Original Article

Intrauterine Insemination in Ovulatory Infertile Patients

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Abstract

Aim: Although there are many studies in literature comparing intrauterine insemination (IUI) and timed intercourse, there are only a few studies examining the use of clomiphene citrate (CC) in ovulatory infertile patients. The aim of this study was to compare IUI following CC-induced ovulation and timed intercourse following CC-induced ovulation in ovulatory infertile patients. **Methods:** Hundred patients who had IUI or timed intercourse following ovulation induction (OI) via CC between 2012 and 2014 are prospectively scanned. Both groups were consisted of 50 patients. Both in groups 1 and 2 patients, the treatment with clomiphene citrate was started on the 3rd day of the menstrual cycle with a dose of 50 mg/day and was continued for 5 consecutive days. On the 13th day of the cycle, the patients were called for examination and folliculometry tests were performed via transvaginal ultrasonography. Human chorionic gonadotropin (HCG, a prepared syringe containing 250 μg/0.5 ml [6,500 IU equivalent] choriogonadotropin alpha) was given to all patients with a sufficient size follicle (18–20 mm). Group 1 patients were recommended to have coitus regularly for a week after the HCG treatment. In group 2, IUI was performed 36 h after the HCG treatment. **Results:** Clinical pregnancy was provided in 28 patients in 100 patients. In group 1, the pregnancy rate per person was 6%, the pregnancy rate per cycle was 2.3%, and live birth rate was 6%. In group 2, the pregnancy rate per person was 22%, the pregnancy rate per cycle was 8.3%, and live birth rate was 23%. A statistically significant difference was observed between groups 1 and 2 in terms of pregnancy per person rate, pregnancy per cycle rate, and live birth rate. **Conclusion:** In the patients who had OI via CC, the pregnancy rates obtained with IUI were statistically significantly higher than timed intercourse.

Keywords: *Clomiphene citrate, intrauterine insemination, ovulation induction*

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Introduction

Infertility is a disease of the reproductive system, which is defined as the failure to achieve a clinical pregnancy after a time period of 12 months or longer of regular unprotected sexual intercourse. The general infertility incidence has been reported as 10–15% and it constitutes one of the most common problems of married couples worldwide.[1-3] Many researches have been conducted for the solution of this problem and also significant developments have been achieved.[4,5] Among the treatment methods to overcome this problem, intrauterine insemination (IUI) following ovulation induction (OI) forms the base of the infertility treatment. Clomiphene citrate (CC) is a drug that is used for the controlled ovarian-stimulation; it is cost-effective and less invasive than gonadotropin.

CC is used in ovulatory infertile patients with polycystic ovary syndrome.[6] In the current study, CC was used on ovulatory infertile patients. Although there are many studies in the literature, which have compared IUI and timed intercourse, there are only a few studies related

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to the use of CC in normal ovulatory patients.[7,8] In this study, IUI and timed intercourse following CC-induced ovulation in normal ovulatory infertile patients are compared.

Clomiphene is a selective estrogen receptor modulator. Its basic action is to block the negative feedback of estrogen on the brain, so the pituitary releases FSH and LH, and follicle development occurs. If the hypothalamic-pituitary unit is functional, ovulation should occur. However, clomiphene will fail with hypothalamic or pituitary dysfunction, or resistant or failing ovaries. Clomiphene is a long trusted oral medication relied upon for its safety, effectiveness, and relatively low cost.

The aim of this study is examining the outcomes of IUI and timed intercourse in normal ovulatory infertile patients after OI via CC prospectively. Patients applied to the Infertility Polyclinic of the Gynecology and Obstetrics Department of Bulent Ecevit University Medical Faculty between March 2012 and March 2014 were included in the study.

Materials and Methods

Ethics committee approval

Approval for the study was granted by the Scientific Research Ethics Committee of Bulent Ecevit University Medical Faculty (approval no. 2011/7 dated 07.19.2011; supplement 1). Study subjects were selected from the patients between the ages 18 and 35 years old (median 29 years) who presented at the Infertility Polyclinic of the Gynaecology and Obstetrics Department of Bulent Ecevit University Medical Faculty between March 2012 and March 2014. Hundred patients who had IUI or timed intercourse following OI using CC treatment were prospectively scanned. A total of 265 cycles evaluated, 100 patients on the first cycle, 87 patients on the second cycle, and 78 patients on the third cycle were examined.

