Ann Med Res 2020;27(4):1099-102

Annals of Medical Research

DOI: 10.5455/annalsmedres.2019.12.877

Original Article

Comparison of pregnancy outcomes in CC resistance PCOS patients undergoing CC plus letrozole and intra uterine insemination treatment with different follicular diameters

Serhat Ege

Health Sciences University, Gazi Yasargil Training and Research Hospital, Department of Gynecology and Obstetrics, Diyarbakir, Turkey

Abstract

Aim: Using Clomiphene citrate (CC) plus letrozole combination to determine the effect of follicular diameter on pregnancy outcomes in CC resistance Polycystic ovary syndrome (PCOS) patients during intra uterine insemination cycles.

Material and Methods: The records of infertile patients who presented to the outpatient clinic were retrospectively analysed. PCOS was diagnosed in 536 (23%) patients, 71 (18%) of whom had CC-resistant PCOS using CC plus letrozole. The patients were divided into two groups; follicular diameter 17-19 mm (group 1, n = 31) and 20-22 mm (group 2, n = 40).

Results: The pregnancy rate in group 1 was 20% (6/30), the abortion rate was 17% (1/6), and the multiple pregnancy rate was 17% (1/6). In group 2, the pregnancy rate was 17% (7/41), the abortion rate was 14% (1/7) and the multiple pregnancy rate was 14% (1/7). There was no statistically significant between-group difference in the pregnancy (p =0.3), abortion (p = 0.8) or multiple pregnancy rates (p =0.8).

Conclusion: In PCOS patients with CC plus letrozole and intra uterine insemination ovulation induction, pregnancy rate is not related to follicular size between 17-22 mm on hCG day. Although there was no direct relationship between follicular size and endometrial thickness, it was found that delaying HCG was not significant for better results.

Keywords: CC resistance; clomiphene citrate; follicular diameters; letrozole; PCOS

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common cause of infertility and affects 6% of population (1). Clomiphene citrate (CC) is considered the primary treatment for inducing ovulation in PCOS patients. CC binds to estrogen receptors and acts as a selective estrogen receptor modulator. As negative feedback from estrogen decreases, gonadotropic hormones are secreted, which induces follicular growth (2).

Letrozole used for ovulation induction and inhibits androgen-estrogen conversion, which leads to the secretion of follicle-stimulating hormone (FSH) by suppression of estrogen production (3). Several studies have demonstrated the efficacy of aromatase inhibitors in patients with CC resistant PCOS (4).

The timing of HCG plays an important role in the intra uterine insemination (IUI) cycle. Stimulation of the premature follicle with HCG may cause oocyte excretion in the follicle or an underdeveloped ovulation (5,6).

Although CC has been used for a long time, the timing of hCG administration has not been well clarified. In addition, the relationship between follicle optimal diameter and pregnancy was evaluated and different results were found. In addition, there are few studies on the effect of follicle size on pregnancy rate due to endometrial thickness (2,7,8).

The aim of this study was to compare the effect of different follicular diameters on gestational outcomes using CC plus letrozole combination.

MATERIAL and METHODS

The records of infertile patients who presented to the outpatient clinic were retrospectively analysed. PCOS was diagnosed in 536 (23%) patients, 71 (18%) of whom had CC-resistant PCOS using CC plus letrozole. The

Received: 20.02.2020 **Accepted:** 01.04.2020 **Available online:** 16.04.2020
Corresponding Author: Serhat Ege, Health Sciences University, Gazi Yasargil Training and Research Hospital, Department of Gynecology and Obstetrics, Diyarbakir, Turkey **E-mail:** serhatege782@gmail.com

patients were divided into two groups: follicular diameter 17-19 mm group (group 1, n = 31) and 20-22 mm group (group 2, n = 40).

The primary outcomes were 1) ovulation, defined as a progesterone level of > 3 ng/ml between D 21 and 23 and 2) The presence of sac with ultrasound was defined as pregnancy. Secondary outcomes included multiple pregnancies and pregnancy loss.

Couples were evaluated using transvaginal ultrasound, basal hormone tests, hysterosalpingography and spermiogram. PCOS was diagnosed according to the Rotterdam criteria: 1) oligomenorrhoea or chronic anovulation, 2) hyperandrogenism (clinical or laboratory) and 3) polycystic ovary appearance on ultrasound (9). CC resistance was defined as failure to ovulate, despite receiving 150 mg of CC for 5 days during successive menstrual cycles for three months (10).

Female patients were between 18 and 39 years of age with CC resistant PCOS had a healthy uterine cavity with at least one patent fallopian tube, and had a male patient with a semen specimen of at least 5 million sperm per milliliter and no pathological findings (sub-mucous myomas, endometrial polyps, uterine septum). Patients with endometriosis, body mass index (BMI)> 30 kg / m2, basal follicle stimulating hormone (FSH) > 12 mIU/mL were not included in the study.

