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Research

An Inexpensive Way for Ovarian Stimulation with Only Clomiphene Citrate in Women with Diminished Ovarian Reserve

Azalmış Over Rezervi Olan Kadınlarda Overyan Stimülasyonu Amacıyla Yalnızca Klomifen Sitrat Kullanımının Ekonomik Bir Yaklaşım Olarak Değerlendirilmesi

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ABSTRACT

Objective: Clomiphene citrate (CC) is commonly used for various indications related to ovarian stimulation in assisted reproductive technology. There is limited information on the effectiveness of clomiphene for ovarian stimulation when used alone in women with diminished ovarian reserve (DOR).

Methods: This retrospective analysis included women stimulated with CC only; a total of 840 cycles from 381 couples were analyzed.

Results: The median age was 39 years. All women had an antral follicle count <5, and the median anti-Müllerian hormone was 0.34 ng/mL. CC was given for 5 days, and stimulation lasted for 8 days. Among 840 cycles, 344 (%) cycles were cancelled. The reasons for cancellation were: premature ovulation, 119 (14.2%); no follicular growth, 98 (11.7%); no oocyte yield at oocyte pick-up, 66 (7.9%); and no metaphase II oocyte yield, 61 (7.3%). The number of cycles with no embryos was 2 (0.4%). The remaining 494 cycles (58.8%) proceeded to embryo transfer (ET). The median numbers of oocytes collected, mature oocytes, and 2 pronuclei embryos were each 2. Frozen ET was performed in 443 (89.1%) cycles, and fresh ET was performed in 51 (10.3%) cycles. The pregnancy test was positive in 131 cycles; there were 96 live births (one twin birth), and the live birth rate per ET was 19.5%.

Conclusion: CC alone seems capable of preventing a premature luteinizing hormone surge in the majority of women with severely DOR. CC-only stimulation is an effective and inexpensive approach to ovarian stimulation in women with severely DOR.

Keywords: Ovarian stimulation, clomiphene citrate, decreased ovarian reserve

ÖZ

Amaç: Klomifen sitrat (CC), yardımcı üreme teknolojilerinde overyan stimülasyon için çeşitli endikasyonlarla yaygın olarak kullanılan bir ajandır. Bununla birlikte, düşük over rezervine (DOR) sahip kadınlarda yalnızca CC kullanılarak yapılan overyan stimülasyonun etkinliği hakkında sınırlı bilgi bulunmaktadır.

Gereç ve Yöntem: Yalnızca CC ile stimüle edilen kadınlar retrospektif olarak analiz edilmiştir. Toplamda 381 çifte ait 840 siklus dahil edilmiştir.

Bulgular: Dahil edilen kadınların median yaşı 39, antral folikül sayısı <5 ve anti-Müllerian hormon değeri 0,34 ng/mL idi. CC beş gün süreyle uygulanmış ve toplam stimülasyon süresi 8 gün olarak kaydedilmiştir. Toplam 840 siklusun 344'ü (%41) iptal edilmiştir. İptal nedenleri şunlardır: prematür ovulasyon: 119 (%14,2); foliküler gelişim olmaması: 98 (%11,7); oosit toplama işlemi sırasında oosit elde edilememesi: 66 (%7,9); olgun (metafaz II) oosit elde edilememesi: 61 (%7,3). Embriyo oluşmayan siklus sayısı yalnızca 2 (%0,4) idi. Geriye kalan 494 siklus (%58,8) embriyo transferine (ET) ilerlemiştir. Toplanan oositlerin medyan sayısı 2, metafaz II oosit sayısı 2 ve 2 pronükleus embriyo sayısı da 2 idi. ET yapılan 494 siklusun 443'ünde (%89,1) donmuş transfer, 51'inde (%10,3) taze transfer uygulanmıştır. Toplam 131 siklusta gebelik testi pozitif bulunmuş ve 96 canlı doğum (biri ikiz) gerçekleşmiştir. ET başına canlı doğum oranı %19,5 olarak hesaplanmıştır.

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ÖZ

Sonuç: Yalnızca CC kullanımı, şiddetli DOR olan kadınların büyük çoğunluğunda erken luteinizan hormon yükselmesini önlemede etkili görünmektedir. Bu yaklaşım, etkili ve düşük maliyetli bir overyan stimülasyon yöntemi olarak değerlendirilebilir.