Criteria

Study inclusion criteria were as follows; female age <35 years and male age <40 years, duration of infertility of >1 year and for the female patient normal hormone profile (TSH, PRL, LH, E2) and 3rd day FSH <12 IU/L. An infertility evaluation is usually initiated after 1 year of regular unprotected intercourse in women under age 35 years and after 6 months of unprotected intercourse in women age 35 years and older.[9] Ovarian reserve, oocyte quality, oocyte quantity, or reproductive potential may diminish after the age 35 years.[10] Therefore, the upper limit is defined as 35 years for a female. Epidemiology studies suggest that fertility rates are lower in men over the age 40 years.[11,12] Therefore, the upper limit is defined as 40 years for a male.

Oligomenorrhea, polymenorrhea patients, patients with any menstrual cycle disorder, patients who were known to be an ovulatory, such as polycystic ovary syndrome were not included in the study. Patients with regular menstrual cycle were included in the study. Ovulation was assumed to have occurred when mid-luteal serum P exceeded 5 ng/ml.[8]

Patients were excluded from the study if they previously had received any infertility treatment. The other exclusion reasons were as follows: if the female had any known health problem that could be a reason for infertility such as PCOS, tubal factor, severe endometriosis, or uterus anomaly, either the male or female had any systemic disease or if the male partner had a sperm count <15 million/ml and sperm morphology <4% according to Kruger.

Patients with 12 or more antral follicles with a diameter of 2–9 mm in one or both of the ovaries or elevated ovary-volume up to 10 ml were evaluated according to the Rotterdam criteria and diagnosed with PCOS. Two of the following three criteria are required for the diagnosis of PCOS: oligo/anovulation, hyperandrogenism, polycystic ovaries on ultrasound. Patients diagnosed with PCOS were excluded from the study.

Patients who met the study criteria and agreed to participate in the study were separated as group 1 and group 2 according to the presentation order at the polyclinic. Following OI using CC, timed intercourse was planned for the patients in group 1 and IUI performed on the patients in group 2. The first evaluation of the patients was carried out on the 3rd day of the menstrual cycle. On the first presentation, a blood test was requested for the examination of FSH, LH, E_2, prolactin, and TSH hormones and for the evaluation of any uterine, ovarian, or tubal pathology transvaginal ultrasonography was performed. A general physical examination performed for the evaluation of systemic diseases. Between the 6th and 10th days of the cycle, all patients went through hysterosalpingography to evaluate the tubal passage and patients with tubal pathology were excluded from the study. The male partner's semen was analyzed and those with sperm count under 15 million/ml and sperm morphology <4% according to Kruger were excluded from the study.[13]

Measurements

After completion of the initial routine infertility analyses, the patients in both groups were called on the 3rd day of their cycle to start treatment. Treatment with CC at a dose of 50 mg/day was started on the 3rd day of

the menstrual cycle and was continued for the following 5 days. On day 13 of the cycle, the patients were called for examination; folliculometry was performed via transvaginal ultrasonography and follicle development was evaluated. Patients with insufficient follicular development were followed up every 2 days for 10 days and in patients with no follicular development, the cycle was canceled and excluded from the study, then treatment was initiated again in the next cycle using CC at a dose of 100 mg/day. In all patients where follicle size reached an appropriate size (18–20 mm), human chorionic gonadotropin (HCG) was applied (a prepared syringe containing 250 μg/0.5 ml [6,500 IU equivalent] choriogonadotropin alpha).

