Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1128579
J Health Sci Med 2022; 5(5): 1286-1291

Effect of oral estrogen supplement on gonadotropin-induced intrauterine insemination: A retrospective cohort study

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Cite this article as: Özgökçe Ç, Öcal A, Ege S. Effect of oral estrogen supplement on gonadotropin-induced intrauterine insemination: A retrospective cohort study. J Health Sci Med 2022; 5(5): 1286-1291.

ABSTRACT

Aim: The effect of estrogen on gonadotropin-induced intrauterine insemination (GI-IUI) is not well studied. Furthermore, risk factors for clinical pregnancy rates are not clearly defined. This study aimed to evaluate the effects of oral estrogen supplementation and clinical pregnancy rates on GI-IUI.

Material and Method: Patients treated with primary and secondary infertility were retrospectively analyzed between September 2016 and September 2019. IUI session was performed after ovarian stimulation with human chorionic gonadotropin. Patients were supplemented with a vaginal gel containing progesterone and oral estrogen (Group A) or only the vaginal gel (Group B). The differences between the groups in pregnancy rate and endometrial thickness and the risk factors associated with clinical pregnancy were determined as primary and secondary outcomes, respectively.

Results: A total of 112 couples were evaluated, where the mean age for females was 31.3±6.1 years. Group A and Group B had 33 (29.5%) and 79 patients (70.5%), respectively. Duration of infertility, number of follicles, and endometrial thickness were significantly different between the two groups. The rate of pregnancy was significantly higher in Group A (51.5%) than in Group B (19%) (p=0.001). There were significant differences between positive and negative pregnancy cases in terms of age, type and duration of infertility, estradiol level, motile sperm number and morphology, number of follicles, and endometrial thickness. The follicle count and estradiol levels were significant risk factors for clinical pregnancy.

Conclusion: Estrogen has a positive effect on pregnancy rates in GI-IUI. The follicle number and estradiol level can be used as a risk factor for IUI.

Keywords: Infertility, intrauterine insemination, gonadotropins, estrogen, clinical pregnancy

INTRODUCTION

Intrauterine insemination (IUI) is preferred, especially in cases of unexplained infertility or cases with mild to moderate endometriosis and/or infertility associated with the mild male factor (1,2). The IUI cycles performed using different agents cause an increase in estrogen levels with the effect of formed ovarian follicles, thereby the thickening of the endometrium (1). In cases where IUI was performed using clomiphene citrate, it has been reported that the endometrial thickness induced by the anti-estrogenic effect of clomiphene at the endometrial level was lower than the thickness induced by natural cycles (3-5). In contrast, it has been speculated that endometrial thickness will not be adversely affected in gonadotropin-induced IUI since injectable gonadotropins do not have a regulatory effect on estrogen (1). However, the possible relationships between gonadotropin-induced IUI, estrogen level, and endometrial thickness have not been studied in detail.

Estrogen is known to positively affect the pregnancy-related endometrial thickness, cervical mucus, and uterine blood flow (6). Therefore, it may be possible to prevent events such as impaired endometrial development and decreased uterine blood flow, especially in IUI, with exogenous estrogen support.

The studies available in the literature addressed the effect of estrogen in IUI performed using clomiphene citrate with or without ethinyl estradiol. In one of these studies, Gerli et al. (7) demonstrated that the use of clomiphene citrate and ethinyl estradiol caused an increase in endometrial thickness. In another study, Unfer et al. (8) reported that even low doses of ethinyl estradiol have a

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Received: 09.06.2022 **Accepted:** 20.07.2022

significant effect on endometrial thickness, histological matching, and morphological characteristics of the endometrium. On the other hand, the effect of estrogen in gonadotropin-induced IUI has not been adequately studied. In this context, the objective of this study is to investigate the effect of oral estrogen supplementation on pregnancy outcomes in IUI performed with injectable gonadotropin and determine the variables that affect clinical pregnancy rates in gonadotropin-induced IUI.

MATERIAL AND METHOD

Research Design

This study has been designed as a retrospective study of patients who underwent infertility treatment with IUI between September 2016 and September 2019. The study was carried out in accordance with the ethical standards set forth in the Declaration of Helsinki. This study was approved by Van Training and Research Hospital Clinical Research Ethics Committee (Date: 09.01.2020, Decision No: 2020/01). Written informed consent was not obtained from the patients due to the study's retrospective nature.

