Success Rates of Clomiphene Citrate and Recombinant Gonadotropin Cycles: A Single-Center Experience

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ABSTRACT

OBJECTIVE: This aim of this study is to assess the ovulation induction cycles based on clomiphene citrate and gonadotropin administration and specify the factors associated with successful outcomes.

STUDY DESIGN: This is a prospective study of 631 patients who underwent 917 ovulation induction cycles. While clomiphene citrate was used in 680 cycles (74.2%) and recombinant follicle-stimulating hormone was administered in 237 cycles (25.8%).

RESULTS: A total of 153 pregnancies were achieved in 917 ovulation induction cycles, indicating a clinical pregnancy rate of 16.7%. The ovulation induction cycles which ended up with clinical pregnancy had a significantly lower frequency of smoking (p=0.005), shorter infertility duration (p=0.001), higher basal luteinizing hormone (p=0.021) and lower basal progesterone (p=0.008) than unsuccessful cycles. The clomiphene citrate cycles which ended up with clinical pregnancy had a significantly lower frequency of smoking (p=0.011), shorter infertility duration (p=0.001) and lower basal progesterone (p=0.013) than the unsuccessful cycles. The recombinant follicle-stimulating hormone cycles which ended up with clinical pregnancy had a significantly higher basal luteinizing hormone (p=0.008) than the unsuccessful cycles. Basal luteinizing hormone and progesterone concentrations could significantly distinguish the patients who were able to conceive in ovulation induction cycles (p=0.021 and p=0.008, respectively).

CONCLUSIONS: Smoking, longer duration of infertility, and elevated basal progesterone are poor prognostic factors for clinical pregnancy in clomiphene citrate and recombinant follicle-stimulating hormone cycles.

Keywords: Clomiphene, Follicle-stimulating hormone, Ovulation induction, Pregnancy, Progesterone

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Introduction

Infertility is a public health concern that drives many couples to search for the help of assisted reproductive technology (ART) methods. In vitro, fertilization has been addressed as the most successful ART procedure, but it is relatively expensive and less available. Therefore, less invasive and more affordable procedures such as ovulation induction and intrauterine insemination (IUI) have become popular (1-3).

Clomiphene citrate (CC) has been traditionally used as the first-line drug for ovulation induction in women with chronic anovulation. Gonadotropins are an alternative, especially for women with CC resistance. However, the optimal choice that combines optimal effectiveness, safety, and costs are subject to debate. Although ovarian stimulation aims to achieve multifollicular growth in women with unexplained infertility, mono-follicular growth appears to be sufficient for women who are to undergo ovulation induction due to chronic anovulation. Various success rates have been yielded for various populations of infertile couples, 30% percent of the total pregnancy rates have been reported for ovulation induction cycles followed by IUI (3-5).

The infertile couples undergoing ovulation induction cycles are keen to know their chances of success as they are most likely to have emotional distress. Thus, it would be prudent to determine the factors favoring pregnancy in ovulation induction cycles (6,7). The factors associated with the success of ovulation induction cycles have been identified as female age, type, and duration of infertility, the number of mature follicles recruited and endometrial thickness (8-10). Although results usually compromise with some of these factors, there is still a lack of consistency in terms of other factors such as sex hormones.

This aim of this study is to assess the ovulation induction cycles based on CC and gonadotropin administration and specify the factors associated with successful outcomes.

Material and method

The present study was approved by the Ethical Committee of Dr. Zekai Tahir Burak Research Hospital (Approval no: 10), where it was undertaken between March 2008 and April 2010. The study protocol was undertaken in accordance with the principles of the Declaration of Helsinki and all participants gave their written informed consent. This is a prospective evaluation of 631 patients who underwent 917 ovulation induction cycles at Department of Reproductive Endocrinology, Zekai Tahir Burak Women's Health and Research Hospital, Ankara, Turkey.

Clomiphene citrate was used for ovulation induction in 680 cycles (74.2%), and recombinant follicle-stimulating hormone (rFSH) was administered for ovulation induction in 237 cycles (25.8%).

