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Clomiphene citrate versus tamoxifen for ovulation induction in women with PCOS: a prospective randomized trial

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ABSTRACT

Objective: To reevaluate the efficacy of induction of ovulation with CC versus TMX in a group of anovulatory subfertile women with PCOS in a randomized controlled trial.

Study design: A prospective randomized controlled study in which 371 PCOS patients were randomly allocated into two treatment groups: group A (187 patients) where women received CC and group B (184 patients) where they received Tamoxifen for one treatment cycle. The outcome measures were number of growing and mature follicles, serum E_2 (pg/ml), serum progesterone (ng/ml) and endometrial thickness, the occurrence of pregnancy and miscarriage.

Results: The number of stimulated follicles reaching ≥16 mm diameter was significantly more in the CC group compared to Tamoxifen stimulated group (2.1 SD ± 0.1 vs. 1.1 SD ± 0.7, $p < 0.0001$). The endometrium at the time of hCG administration was significantly thicker in the TMX group (10.1 ± 0.1 mm vs. 9.3 ± 0.4 mm,). Ovulation occurred in 120/187 cycles (64%) in the CC group and 95/184 cycles (51.6%) in the TMX group with significant difference between two groups in favors of clomiphene ($p = 0.01$). Serum E_2, on the day of hCG administration, was significantly higher in the clomiphene group ($p < 0.0001$). Pregnancy occurred in 37 cycles in group A (18.7%) and 20/184 cycles (10.8%) in group B and the difference was statistically significant ($p = 0.04$).

Conclusions: Clomiphene citrate is more successful than tamoxifen as a first line therapy for ovulation induction in women with PCOS.

1. Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder affecting women of reproductive age [1]. According to a consensus between the European Society of Human Reproduction Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), two of the following three factors are required for diagnosis of PCOS: oligomenorrhea or amenorrhea; clinical and biochemical signs of hyperandrogenism, or both; polycystic ovaries as seen on ultrasound scanning [2]. In anovulatory subfertile women with PCOS, ovulation induction has been successfully conveyed with a number of medical and/or surgical interventions [3–5].

Clomiphene citrate (CC) is a synthetic compound composed of a mixture of two isomers, enclomiphene and zuclomiphene [6]. It has been used for ovulation induction for almost 50 years [7]. Clomiphene citrate acts primarily by occupying the hypothalamic estrogen receptors for a longer period than estrogens [8,9]. Consequently, it increases the release of GnRH with an ultimate increase in serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels. This temporary increase in endogenous gonadotropins stimulates the ovary, when occurs early in follicular phase, and increases the number of follicles reaching ovulation [9]. It was apparent that clomiphene citrate has both estrogenic and anti-estrogenic effects [10]. Concerns about its anti-estrogenic effect on the whole reproductive tract have led some clinicians to recommend other anti-estrogens as tamoxifen (TMX) as an alternative to clomiphene for ovulation induction in anovulatory women with PCOS [11–13]. Either clomiphene citrate or Tamoxifen had been suggested as the first line drug for ovulation induction in anovulatory women with PCOS [14]. But, are both drugs equally effective in that respect? In a recent Cochrane review, there was no evidence of a difference in effect between clomiphene versus tamoxifen for ovulation induction [15]. However, the total number of the included participants was too small to be conclusive. The purpose of this trial was to reevaluate the efficacy of induction of ovulation with CC versus TMX in a group of anovulatory subfertile women with PCOS in a randomized controlled trial.

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2. Materials and methods

The study comprised of 371 women with PCOS among those attending the Outpatient Clinic in Mansoura University Hospitals, Mansoura University, Egypt, and a private practice setting in the period from December 2005 to December 2009. Diagnosis of PCOS based on the revised 2003 consensus on diagnostic criteria (ESHRE/ASRM 2003). All patients had patent Fallopian tubes proved by hysterosalpingography and normal semen analysis for their partners according to the modified criteria of World Health Organization (1999). The study was approved by the local Research Ethics Committee and all participants gave informed consent before inclusion in the trial.

