ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Cost-effectiveness of Clomiphene Citrate Against Gonadotropin Therapy in Women with Unexplained Infertility

Açıklanamayan İnfertilitesi Olan Kadınlarda Klomifen Sitratın Gonadotropin Tedavisine Karşı Maliyet Etkinliği

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ABSTRACT

Aim: *Clomiphene citrate (CC) is the most frequently used agent for ovarian stimulation (OS). Gonadotropin (GND) treatment can be encouraged as a next step in women who are not able to become pregnant with CC. We aimed to determine the efficacy and cost-effectiveness of CC and GND in patients with unexplained infertility undergoing OS and intrauterine insemination.*

Material and Method: *The cost-effectiveness and success of CC and GND were retrospectively evaluated in 358 infertile women, of whom 247 received CC and 11 received GND treatment. The total CC/GND dose, endometrial thickness, semen parameters, duration of OS, follicle size, and pregnancy outcome were recorded. The medical costs of both strategies were analyzed, including the costs of medication and cycle monitoring. The cost of insemination was not evaluated since it was applied in both groups. The Shapiro-Wilk test, Student's t-test and Mann-Whitney U test were used for statistical analyses.*

Results: *There were no statistically significant differences between the groups in terms of cycle characteristics, semen analysis, total drug dose used, duration of OS, and dominant follicle size (p>0.05 for all). The pregnancy rate was 23.5% among the 264 (73.7%) patients with primary infertility and 17% among the 94 (26.3%) patients with secondary infertility. No significant difference was observed between the CC and GND groups with regard to the achieved pregnancy rate (21.1% vs. 23.4%, p=0.615). No side effect was observed. The cost of treatment for a couple with unexplained infertility was 1,716.42 TL for GND and 30.67 TL for CC.*

Conclusion: *The treatment success of OS with CC and GND seems to be similar in patients with unexplained infertility. Therefore, considering the cost-effectiveness and side effects of GND medication, the first choice should be CC in these patients.*

Keywords: *clinical pregnancy; clomiphene citrate; gonadotropin; ovulation induction; unexplained infertility*

ÖZET

Amaç: *Klomifen sitrat (CC), over stimülasyonu (OS) için en sık kullanılan ajandır. Klomifen sitrat ile gebe kalamayan kadınlarda gonadotropin (GND) tedavisi bir sonraki adım olarak teşvik edilebilir. Biz bu çalışmada açıklanamayan infertilitesi olan OS ve intrauterin inseminasyona giden hastalarda CC ve GND'nin etkisini ve maliyet etkinliğini belirlemeyi amaçladık.*

Materyal ve Metot: *CC ve GND'nin maliyet etkinliği ve başarısı, 247'si CC ve 11'i GND tedavisi alan 358 infertil kadında geriye dönük olarak değerlendirildi. Toplam CC/GND dozu, endometriyal kalınlık, semen parametreleri, OS süresi, folikül boyutu ve gebelik sonucu kaydedildi. İlaç maliyetleri ve döngü izleme dahil olmak üzere her iki stratejinin tıbbi maliyetleri analiz edildi. Her iki grupta da inseminasyon uygulandığı için onun maliyeti değerlendirilmemiştir. İstatistiksel analizler için Shapiro-Wilk testi, Student's t-testi ve Mann-Whitney U testi kullanıldı.*

Bulgular: *Siklus özellikleri, semen analizi, kullanılan toplam ilaç dozu, OS süresi ve dominant folikül boyutu açısından gruplar arasında istatistiksel olarak anlamlı fark yoktu (tümü için p>0,05). Primer infertilitesi olan 264 (%73,7) hastada gebelik oranı %23,5, sekonder infertilitesi olan 94 (%26,3) hastada ise %17 idi. Elde edilen gebelik oranı açısından CC ve GND grupları arasında anlamlı bir fark gözlenmedi (%21,1'e %23,4, p=0,615). Herhangi bir yan etki gözlenmedi. Açıklanamayan infertilitesi olan bir çiftin tedavi maliyeti GND için 1.716,42 TL ve CC için 30,67 TL idi.*

Sonuç: *Açıklanamayan infertilitesi olan hastalarda OS'nin CC ve GND ile tedavi başarısı benzer görünmektedir. Bu nedenle GND tedavisinin maliyet etkinliği ve yan etkileri göz önüne alındığında bu hastalarda ilk tercih CC olmalıdır.*

Anahtar Kelimeler: *klinik gebelik; klomifen sitrat; gonadotropin; ovulasyon endüksiyonu; açıklanamayan infertilite*

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Introduction

Infertility is defined as the inability of couples to obtain pregnancy despite at least one year of unprotected sexual intercourse[1]. Ovulation stimulation (OS) with intrauterine insemination (IUI) is recommended as a primary treatment option for infertility due to mild male factor, unexplained infertility[2]. Clomiphene citrate (CC) is the most frequently used agent in clinical practice for OS[3]. Pregnancy rates per cycle range from 10 to 20% in CC treatment[4].