The women with one-year-long primary infertility and six-month-long secondary infertility were included in this study. The women aged ≥ 40 years, the women with body mass index (BMI) >29.9 kg/m^2, the women with poor ovarian reserve (with antral follicles of less than 5 to 7), the women who underwent ovarian and/or tubal surgery or with bilateral tubal factor, the women with male infertility, the women with endometriosis, women with uterine factor (fibroids, polyps and malformations), the women with systemic chronic diseases and women with endocrinopathies (diabetes mellitus, thyroid dysfunction, hyperprolactinemia, Cushing syndrome and late-onset congenital adrenal hyperplasia) were excluded.

Body mass index (BMI) was calculated as follows:
Body mass index (kg/m^2)=Body weight (kg)/Height^2 (m^2)

Ovulation Induction

Basal serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and progesterone levels were measured on day 3 of the menstrual cycle by automated Elecsys Immunoanalyser (Roche Diagnostics, Mannheim, Germany). The intra-assay and inter-assay coefficients of variation (CVs) were < 3% and < 6% for FSH, <3% and <4% for LH, <5% and <10% for estradiol and <3% and 5% for progesterone. Moreover, endometrial thickness and antral follicle count were evaluated on day 3 by transvaginal ultrasonography.

Ovulation induction by was begun on day 3 of the menstrual cycle. was given orally at a dose of 50 to 150 mg/day for five days. Ovulation induction by rFSH was begun at an initial subcutaneous dose of 50-100 IU/day 3 of the menstrual cycle. The rFSH dose was modified by the follicular growth, endometrial thickening, and serum estradiol levels. When at least one mature follicle reached a diameter of at least 18 mm in ovulation induction cycles, ovulation triggering was performed by intramuscular administration of 10000U IU human chorionic gonadotropin. None of the patients underwent a session of IUI.

The ovulation induction cycles were canceled if there were no mature follicles, more than four mature follicles were monitored, or serum estradiol concentrations were above 2000 ng/mL.

A clinical pregnancy is defined by the presence of an intrauterine embryo with a heartbeat, whereas an ongoing pregnancy was defined as a normally developing and living embryo beyond 12 weeks.

Statistical Analysis

Collected data were analyzed by Statistical Package for Social Sciences version 18.0 (SPSS IBM, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (range: minimum-maximum), and categorical variables were denoted as numbers or percentages where appropriate. Normally distributed continuous variables were analyzed by the independent samples t-test, and categorical variables were analyzed by Fisher's exact test. Receiver operating characteristic (ROC) curves were drawn to specify the predictive power of early follicular phase hormones (FSH, LH, estradiol, and progesterone), endometrial thickness and antral follicle count in distinguishing between the patients who were able to conceive and those who were unable. Two-tailed p values less than 0.05, with a confidence level of 95% were accepted to be statistically significant.

Results

Table I summarizes the demographic and clinical characteristics of groups with and without clinical pregnancy after ovulation induction. A total of 153 pregnancies occurred in 917 ovulation induction cycles, indicating a clinical pregnancy rate of 16.7%. Compared to unsuccessful ovulation induction cycles, the cycles ending up with pregnancy had a significantly lower frequency of smoking (p= 0.005), shorter infertility duration (p= 0.001), higher basal LH (p= 0.021), and lower basal progesterone (p= 0.008).

Table I: *Demographic and clinical characteristics of groups with and without clinical pregnancy after ovulation induction*

	Total (n=917)		
	Clinical pregnancy (n=153)	No clinical pregnancy (n=764)	*p*
Age[a] (years)	26.0±3.7	26.3±3.8	0.426
Body mass index[a] (kg/m^2)	23.5±3.0	23.3±3.0	0.520
Smoking[b] (n)	11 (7.2%)	121 (15.8%)	0.005*
Primary infertility[b] (n)	122 (79.7%)	607 (79.5%)	0.994
Secondary infertility[b] (n)	31 (20.3%)	157 (20.5%)	0.994
Infertility span[c] (years)	2 (1-16)	3 (1-19)	0.001*
Basal FSH[c] (mIU/mL)	6.3 (3.3-10.0)	6.4 (0.03-10.5)	0.946
Basal LH[c] (mIU/mL)	5.9 (0.9-13.8)	5.4 (1.0-13.9)	0.021*
Basal estradiol[c] (pg/mL)	42.6 (12.0-108.0)	41.6 (0.7-100.0)	0.654
Basal progesterone[c] (ng/mL)	0.700 (0.03-2.45)	0.80 (0.01-6.00)	0.008*
Basal endometrial thickness[c] (mm)	4 (4-5)	4 (4-9)	0.996
Basal antral follicle count[b] ≤10	87 (56.9%)	411 (53.8)	0.469
Basal antral follicle count[b] >10	66 (43.1%)	353 (46.2)	0.469

