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Factors affecting success in intrauterine insemination cycles; 2-year single center experience

İntrauterin İnseminasyon Sikluslarında başarıyı etkileyen faktörler; tek merkezin iki yıllık deneyimi

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ÖZ

Amaç: Bu çalışmanın amacı; ovulatuar disfonksiyonu veya açıklanamayan infertilitesi olan hastalarda, klomifen sitrat ve gonadotropinler ile yapılan ovulasyon indüksiyonu ve intrauterin inseminasyon sikluslarının başarı oranlarını değerlendirmek ve başarıyı etkileyen faktörleri incelemektir.

Gereç ve Yöntemler: Haziran 2017 ve Ekim 2019 yılları arasında ovulatuar disfonksiyon veya açıklanamayan infertilite tanısı konan 152 infertil çiftte yapılan 223 intrauterin inseminasyon siklusu kayıtları retrospektif olarak tarandı.

Bulgular: Toplamda 33 pozitif gebelik test sonucu elde edildi ve gebelik başarı oranımız %14,8'di. Gonadotropin IUI sikluslarında gebelik başarı oranı %16,6 ve klomifen sitrat IUI sikluslarında gebelik başarı oranı %9,3'dü. Gebe kalan ve kalmayan gruplar karşılaştırıldığında her iki grup kadın yaşı, BMI, infertilite süresi, bazal FSH, LH, östradiol düzeyleri ve trigger günü endometrial kalınlık açısından benzerken sigara kullanımı gebe kalan grupta istatistiksel anlamlı olarak daha düşüktü (p=0.012).

Sonuç: Ovulatuar disfonksiyonu ve açıklanamayan infertilitesi olan infertil hastalarda sigara kullanımı IUI sonuçları üzerinde olumsuz etki etmektedir.

Anahtar Kelimeler: Ovulasyon indüksiyonu, intrauterin inseminasyon, prognostik faktörler, gebelik oranı

ABSTRACT

Objective: The aim of this study is to evaluate the success rates of intrauterine insemination cycles due to ovulation induction with clomiphene citrate and gonadotropins, and to identify factors associated with successful outcomes in women with unexplained infertility and ovulatory dysfunction.

Material and Methods: Between June 2017 and October 2019, 223 intrauterine insemination cycle records were scanned retrospectively in 152 infertile couples diagnosed with ovulatory dysfunction or unexplained infertility.

Result: A total of 33 positive pregnancy test results were obtained, which had shown a pregnancy success rate of 14.8%. Pregnancy success rate in Gonadotropin IUI (Intrauterine Insemination) cycles was found as 16.6% and pregnancy success rate in CC (Clomiphene Citrate) IUI cycles was found as 9.3%. When the groups that conceived and did not conceive were compared, both groups were similar in terms of female age, BMI, duration of infertility, basal FSH, LH, estradiol levels and endometrial thickness on trigger day, while smoking was statistically significantly lower in the group that conceived (p = 0.012).

Conclusion: Smoking negatively affects IUI results in infertile patients with ovulatory dysfunction and unexplained infertility.

Key Words: Ovulation induction, intrauterine insemination, prognostic factors, pregnancy rate

INTRODUCTION

Infertility is a condition wherein pregnancy cannot be achieved despite of unprotected sexual intercourse for a period of at least 12 months. Up to 85% of the couples who want a progeny can usually manage to achieve a successful pregnancy in the first year. As for the remaining couples, the causes that prevent pregnancy should be investigated before an infertility treatment can begin. Among the causes of infertility between couples, male factors (25% -30%), ovulatory dysfunctions (21% -25%), tubal factors (14% -20%) and unexplainable causes (25%

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-28%) exist; however, more than one reason was observed in 40% of these couples (1).

The process of using medications to stimulate normal ovulation in women with ovarian dysfunction is known as ovulation induction. For a female partner with unexplained infertility or ovulatory dysfunction, and at least one fallopian tube confirmed to be open in imaging with hysterosalpingography, and a male partner with enough sperm count and mobility, the simplest method of treatment is ovulation induction and planned coitus. Pregnancy success rate has been shown to increase up to 16% due to ovulation induction and planned coitus for well-chosen infertile couples (2). Clomiphene citrate (CC) has traditionally been used as a first-line medication for ovulation induction. Gonadotropins, on the other hand, are an alternative for women who have had CC resistance or failed CC treatment. Additionally, despite being an off-label drug that functions as an aromatase inhibitor, letrozole has been proposed as a front-line drug in the 2018 treatment guideline titled "Evidence Based Treatment of PCO and Infertility", especially for women diagnosed with anovulatory infertility based on polycystic-ovary syndrome (3).