Patients were randomly allocated into two treatment groups: group A (187 patients) where women received CC and group B (184 patients) where they received Tamoxifen for one treatment cycle. Randomization was done using a computer generated random table for the whole group and allocation was done by the investigators. Neither the patients nor the investigators were blinded to the therapy as the outcome was objectively measured. Withdrawal bleeding was achieved using 10 mg of dydrogesterone tablets for 10 days before stimulation. Patients in CC group took 100 mg of CC oral tablets (Clomid; Hoechest Marion Russel, Cairo, Egypt) daily from day 3 of the menses for 5 days (187 patients, 187 cycles), whereas patients in the TMX group took 20 mg of tamoxifen oral tablets (Nolvadex; AstraZeneca Ltd, Herts, UK) daily from day 3 of the menses for 5 days (184 patients, 184 cycles). All patients were monitored by transvaginal ultrasound for the mean follicular diameter and endometrial thickness in the days 10, 12, and 14 of the cycle. Serum esrtadio (E_2) (pg/ml) was measured at the time of hCG injection b using direct double antibody kits (Pantex, Santa Monica, CA) serum P (ng/ml) was measured on days 21–23 of the cycle by using antibody coated-tube method (Coat-A-Count; Diagnost Product Corporation, Los Angeles, CA). Human c gonad otropin injection (hCG) (5000–10,000 IU IM, P meyl; ganon, Oss, Holland) was given when one follic easur t least 18 mm was found. Patients were advised to have intercourse 24–36 h after hCG injection. Serum P (ng/ml) was measured on day 8 post to hCG administration for confirmation of ovulation. Values greater than 7 ng/ml were considered a proof of ovulation. Serum hCG was determined 2 weeks after hCG injection in the absence of menstruation for diagnosis of pregnancy. Transvaginal ultrasound was performed 5 weeks post hCG administration for women with positive pregnancy test in blood. The researcher who was involved in collecting data as regards the outcomes was blinded to women allocation to the treatment groups. Primary outcome measures were the number of growing and mature follicles, serum E_2 (pg/ml) at the day of HCG administration, and endometrial thickness (mm) on the d dministration, ovulation rate.

The secondary outcome measu s clinical p nancy rate. Clinical pregnancy rate was efine the pr nce of an intrauterine gestational sac h evide tal r and cardiac pulsation by TVS five wee ost to CG adm ation in women with positive pregnanc t in b d. Miscarr ge was defined as absence of fetal p o c pulsa n in an intrauterine gestational sac de ed by 1 week st hCG administrated in a woman with sitive pregn st in blood.

2.1. Statistical analys

ta obtained were tistically analyzed using statistical pa age for social science (SPSS 16) (SPSS Inc., Zonguldak K elmas Univ ty, Zonguldak, Turkey). Sample size calculation, be the study owed that each arm should contain at least 180 patie ha 0% power of the study at 95% confidence interval (CI) wh 15% difference in pregnancy rate was expected ween the two groups. Data analyzer was blinded to patients' g nt. Student's *t*-test was used for comparing quantitative data while proportions were analyzed using the χ^2 test. Results were expressed as mean ± standard deviation for continuous data and percentages for qualitative ones. The differences were considered to be statistically significant whenever $p < 0.05$.

Table 1
Characteristics of the patients.