*FSH: Follicle-stimulating hormone, IUI: Intrauterine insemination, LH: Luteinizing hormone. [a]:Data were shown as mean ± standard deviation, [b]: As the number of cases and (%), [c]: As the median (minimum-maximum). *p < 0.05 was accepted to be statistically significant.*

Table II demonstrates the demographic, clinical characteristics and pregnancy outcomes of patients assigned to receive either CC or rFSH for ovulation induction. When compared to the women in the CC group, the women in the rFSH group had significantly older age (p=0.001), higher BMI (p=0.002), higher incidence of primary infertility (p=0.005), longer infertility span (p=0.001), lower basal LH (p=0.001), and lower cycle cancellation rates (p<0.001). Clinical and ongoing pregnancy rates were statistically similar between groups.

Table III displays the demographic and clinical characteristics of groups with and without clinical pregnancy after ovulation induction with CC or rFSH. When compared to unsuccessful CC cycles, the CC cycles ending up with pregnancy had a significantly lower frequency of smoking (p=0.011), shorter infertility duration (p=0.001), and lower basal progesterone (p=0.013). The patients who conceived after rFSH treatment had significantly higher basal LH (p=0.008) compared to the patients who were unable to conceive after rFSH treatment.

Table II: *Demographic, clinical characteristics, and pregnancy outcomes of patients assigned to receive either clomiphene citrate or recombinant follicle-stimulating hormone for ovulation induction*

	Recombinant FSH (n=237)	Clomiphene citrate (n=680)	*p*
Age[a] (year)	27.4 ± 3.7	25.8 ± 3.7	<0.001*
Body mass index[a] (kg/m^2)	23.9 ± 3.0	23.2 ± 3.0	0.002*
Smoking[b] (n)	34 (14.3%)	98 (14.4%)	0.980
Infertility span[c] (years)	5 (1-19)	3 (1-17)	<0.001*
Primary infertility (n)	204 (86.1%)	525 (77.2%)	0.005*
Secondary infertility (n)	33 (13.9%)	155 (22.8%)	0.005*
Basal FSH[c] (mIU/mL)	6.4 (2.4-10.5)	6.3 (0.03-10.1)	0.296
Basal LH[c] (mIU/mL)	4.8 (1.0-13.9)	5.6 (0.86-13.9)	<0.001*
Basal progesterone[c] (ng/mL)	0.77 (0.08-4.68)	0.8 (0.01-6.0)	0.294
Basal estradiol[c] (pg/mL)	40 (12-100)	42.3 (0.7-108)	0.120
Basal endometrial thickness[c] (mm)	4 (4-6)	4 (4-9)	0.608
Basal antral follicle count[b] ≤10 (n)	138 (58.2%)	360 (52.9)	0.196
Basal antral follicle count[b] >10 (n)	99 (41.8%)	320 (47.1)	0.196
Cycle cancellation[b] (n)	18 (7.6%)	121 (17.8)	<0.001*
Clinical pregnancy[b] (n)	37 (15.6%)	116 (17.1)	0.607
Ongoing pregnancy[b] (n)	31 (13.0%)	107 (17.5%)	0.439

*FSH: Follicle-stimulating hormone, IUI: Intrauterine insemination, LH: Luteinizing hormone, [a]: Data were shown as mean ± standard deviation, [b]: As the number of cases and (%), [c]: As the median (minimum-maximum). *p<0.05 was accepted to be statistically significant.*

Table III: *Demographic and clinical characteristics of groups with and without clinical pregnancy after ovulation induction with clomiphene citrate or recombinant follicle-stimulating hormone*