Population and Sample

The study population comprised the couples with no pregnancy despite having regular sexual intercourse at least twice a week for at least one year, couples in which the female partner has been shown to have at least one tube passage and peritoneal distribution by hysterosalpingography performed in the last two years, couples in which the male partner had no azoospermia, and couples with unexplained primary and secondary infertility. Demographic and clinical data of all patients who were treated for infertility in the clinic where this study was conducted were concurrently recorded in a computerized recording system from the time of admission to the end of the treatment. Obstetric and gynecological backgrounds and menstrual cycle patterns of the patients were investigated. All patients underwent a physical examination. Additionally, the necessary laboratory tests, i.e., thyroid-stimulating hormone (TSH), prolactin, and testosterone tests, were performed in order to detect endocrine and metabolic diseases, if any. Patients with infertility duration of 10 years or longer, patients with a basal follicle-stimulating hormone (FSH) level of >10 IU/L and a basal estradiol (E2) level of >80 pg/mL on the 2nd or 3rd day of menstruation, patients with additional endocrine and metabolic diseases, and patients with solid or cystic mass detected on transvaginal ultrasound (TVUS) were excluded from the study. All male patients were evaluated with urology examination and at least two spermiogram tests performed at different times. Couples with severe male factor were excluded from the study. In the end, 112 primary and secondary infertile couples were included in the study sample (**Figure 1**).

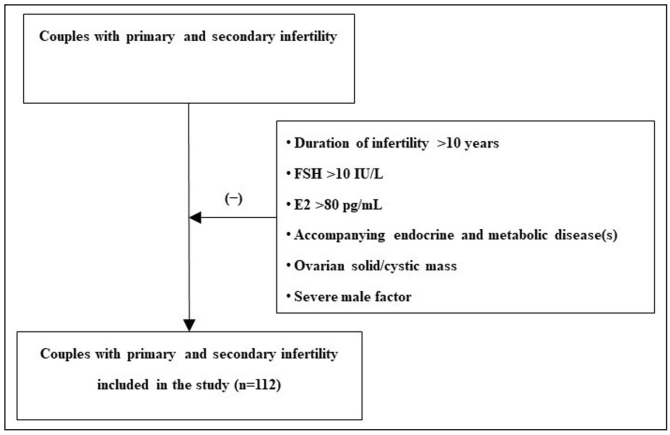

Figure 1. Flow chart of the study.

Ovarian stimulation and IUI protocol

Ovarian stimulation was performed on the 3rd day of menstruation in patients with regular cycles or on the 3rd day of presumed menstruation in oligomenorrhea patients without regular cycles. 50 to 150 IU of recombinant FSH (GonalF®; Merck Serono, Italy, Puregon®; Merck-Sharp & Dohme, Australia) was administered to the patients, taking into account their age, body mass index (BMI), ovarian reserve status, and response to previous treatments, if any. TVUS and serum E2, luteinizing hormone (LH), and progesterone measurements were employed for cycle monitoring. Ovarian follicle detection and endometrial thickness (mm) measurements were performed by TVUS.

In cases with a follicle size of 18 mm and above and spontaneous LH surges, a single IUI session was performed at the 36th hour following the administration of 10.000 IU human chorionic gonadotropin (hCG) (Pregnyl®; Organon, the Netherlands) intramuscularly or 250 µg recombinant hCG (Ovitrelle®; Merck-Serono, Italy) subcutaneously. The vulva was washed with physiological saline solution during the procedure, and then 0.5 mL of sperm was injected into the intrauterine cavity using a soft insemination catheter (Ainseblue-R RI. Mos., Italy). The procedure was terminated after 15 minutes of resting in the supine position.

Luteal phase support was provided with micronized vaginal gel (Crinone 8% vaginal gel, Merck Pharmaceuticals, Bedfordshire, England) containing 90 mg progesterone and continued until the 12th week in patients who developed pregnancy. Oral estrogen supplementation [Estrofem (once daily 2 mg tablet) Novo Nordisk, İstanbul, Turkey] was given to some of the patients, according to the decision of the primary researcher. The patients were divided into two groups according to whether they were administered oral estrogen therapy: patients who were administered vaginal progesterone gel and oral estrogen therapy (Group A) and patients who were administered only vaginal progesterone gel (Group B).

Data Collection

Patients' age (years), type of infertility (primary or secondary), duration of infertility (years), FSH (IU/L) and E2 (pg/mL) levels, antral follicles detected by TVUS (n), and endometrial thickness (mm) measured on the day of administration of hCG were recorded. The total progressive motile sperm count (TPMSC) (n/mL) in men and the percentage (%) of sperms with normal sperm morphology according to Kruger criteria were recorded in the database. Couples were evaluated in two subgroups according to their TPMSCs: couples with>10 million progressive motile sperms per mL and couples with <10 million progressive motile sperms per mL. In addition, couples were divided into two subgroups according to the male partner's percentage of sperms with normal sperm morphology: couples who had >4% sperms with normal morphology and couples who had <4% sperms with normal morphology. Pregnancy was assessed with hCG measurement on the 14th day after the IUI application and confirmed clinically by the presence of a heartbeat in TVUS performed at the 7th week on average.