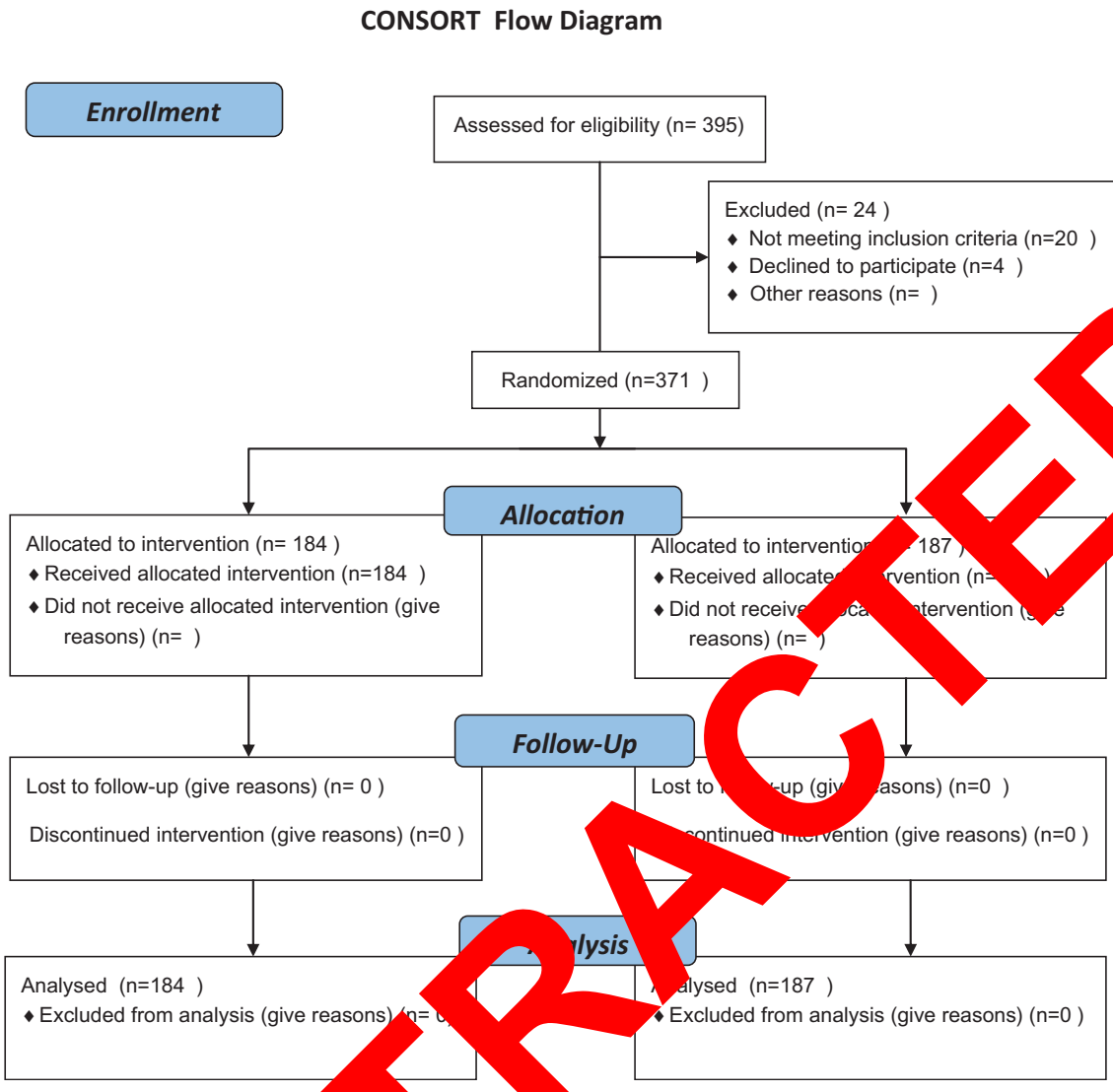
	roup A (Clomiphene group)	Group B (Tamoxifen group)	p[a]
Number of women (cycles)	87 (187)	184 (184)	
Age (years)[b]	25.8 ± 2.1	26.2 ± 2.2	0.07
BMI (kg/m^2)[b]	29.9 ± 3.1	30.5 ± 2.8	0.06
Parity			
Nuliparaous	111 (59.3%)	106 (57.6%)	0.8
Multiparous	76 (40.7%)	78 (42.4%)	
Day 2 seru H (IU/m	5.3 ± 2.0	5.6 ± 2.1	0.1
Duration bfertili be)[b]	18.0 ± 7.2	16.8 ± 6.0	0.08

[a] None of th ces were tistically significant ($p > 0.05$).
[b] Mean ± SD.

Table 2
Outcomes in clomiphene citrate (CC) and tamoxifen groups.

	Group A (Clomiphene group)	Group B (Tamoxifen group)	p value	CI
Ovulation rate	120/187 (64%)	95/184 (51.6%)	0.01[a]	22.80–45.01
Pregnancy rate	35/187 (18.7%)	20/184 (10.8%)	0.04[a]	21.10–43.12
Pregnancy rate/ovulation	35/120 (29.2%)	20/95 (21.1%)	0.045[a]	22.80–42.91
Miscarriage rate	5/35 (14%)	4/20 (25)	0.7	18.55–23.36
Serum E_2 (pg/ml)[b]	516 ± 42.2	399 ± 48.3	0.0001[a]	12.20–20.01
Number of follicles reaching 18 mm[b]	2.1 ± 0.1	1.1 ± 0.7	0.0001[a]	15.55–23.22
Endometrial thickness (mm)[b]	9.3 ± 0.4 mm	10.1 ± 0.1	0.0001[a]	26.25–32.21

[a] The differences were statistically significant ($p < 0.05$).
[b] Mean ± SD.



3. Results

We approached 395 women, 371 women agreed to participate and signed consent. The study comprised of 371 patients (371 cycles) in total. There were no statistical significant differences between the two groups in regard age, duration of infertility, type of infertility, body mass index (BMI), day 2 serum FSH or the presenting symptoms and signs (Table 1).