	Clomiphene citrate (n=680)			Recombinant FSH (n=237)		
	Clinical pregnancy (n=115)	No clinical pregnancy (n=565)	*p*	Clinical pregnancy (n=38)	No clinical pregnancy (n=199)	p
Age[a] (years)	25.8±3.6	25.9±3.8	0.837	26.8±3.9	27.6±3.7	0.279
BMI[a] (kg/m^2)	23.2±2.9	23.2±3.0	0.964	24.5±3.1	23.8±3.0	0.185
Smoking[b] (n)	8 (6.9%)	90 16.0%)	0.011*	3 (8.1%)	31 (15.5%)	0.239
Primary infertility[b] (n)	87 (75.0%)	438 (77.7%)	0.444	35 (94.6%)	169 (84.5%)	0.092
Secondary infertility[b] (n)	29 (25.0%)	126 (22.3%)	0.444	2 (5.4%)	31 (15.5%)	0.092
Infertility span[c] (years)	2 (1-16)	3 (1-17)	0.001*	3 (1-15)	5 (1-19)	0.055
Basal FSH[c] (mIU/mL)	6.3 (3.3-10)	6.3 (0.03-10.1)	0.647	6.3 (3.8-10.0)	6.5 (2.4-10.5)	0.359
Basal LH[c] (mIU/mL)	5.8 (0.9-13.8)	5.6 (1.3-13.9)	0.270	6.1 (1.9-13.4)	4.7 (1.0-13.9)	0.008*
Basal estradiol[c] (pg/mL)	42.7 (13.4-108)	42.2 (0.7-100)	0.382	40 (12-100)	40.1(13-94.8)	0.596
Basal PG[c] (ng/mL)	0.7 (0.03-2.4)	0.8 (0.01-6.0)	0.013*	0.7 (0.08-1.6)	0.8 (0.2-4.7)	0.287
Basal ET[c] (mm)	4 (4-5)	4 (4-9)	0.864	6.3 (3.8-10.0)	6.5 (2.4-10.5)	0.359
Basal AFC[b] ≤10	65 (56.0%)	295 (52.3%)	0.399	22 (59.5%)	116 (58.0%)	0.990
Basal AFC[b] >10	51 (44.0%)	269 (47.7%)	0.399	15 (40.5%)	84 (42.0%)	0.990

*BMI: Body mass index, AFC: Antral follicle count, ET: Endometrial thickness, FSH: Follicle-stimulating hormone, IUI: Intrauterine insemination, LH: Luteinizing hormone, PG: Progesterone, [a]: Data were shown as mean ± standard deviation, [b]: As the number of cases and (%), [c]: As the median (minimum-maximum). *p < 0.05 was accepted to be statistically significant.*

Figure 1 indicates that the ROC curve drawn for basal LH had a significantly larger area with a cut-off point of 5.56 mIU/mL (AUC: 0.559; 95% confidence interval: 0.509-0.610; *p*=0.021).

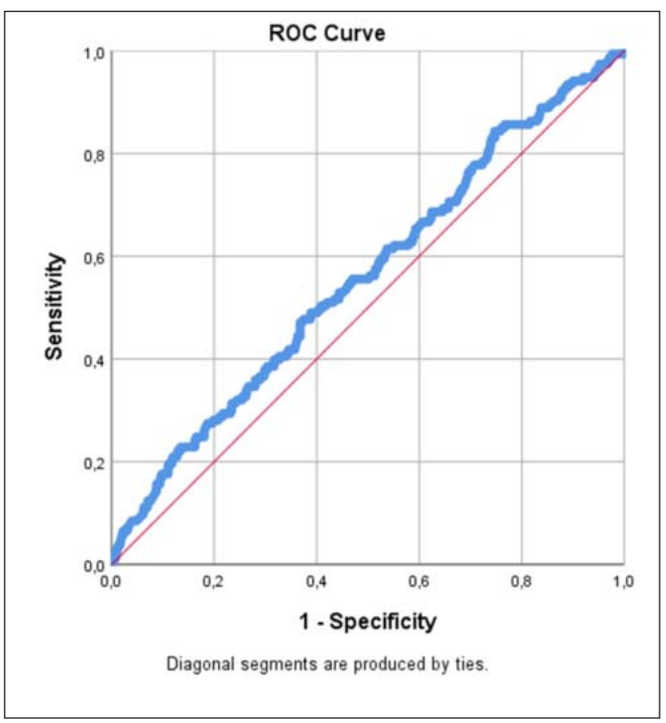

Figure 1: *Receiver operating characteristic curves of serum luteinizing hormone concentration on day 3 of the menstrual cycle for predicting pregnancy*

