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Original Article

Intrauterine insemination versus timed intercourse in ovulation induction cycles with clomiphene citrate for polycystic ovary syndrome: A retrospective cohort study

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ABSTRACT

Aim: The aim of this study is to evaluate the effect of intrauterine insemination (IUI) on clinical pregnancy rates in women with polycystic ovary syndrome (PCOS) undergoing ovulation induction (OI) cycles.
Methods: We evaluated the medical records of one hundered and forty-seven infertil anovulatory women with PCOS who attended to the infertility outpatiens clinics of the current hospital. All women underwent either IUI or timed intercourse (TIC) following OI with clomiphene citrate (CC) according to their requests. Some demographic and clinical features, baseline hormone levels and treatment cycle characteristics were recorded for each woman.
Results: Of a total 147 cycles, 56 cycles were with IUI and 91 others with TIC. The IUI and TIC groups were similar in terms of age, BMI, gravidity numbers, parity numbers, number of abortion and infertility duration ($p > 0.05$). There were also no significant differences in hormone parameters ($p > 0.05$). Moreover, no significant difference was observed between the groups regarding semen parameters and weekly coit frequency. However, a significant difference was found in clinical pregnancy rates between the IUI group (48.2%) and the TIC group (11%) ($p < 0.001$).
Conclusion: Compared to TIC, IUI increases clinical pregnancy rates in infertile women with PCOS who underwent OI with CC.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopaties in women of reproductive age, affecting between 6.5 and 8% of women overall [1,2]. PCOS as it defines a syndrome, has a multiple potential etiologies and variable clinical presentations. Oligo- or anovulation and hyperandrogenism are the most common findings of PCOS. Other features are polycystic ovaries on pelvic ultrasonography, infertility due to oligoovulation, obesity, and insülin resistance. The main cause of infertility in women with PCOS is chronic anovulation [3]. Although significant progress has been made towards the universally accepted diagnostic criteria for PCOS, the optimal treatment for infertile women with PCOS is various. Treatments include lifestyle modifications and pharmaceutical agents such as clomiphene citrate (CC), gonadotropins and letrozol. However, CC is still the first choice for ovulation induction (OI) in those anovulatory women [4].

Intrauterine insemination (IUI) is a simple, cheap and non-invasive method which widely used in treatment of many infertility problems, although it is not considered as an assisted reproductive technique. The selection of accurate patient group, patient's age, permeability of fallopian tubes, duration of infertility, total motile sperm count, sperm morphology and preovulatory follicle number are important determinants for success in predicting the outcomes of this method. Although the necessity of IUI in women with unexplained or mild male subfertility who have undergone OI with CC is widely accepted [5–9], its role and success for anovulatory patients remains unclear [10,11].

In this study, we aimed to evaluate the effect of IUI on clinical pregnancy rates in women with PCOS undergoing OI cycles with CC.

Materials and methods

We evaluated the medical records of one hundred and forty-seven infertile women with PCOS who attended University of Health Sciences Zekai Tahir Burak Women's Health Research and Education Hospital, for infertility treatment between June 2017 and January 2018. All consecutive patients diagnosed with

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anovulatory PCOS were included in the study. PCOS was diagnosed by using the Rotterdam criteria of of European Society of Human Reproduction and Embryology (ESHRE)-American Society for Reproductive Medicine (ASRM) [12]. Chronic anovulation was confirmed by displaying a serum level of progesterone < 3 ng/mL during the midluteal phase. All semen parameters were evaluated according to the modified criteria of World Health Organization [13] and normozoospermia was shown on all semen analysis. All of the patients underwent hysterosalpingography which showed patency at least one tube. All women initially had the following basal hormonal assays including follicule stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), prolactin on Day 2 or 3 spontaneus or progestrone-induced menstruation, and mid-luteal progestrone. Hormone parameters were run with UnicelDxI 800 Immunoassay System (Beckman Coulter, Fullerton, CA, USA).

During the study period, only the last cycles of 147 patients were included. Exclusion criterias were other causes of infertility, semen analysis levels which suboptimal for IUI, women who had received ovarian stimulation with gonadotrophins, who had systemic medical conditions and age under the 18 years or above the 40. The study was approved by the Zekai Tahir Burak Women's Health Research and Education Hospital Ethics Committee.