The process of delivering the washed sperm sample into the uterine cavity via a catheter is called intrauterine insemination (IUI). IUI is a low-cost and non-invasive method, especially for selected patients with functionally normal tubes but with infertility due to certain cervical factors, anovulation, milde male factors, and unexplained factors. According to relevant studies, the pregnancy success rate observed with intrauterine insemination after ovulation induction has been stated as between 5% and 31% (4–7).

This study aims to evaluate the success rates of IUI cycles after ovulation induction based on clomiphene citrate and gonadotropin administration, and to identify factors associated with a positive pregnancy test result in women that have unexplained infertility and ovulatory dysfunction.

MATERIAL AND METHODS

Couples who applied to the infertility outpatient clinic of Umraniye Training and Research Hospital, Istanbul, Turkey between June 2017 and October 2019 were included in the study. Primary infertility defined as the couples who have not had a pregnancy despite one year of unprotected intercourse and secondary infertility defined as the couples who could not conceive despite unprotected intercourse for six months. Ovulation induction by clomiphene citrate and recombinant FSH with intrauterine insemination cycles in primary and secondary infertile couples were retrospectively screened. 441 treatment cycles which were applied on 272 infertile couples, along with their treatment cycle files, were analyzed. Patients with the following features were excluded from the study; those over the age of 40 during treatment, those whose BMI is 30 kg/m2 or more, those that were taking medication because of insulin resistance, diabetes mellitus, hypo or hyperthyroidism, patients with hypogonadotropic hypogonadism, patients with endometriosis, history of ovarian or tube surgery, patients with conditions that cause cavity deformations such as fibroids, polyps, and congenital uterine malformations, patients with male infertility factors, patients undergoing various treatments except clomiphene citrate and gonadotropin treatments, individuals who received intrauterine insemination in their natural cycle, and patients who have experienced spontaneous ovulation and were not inseminated.

A total of 223 cycle implementations were performed in 152 infertile couples with ovulatory dysfunction and unexplained infertility. The participation criteria were as follows; patients under the age of 40 during treatment, those with a BMI of 29.9 kg/m2 or less, least one tube shown to be open according to the results of hysterosalpingography and couples with the male partner possessing a "total post-washing progressive motile sperm count" as greater than 5 million.

Ovulatory dysfunction defined as; patients who has not have spontaneous follicle development and ovulation in previous examinations or patients with detecting a progesterone level below 3 ng/mL tested seven days after the expected ovulation day depending on the cycle duration.

Body mass index (BMI) had been measured as; BMI (kg/m2) = Body weight (kg)/Height2 (m)

The Local Ethics Committee of Umraniye Training and Research Hospital, Istanbul, Turkey have approved this study (Ethics Committee Approval No: B.10.1.TKH.4.34.H.GP.0.01/205)

Ovulation Induction

The patients applied to our outpatient clinic on the third day of their cycle. Patient's basal endometrium thickness and antral follicle count were assessed by ultrasound. Blood samples were taken the same morning after 8 hours of fasting. Basal FSH, LH and estradiol levels of the patients were analyzed with the Abbott Architect i200 SR device in accordance with the manufacturer's recommendations. Ovulation induction was performed between the 5th and 9th days of the cycle via Clomiphene Citrate (CC) with a daily dose range of 50-150 mg/day. Ovula-

tion induction via gonadotropin were started on the 3rd day of the cycle via recFSH (Gonal-f Merck İlaç Ecza ve Kimya Tic. A.Ş., Puregon Merck Sharp Dohme İlaçları Ltd. Şti., Fostimon IBSA İlaç San. Ve Tic. Ltd. Şti.) administration, with a daily starting dose of 75 IU/day. The dose was increased by 37.5 IU/day in tandem with follicle development. As soon as the dominant follicle reached 18mm in size, ovulation was triggered with 250 mcg rechCG (Gonal-f Merck İlaç Ecza ve Kimya Tic. A.Ş). Ultrasonography (Hitachi Aloka Prosound F37) was used for basal ultrasound examinations and follicle follow-up of patients.

Sperm Preparation

After 3-7 days of sexual abstinence, sperm samples were taken to the andrology laboratory of our hospital on the morning of intrauterine insemination. Sperm samples to be used in insemination were prepared by two-layer gradient swim-up technique.

Intrauterine Insemination

36 hours after the trigger intrauterine insemination was performed by a soft cannula. After the insemination all patients were given a 15-minute rest period to have rest and did not received any medication for luteal phase support. In order to apply legal regulations in our country to prevent multiple pregnancies; rechCH was not applied in the presence of more than two follicles greater than 16 mm, insemination procedure was canceled, and couples were advised not to have sexual intercourse. As the primary outcome in our study, Beta-hCG was examined in the patient's blood 14 days after intrauterine insemination and a value of 50 and above was evaluated as a positive pregnancy test result.