Figure 2 shows that the ROC curve drawn for basal progesterone had a significantly larger area with a cut-off point of 0.642 ng/mL (AUC: 0.568; 95% confidence interval: 0.518-0.618; *p*=0.008). That is, basal LH and progesterone concen-

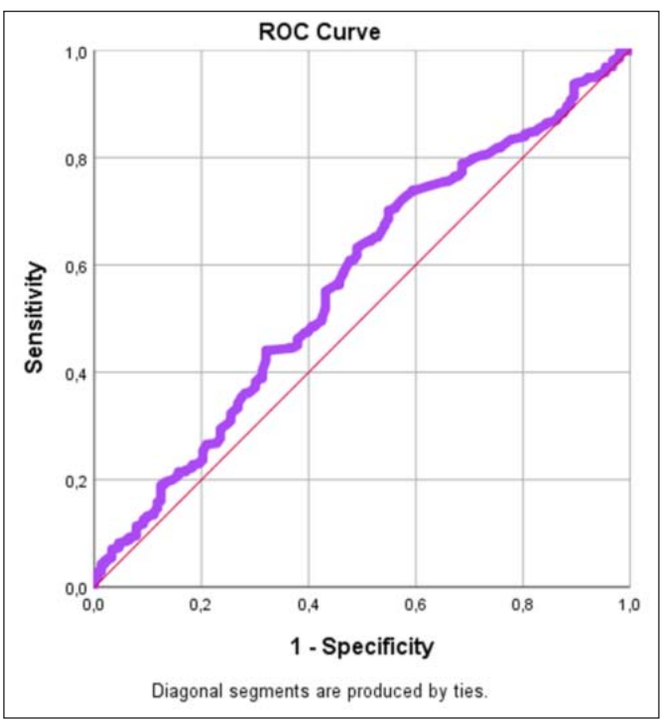

Figure 2: *Receiver operating characteristic curves of serum progesterone concentration on day 3 of the menstrual cycle for predicting pregnancy*

trations could significantly distinguish the patients who were able to conceive in ovulation induction cycles.

Discussion

According to a Cochrane review published in 2007, rFSH is the drug of choice for ovarian stimulation in women undergoing IUI (11). This meta-analysis of seven studies examining 556 women showed significantly higher pregnancy rates for rFSH when compared to CC (Odds ratio=1.8, 95% CI: 1.2-2.7) (11). A randomized controlled trial published in 2015 also indicated significantly higher live birth rates for rFSH when compared to CC in IUI cycles (12).

On the other hand, Danhof et al. claimed that they had adequate power to show that there is no statistically significant difference between rFSH and CC in IUI cycles with respect to cumulative ongoing pregnancy rates (Absolute rate difference =0.04, 95% CI:-0.02 to 0.11) (9). Similarly, Huang et al. concluded that CC and gonadotropins were equally efficient and safe in PCOS patients who are to undergo IUI after ovulation induction (10). In that study, clinical pregnancy rates were computed as 17.7% vs 17.5% for CC and gonadotropin cycles, respectively (10).

Accordingly, this study found CC and rFSH similarly effective for achieving clinical pregnancy in ovulation induction cycles (15.6% vs 17.1%, respectively). It was found that multi-follicular growth did not increase live birth rates, but significantly increased multiple pregnancy rates from 0.8% to 15.5% (10). A meta-analysis by van Rumste pointed out that multiple pregnancy rate was increased without a substantial gain in overall pregnancy rate whenever multi-follicular growth was achieved in ovulation induction-IUI cycles (13). The findings of the present study suggest that CC cycles might have outcomes that are as favorable as those of rFSH cycles. This unexpected result may be due to the significantly younger age, lower BMI, shorter infertility duration and higher secondary infertility rate of the women who underwent ovulation induction by CC administration.