The patients received a combination of 2.5 mg of letrozole (Femara; Novartis, Basel, Switzerland) for 3 D (D5–D7) and 100 mg of CC (Serophene; Serono, Geneva, Switzerland) for 5 D (D3–D7) for one treatment cycle. All the patients were evaluated using transvaginal ultrasonography on D 7 of menstruation or after the diameter of the largest follicle had reached 14 mm. If a dominant follicle was present, the patients received a human chorionic gonadotropin (HCG) trigger (Ovitrelle; Serono, Geneva, Switzerland) in a single dose via the subcutaneous routewhen the follicle size reached (17-22 mm), followed by IUI 36–38 h later.

Treatment cycles were divided in two groups according to the size of the leading follicle at the time of the hCG (17≤ 20 mm,20 ≤ 23 mm). These cut off values were selected because the highest pregnancy rates have been reported for a leading follicle size of 17–22 mm (8).

The study protocol was approved by the regional ethics committee (no: 375/2019).

Statistical analysis

The mean ± standard deviation (sd) were calculated for quantitative variables. Qualitative variables are presented as frequencies.The normally of the data was checked using the Kolmogorov-Smirnov test. Using an alpha value of 0.05, the power of our study was calculated as 99%.The Student's t-test and Mann–Whitney U test was performed to compare continuous variables with and without a normal distribution in the two groups. The proportional data were compared using a chi-squared test and Fisher's exact test. A p-value of < 0.05 was considered significant. All statistical analyses were performed using R-software v.3.5.1 (R Statistics Software; Institute for Statistics and Mathematics, Vienna, Austria).

RESULTS

The pregnancy rate in group 1 was 20% (6/30), the abortion rate was 17% (1/6), and the multiple pregnancy rate was 17% (1/6). In group 2, the pregnancy rate was 16% (1/7), the abortion rate was 14% (1/7) and the multiple pregnancy rate was 14% (1/7). There was no statistically significant between-group difference in the pregnancy (p =0.3), abortion (p = 0.8) or multiple pregnancy rates (p =0.8).

Clinical pregnancy rates observed with follicular size and endometrial thickness Table 1 is shown. Although endometrial thickness was different between groups, pregnancy status was not affected.

Table 1. Demographic characteristics of the study participants stratified by follicular size

	Group 1 17<20 mm (n=30)	Group 2 20<23 mm (n=41)	P value
Age (y) (mean ± SD)	29.40 ± 7.33	30.39 ± 6.25	0.5
BMI(kg/m^2) (mean ± SD)	21.47 ± 1.36	21.66 ± 2	0.6
Endometrial thickness at triggering HCG (mm)	8.8 ± 1.21	9.49±1.14	0.02
Basal E_2 (pg/ml) (mean ± SD)	46 ± 13.31	46.54 ± 10.36	0.8
LH (IU/mL) (mean ± SD)	5.20 ± 1.75	4.98 ± 1.81	0.5
FSH(IU/mL) (mean ± SD)	5.07 ± 1.36	5.41 ± 1.45	0.3
Pregnancy n %	6/30 ± (20)	7/41 ± (17)	0.3
Abortus n %	1/30 ± (3)	1/41 ± (2.4)	0.8
Multiple pregnancy n %	1/30 ± (3)	1/41 ± (2.4)	0.8

Data are mean ± standard deviation or n (percentage).
BMI: body mass index; FSH: follicle-stimulating hormone;
E_2:oestrodiol ; HCG: human chorionic gonadotropin;
LH: luteinizing hormone;

DISCUSSION

The optimum follicle diameter is essential for the timing of HCG administration. The timing of hCG addition is critical, because premature administration of hCG may result in follicular atresia, on the other hand, delayed hCG trigger can happen after ovulation has already occurred. In this study, we did not find any significant difference in the relationship between endometrial thickness and follicular size or in pregnancy rates.

Initial studies were examining follicular dimensions to trigger ovulation. Studies comparing natural cycles with CC cycles indicated that CC cycles had a wider (18-30 mm) follicular range. This wide range has not been a predictive measure. Therefore, many studies have been conducted on follicle size and outcomes (11–14).

Farhi et al. (8) show that the ideal hCG interval in PCOS patients receiving CC was 18-22 mm. Similarly, Shalom-Paz et al. (7) stated that hCG application has increased pregnancy rates when the dominant follicle reaches 20 mm. On the other hand, Palatnik et al. (15) show that high pregnancy rates during the follicle range 23-28 mm. In addition, the optimal size of follicles in CC and letrozole induction was similar for both. Buzaglo et al. (16) reported clinical pregnancy rates of 32.6%, 30.4%, 44.1% and 34.2% for dominant follicular diameters of 17 mm, 18 mm, 19 mm and 20 mm, respectively. Although the highest pregnancy rate was found to be 19 mm follicular sizes, there was no significant difference between the four groups in pregnancy rates. In this study, CC resistant PCOS patients with CC plus letrozole treatment were divided into two groups (17-19 mm and 20-22 mm). There was no statistically significant between-group difference in the pregnancy (p =0.3), abortus (p = 0.8) or multiple pregnancy rates (p =0.8).