Following HCG, group 1 patients were recommended to have coitus on alternate days for 1 week. Group 2 patients were called to the clinic together with their partners 36 h after the application of HCG. A sperm sample was taken from the partners. The semen samples were collected by masturbation after a 3-day period of sexual intercourse fasting, prior to the planned IUI procedure. The semen samples were processed with the separation-washing method based on the density gradient enrichment using Sil-Select Plus solution. The kit and materials used with the samples were brought to 37°C. An upper layer of 2.5 ml Sil-Select Plus was placed in a sterile centrifuge tube with a sterile syringe. Then a lower layer of 3 ml Sil-Select Plus was placed slowly on the upper section of the upper layer of the tube with a sterile syringe. The desired gradient between the upper and lower layers was observed stable for a maximum of 1 h. Using a transfer pipette, 2.3-ml liquefied semen was transferred over the upper layer. These three phase tubes were centrifuged for 20 min at 350–450 g. At the end of centrifugation, samples, where a pellet section was not visible, were centrifuged again. The pellet was removed by taking the supernatant immediately at the end of centrifugation. With a sterile syringe, 2.5–3 ml sperm washing solution was added, without rinsing the pelleta suspension was obtained. The suspension mixture was centrifuged for 8–10 min at 300–400 g. The pellet was removed by taking the supernatant. Finally, by separating immotile or abnormal sperm, leukocytes and other cellular extra entities found in the semen, only motile and healthy sperms obtained. After the patient positioned on a gynecological examination table, IUI catheter inserted into the cervix and IUI applied. Following IUI, coitus on the alternate days was recommended for 1 week.

The patients were told to attend the clinic immediately if they had any discomfort, otherwise, a follow-up examination was planned for 2 weeks later. In patients who did not menstruate following IUI, serum β-HCG was examined to determine pregnancy. Patients with β-HCG positivity were followed up by ultrasonography. Clinical pregnancy was accepted in the cases who had an amniotic sac and cardiac activity in the endometrial cavity. The same treatment was applied for 3 months if the patient had not conceived in that period. The pregnant patients were followed up until the end of the birth and the number of live births was recorded. The results are shown in Tables 1–3.

Statistical analysis

Statistical evaluations were made using SPSS 19.0 software (SPSS Inc. Chicago, IL, USA). Conformity to the normal distribution of numerical variables was examined with the Kolmogorov–Smirnov test. Numerical variables were stated arithmetically using descriptive statistics as the mean ± standard deviation (SD), median (minimum–maximum) and categorical data, which were stated as number (*n*) and percentage (%). Differences between the groups in terms of categorical variables were examined with the Fisher exact test. Odds ratio (OR) was calculated in a 95% confidence interval (CI) in 2 × 2 tables. In the comparison of two groups in terms of quantitative variables, significance test between the two averages was used when the parametric test hypothesis was met, otherwise, the Mann Whitney U-test was used. A value of $P < 0.05$ was accepted as statistically significant.

Results

Demographic data

In this study, 100 patients who had IUI or timed intercourse following OI using CC were prospectively scanned. Patients divided into two groups each containing 50 patients. Informed consent was obtained from all participants. A total of 265 cycles evaluated, the first cycle had 100, the second cycle had 87, and the third cycle had 78 patients.

Table 1: Comparison of the pregnancy outcomes according to the patients in both groups

	Group 1, *n* (%)	Group 2, *n* (%)	Total, *n* (%)	OR (95% CI)	*P*
Pregnant	6 (6)	22 (22)	28 (28)	5.762 (2.079-15.971)	
Not pregnant	44 (44)	28 (28)	72 (72)		0.001*
Total	50 (50)	50 (50)	100 (100)		

Cases are shown as number (percentage of total). The Chi-square test was used in the comparison of the groups. *P<0.05 is significant

Table 2: Comparison of the pregnancy outcomes according to the number of cycles in both groups

	Group 1, *n* (%)	Group 2, *n* (%)	Total, *n* (%)	OR (95% CI)	*P*
Pregnant	6 (2.3)	22 (8.3)	28 (10.6)	5.023 (1.965-12.844)	
Not pregnant	137 (51.7)	100 (37.7)	237 (89.4)		0.001*
Total	143 (54)	122 (46)	265 (100)		

Cases are shown as number (percentage of total). The Chi-square test was used in the comparison of the groups. *P<0.05 is significant

Table 3: Comparison of the difference between the groups in respect of the cycle in which pregnancy occurred

	Group 1, *n* (%)	Group 2, *n* (%)	Total, *n* (%)	*P*
Pregnancy in the 1st cycle	2 (7.1)	11 (39.3)	13 (46.4)	0.007*
Pregnancy in the 2nd cycle	3 (10.7)	6 (21.4)	9 (32.1)	0.164
Pregnancy in the 3rd cycle	1 (3.6)	5 (17.9)	6 (21.4)	0.034*
Total	6 (21.4)	22 (78.6)	28 (100)	<0.001*