Women who have not been able to become pregnant with CC may be encouraged to try gonadotropin (GND) as a next step. The advantage of the latter is that the dosage can be adjusted in the same cycle. The cost of GND therapy is significantly higher than in CC. However, it also has the disadvantages of requiring monitoring during treatment, involving the risk of ovarian hyperstimulation, and having a high rate of multiple pregnancies. Clomiphene citrate also has an anti-estrogenic effect on the endometrium and cervical mucus[5]. Recently, there has been a debate concerning whether GND treatment is unnecessary and extends the time to reach pregnancy, especially in couples with unexplained infertility following CC treatment.

The real cost of IUI treatment differs from one country to another, mainly due to the different costs of healthcare services and medicine. The Turkish Social Security Institution (SGK), the main governor of healthcare insurance in Türkiye, reimburses patients for the costs of cycle monitoring, IUI, and medication to a certain extent according to Supplement-2C of the Health Application Statement (SUT-Ek-2C) (http://www.sgk.gov.tr).

In our study, we aimed to investigate whether there was any difference between the treatment efficacy and pregnancy outcome of patients treated with CC and GND and determine the cost-effectiveness of the two methods for patients with unexplained infertility.

Material and Methods

This retrospective study included 358 women diagnosed with unexplained infertility who presented to the reproductive endocrinology and infertility clinic of Zekai Tahir Burak Women's Health Research and Education Hospital between June 2013 and April 2015. The study was approved by the ethics committee and institutional review board of the hospital (date and decision number: 04.27.2016-21). All the consecutive patients who met the study criteria were included in the sample. The sample comprised 358 patients aged 22–45 years who had an unexplained infertility diagnosis and underwent IUI after CC/GND and Ovulation Induction. On the third day of menstrual cycle, an ultrasonographic examination was performed and serum baseline hormones, such as follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), thyroid-stimulating hormone (TSH), prolactin (PRL), free testosterone, and dehydroepiandrosterone-sulfate were evaluated. All the patients underwent hysterosalpingography (HSG), and at least one tube showed patency with normal uterine cavity. Semen specimens were collected after at least two to five days of sexual abstinence, and the results were recorded in order to exclude the male factor. Semen parameters were analyzed according to the WHO 2010 criteria[6]. One IUI procedure was performed in each patient. Patients with severe male infertility, stage 3–4 endometriosis, polycystic ovarian syndrome , bilateral tubal occlusion according to HSG, ovarian hyperstimulation during treatment, additional drug use, thyroid dysfunction, or hyperprolactinemia were excluded from the study.

Clinical and demographic features, such as basal hormone (FSH, LH, and E2) levels, sperm count, morphology and volume, duration of OS, total CC/GND dose for induction, endometrium thickness on the day of human chorionic gonadotropin (hCG), and follicle size were recorded from the patients' files. Clomiphene citrate was used as the first step treatment in patients with unexplained infertility. Women who were not able to conceive with CC were treated with GND as the next step. However, patients who did not want to use CC treatment, those aged over 35 years, and those with a long duration of infertility underwent direct GND treatment. Multiple clinicians were involved in the treatment of patients evaluated in the study. In the group receiving CC treatment, 50–100 mg/day CC was initiated on the third to fifth day of menstrual cycle, while the GND group received 37.5–75 IU/day follicle-stimulating hormone/human menopausal gonadotropin (FSH/HMG) therapy starting from the second or third day of menstrual cycle. Serial transvaginal ultrasonography examinations were performed during OS. When at least one follicle reached a maximum diameter of 18–20 mm, 10.000 IU hCG was administered intramuscularly. Intrauterine insemination was performed 24/36 hours after administering hCG. The dosage of the drug was individualized according to the response of each patient and/or the data from their previous cycles. Luteal phase

support was provided with vaginal progesterone 200 mg/day for the patients in the GND group.