Statistical Analysis

The primary outcomes of the study were the differences between the treatment groups in pregnancy rates and endometrial thickness, whereas the secondary outcomes were the risk factors that affected the success of clinical pregnancy. The descriptive research data were tabulated as mean±standard deviation or median (interquartile range) values in the case of continuous variables and expressed as numbers and percentages in the case of categorical variables. The Kolmogorov-Smirnov test was used to determine whether the numerical variables conformed to the normal distribution. In the comparisons between the groups, the independent samples t-test was used in cases where numerical variables conformed to the normal distribution, and the Mann-Whitney U test was used in cases where numerical variables did not conform to the normal distribution. The Pearson's chi-squared test or the Fisher's exact test was used for comparisons between categorical variables by groups. The univariate and multiple logistic regression models were used to investigate the risk factors affecting the pregnancy test results. The results of the univariate and multiple logistic regression analyses were given in terms of odds ratio (OR) values within 95% confidence interval (CI). Statistical analyzes were performed with the Jamovi 1.0.7 (Jamovi Project, version 1.0.7, 2019, retrieved from https://www.jamovi.org) and JASP 0.11.1 (Jeffreys's Amazing Statistics Program, version 0.11.1, retrieved from https://jasp-stats.org) software packages. Probability (p) values of <0.05 were deemed to indicate statistical significance in all statistical analyses.

RESULTS

A total of 112 couples were evaluated within the scope of the study. The mean age of female patients was 31.3±6.1 years. Primary infertility was detected in 87 (77.7%) of the couples. The median duration of infertility was 5 (min.:3, max:7) years.

There were 33 (29.5%) patients in Group A and 79 (70.5%) patients in Group B. There was no significant difference between the groups in terms of age, infertility type, FSH, and E2 levels (p>0.05 for all cases) (**Table 1**). However, the median duration of infertility in Group A, the study group, was significantly shorter than in Group B [3 (min.3-max.6) years vs. 6 (min.5-max.7) years, respectively] (p=0.022). Additionally, the rate of couples with TPMSC>10 million/mL and the rate of couples with sperms with normal sperm morphology >4% were significantly higher in Group B than in Group A (p=0.022 and p=0.036, respectively). In Group A, the median number of antral follicles was determined as 5 (min.:3, max.:6), and the median endometrial thickness was determined as 7.0 (min.:6, max.:9) mm, indicating a significant difference between the groups in favor of Group A (p=0.013 and p=0.004, respectively). The rate of couples with positive pregnancy was 51.5% (17 couples out of 33 couples) in Group A and 19% (15 out of 79 couples) in Group B, indicating a significant difference between the groups in favor of Group A(p=0.001) (**Table 1**). The overall clinical pregnancy rate in the study sample was determined as 28.6% (32 out of 112 couples).

Table 1. Demographic and clinical characteristics of the study group (Group A) and the control group (Group B).

	Group A (n=33)	Group B (n=79)	p
Age (years)[a]	30.5±5.7	31.5±6.2	0.414
Type of infertility (%)[b]			0.154
Primary	29 (87.9)	58 (73.4)	
Secondary	4 (12.1)	21 (26.6)	
Duration of infertility (years)[c]	3.0 [3.0- 6.0]	6.0 [5.0- 7.0]	0.022
FSH (IU/L)[a]	7.9±1.5	7.5±1.3	0.204
E2 (pg/mL)[a]	39.0±14.3	37.1±11.5	0.489
TPMSC (%)[b]			0.022
<10 million/mL	11 (33.3)	10 (12.7)	
>10 million/mL	22 (66.7)	69 (87.3)	
Sperms with normal morphology (%)[b]			0.036
<4%	11 (33.3)	11 (13.9)	
>4%	22 (66.7)	68 (86.1)	
Number of antral follicles[c]	5.0 [3.0-6.0]	3.0 [2.0-4.0]	0.013
Endometrial thickness (mm)[c]	7.0 [6.0-9.0]	6.0 [5.0-7.0]	0.004
Pregnancy (%)[b]			0.001
Negative	16 (48.5)	64 (81.0)	
Positive	17 (51.5)	15 (19.0)	

[a]Mean±standard deviation (independent samples t-test), [b]Number (%) (Pearson's chi-squared test), [c]Median [interquartile range] (Mann-Whitney U test), FSH: follicle-stimulating hormone. TPMSC: total progressive motile sperm count. E2: estradiol