Cases are shown as number (percentage of total). The Chi-square test was used in the comparison of the groups. *P<0.05 is significant

Table 4: Comparison of the pregnancy outcomes of groups 1 and 2

	Group 1	Group 2
Number of cycles	143	122
Total pregnancies	6	22
Multiple pregnancies	0	2*
Abortus	0	2
Ectopic pregnancy	0	0
Live birth rate	6	23

*Multiple pregnancies comprised one set of twins and one set of triplets

Table 5: Comparison of the live birth rate outcomes according to the patients in both groups

	Group 1, *n* (%)	Group 2, *n* (%)	Total, *n* (%)	OR (95% CI)	*P*
Live birth	6 (6)	23 (23)	29 (29)	0.160	
None	44 (44)	27 (27)	71 (71)	(0.058-0.443)	0.001*
Total	50 (50)	50 (50)	100 (100)		

Cases are shown as number (percentage of total). The Chi-square test was used in the comparison of the groups. *P<0.05 is significant

Table 6: Comparison of the live birth rate of groups 1 and 2

	Group 1, *n* (%)	Group 2, *n* (%)	Total	*P*
Live birth rate in the 1st cycle	2 (6.9)	12 (41.3)	14 (48.2)	0.004*
Live birth rate in the 2nd cycle	3 (10.3)	7 (24.1)	10 (34.4)	0.080
Live birth rate in the 3rd cycle	1 (3.4)	4 (13.8)	5 (17.2)	0.065
Total	6 (20.7)	23 (79.3)	29 (100)	<0.001*

Comparison of the methods

Twenty-eight clinical pregnancies were achieved from 100 patients following OI using CC, timed intercourse was planned for the patients in group 1 and IUI planned for the patients in group 2. In group 1, the pregnancy rate per person was 6%, the pregnancy rate per cycle was 2.3%, and live birth rate was 6%. In group 2, the pregnancy rate per person was 22%, the pregnancy rate per cycle was 8.3%, and live birth rate was 23%. A statistically significant difference was observed between groups 1 and 2 in terms of pregnancy per person rate, pregnancy per cycle rate and live birth rate. The pregnancy rate of patients with IUI after CC-induced ovulation was determined to be statistically significantly higher compared to timed intercourse patients. The results are shown in Tables 2–5.

Of the six clinical pregnancies in group 1, two were achieved after the first cycle, three after the second cycle, and one after the third cycle. Of the 22 clinical pregnancies in group 2, 11 were achieved after the first cycle, six after the second cycle, and five after the third cycle. The results are shown in Table 6.

There were a total of two multiple pregnancies, both patients were in group 2 and one patient was pregnant with twins and other patient was pregnant with triplets. No statistically significant difference was seen between the groups in terms of multiple pregnancies. Two of the clinical pregnancies resulted with abortus in group 2. Although abortus was not seen in group 1, no statistically significant difference was determined between the groups. Ectopic pregnancy was not observed in both groups. The results are shown in Table 1.

There were six live births in group 1 and 23 in group 2. There was a statistically significant difference in live birth rate between groups 1 and 2. The results are shown in Tables 2 and 3.

Discussion

CC is used in the infertility treatment of ovulatory patients.[14] However, in the current study, CC was used on ovulatory infertile patients. A comparison was made between IUI following CC-induced ovulation and timed intercourse following CC-induced ovulation in ovulatory infertile patients.

There are many trials in the Cochrane review that was updated in 2016.[15] In a study comparing IUI versus timed intercourse or expectant management of both in

the natural cycle, there was no evidence of a difference in the cumulative live births between the two groups. In our study we used CC instead of the natural cycle and pregnancy rates were found higher in those who had CC and subsequent IUI. In a study comparing IUI versus TI or expectant management of both in the stimulated cycle in ovulatory infertile patients, there was no evidence of a difference between the two treatment groups. Although our work is a similarly conducted study, the results are quite different. In this study, ovulatory infertile patients were included in the study. In our study, normal ovulatory infertile patients were included in the study and pregnancy rate was found to be greater after the IUI application. In a study comparing IUI in a natural cycle versus IUI in a stimulated cycle, an increase in live birth rate was found for women who had stimulated cycle and subsequent IUI compared with those who underwent IUI in a natural cycle. In a study comparing IUI in a stimulated cycle versus TI or expectant management in a natural cycle, there was no evidence of a difference in live birth rates between the two treatment groups. In a study comparing IUI in natural cycle versus TI or expectant management in a stimulated cycle, there was evidence of an increase in live births for IUI. Many factors such as patient's age, ovary reserve, oocyte quality, oocyte quantity, lack of additional infertility factors, patient compliance, and the experience of the clinician affect the result of the studies.