Cigarette smoke contains several toxic chemical compounds which induce oxidative stress. Due to the enhancement in oxidative stress, smoking women have significantly higher basal FSH, lower serum anti-Müllerian hormone (AMH) and lower oocyte fertilization, which exerts a negative impact on ovarian reserve in in-vitro fertilization (IVF) cycles (14-16). In parallel, the results of this study indicate that ovulation induction cycles ending up with clinical pregnancy have a significantly lower frequency of smoking.

On the other hand, Farhi and colleagues did not identify significant differences in pregnancy rates of smokers and non-smokers (16.3% and 15.8%, respectively) in a retrospective review of 885 couples undergoing IUI after ovulation induction. However, a higher dose of gonadotropins was required in smokers (17). Another analysis of 900 couples with unexplained infertility was unable to detect a correlation between smoking and live birth in ovulation induction-IUI cycles (18). Similarly, a Turkish study was unable to address female smoking as a predictive factor for clinical pregnancy in the first IUI cycles (19). These discrepant results might be attributed to the relatively small number of smoking women, lack of longitudinal data and heterogeneity in studied populations.

Duration of infertility also affects the success of ovulation induction cycles (20,21). Jeon et al. assessed 348 IUI cycles using CC or letrozole combined with gonadotropins, or gonadotropins only and described the longer duration of infertility as an unfavorable factor for clinical pregnancy in IUI cycles (20). The longer duration of infertility has also been associated with lower clinical pregnancy and live birth rates in couples with unexplained infertility (18). A study evaluating Turkish couples with unexplained infertility and mild male infertility concluded that the clinical pregnancy rate was positively affected by a shorter duration of infertility (21). Complying with literature, ovulation induction cycles achieving the clinical pregnancy have a significantly shorter duration of infertility than unsuccessful cycles in this study. It is prudent to expect better outcomes in ovulation induction cycles of couples with shorter infertility span as the factors affecting these couples are probably less severe.

It has been hypothesized that incomplete destruction of a preceding corpus luteum and excessive production within the adrenal gland can lead to an early elevation of serum progesterone before ovulation. This premature rise of progesterone might force the endometrium to advance earlier, disturb synchronization between endometrium and transferred embryos and, thus, affect endometrial receptivity in IVF cycles (22, 23). Kolibianakis et al. were the first to find that the ongoing pregnancy rate was significantly lower in IVF cycles with elevated basal progesterone levels (24). Blockeel et al. used gonadotropin-releasing hormone (GnRH) antagonist for 3 days in cycles with elevated basal progesterone (>1.5 ng/mL) so that these women had statistically similar clinical pregnancy rates (25). Hamdine et al. also concluded that there was a lower chance of achieving an ongoing pregnancy in case of early basal progesterone rise (>1.5 ng/dL) (26). In contrast, Mutlu et al. were unable to specify an association between basal progesterone levels and pregnancy outcomes. They argued that canceling cycles with elevated basal progesterone might be the underlying reason (27).

As for the present study, ovulation induction cycles ending up with clinical pregnancy had significantly lower basal progesterone than unsuccessful cycles. Moreover, progesterone concentrations <0.642 ng/mL could distinguish the patients who were able to conceive in ovulation induction cycles. However, the detection of a significant difference for basal progesterone did not correspond to a meaningful clinical im-

plication. This incompetency can be attributed to the relatively small cohort size as well as the relatively higher cycle cancellation rates in both CC and rFSH cycles.

In conclusion, smoking, longer duration of infertility and elevated basal progesterone appear to be related to failure to conceive in ovulation induction cycles. However, this conclusion should be considered carefully as the power of this study is limited by several factors, including relatively small cohort size, and the lack of randomization, longitudinal data, and data related to AMH levels. Further research is warranted to clarify the factors associated with the success of CC and gonadotropin use in anovulatory women undergoing ovulation induction.

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