Anahtar Kelimeler: Overyan stimulasyon, klomifen sitrat, düşük over rezervi

INTRODUCTION

Ovarian stimulation (OS) is employed to induce multifollicular growth for in vitro fertilization (IVF) treatments. As the number of oocytes retrieved increases, the probability of live birth increases. Diminished ovarian reserve (DOR) limits the response to OS. Women with DOR constitute 9-24% of infertile patients (1,2). They have increased follicle-stimulating hormone (FSH) level and decreased anti-Müllerian hormone (AMH) levels, and their antral follicle count (AFC) is 5-7 or fewer follicles (3,4). In DOR, multifollicular growth during OS is not possible (5). Since ovarian response to stimulation treatments is inefficient, clinicians have experimented with various protocols to achieve satisfactory results.

For mild stimulation, alternative treatments include: i) low-dose gonadotropins; ii) oral treatments such as letrozole or clomiphene citrate (CC) (6). With mild stimulation, the cost of treatment and the number of drug injections are reduced, ultimately rendering treatment more accessible for these patients who may need several treatment cycles.

CC is a selective estrogen receptor modulator (7). It acts as an antiestrogen at normal estrogen levels. CC blocks the estrogen receptors in the hypothalamus, thereby inhibiting endogenous estrogen's negative-feedback effect, which results in an increased pulse frequency of gonadotropin-releasing hormone (GnRH) secretion and a subsequent rise in FSH and luteinizing hormone (LH) (8). This eventually stimulates follicular growth and ovulation. The advantages of CC used in OS during IVF include reduced gonadotropin administration, lower treatment cost, fewer side effects, and no decrease in oocyte quality (9). However, the anti-estrogenic effect of CC may impair endometrial growth.

Few studies have examined CC stimulation in DOR. Herein, we report a large series of women with DOR who underwent OS with CC.

METHODS

This retrospective descriptive study was conducted at an assisted reproductive technology center. Electronic records of the Clinique were screened to identify who underwent OS with CC only from January 2016 to December 2019. The study protocol was approved by the Koç University Clinical Research Ethics Committee (protocol no: 2022.431.IRB1.157, date: 05.12.2022).

CC-only stimulation was offered when the patient was not expected to develop more than 3 follicles, e.g., AFC ≤4 and/or serum AMH ≤1.1 ng/mL.

All women who met the above criteria and underwent CC-only OS were included in the study. Exclusion criteria were a body mass index over 30 kg/m^2 or oocyte cryopreservation. Those who received CC with gonadotropins or GnRH antagonists were also excluded.

Stimulation Protocols and Pituitary Suppression

A baseline scan was performed on the second or third day of the menstrual period to exclude any follicles greater than 12 mm in diameter. CC 100 mg/day orally (Klomen®, Koçak Farma, Türkiye) was administered for 5 days. Ovarian response was monitored by ultrasound and by measurement of serum estradiol, LH , and progesterone levels every 2-3 days, according to the physician's evaluation. If there were growing follicles >10 mm, monitoring was continued spontaneously; however, if there was no follicular activation, CC was continued for up to 10 days at the treating physician's discretion.

When the leading follicle was 18 mm, final oocyte maturation was induced with 250 µg recombinant human chorionic gonadotropin (250 µg/0.5 mL; Merck, Italy).

Transvaginal oocyte pick-up (OPU) under general anesthesia was performed 32 hours after the human chorionic gonadotropin injection. Generally, embryos were cultured until the day-5 stage. However, embryos with early-stage fragmentation were frozen on day 3 or day 4. Luteal phase support with vaginal micronized progesterone gel (crinone 8% vaginal gel, Merck, England) 90 mg twice a day, was started on the evening of embryo transfer (ET), and continued until a negative pregnancy test or 6th week of gestation. Additionally, weekly depot progesterone (500 mg) was administered intramuscularly (Proluton Depot, Bayer, Germany) until a negative pregnancy test or until the 10th week of gestation.

The outcomes were: duration of stimulation, total CC dosage used, number of oocytes retrieved, number of metaphase II oocytes retrieved, oocyte maturation rate, number of embryos, pregnancy rate, and live birth rate. Oocyte maturation rate was defined as the proportion of metaphase II oocytes among all collected oocytes per woman.