Statistical Analysis

Statistics were performed with the SPSS 25.0 package program. The distribution of the data was found to be normal with the Kolmogorov Smirnov test. In addition to descriptive statistical methods (mean, standard deviation, frequency, etc.), t-test and chi-square tests were also used alongside parametric data while evaluating the findings of this study. Significance has been determined at $p < 0.05$ levels for all values.

RESULTS

33 positive pregnancy test result were recorded from 223 cycles, 54 of which CC treatment and 169 of the gonadotropin treatments. The overall positive pregnancy test result rate, obtained from ovulation induction and intrauterine insemination cycles, was 14.8%. While 5 positive pregnancy results (9.3% success rate) was obtained with CC and IUI cycles, 28 positive pregnancy results (16.6% success rate) was obtained with gonadotropin and IUI cycles. Out of 33 pregnancies, live birth occurred in 15 of them, ongoing pregnancy more than 12 weeks in 10 of them, and chemical pregnancy occurred in 8 of them.

In comparison between the group with positive pregnancy result and the group with negative pregnancy test result, no significant difference was found in parameters such as age, BMI, basal FSH, basal LH, basal estradiol levels, endometrial thickness on basal and trigger days, and infertility type and duration. Only smoking was found to be statistically higher in the negative pregnancy test group (p=0.012). (Table 1)

Table 1: Demographic characteristics, baseline hormone values and cycle characteristics of the patients.

	Pregnancy Positive (n=33)	Pregnancy Negative (n=190)	p
Age (years)*	30.4±4.70	31.1±4.84	0.447
Body Mass Index (kg/m^2)*	23.3±3.64	23.6±3.44	0.642
Duration of infertility (years)*	2.46 (1-10)	3.02 (1-13)	0.244
Basal FSH (mIU/mL)*	5.8(3.1-11.4)	5.9(2.3-16.0)	0.776
Basal LH (mIU/mL)*	5.7(1.9-14.2)	4.9(1.6-18.4)	0.084
Basal Estradiol (pg/mL)*	46.6(21.0-102.0)	47.6(15.0-119.0)	0.802
Tobacco consumption (n)**	6 (14.6%)	35 (85.4%)	0.012
Primary infertility (n)**	24 (72.7%)	127(66.8%)	0.552
Secondary infertility (n)**	9(27.3%)	63(33.2%)	0.552
Basal endometrial thickness(mm)*	2.96(2-6)	3.32(2-9)	0.200
Trigger day endometrial thickness (mm)*	8.8(5-19)	9.0(5-22)	0.607

* T-test, ** chi-square

Comparing the group with clomiphene-citrate-based ovulation induction treatment to the group with gonadotropin-based ovulation induction treatment also showed no significant difference on BMI, basal FSH, basal LH, basal estradiol levels, smoking, recHCG, trigger day endometrial thickness, and infertility type and duration. The only statistically significant difference between parameters was found to be basal endometrial thickness. (p=0.001). (Table 2)

Table 2: Demographic characteristics, baseline hormone values and cycle characteristics of clomiphene citrate and gonadotropin groups.

	Clomiphene Citrate (n=54)	Recombinant FSH (n=169)	p
Age (years)*	30.8±5.36	31.1±4.65	0.744
Body Mass Index (kg/m²)*	23.4±3.35	23.5±3.51	0.856
Duration of infertility (years)*	3.20 (1-10)	2.86(1-13)	0.393
Basal FSH (mIU/mL)*	5.54(3.10-16.0)	6.03(2.3-16.0)	0.109
Basal LH (mIU/mL)*	4.66(2.0-8.5)	5.24(1.6-18.4)	0.119
Basal Estradiol (pg/mL)*	4.72(20-119)	48.4(15-108)	0.242
Tobacco consumption (n)**	11 (20.4%)	30(17.8%)	0.688
Primary infertility (n)**	32(59.3%)	119(70.4%)	0.135
Secondary infertility (n)**	22(40.7%)	50(29.6%)	0.135
Basal endometrial thickness (mm)*	3.81(2-9)	3.09(2-9)	0.001
Trigger day endometrial thickness (mm)*	8.96(5-15)	9.05(5-22)	0.815
Ovulatory dysfunction**	14(25.9%)	46(27.2%)	1.000
Unexplained infertility**	40(74.1%)	123(72.8%)	1.000
Positive pregnancy test result**	5(9.3%)	28(16.6%)	0.270
Negative pregnancy test result**	49(90.7%)	141(83.4%)	0.270