The cost-effectiveness analysis was performed from a health care perspective by taking into account the current direct medical costs of IUI. The fees for the gynecologist's cyclic monitoring or IUI treatment were not included in the calculation due to the absence of any difference in the fees of gynecologists working in state hospitals. The medication costs were calculated based on the total number units of GND or milligram of CC and the ovulation trigger used. In this process, the costs and reimbursement amounts for cycle monitoring and IUI and other costs of medication were obtained from Supplement 2C of the Health Application Statement presented on the SGK website (http://www.sgk.gov.tr).

The serum β-hCG test was performed at nearly two weeks after IUI. The diagnosis of clinical pregnancy was made six weeks after IUI based on the fetal heartbeat. The patients were divided into two groups according to pregnancy success (n=280) or failure (n=78). The groups were statistically compared in terms of the variables mentioned. There was one twin pregnancy but there no ectopic pregnancy. It was calculated that a total sample size of 357 infertile women would be needed for the expected pregnancy rate of 10% estimated from the existing literature data, with a power of 0.95 and a significance level of 5%.

Statistical Analysis

All statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS) program version 17 for Windows. The Kolmogorov-Smirnov test was used to test the normality of data distribution. Normally distributed continuous variables were expressed as mean standard deviation, and those that were not normally distributed were shown as median (minimum–maximum) values. Categorical variables were presented with number and percentages. The independent-samples t-test was used for the comparison of the groups when the parametric test conditions were met, and the Mann-Whitney U test otherwise. In order to compare categorical variables between the groups, the chi-square test was used. A p value of less than 0.05 was considered statistically significant.

Results

Of the 358 patients included in the study, 78 achieved pregnancies with the treatment applied, and their mean age was 27.3 (5.04) years. In the pregnant group, the mean age of the partners was 30.4 (5.15) years. Among the 280 patients without pregnancy, the mean age was 27.6 (5.06) years and that of their partners was 30.48 (5.22) years. There was no statistically significant difference between the groups in terms of age, body mass index, number of treatment cycles, sperm count, morphology, total CC dose, total GND dose, duration of treatment, dominant follicle diameter, and pregnancy outcomes (p>0.05)

Table 1. *Demographic and clinical characteristics of the patients*

	Pregnancy Outcome				
	Not Pregnant (n=280)		Pregnant (n=78)		
Variables	Mean (SD)	Median (Min-Max)	Mean (SD)	Median (Min-Max)	p-value
Age, woman (years)	27.60 (5.06)	28.00 (19.00–44.00)	27.38 (5.04)	26.50 (19.00–40.00)	0.665
Age, man (years)	30.48 (5.22)	30.00 (20.00–54.00)	30.40 (5.15)	29.50 (20.00–54.00)	0.798
BMI (kg/m^2)*	27.92(5.33)	27.54 (17.80–44.73)	28.92 (4.94)	28.06 (20.70–40.00)	0.101
Number of cycles	2.46 (1.37)	2.00 (1.00–6.00)	2.10 (1.06)	2.00 (1.00–6.00)	0.072
Sperm count (mil)	52.33 (24.51)	44.50 (7.00–152.00)	49.23 (20.17)	44.50 (15.00–152.60)	0.601
TMSC (mil)**	37.73 (11.48)	35.00 (18.00–81.00)	34.91 (10.17)	33.00 (12.50–63.00)	0.086
Morphology (%)	8.50 (5.39)	7.00 (3.00–50.00)	7.64 (3.06)	6.50 (5–17.40)	0.174
Sperm volume (ml)	2.59 (1.06)	2.00 (0.70–6.50)	2.52 (0.88)	2.00 (1.5–7.00)	0.798
Dominant follicle diameter (cm)	18.82 (2.04)	19.00 (10.00–26.00)	18.76 (1.72)	19.00 (14.00–24.00)	0.980
Endometrial thickness (mm)	8.90 (2.27)	9.00 (4.00–19.00)	9.05 (2.09)	9.00 (5.00–14.00)	0.509
Infertility duration (years)	3.73 (2.34)	3 (1–16)	3.41 (1.72)	3 (1–9)	0.624
	n (%)		n (%)		
Multifollicular development	109 (38.9%)		26 (33.3%)		0.367

*BMI: Body Mass Index; SD: Standart Deviation **TMSS: Total Motile Sperm Count

Table 2. *Pregnancy outcome according to the infertility type and treatment groups*

Variables		Pregnancy Outcome		p value
		Not Pregnant (n=280)	Pregnant (n=7 8)	
Infertility type, n (%)	Primary	202 (76.5)	62 (23.5)	0.192
	Secondary	78 (83.0)	16 (17.0)	
Treatment, n (%)	CC	195 (78.9)	52 (21.1)	0.615
	GND	85 (76.6)	26 (23.4)	

CC: Clomiphene sitrate; GND: Gonadotropin.