Clinical pregnancy was defined as visualization of a gestational sac on ultrasound 4-6 weeks after ET. Ongoing pregnancy was defined as pregnancy continuing beyond 24 weeks' gestation. Live birth was defined as any pregnancy that resulted in the birth of an infant with heartbeat after the 24th gestational week. Electronic records of all patients during the aforementioned time periods were screened for demographic, stimulation, laboratory, and clinical data.

Statistical Analysis

Variable distributions were evaluated visually using histograms. Continuous variables were summarized as mean (standard deviation) or median (25th-75th percentiles), depending on their distributional characteristics. Categorical variables were defined with numbers and percentages. Sample size calculation was not performed for this retrospective analysis; however, all cycles meeting the inclusion criteria within the specified period were included.

RESULTS

A total of 840 cycles from 381 women were included in the analysis. Median age was 39 years. Median AFC and AMH were 3 and 0.34 ng/mL, respectively. CC was administered for a median of 5 days, and stimulation lasted a median of 8 days. Baseline characteristics are summarized in Table 1.

Of 840 cycles, 217 (25.9%) were cancelled before OPU due to premature ovulation and the absence of follicular growth (Table 2). The remaining 623 cycles (74.1%) proceeded to oocyte retrieval. No oocytes were retrieved in 66 cycles (7.9%), and in 61 cycles (7.3%) all retrieved oocytes were immature (Table 2).

The median number of oocytes collected, mature oocytes, and 2 pronuclei embryos was 2 in 496 cycles. Two cycles (0.4%) had no embryos (Table 3).

Endometrial thickness on the day of ET was 9.0 mm. Frozen ET was performed in 443 cycles (89.1%) and fresh ET in 51 cycles (10.3%). One ET was performed in 229 cycles, and two ETs were performed in 265 cycles. Pregnancy tests were positive in 131 cycles (15.6% per started cycle; 21.0% per OPU; 26.6% per ET). There were 96 live births (one was a twin birth); the live birth rate per ET was 19.5% (11.4% per started cycle; 15.4% per OPU).

DISCUSSION

CC alone seems to be an inexpensive and effective agent for OS herein in patients with severe DOR. As highlighted by meta-analyses and other studies, no single treatment approach has been established as superior for women with DOR (6,9,10). The number of oocytes retrieved and

Table 1. Baseline characteristics of the patients

	Median (25th-75th quartiles)
Age	39 (35-43)
Parity	0
Number of abortions	0
Number of previous IVF treatments	3 (2-6)
Infertility duration (months)	48 (24-90)
BMI (kg/m^2)	24.1 (22.0-27.1)
AFC	3 (2-4)
AMH (ng/dL)	0.34 (0.21-0.49)
Day 3 estradiol (pg/mL)	38 (29-59.3)
Day 3 progesterone (pg/mL)	0.2 (0.1-0.5)

IVF: In vitro fertilization, BMI: Body mass index, AFC: Antral follicle count, AMH: Anti-müllerian hormone

Table 2. Cancellation reasons and rates in all cycles

	Number of cycles, (% in total number of cycles)
Number of cancelled cycles before OPU	217 (25.9)
No growing follicles	98 (11.7)
Premature ovulation	119 (14.2)
Number of cancelled cycles after OPU	127 (15.2)
No oocytes in OPU	66 (7.9)
All immature oocytes	61 (7.3)

Total number of cycles: 840. OPU: Oocyte pick-up

Table 3. Fertility outcomes of the clomiphene induced cycles

	Median (25th-75th quartiles)
HCG day estradiol (pg/mL)	464.5 (295.0-693.0)
HCG day progesterone (pg/mL)	0.14 (0.1-0.27)
Endometrial thickness at ET day (mm)	9.0 (8.5-11.0)
Starting gonadotropin dose	100
Duration of treatment (days)	5
Total gonadotropin dose	500
Number of total oocytes	2 (1-3)
Number of MII oocytes	2 (1-3)
Number of 2PN embryos	2 (1-2)
Number of blasts	0 (0-1)
Number of day 5 blasts	0
Ratio of MII oocytes to total number of oocytes	1
Fertility rate	1 (0.81-1)