* T-test, ** chi-square

DISCUSSION

Pregnancy success rates in intrauterine insemination cycles in the related literature was found to vary; depending on the agents used for the ovulation induction procedure and the characteristics of the study population. As an example; in a study comparing expectant management with intrauterine insemination in infertile patients with isolated cervical factor, at the end of six months follow up, the cumulative pregnancy rate in the insemination group was found to be higher than the expectant management group (51% and 33% respectively) (8). In another randomized controlled study in which the expectant management group were compared with the unexplained infertility group undergoing ovulation induction with oral agents and IUI procedure; the cumulative live birth rate in the IUI group was recorded at 31%, with the rate being relatively higher than the expectant management group, which was recorded at 9% (RR: 3.41 95% CI 1.71-6.79) (7). Similarly, as shown in a study in 2018; ovulation induction and intrauterine insemination is associated with higher chances of ongoing pregnancy compared to expectant management group of couples with unexplained subfertility and poor prognoses of natural conception (Overall hazard ratio: 1.96 95% CI: 1.47-2.62) (9). Considering the success of pregnancy, intrauterine insemination treatment on well-selected infertile patient population is apparently much more effective than expectant management.

As stated in the Cochrane Review (published in 2007), in which pregnancy rates are analyzed in intrauterine insemination treatments through oral agents and gonadotropins, gonadotropins are expressed as the most effective form of medication. Meta-analysis of 7 studies involving 556 infertile patients in total, has shown that IUI administered via gonadotropins provided statistically higher pregnancy rates than IUI administered via CC (Odds ratio=1.8, 95% CI: 1.2-2.7) (10). In addition, a randomized controlled prospective study conducted by Diamond et al. in 2015 suggests that clinical pregnancy and live birth rates are higher in IUI cycles with recFSH than with CC (11). In accordance with the current literature, our study has showed that pregnancy rates in IUI cycles with gonadotropin were much higher than those performed with CC, with the rates being 16.6% of gonadotropins and 9.3% for CC.

On the other hand, as seen in the review published by Danhof et al. in 2018, it was claimed that due to strict cancellation criteria at IUI, recFSH with ovarian stimulation was not superior to CC in terms of cumulative ongoing pregnancy rate. (Absolute Ratio Difference = 0.04, 95% CI: −0.02 to 0.1) (12). Similarly, in another study conducted by Ejzenberg et al., there was no statistical difference in terms of positive pregnancy test results between IUI cycles with CC and gonadotropin (p=0.300) (6). Also, Huang et al. concluded that CC and gonadotropins are equally effective in PCOS patients undergoing IUI after induction of ovulation, in which clinical pregnancy rates were recorded as 17.7% and 17.5% for CC and gonadotropin cycles, respectively (13).

Our country implements a legal regulation managed by the Ministry of Health to prevent multiple pregnancies. This arrangement states that; if more than two follicles greater than 16 mm develops during ovulation induction, the treatment cycle will be canceled. Naturally, we also apply these strict cycle cancellation criteria in our hospital within the framework of this legislation. Indeed, in this study, multiple pregnancies were not detected in any of the 33 pregnancy cases, which is equally important for us in terms of the success of the treatment. This approach was also supported by a meta-analysis published in 2008. According to this meta-analysis of 14 studies involving a total of 11599 insemination cycles; IUI, when co-administered with COH (Controlled Ovarian Hyperstimulation), should not target more than two follicles. This study shows that, given cycles with three or four follicles, there is an increase in multiple pregnancy rates, with no significant gain shown in overall pregnancy rate (14).

The relevant literature contains an extensive research archive of factors affecting success rates in intrauterine insemination. A retrospective study which examined a total of 1171 IUI cycles, claimed that increased female age negatively affected IUI

results (15). In addition, another study involving 1038 IUI cycles showed that female age is an important predictive factor for treatment success among all causes of infertility. This study claimed that the ongoing pregnancy rate per couple was 38.5% for those under 30 years of age, and 12.5% for those over 40 years of age (16). Different from these studies, in our study, no relation was found between the age of women and the success of IUI. This difference may have occurred due to the fact that we have conducted our study with infertile patients younger than 40 years of age and preferred IVF especially for primary infertile patients over 40 years of age. As a supporting argument for our approach, a study by Bou Nemer et al. explained that IVF treatment had a statistically higher live pregnancy rate per cycle for patients aged 40 years and older compared to mild stimulation intrauterine insemination. (9.2%, 1.28%, p <0.001, respectively) (17).