Kirby *et al*.[16] and Guzick *et al*.[17] showed that the application of IUI in the natural cycle in unexplained infertile patients increases the chances of conception only slightly (OR = 2.7, 95% CI 1.0–4.4). In the prospective, randomized, controlled multi-center study by Guzick *et al*. on 932 couples with unexplained infertility, the results provided important data about the evaluation of the therapeutic efficacy of both IUI and controlled ovarian hyperstimulation (COH). According to the results of this study, the chance for pregnancy for a couple diagnosed with unexplained infertility and applied IUI and COH with gonadotropin was 3.2 times greater compared to the patients who had intracervical insemination only, representing natural intercourse, and 1.7 times greater than those applied with IUI without COH. This suggests that the highest therapeutic effect was provided by the application of COH and IUI together in couples with unexplained infertility. In our study, we applied COH with CC to both groups. CC is a cost-effective and a less invasive agent than gonadotropin. Therefore, we chose CC as the first option.

In the studies comparing timed intercourse with IUI in the COH applied cycles, it has been observed that the probability of pregnancy in couples with unexplained infertility is significantly higher with IUI compared to timed intercourse.[18] Although those studies were conducted on patients with unexplained infertility, in our study normal infertile patients were included. Similar results were obtained in both studies. In the meta-analysis of seven prospective randomized studies comparing IUI and timed intercourse in COH cycles by Zeyneloglu *et al*., the pregnancy rate per cycle was 20% for IUI and 11% for timed intercourse in a total of 980 gonadotropin cycles.[19-25] In all the seven studies evaluated in that meta-analysis, an increased likelihood of pregnancy with the addition of IUI to the COH cycles in couples with unexplained infertility was seen (OR = 1.84, 95% CI 1.3–2.6). In our study, a comparison was made between IUI and timed intercourse following CC-induced ovulation in ovulatory infertile patients and an increase in the likelihood of pregnancy with the addition of IUI to the COH cycles was observed.

However, in some studies, it has been reported that IUI had no superiority over waiting for treatment in couples with unexplained infertility.[26-28] Unstimulated IUI was evaluated in one of these studies.[26] In our study, IUI following CC-induced ovulation was evaluated. For this reason, the success rate of unstimulated IUI may be low. Again in a study comparing IUI with timed intercourse with CC in patients with polycystic ovary syndrome, no statistically significant difference was found between timed intercourse and IUI.[28] In another study, there was no statistically significant difference in clinical pregnancy rates between timed intercourse and IUI after CC on ovulatory infertility patients with polycystic ovary syndrome.[29] Polycystic ovary syndrome is a CC-resistant disease. In our study, patients with polycystic ovary syndrome were excluded hence the infertility is an ovulatory. Although there are many studies in the literature comparing IUI and timed intercourse,[16-28] there are only a few studies related to the use of CC in normal ovulatory patients.

In the current study, CC was used in ovulatory infertile patients. Among the patients with unexplained infertility patients who had ovulation via CC were included in the study, and IUI treatment was found to be significant.

Conclusion

In conclusion, in ovulatory infertile patients with CC-induced ovulation, the likelihood of pregnancy was found to be higher with subsequent IUI compared timed intercourse [Table 4]. By taking other factors into consideration that could be a reason for infertility in ovulatory infertile patients, such as patient's age, hormone profile, additional diseases, and spermiogram

results, timed intercourse may be planned after CC-induced ovulation as it is a low-cost and less invasive method, but in our study IUI with CC-induced ovulation had higher live birth rates. There is a need for further studies on the use of CC in ovulatory infertile patients.

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Conflicts of interest

There are no conflicts of interest.

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