Shalom-Paz et al. (7) show that larger follicles could allow increased estrogen levels and improved endometrial uptake. Similarly, Palatnik et al. (15) reported a higher pregnancy rate in cases with a thicker endometrium. Other hands, Seckin et al. (17) show that the pregnancy rate in PCOS patients who underwent ovulation induction by CC is not related to the leading follicular size on the day of hCG. Also, they demonstrated that pregnancy rates of women with different follicular sizes were not affected by endometrial thickness. Similarly; In this study, we did not find any significant difference in the relationship between endometrial thickness and follicular size.

This study has several limitations; we did not study neonatal outcomes because pregnancies were not followed up to delivery. Secondly two groups were created and working ranges were kept wide. Last this study is retrospective, it should be supported in randomized studies based on similar studies.

CONCLUSION

In PCOS patients with CC plus letrozole and IUI ovulation induction, pregnancy rate is not related to follicular size between 17-22 mm on hCG day. Although there was no direct relationship between follicular size and endometrial thickness, it was found that delaying HCG was not significant for better results.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: The study protocol was approved by the regional ethics committee (no: 375/2019).

Serhat Ege ORCID: 0000-0001-5430-602X

REFERENCES

1. Tarlatzis BC, Fauser BCJM, Legro RS, et al. Consensus on infertility treatment related to polycystic ovary syndrome. In: Human Reproduction 2008;23:462-77.
2. Nakamura Y, Sugino N, Mioko O, et al. Effects of clomiphene citrate on the endometrial thickness and echogenic pattern of the endometrium. Fertil Steril 1997;67:256-60.
3. Holzer H, Casper R, Tulandi T. A new era in ovulation induction. Fertil Steril 2006;85:277-84.
4. Mitwally MFM, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril 2001;75:305-9.
5. Stanger JD, Yovich JL. Failure of human oocytes release at ovulation. Fertil Steril 1984;41:827-32.
6. Cohlen BJ. Should we continue performing intrauterine inseminations in the year 2004? Gynecol Obstet Invest 2005;59:3-13.
7. Shalom-Paz E, Marzal A, Wiser A, et al. Does optimal follicular size in IUI cycles vary between clomiphene citrate and gonadotrophins treatments? Gynecol Endocrinol 2014;30:107-10.
8. Farhi J, Orvieto R, Gavish O, et al. The association between follicular size on human chorionic gonadotropin day and pregnancy rate in clomiphene citrate treated polycystic ovary syndrome patients. Gynecol Endocrinol 2010;26:546-8.
9. Fauser BCJM. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19-25.
10. Homburg R. Clomiphene citrate-end of an era? A mini-review. Hum Reprod 2005;20:2043-51.
11. Nilsson L, Wikland M, Hamberger L, et al. Simplification of the method of in vitro fertilization: Sonographic measurements of follicular diameter as the sole index of follicular maturity. J In Vitro Fert Embryo Transf 1985;2:17-22.
12. Haritha S, Rajagopalan G. Follicular growth, endometrial thickness, and serum estradiol levels in spontaneous and clomiphene citrate-induced cycles. Int J Gynaecol Obstet 2003;81:287-92.
13. Messınıs IE, Templeton A. Urinary oestrogen levels and follicle ultrasound measurements in clomiphene induced cycles with an endogenous luteinizing

hormone surge. BJOG: An International J Obstetrics & Gynaecology 1986;93:43-9.
14. Ibérico G, Vioque J, Ariza N, et al. Analysis of factors influencing pregnancy rates in homologous intrauterine insemination. Fertil Steril 2004;81:1308-13.
15. Palatnik A, Strawn E, Szabo A, et al. What is the optimal follicular size before triggering ovulation in intrauterine insemination cycles with clomiphene citrate or letrozole? An analysis of 988 cycles. Fertil Steril 2012;97:1089-94.
16. Buzaglo K, Velez M, Shaulov T, et al. Leading follicle size in modified natural cycle IVF- predictor of successful outcome? Fertil Steril 2012;98;267-75.
17. Seckin B, Pekcan MK, Bostanci EI, t al.Comparison of pregnancy rates in PCOS patients undergoing clomiphene citrate and IUI treatment with different leading follicular sizes. Arch Gynecol Obstet 2016; 293:901-6.