Table 3. *Resource use per woman*

	Gonadotropin (n=111)			Clomiphene Citrate (n=247)			
Pregnancy Outcome	(n)	Total dose (IU) Mean (SD)	Median (Min-Max)	(n)	Total dose (mg)	Median (Min-Max)	p-value
Pregnant	26	926.64(498.22)	825 (375–2.550)	52	407.87(149.98)	500(125–750)	0.824
Non Pregnant	85	951.81(645.07)	750.00 (300–4.450)	195	411.57(144.43)	500(125–750)	0.743
Cost (TL)							
Pregnant	26	1.716.42			30.67		
Non-Pregnant	85	1.763.03			30.95		<0.001

(Table 1). Ovarian hyperstimulation syndrome (OHSS) did not develop in any of the patients. A total of 264 (73.7%) patients had primary infertility, and their pregnancy rate was 23.5%, while the remaining 94 (26.3%) had secondary infertility and had a pregnancy rate of 17%. According to the treatment applied, the rate of pregnancy was determined as 21.1% for the CC group and 23.4% for the GND group. Twin pregnancy occurred in one (1.3%) patient who had been treated with GND. No statistically significant difference was observed between the treatment groups in terms of pregnancy outcome. There was also no statistically significant difference in relation to the infertility type, total CC/GND dose, and follicle count and size (p>0.05) (Table 2). However, a statistically significant difference was detected in the costs of GND and CC in the treatment of patients with unexplained infertility (p<0.001) (Table 4).

Table 4. *Unit and total costs of the treatments*

Cost Item	Unit	Unit Costs (€) *	TL **
Medication			
Gonadotropin	75 IU	24.75	1.852 TL
Clomiphene citrate	50 mg	0.53	1.8/25 mg
HCG for ovulation induction	5.000 IU	5.83	132.4

* Costs were derived from the expert panel of the Dutch Consortium for Research in Women's Health.
** Prices of pharmaceuticals were obtained from the Turkish Social Security Institution website (htpp://www.sgk.gov.tr)

Discussion

Clomiphene citrate is the first-line agent in the treatment of women with anovulatory infertility. Many factors play a role in the selection of the induction protocol to be administered, including patient age, result of ovarian reserve tests, and semen parameters. Clomiphene citrate is especially preferred in young, non-obese women, and in those that will receive treatment for the first time, whereas GND is preferred in patients who have not responded to CC and have additional risk factors, such as advanced age and moderate male factor. However, careful attention should be paid to possible complications, such as multifollicular development, OHSS, and multiple gestation during GND therapy.

In our study, when we compared the GND and CC groups, we found no difference in terms of pregnancy achievement rates. Based on our findings, CC presents as a more cost effective treatment in eligible patients. In addition, GND has certain disadvantages, including requirement of daily injections and a close follow-up, as well as side effects, such as pain and redness. In addition, the risk of multifollicular development is lower with the use of low-dose drugs, which reduces the possibility of OHSS. Observational studies conducted with large populations showed a pregnancy rate of 10% per cycle and a multiple pregnancy rate of 30% after GND and IUI[7,8]. In another prospective, randomized, controlled trial comparing letrozole + HMG stimulation with CC + HMG, the incidence of OHSS was determined 3% in

the CC + HMG group, while no OHSS was observed in the letrozole + HMG stimulation group[9]. The cost of treatment is another important factor to be considered. Karen et al.[10] showed that although HMG treatment was more expensive than CC treatment, it had better clinical pregnancy outcomes per cycle.