Ovulation induction protocol

The patients were administered CC (Klomen®, Kocak Farma, Istanbul, Turkey) 50–150 mg/day from day 2 to 5 of the spontaneous or induced cycle after basal transvaginal ultrasonography. The doses were determined based on the patient characteristics such as body mass index (BMI) and previous cycle features. All women were monitored by serial transvaginal ultrasound with Logiq ProSeries 200 ultrasound device (General Electrics Company, Niskayuna, NY, USA) equipped with 6.5 mHz transvaginal probe for mean follicular diameter and endometrial thickness during OI. Follicle diameters were measured on two planes and their mean diameters were taken. When at least one follicle reached a maximum diameter of 17–18 mm, 250 mcgr of recombinant human chorionic gonadotropin (rhCG) was administered subcutaneously. The decision whether or not to perform IUI was made according to the couple's decision. IUI was performed 34–36 h after hCG injection. A single insemination catheter (TecnoCath insemination catheter, Ankara, Turkey) was used for IUI. The cervix was exposed with a bivalve speculum, the mucus was removed with a cotton swab, and the tip of the catheter was gently introduced into the uterus until it lay about 0.5 cm from the top of the uterine cavity in the fundal region. An experienced infertility specialist performed the all IUI procedures. Women remained supine position for 10 min after the procedure. For those who did not undergo IUI, the couples were instructed to have unprotected TIC on hCG day and every two days for subsequent one week. After the each sexual intercourse, women were recommended to lie on her back with a slight lifting of her hips for at least ten minutes. According to our clinical policy, all patients were observed for any evidence of ovulation with monitoring midluteal serum progesterone level. No luteal phase support was given to these patients.

Sperm preperation

Semen samples were collected from the patients by masturbation in a private room nearby the laboratory. After liquefaction for 20 min at the vacuum furnace, the collected semen specimens (pre-washed) were assessed for conventional semen parameters including sperm concentration and sperm motility by the computer-assisted semen analyzer. The rest of the semen was processed using standard swim up method with a sperm preparation media (SpermRinse Solution, Vitrolife, Gothenburg, Sweden). The swim-up process which is a method of floating of progressive motility sperm in the medium, started with the placement of semen sample in a falcon conical centrifuge tube. Media and sperm were mixed at a ratio of 1/1. After pipetting, the sample was centrifuged at 1200–1500 rpm for 10 min. The supernatant was removed using a pipette. After the supernatant was dumped, 1 ml of the same medium was added and the same cycle was repeated for 5 min. The tube was placed at an angle of 45 degrees and 0.5–1 mL of medium was added onto the pellet. This was incubated for 1 h at 37 °C without deterioration of the angle. A small amount was taken from the supernatant, and post wash analysis was again performed by the computer-assisted semen analyzer and recorded. Finally, the sperm solution was withdrawn from the tube surface with a pipette to aid in totaling 0.5–1 mL of the tube without distortion the angle, and it was transferred in to falcon 5 mL tube to be used for IUI. Sperm analysis was performed by the same andrology laboratory technician according to a quality control program at the Andrology Laboratory of the current hospital.

Evaluation of pregnancy

All women underwent serum beta chronic gonadotrophin (ß -hCG) measurement 14 days after IUI and TI. Patients with ß-hCG >10 mIU/ mL were accepted pregnant. In patients with positive pregnancy test, the increase in ß-hCG was evaluated after 2 days. Patients who had an increase in ß-hCG rather than normal doubling in serial measurements (non viable pregnancy), whose ß-hCG value is decreasing while their vaginal bleeding starts or those with pregnancy of unknown location (no visible intrauterine or extrauterine pregnancy on ultrasound) at the 6th weeks of gestation were accepted as biochemical pregnancy. Clinical pregnancy was diagnosed 5 weeks after the IUI by evidence of intrauterine gestational sac and/or fetal heart activity.