The number of stimulated follicles reaching ≥16 mm diameter was significantly more in the CC group compared to Tamoxifen stimulated group (2.1 SD ± 0.1 vs. 1.1 SD ± 0.7, $p < 0.0001$). The endometrium at the time of hCG administration was significantly thicker in the CC group (10.1 ± 0.1 mm vs. 9.3 ± 0.4 mm, $p < 0.0001$). Ovulation occurred in 120/187 cycles (64%) in the CC group and 95/184 cycles (51.6%) in the TMX group with a significant difference between two groups in favors of clomiphene ($p = 0.01$). Serum E_2, on the day of hCG administration, was significantly higher in the clomiphene group (0.0001). Pregnancy occurred in 35/187 (18.7%) cycles and 35/120 (29.2%) ovulations in group A and 20/184 (10.8%) cycles and 20/95 (21.1%) ovulations in group B and the differences were statistically significant. There was no significant difference between miscarriage rates among pregnant women in both groups (Table 2). Two twin pregnancies occurred in the clomiphene group and none in the tamoxifen group. No higher order pregnancies or OHSS occurred in both groups.

4. Comments

This randomized trial showed that clomiphene citrate was superior to tamoxifen for ovulation induction in women undergoing ovulation induction in terms of clinical pregnancy rate per woman. This is in contrast to previous non-randomised reports that praised TMX as a better ovulation induction drug in this group of patients [16]. A Cochrane review had shown both drugs to be equally effective in terms of pregnancy rate per woman [15]. However, results were pooled from only two RCTs with a total number of participants of 190 women. A previous larger systematic review and meta-analysis that aggregated results from four randomised trials on anovulatory women, whether PCOS or not, had also shown no difference between the two medications [17]. Our study has strict inclusion criteria that involved only women with PCOS.

It is vexing that the re-establishment of ovulation by CC does not produce a much higher pregnancy rate. This discrepancy between ovulation and pregnancy rates (only 50% of those who ovulate will conceive) may be partly explained by the peripheral anti-estrogenic effects of CC at the level of the endometrium and cervical mucus or by hypersecretion of LH [18]. While the depression of the cervical mucus may be overcome by performing IUI, suppression of endometrial proliferation, unrelated to dose or duration of treatment but apparently idiosyncratic, indicates a

poor prognosis for conception if the endometrial thickness on ultrasound scanning does not reach 8 mm at ovulation [6]. CC not only increases the desired FSH but also produces an increase in LH concentrations. This increase in LH, whose basal level is often already high in women with PCOS, may compromise pregnancy rates in those receiving CC [18].

However, there is little or no compelling evidence to support these notions. The quality and quantity of cervical mucus production in CC treatment cycles may sometimes be reduced [19], but rarely to an extent that jeopardizes the effective capture, survival, or transport of sperm. Limited endometrial proliferation has been observed in some CC-treated patients, but the effect is minor or not at all evident in the large majority of women [20–22]. Although some studies have suggested that fecundity may relate to endometrial thickness, others have failed to demonstrate any significant correlation. CC has indeed been shown to inhibit steroid hormone production by cultured avian [23], ovine [24], and human granulosa/luteal cells [25], but estrogen and progesterone levels in CC-induced cycles are typically significantly higher, not lower, than in spontaneous cycles. Adverse effects of CC on mouse ovum fertilization and embryo development have been demonstrated in vitro [26], but circulating levels of CC never reach the concentrations required to produce these effects, even after several consecutive treatment cycles [27]. Taken together, available evidence and accumulated clinical experience suggest that any adverse antiestrogenic effects of CC present no significant obstacle in the majority of treated women.

TXN had been suggested to improve cervical mucus [28]. Any potential favorable effect of TXN had failed to be translated into a better pregnancy rate in our study. The elevated serum E_2 with CC compared to TXN may reflect a larger increase in endogenous gonadotropins secondary to stimulation with CC that led to more recruitment of more follicles and hence more E_2 secretion. The higher serum E_2 level may explain, together with the better ovulation rate, the increased pregnancy rates. Some researchers had advocated the concomitant use of tamoxifen with clomiphene citrate for a few cycles [11,29]. Despite other recommended the addition of adjuvants as dexamethasone for clomiphene resistant cases [30,31]. In our series, we used a high ovulation rate in favor of clomiphene in women with PCOS who were undergoing ovulation induction for the first time. In agreement with others, we have not detected any case of OHSS with CC or did we with TXN. Miscarriage rate was not significantly different between both drugs [13,32]. So far, there is no formal dose determining trials for tamoxifen. Ovulation was achieved with 20–80 mg daily of tamoxifen in different studies [1,13,17].

To conclude, this study showed that clomiphene citrate is more successful than tamoxifen as first line therapy for ovulation induction in women with PCOS. Clomiphene citrate should be the first drug of choice for ovulation induction in anovulatory women with PCOS.

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