Dankert et al.[11] found that the live birth rates per cycle in the CC and r-FSH treatment groups were 10% and 8.7%, respectively in women treated with IUI. In another prospective study, patients who received CC and FSH therapy were compared, and the pregnancy rate per cycle was reported to be lower in the CC group (4%) than in the FSH group (13%). In our study, the success rate of IUI was 21% (78/358), which is higher than presented in the literature. This may be due to our strict inclusion criteria.

Intrauterine insemination studies reported different results on the endometrial thickness on the day of HCG and pregnancy rates. In one study on CC, the endometrial thickness and pregnancy rate were evaluated and found to have no association with pregnancy[12]. In another study using CC and HMG, a triple-line appearance of the endometrium on the day of IUI had a positive effect on pregnancy[13]. In our study, there was no significant difference between the endometrial thickness and pregnancy rate of the two groups, which is consistent with the literature.

Early stage endometriosis, minimal pelvic adhesions, cervical factor, and subclinical male factor are often assessed in unexplained infertile groups. Badaway et al. concluded that laparoscopy (L/S) could be postponed when proceeding in the management of unexplained infertility until the timed sexual intercourse with OS fails to achieve pregnancy[14]. However, there is still no consensus among researchers in the management of patients after CC therapy failure. Some authors perform L/S on women with pelvic symptoms, such as endometriosis and proceed with GND in women without pelvic symptoms. For symptomatic women, the treatment decision following L/S is taken based on intraoperative findings (e.g., endometriosis and adhesions). For asymptomatic women, OS with GND and IUI is offered as a well-established approach in the treatment of unexplained infertility with a higher rate of conception compared with CC/IUI or aromatase inhibitors[15]. However, patients should be informed that GND/IUI also increases the possibility of multiple gestation, compared with either CC or the aromatase inhibitor letrozole. Some authors perform L/S, rather than offering GND/IUI, as the next treatment step for women unable to pursue in vitro fertilization (IVF). According to these authors, a number of these women will have findings of endometriosis and/or adhesive disease at the time of L/S, regardless of symptomatology, and the surgical treatment of endometriosis will be associated with improved fertility[16]. After L/S, another course of CC/IUI is initiated since GND/IUI is associated with a high rate of multiple gestation and increases the cost out of proportion to the modest improvement in outcome (live birth rate reported as 32% for GND/IUI compared with 23% for CC/IUI)[15] On the other hand, some women who initially decline IVF and do not respond to other treatments may change their decision and pursue IVF rather than GND treatment because the live birth rate is higher with IVF compared with GND (45 versus 32%)[15.17], and their costs are similar.

In general, due to the increased risk of multiple gestation associated with OS with GND and IUI and the increased efficacy of IVF compared with OS, the American Society for Reproductive Medicine practice committee favors IVF rather than GND/IUI in cases where CC/IUI has failed[18] . This approach is supported by a randomized trial that compared the treatment outcomes of couples assigned to receive three cycles of CC/(IUI), three cycles of FSH/IUI, and up to six cycles of IVF (conventional approach)[19]. For the couples who did not conceive with CC/IUI, omitting the FSH/IUI cycles resulted in less time to achieve pregnancy (median time to pregnancy for accelerated or conventional approach: 8 versus 11 months), fewer treatment cycles, and significantly lower total costs. The cumulative pregnancy rate was slightly higher in the accelerated approach group initially but similar to the conventional treatment group after 11 months. The incidence of multiple gestation was also similar in both groups. Although our study was not randomized or prospective, we obtained similar results. In another randomized controlled trial, CC and GND treatments were compared in patients with unexplained subfertility undergoing IUI. The ongoing pregnancy rates were 31% in the GND group and 26% in the CC treatment group[20] . Bordewijk et al. compared the cost-effectiveness of GND versus CC in women with normogonadotropic anovulatory women. The authors found no significant difference in the rate of live births between the CC and GND groups[21] .

Limitations

The limitations of our study include the short follow-up period after pregnancy, resulting in the inability to detect pregnancy outcome in all patients, and serial ultrasonography being performed by more than one sonologist for the evaluation of follicular growth and endometrial thickness. However, we observed no adverse outcomes after either treatment.

Conclusion

In infertile patients, CC seems to be the first-choice treatment due to its ease of use and cost-effectiveness, as well as similar treatment success to GND in OI with IUI cycles. Similar pregnancy rates in both treatment groups suggest that in patients with unexplained infertility, the GND step can be omitted after CC treatment. This can may shorten the time for the patients to achieve pregnancy and reduce the cost of treatment.

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