage and live birth rates.

To the authors' knowledge, there is only one small study (20 patients) in the literature that reported the use of combined CC and tamoxifen citrate in patients with PCOS which was reported by Suginami et al, in 1993 [7].

Letrozole is effective for inducing ovulation in CC-resistant PCOS as demonstrated in previous studies and in recent reviews and guidelines [6,8-10].

The addition of tamoxifen to CC in the current study may be associated with beneficial effect on endometrial thickness which may explain the comparable pregnancy rate with letrozole.

The use of tamoxifen was proved effective in patients with PCOS who failed to CC particularly those with endometrial thickness less than 7 mm when undergoing Intrauterine Insemination Cycles and frozen-thawed embryo transfer cycles as recently reported [11,12].

Ovulation induction with CC might result in lower endometrial thickness (ET) than other ovulation induction regimens. Whether the lower ET caused the lower pregnancy and live birth rates remains to be elucidated as recently reported by systematic review and meta-analysis [13].

Inability to design a randomized trial, to record adverse effects and cost of treatment of both regimens constitutes unintended limitations of the current study.

Larger multicenter studies are warranted to prove or refute the beneficial use of combined CC and tamoxifen in CC-resistant PCOS patients before the resort to the more costly and invasive gonadotrophin therapy or laparoscopic ovarian drilling.

In conclusion: combined use of CC and tamoxifen was comparable to letrozole for inducing ovulation in CC-resistant PCOS in terms of ovulation, pregnancy and live birth rates.

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