In likeness with female age, body mass index is another confounding factor in the success of intrauterine insemination. It has been shown that in overweight women, the incidence of menstrual dysfunction and anovulation is higher, which can cause implantation impairment (18). However, in the study conducted by Yumusak et al., they could not find a significant difference in terms of BMI between the group who became pregnant after IUI cycles and the group who could not conceive (19). Also Raymond Li et al. could not show a significant relationship between BMI and pregnancy rates; although, higher BMI has been associated with a higher threshold dose and longer stimulation time (20). Interestingly, women with higher BMI were found to be more likely to become pregnant than women with lower BMI treated with letrozole (21) and gonadotropins (18), but the findings were not statistically significant. As for this study, no significant relationship has been found between BMI and positive or negative pregnancy test result groups.

The duration of infertility is also examined as a predictive factor in IUI success (6,22). Jeon et al. assessed 348 IUI cycles using only CC, letrozole combined with gonadotropins or gonadotropins only and described the longer duration of infertility as an unfavorable factor for clinical pregnancy in IUI cycles (22). The study by Ejzenberg on the prognostic factors of IUI cycles also showed the negative impact of prolonged infertility on IUI success (6). In a study conducted by Erdogan et al. pregnancy rate after IUI was found to be significantly higher in patients with an infertility duration of less than 3 years compared to those with an infertility duration longer than 3 years (23). Unlike these study results, our study did not state any difference between the positive pregnancy test result group and the negative pregnancy test result group in terms of duration of infertility.

It has been shown that in ovulatory women, a basal FSH level of 8 IU/liter or higher is associated with decreasing fecundity, independent of female age and cycle length (24). In addition to basal FSH, the correlation between basal LH and estradiol levels and IUI success rate was also examined. Among these three basal hormones, there was only a statistically significant correlation of FSH concentration with the percentage of positive β-hCG test results was shown by Ejzenberg et al (6). However, in this study, we did not find a statistical difference between baseline FSH, LH and estradiol levels and positive and negative pregnancy test result groups.

It has already known that smoking influences several aspects of fertility. Female smoking is associated with increased basal FSH and decreased oocyte fertilization (25), decreased serum AMH that indicates a negative impact on ovarian reserve (26) and reduced uterine receptiveness (27). Similarly, our study also suggests that smoking has a negative impact on IUI success rate for the infertile population with ovulatory dysfunction and unexplained infertility. On the other hand, in an analysis which investigated 900 couples with unexplained infertility found no relationship between smoking and live birth in ovulation induction IUI cycles (28). Also in another study evaluating the factors affecting pregnancy success, no significant difference was found between the group who became pregnant after IUI and the group who could not conceive in terms of smoking (23). In addition Farhi et al. could not perceive any significant difference between the smoking group and non-smoking group (16.3% and 15.8%, respectively) regarding pregnancy rates in the retrospective examination of 885 couples who received IUI after ovulation induction. However, a higher dose of gonadotropin was found to be required in smokers (29). We think that these contradictory results may be related to the heterogeneity of the population studied, as well as the type and number of cigarettes used.

Various studies have analyzed the relationship between pre-ovulatory endometrial thickness and insemination outcomes. In a study published in 2019, the endometrial thickness on the trigger day was found to be statistically significantly thicker in the group that conceived after the IUI cycle compared to the group who could not conceive (19). However, a meta-analysis of 23 studies including 3846 women who received intrauterine insemination treatment following ovulation induction via CC, letrozole or gonadotropins suggest that women treated with

CC have less pre-ovulatory endometrium thickness than women treated with gonadotropins, but there is no evidence of a relationship between pre-ovulatory endometrial thickness and pregnancy rates (30). Similar to this meta-analysis published in 2017, in our study, we also found that the endometrial thickness on the trigger day in the ovulation induction cycles made with CC was thinner than the gonadotropin group, but this finding was found to be not statistically significant. Similarly, there was no statistical difference in the endometrial thickness on the trigger day between the group with positive pregnancy test result and the group with negative pregnancy result.

In the literature, differences in the determinants of pregnancy in IUI cycles are most likely due to the heterogeneous nature of the study populations. Being single-center, retrospective nature and the low number of IUI cycles are the limitations of our study.

As a conclusion, this study has shown that; while smoking in the infertile population with ovulatory dysfunction and unexplained infertility has a negative effect on IUI results, in terms of female age, BMI, infertility span, basal FSH, basal LH, estradiol levels and endometrial thickness on trigger day, it has not displayed a correlation with IUI results. Further studies are needed to clarify the factors associated with the success of intrauterine insemination followed up by ovulation induction.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they had obtained appropriate institutional review board approval and had followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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