Statistical analysis

Statistical analysis Statistical Package for the Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Descriptive statistics were used to demonstrate the mean ± standard deviation and median (range) for constant variables, whereas nominal variables were expressed as case number and percentages. As to the analysis of the data, normality in the repeated measures was tested with Shapiro-Wilks test. To determine the differences between the groups, parametric (Independent samples t test) and non-parametric analyzes (Mann–Whitney U) were performed after normality analysis. Proposrtions were compared with Chi Square test or Fisher exact test. Binary logistic regression analysis was used to estimate the association between the treatment modality and possible predictors of pregnancy in OI cycles. P value of less than 0.05 was considered significant.

A minimum of 122 participants was required to demonstrate at least 10% difference between groups with a power of 80 at the 5% significance level. The difference of 10% was taken from both pilot study [14].

Results

Of a total 147 OI cycles which were analyzed, 56 cycles were resulted with IUI and 91 were with TIC. The groups were similar in terms of age, BMI, infertility type, infertility duration, number of gravidity, parity and abortion ($p > 0.05$) (Table 1). Number of smoker were statistically significantly higher in the TIC group than in the IUI group (3.6% vs. %14.3, p:0.049). Weekly frequency of

Table 1
Demographic, clinical and laboratory characteristics of the groups.

Variables	IUI group (n:56)	TIC group (n:91)	P
Age (years)	26(19–35)	24(19–40)	0.197
BMI (kg/m^2)	25.0 ± 3.9	26.2 ± 5.1	0.071
Gravidity	0(0–3)	0(0–4)	0.187
Parity	0(0–3)	0(0–2)	0.177
Number of abortion	0(0–2)	0(0–3)	0.656
Infertility duration(years)	3(1–10)	3(1–13)	0.082
Cigarette smoking	2(3.6)	13(14.3)	0.049
Infertility type			
Primary	49(87.5)	68(74.7)	0.063
Secondary	7 (12.5)	23(25.3)	
Coit frequency/week	2(1–4)	2(1–8)	0.682
TPMSC (mil)	34.8 ± 8.4	35.5 ± 17.3	0.700
Prior surgery			
H/S	3(5.4)	(5.5)	0.884
L/S	2(3.6)	52(2.2)	
FSH(U/L)	6.5 ± 1.4	6.7 ± 1.6	0.543
LH(U/L)	6.0(2.5–37)	5.7(1.6–2.9)	0.180
TSH (U/L)	2.1(0.6–5.3)	2(0.3–5.2)	0.088
PRL (ng/mL)	16.0(2.7–32.0)	14.6(0.8–26)	0.222
E2(pg/mL)	34.5(10.6–98)	36(6–97)	0.230

IUI: intrauterine insemination, TIC: timed intercourse, BMI: body mass index, TPMSC: total progressively motile sperm count, H/S: hysteroscopy, L/S: laparoscopy. FSH: follicle stimulating hormone, LH: luteinizing hormone, PRL: prolactin, TSH: thyroid stimulating hormone, E2: estradiol. Data are presented as mean ± standard deviation, median (minimum-maximum), and number (percentage). P < 0.05 is considered statistically significant.

sexual intercourse and history of gynecologic surgery including operative laparoscopy and hysteroscopy were higher in TIC group compared to IUI group, but the differences were not statistically significant (P > 0.05). Semen analysis revealed that there was no significant difference between groups in terms of total progressively motile sperm count (34.8 ± 8.4 vs. 35.5 ± 17.3 mil., p:0.700). Also, no significant difference was observed between groups regarding the number of previous CC cycles (p > 0.05). Basal E2, FSH, LH, TSH and PRL levels were similar in both groups. CC starting day, number of previous CC cycles, cyles length, dominant follicule size and endometrial thickness on hCG day were similar (p > 0.05) (Table 2). Multifollicular development were also similar in both groups. Multiple pregnancy was not detected in any of the patients, but only one ectopic pregnancy was observed in TIC group. A significant difference was observed in both chemical (58.9% vs. 12.1, p < 0.001) and clinical pregnancy rates (48.2% vs. 11%, p < 0.001) between the 2 groups. Logistic regression method demonstrated that the only significant determinant for predicting clinical pregnancy is the addition of IUI to OI, with an odds ratio of 9.451 (95% confidence interval: 3.330–26.825, p > 0.001) (Table 3).