There were significant differences between cases with positive and negative pregnancy in terms of age, infertility type, infertility duration, E2 level, TPMSC, sperm morphology, antral follicle count, and endometrial thickness (p<0.05 for all cases) (**Table 2**). The positive pregnancy rate was significantly higher among young female patients and in cases with primary infertility, short infertility duration, and low E2 levels. The rate of couples with TPMSC>10 million/mL and normal sperm morphology >4% was higher among the couples with positive pregnancy. In female patients with and without positive pregnancy, the median number of antral follicles was 6 and 3, and the median endometrial thickness was 9.0 mm and 6.0 mm, respectively (p<0.001).

Table 2. Demographic and clinical characteristics of patients with and without clinical pregnancy.

	Clinical pregnancy		
	Negative (n=80)	Positive (n=32)	p
Age (years)[a]	32.4±6.5	28.3±3.2	<0.001
Type of infertility (%)[b]			0.020
Primary	57 (71.2)	30 (93.8)	
Secondary	23 (28.7)	2 (6.2)	
Duration of infertility(years)[c]	6.0 [5.0-7.0]	3.0 [2.0-3.0]	<0.001
FSH (IU/L)[a]	7.7±1.4	7.3±1.3	0.173
E2 (pg/mL)[a]	40.6±13.1	30.3±5.5	<0.001
TPMSC (%)[b]			0.003
<10 million/mL	21 (26.2)	0 (0.0)	
>10 million/mL	59 (73.8)	32 (100.0)	
Sperms with normal morphology (%)[b]			0.002
<4%	22 (27.5)	0 (0.0)	
>4%	58 (72.5)	32 (100.0)	
Number of antral follicles[c]	3.0 [2.0-4.0]	6.0 [5.0-7.0]	<0.001
Endometrial thickness (mm)[c]	6.0 [5.0- .0]	9.0 [8.0-10.0]	<0.001

[a]Mean±standard deviation (independent samples t-test), [b]Number (%) (Pearson's chi-squared test or Fisher's exact test), [c]Median [interquartile range] (Mann-Whitney U test), FSH: follicle stimulating hormone, TPMSC: total progressive motile sperm count, E2: estradiol

The univariate logistic regression analysis revealed that age, infertility type, duration of infertility, E2 levels, and the number of antral follicles were significant risk factors for pregnancy (**Table 3**). The multiple logistic regression analysis of these risk factors revealed that the number of antral follicles [4.47 (2.4-8.32), p<0.001] and low E2 levels [0.87 (0.79-0.96)pg/mL, p=0.004] were significant risk factors for clinical pregnancy.

DISCUSSION

The results of this study indicated that oral estrogen supplementation in gonadotropin-induced IUI was a significant factor in achieving clinical pregnancy. In addition, it has been determined that the number of antral follicles and E2 levels may also be considered positive risk factors in achieving clinical pregnancy.

It was reported in the literature that the use of estrogen in the IUI treatment positively affected the pregnancy rates (7,8). For instance, in the IUI study conducted by Moini et al. (6) on infertile polycystic ovarian patients, a success rate of 29% was obtained in the group where clomiphene citrate and low dose (0.05 mg) ethinyl estradiol were used compared to 10% in the group where only clomiphene citrate was used. Similarly, the clinical pregnancy rates with and without the use of estrogen were determined as 51.5% and 19.5% in this study. In another study, a significant improvement was detected in endometrial thickness (12-15 mm) with the use of ethinyl estradiol together with clomiphene citrate. In the said study, increasing the ethinyl estradiol dosage from 0.02 mg to 0.05 mg did not yield any significant difference in results (8). It has been reported that the endometrial thickness was>6 mm in each case that was administered IUI along with ethinyl estradiol and that the pregnancy rate in these cases was significantly better (18.75% vs. 6.25%) (7). This positive effect of ethinyl estradiol could not be demonstrated in Moini's study (6); however, this result was attributed to the effect of estrogen on endometrial thickness (7). In comparison, the endometrial thickness was significantly higher in the estrogen-administered group (Group A) than in the control group (Group B). As a matter of fact, the higher pregnancy rate observed in Group A was attributed to higher endometrial thickness.