PN: Pronuclei, HCG: Human chorionic gonadotropin, ET: Embryo transfer, MII: Metaphase II

pregnancy rates with CC-only or mild stimulation protocols are comparable to those achieved with standard protocols. Moreover, CC-only and mild-stimulation approaches offer financial advantages (3). However, CC has some undesirable effects, including premature ovulation, insufficient follicular growth, and endometrial thinning (11). In a randomized controlled trial (RCT), Ragni et al. (9) reported similar cycle-cancellation rates in the CC-only and high-dose gonadotropin groups, attributable to premature ovulation or follicular arrest/absence. They used, as treatment groups, 150 mg/day for 5 days starting on the third day of the cycle, and 450 IU recombinant follicle-stimulating hormone plus 0.1 mg GnRH agonist. In our study, we administered CC at 100 mg/day for 5 days, with treatment extended to 10 days for selected patients.

Compared with Ragni et al.'s (9) findings, our study observed a higher incidence of premature ovulation, while the rate of inadequate follicular growth was similar. Although oocyte retrieval rates were higher in the high-dose gonadotropin group, live birth rates remained comparable between groups (9). The average number of oocytes retrieved was 1.1±1.1 in Ragni et al.'s (9) study, ours was 2 (median). Notably, their pregnancy rates were low across both treatment arms, with rates per cycle initiation, per OPU, and per ET of 5%, 6%, and 14%, respectively, and live birth rates of 3%, 4%, and 9%. In contrast, the live birth rate per ET in our study was 19.5%.

Revelli et al. (12) compared mild stimulation with the long GnRH agonist protocol and reported higher cancellation rates (13%) in the mild-stimulation group, along with a shorter duration of stimulation, lower total gonadotropin consumption, and fewer metaphase II oocytes and ETs. However, clinical pregnancy rates, ongoing pregnancy rates (OPR), and OPR per ET were similar between the two protocols. Their OPR per ET rate of 17.8% closely aligns with our findings.

One of the earliest studies comparing mild stimulation with the GnRH agonist long protocol, conducted by D'Amato et al. (13), found a higher cancellation rate in the long protocol group than in the mild stimulation group, particularly among patients older than 35 years. In this age group, the number of oocytes retrieved was lower with the long protocol, and pregnancy rates were lowest, although the differences did not reach statistical significance.

Karimzadeh et al. (14) compared mild stimulation with the microdose flare-up protocol and found that, in the mild stimulation group, endometrial thickness and follicle counts were higher, whereas total gonadotropin consumption was lower. Clinical pregnancy rates per ET and cycle cancellation rates were similar between groups. Because of the adverse effects of CC on endometrial thickness, frozen ET was performed more frequently in our study. Similarly, Ochin et al. (15) reported a higher rate of frozen ET among normoresponsive patients undergoing mild stimulation than among those receiving the long protocol, primarily attributable to inadequate endometrial thickness.

With respect to endometrial thickness, Shakerian et al. (16) demonstrated that it is not predictive of live birth; this finding was later confirmed by additional studies (17). In a multicenter RCT investigating different OS protocols in intrauterine insemination cycles for unexplained infertility, endometrial thickness was lower in CC cycles compared to gonadotropin cycles; however, this difference did not impact live birth rates (18).

Study Limitations

This is a retrospective, descriptive study of patients who underwent OS with only CC. The inclusion of a control group receiving gonadotropins would have strengthened the study's design and enhanced its scientific validity.

CONCLUSION

Given the high cost of gonadotropins and the comparable effectiveness of various OS protocols in women with DOR, CC represents a viable and cost-effective alternative in this clinical setting. A limitation of our study is the absence of a control group undergoing conventional OS with gonadotropins; however, as a descriptive study, it provides valuable insights. If future comparative prospective trials confirm the efficacy of CC, it may serve as a cost-effective alternative, reducing the financial and treatment burdens for women with DOR.

ETHICS

Ethics Committee Approval: The study protocol was approved by the Koç University Clinical Research Ethics Committee (protocol no: 2022.431.IRB1.157, date: 05.12.2022).

Informed Consent: Retrospective study.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: R.Ö., A.K., O.Ö., Concept: R.Ö., A.K., M.B.A., Design: S.G.Ç., A.K., M.B.A., Data Collection or Processing: R.Ö., S.G.Ç., A.K., O.Ö., Analysis or Interpretation: S.G.Ç., M.B.A., Literature Search: R.Ö., S.G.Ç., Writing: R.Ö., S.G.Ç., M.B.A.

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