Discussion

Clomiphene citrate is a nonsteroidal triphenylethylene derivative and acts as a selective estrogen receptor modulatör (SERM). The commercially available form of clomiphene is the dyhidrogene citrate salt and contains two stereoisomers: en-clomiphene (62%) and zu-clomiphene (38%), which were originally called the *cis*-isomer and *trans*-isomer, respectively. En-clomiphene is cleared rapidly, in contrast zu-clomiphene has a long half-life [15], and it remains detectable in the circulation for more than a month after treatment [16]. En-clomiphene is the more potent isomer with greater anti-estrogenic activity and the one primaly responsible for inducing follicular development. CC acts primarily as an anti-estrogen in the uterus, cervix and vagina. Besides this, CC does not produce a much higher pregnancy rate, as only 50% of those who ovulate will conceive [17]. Anti-estrogenic effects of CC at the level of the endometrium and cervical mucus is the cause of this feature [17–19].

IUI is a procedure in which processed and concentrated motile sperm are placed directly into the uterine cavity. Clinical use of IUI is based on the hypothesis that placing a large number of sperm in the reproductive tract enhances the likelihood of conception [20]. The minimum requirements for performing the procedure are ovulation in the IUI cycle, patency of at least one fallopian tube, inseminate with an adequate number of motile sperm, and absence of documented or suspected active cervical, intrauterine, or pelvic infection. The rational of using IUI is to enhance the pregnancy rate by increasing the number of motile sperms to reach the oocycte [20]. In the past, IUI has been used as a treatment for couples with poor post coital tests by passing the hostile cervical factors [21]. Today IUI is widely used for those women with male subfertility and/or unexplained infertility [22]. For cervical factor or mild male factor infertility, IUI allows sperm to bypass potentially hostile cervical factors, thus increasing the number of sperm that gain access to the uterine cavity (and oocyte). For women undergoing OI, including those with unexplained infertility or minimal or mild endometriosis, pregnancy rates are thought to be higher when IUI is used as an adjunctive procedure instead of timed natural intercourse. In these couples, IUI is often used as an intermediate level and cost-effective intervention prior to proceeding to in vitro fertilization (IVF). The pregnancy rate after IUI depends on male factors, female factors and technical factors.

Table 2
Cycle characteristics of the patients among the groups.

Variables	IUI group (n:56)	TIC group (n:91)	P
CC starting day of cycles			
2nd	4(7.1)	13(14.3)	0.348
3th	38(67.9)	57(62.6)	
4th	5(8.9)	12(13.2)	
5th	9(16.1)	9(9.9)	
CC dose			
50 mg	50(89.3)	69(75.8)	0.019
100 mg	3(5.4)	20(22)	
150 mg	3(5.4)	2(2.2)	
Number of previous CC cycle	1(1–3)	2(1–4)	0.425
Cycle lenght (days)	13.5(10–23)	13(9–25)	0.891
Endometrial thickness on hCG day (mm)	8.5 ± 2.0	8.8 ± 2.2	0.413
Dominant follicle size on hCG day (mm)	20(17–28)	19(17–26)	0.058
Multifollicular development	21(37.5)	33(36.3)	0.880
Biochemical pregnancy	33(58.9)	11(12.1)	<0.001
Clinical pregnancy	27(48.2)	10(11)	<0.001

IUI: intrauterine insemination, TIC: timed intercourse, CC: clomiphene citrate, Data are presented as mean ± standard deviation, median (minimum-maximum), and number (percentage). P < 0.05 is considered statistically significant.

Table 3
Multivariable logistic regression analysis of risk factors for predicting clinical pregnancy.