In a systematic review, it was demonstrated that the administration of additional estrogen to progesterone as luteal phase support for in vitro fertilization, one of the assisted reproductive treatment methods, increased the clinical pregnancy rates by 1.66 times (9). Additionally, it has been speculated that phytoestrogen supplementation would positively affect pregnancy rates (10). However, further prospective studies are needed to determine the net effect of estrogen support on assisted reproductive treatment methods since the studies available in the

Table 3. Univariate and multiple logistic regression analysis for pregnancy development

	Model 1			
	Univariate		Multiple	
	OR (%95 CI)	p	OR (%95 CI)	p
Age (years)	0.86 [0.79- 0.95]	0.002	0.93 [0.79- 1.08]	0.328
Type of infertility (secondary/primary)	0.17 [0.04- 0.75]	0.020	0.08 [0- 2.89]	0.170
E2(pg/mL)	0.91 [0.87- 0.96]	<0.001	0.87 [0.79- 0.96]	0.004
Number of antral follicles	4.4 [2.56- 7.56]	<0.001	4.47 [2.4- 8.32]	<0.001
Duration of infertility(years)	0.23 [0.13- 0.39]	<0.001	-	-

Dependent variable: clinical pregnancy. OR: odds ratio, CI: confidence interval, E2: estradiol.

literature on the assisted reproductive treatment methods and risk factors for the clinical pregnancy, though they are detailed, do not provide clearly defined numerical values. The studies that investigated the relationship between the number and size of antral follicles and pregnancy rates also do not provide clearly defined limit values. In the study of Sun et al. (11), it was reported that the highest pregnancy rates were obtained in cases with a follicle size between 19 and 21 mm and that the lowest pregnancy rates were obtained among cases with a follicle size larger than 21 mm. On the other hand, Merviel et al. (12) reported >16 mm as the optimum follicle size for higher pregnancy rates. In comparison, a limit value was not determined in this study; instead, the evaluations were made based on the comparison of the results of measurements between the groups investigated within the scope of the study.

In a study conducted by Liu et al. (1), no positive correlation was found between endometrial thickness and pregnancy rates in cases administered gonadotropin-induced IUI. Similarly, the meta-analyses available on the subject did not reveal a positive correlation between endometrial thickness and clinical pregnancy rates in cases administered gonadotropin-induced IUI (13). In contrast, some studies reported low pregnancy rates among cases with an endometrial thickness of <6 mm (14). In comparison, although the multiple regression analysis conducted within the scope of this study did not reveal endometrial thickness as one of the significant positive risk factors for the clinical pregnancy, the estrogen-administered group (Group A) and cases where clinical pregnancy was achieved had significantly higher endometrial thicknesses. Additionally, the subgroup analyses revealed significantly more clinical pregnancies in cases with endometrial thickness between 10.5 mm and 13.9 mm, indicating the non-linear relationship between endometrial thickness and clinical pregnancy. The fact that no significant difference was found in endometrial thickness between the estrogen-administered group and the control group in other studies available in the literature was attributed to the small sample size employed in these studies and the non-linear relationship between the pregnancy rate and the endometrial thickness (1).

In a study conducted by Bakas et al. (2) on the effect of changes in estrogen levels observed during the IUI process on clinical pregnancy rates, it was determined that the percent change observed in estrogen levels between the 6th and 10th day following the start of the IUI process was less in cases with clinical pregnancy than in other cases, which was thus suggested as a predictor for clinical pregnancy. Similarly, it was reproducibly shown that the pregnancy rates were positively correlated with the estrogen levels (>500 pg/mL) observed during hCG administration but not with the E2 levels measured on the 3rd day of the cycle (12). In parallel, in a prospective study, no correlation was found between E2 levels and pregnancy rates (15). In comparison, only the baseline FSH and E2 levels before the start of the IUI treatment were investigated in this study, whereas the change in estrogen levels or the estrogen levels during hCG administration were not. Consequentially, it was determined that the E2 levels of the cases with clinical pregnancy were significantly lower. In addition, low E2 levels were detected as a risk factor in the multiple regression analysis. Further prospective studies may clarify the reciprocal interaction between the number and size of antral follicles and the hormone levels of patients in the context of the medical treatment to be administered for the stimulation of the ovaries.

Limitations of the Study

There were some limitations to this study. First, detailed clinical data of the patients could not be obtained due to the study's retrospective design. Secondly, the relatively small number of couples included in the study may be deemed as another limitation.

CONCLUSION

The findings of the study indicated that estrogen supplementation in cases who were administered gonadotropin-induced IUI positively affected the pregnancy rates. In addition, the number of antral follicles and E2 levels were found as risk factors for IUI success. Further large-scale prospective studies are needed to corroborate the results of this study.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Van Training and Research Hospital Clinical Research Ethics Committee (Date: 09.01.2020, Decision No: 2020/01).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have participated in the design, execution, and analysis of the paper, and that they approved the final version.

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