Model	ß	SE	Wald	P	OR	95% CI
Age (years)	−0.107	0.062	2.989	0.084	0.899	0.796–1.014
BMI (kg/m^2)	0.014	0.053	0.075	0.784	1.015	0.915–1.125
Basal FSH (U/L)	0.065	0.163	0.160	0.689	1.067	0.776–1.469
Infertility duration (years)	0.112	0.125	0.804	0.370	1.119	0.875–1.431
Smoker (Yes/No)	1.411	1.119	1.589	0.207	4.098	0.457–36.726
Coit freuency (/week)	−0.407	0.322	1.596	0.207	0.666	0.354–1.252
TPMSC (mil)	−0.022	0.014	2.440	0.118	0.978	0.951–1.006
Endometrial thickness (mm)	0.108	0.109	0.991	0.319	1.115	0.900–1.380
Treatment modality (IUI/TIC)	2.246	0.532	17.807	<0.001	9.451	3.330–26.825
Multifollicular development (>1)	0.212	0.512	0.172	0.678	1.236	0.454–3.370
CC starting day (2nd-3rd/4th-5th)	−0.119	0.522	0.052	0.819	0.887	0.319–2.470
Infertility type (Primary/secondary)	−0.462	0.660	0.491	0.483	0.630	0.173–2.295
CC dose (>50 mg)	−0.168	0.618	0.074	0.786	0.845	0.252–2.840
Cycle lenght (days)	−0.075	0.092	0.673	0.412	0.927	0.774–1.110
Follicle size (>20 mm)	−0.624	0.490	1.621	0.203	0.536	0.205–1.400
Constant	0.670	3.278	0.042	0.838	1.954	

BMI: body mass index, FSH: follicle stimulating hormone, TPMSC: total progressively motile sperm count, IUI: intrauterine insemination, TIC: timed intercourse, CC: clomiphene citrate, SE: standard error, OR: odds ratio, CI: confidence interval. $P < 0.05$ is considered statistically significant.

The main cause of infertility in women with PCOS is ovulatory disorder and hence the treatment is OI [23]. It appears reasonable to combine OI with IUI in women with PCOS having male factor subfertility, but we aimed to show the benefits of adding IUI to couples without male factor infertility. The first randomized trial comparing the addition of IUI to CC in women with PCOS and normal semen analysis was reported recently [24]. They suggest that there were no differences between the IUI and TIC groups regarding the clinical pregnancy rate per cycle. Also they found no difference between the groups regarding age, duration of infertility, anthropometric variables and hormone profiles. Compitable with this study, our results showed that the groups were similar in terms of age, BMI, duration of infertility, endometrial thickness at the time of hCG administration day, cycle length, basal FSH, LH, TSH and E2 levels. We also evulate weekly frequency of sexual intercourse, history of infertility surgery and infertility type. Sexual intercourse fequencies were similar between two groups and history of infertility surgery were higher in TIC group compared to IUI group, but the differences were not statistically significant. However, our data are disagree with the recent study among clinical pregnany rates and we conversely demonstrated the beneficial effect of IUI for those undergoing OI with CC cycles. In our study, a significant difference was observed in both biochemical (58.9% vs. 12.1, $p < 0.001$) and clinical pregnancy rates (48.2% vs. 11%, $p < 0.001$) between the 2 groups. Unlike to this study, we include our study both primary and secondary infertile women and women who had infertility treatment with CC before. Also, PRL was found to be higher in IUI group and it is known that this is a cause of anovulatory infertility like PCOS. However, there was no hyperprolactinemic cases in our study and all PRL values were in normal range in both groups. Therefore we think that this difference had no significant affect on the outcomes. Additionally, TIC group have higher BMI and number of previous CC cycle. The daily dose of CC used in TIC group was higher accordingly. This result suggest that TIC group may have more insulin resistance related to higher BMI values and needed higher doses.

Although anovulatuary factors is the main cause of infertility in women with PCOS; our study suggest it could be also some unknown cervical factors might be present in those women. Anti-estrogenic effects of CC on cervix might contribute to these cervical factors. Thus, adding IUI which eliminates these cervical factors in anovulatory women with PCOS to the CC cycles may improve the pregnancy rates.

The main drawback of our study is retrospective nature. Another limitation includes the convenience sampling technique employed during patient selection. Hovewer it provides information about the lack of efficacy of TIC in treatment among women with PCOS. It is well known that compared to fertile women, infertile women are already stressed [20] and this psycological stress can be a negative impact on infertility treatment [25]. Beside this, TIC is certainly less stressfull than IUI. We did not evaluate the stress level of our patients, but it seems that IUI related stress does not remarkably affect the treatment outcomes.

We conclude that compared to TIC, IUI significantly increases both biochemical and clinical pregnancy rates in infertile women with PCOS who have undergone OI with CC.

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