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Original Article

Does intrauterine insemination timing matter for achieving pregnancy during ovulation induction using gonadotropins? A retrospective cohort study

Omer Hamid Yumusak [a,*], Serkan Kahyaoglu [a], Meryem Kuru Pekcan [a], Esra Isci [b], Mehmet Cinar [a], Yasemin Tasci [a]

[a] *Department of Reproductive Endocrinology, Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey*
[b] *Department of Gynecological Oncology, Gazi University, Ankara, Turkey*

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Abstract

Background: Intrauterine insemination (IUI) is a commonly used procedure to increase the infertile couples' chance of pregnancy. Single or double insemination and different timing choices are modifications of this intervention. The aim of this study was to elucidate the effect of the IUI procedure on clinical pregnancy rates when performed at 24 hours or 36 hours after ovulation triggered by human chorionic gonadotropin (hCG) following ovulation induction with gonadotropins.

Methods: One hundred and thirteen women diagnosed with polycystic ovarian syndrome (PCOS) (as per Rotterdam's criteria) or unexplained infertility, who were treated using gonadotropins for ovulation induction and IUI for increasing fertilization potential, were recruited from the medical records of the infertility clinic. Demographic features, cycle outcomes, and clinical pregnancy rates of the patients were compared based on two different timing strategies of IUI (24 hours and 36 hours) following ovulation trigger using hCG.

Results: Clinical pregnancy rates per cycle were 22.9% in the PCOS group and 26.9% in the unexplained group. The clinical pregnancy rates according to the timing of IUI were found to be similar for PCOS patients, unlike patients with unexplained infertility whose clinical pregnancy rates were significantly better when the IUI procedure was performed 24 hours following the hCG trigger. The cycle day of hCG trigger was also found to be significantly related to clinical pregnancy rate as utilizing a later hCG trigger day appeared to positively affect the odds of clinical pregnancy establishment.

Conclusion: IUI performed at either 24 hours or 36 hours after ovulation triggered by hCG injection does not change clinical pregnancy rates for PCOS patients. Patients with unexplained infertility seem to benefit from earlier IUI procedures, which increases their fertility potential during ovulation induction with gonadotropins. Avoiding earlier than physiologically needed artificial-hCG triggering before IUI procedures results with better pregnancy rates.

Keywords: clinical pregnancy; gonadotropin; infertility; intrauterine insemination

1. Introduction

Intrauterine insemination (IUI) with or without ovarian stimulation is a common treatment for infertility. Despite the popularity of this assisted reproductive technique, IUI is widely used to improve pregnancy rates with mild male factor, unexplained infertility, cervical factor, anovulation, and

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* Corresponding author. Dr. Omer Hamid Yumusak, Zekai Tahir Burak Women's Health Education and Research Hospital, Reproductive Endocrinology Clinic, Hamamonu-Altindag, Ankara, Turkey.

E-mail address: omeryum@hotmail.com (O.H. Yumusak).

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minimal and mild endometriosis.[1] It is a simple and relatively less invasive and less expensive procedure than other forms of assisted reproductive technology.[2] The minimum requirements for performing the procedure are: (1) ovulation in the IUI cycle; (2) patency of at least one fallopian tube; (3) insemination with an adequate number of motile sperm; and (4) the absence of documented or suspected active cervical, intrauterine, or pelvic infection.[1]

Stimulated IUI is much more effective than natural cycle or controlled ovarian hyperstimulation treatment. In four randomized trials of patients with unexplained subfertility, pregnancy rates were higher when IUI was performed in stimulated cycles than in natural cycles [odds ratio (OR): 2.14; 95% confidence interval (CI): 1.26−3.61; pregnancy rates: 25% vs. 14% for stimulated and natural cycles, respectively, where 26 patients received clomiphene citrate, and 370 patients received gonadotropins].[3] According to the 2009 European Society of Human Reproduction and Embryology Capri Workshop, the pregnancy rates with clomiphene citrate and IUI were 7%, and with follicle stimulating hormone (FSH) ovarian stimulation and IUI they were 12% per cycle.[1] However, there are various criteria affecting the success rate of IUI including age, indications of IUI, the optimal procedures for sperm preparation, insemination methods, and timing.[1,4]

There is not a consensus on the optimal timing of IUI. In the large majority of published studies, insemination is performed 32−36 hours following human chorionic gonadotropin (hCG) administration. A 2014 systematic review compared the optimum time interval from hCG injection to IUI, comparing different time frames ranging from 24 hours to 48 hours, and found no difference in the pregnancy rate per couple.[5] Luciano et al[6] showed that ultrasound-confirmed follicle rupture occurred on Day +1 of the luteinizing hormone (LH) surge in 6% of patients, on Day +2 in 72%, and on Day +3 in 21%. In light of this finding, it seems probable that IUI on Day +1 after hCG injection, plus properly timed intercourse, could achieve results similar to those obtained with IUI on Day +2 after hCG injection in infertile couples with normal spermiograms. The clinical effect of IUI on pregnancy rates for different infertility etiologies such as polycystic ovary syndrome (PCOS) and unexplained infertility has not yet been extensively evaluated. Although the efficiency of IUI procedures for unexplained infertility in patients has been proven, the clinical benefit of this procedure is not clear for PCOS patients whose central problem is anovulation rather than fertilization. The primary aim of this study was to elucidate the effect on clinical pregnancy rates of the IUI procedure performed at 24 hours or 36 hours after ovulation triggered by hCG, following ovulation induction with gonadotropins. The secondary aim of the study was to compare the clinical pregnancy rates for PCOS and unexplained infertility that is associated with the timing of IUI procedures, during ovulation induced by gonadotropins.

2. Methods

This retrospective study was approved by the ethics committee of the Zekai Tahir Burak Women's Health Research and Education Hospital, Ankara, Turkey. One hundred and thirteen women diagnosed with PCOS (as per Rotterdam's[7] criteria) or unexplained infertility were recruited from the medical records of the infertility clinic. Couples were evaluated with semen analyses, hysterosalpingogram and/or laparoscopy, and transvaginal sonographic screening performed in the early follicular phase of cycle and midluteal serum progesterone. The husbands of all patients had normal spermiogram results based on at least two semen analyses according to the World Health Organization 2010 criteria. All women had at least one tubal patency, documented by hysterosalpingogram and in some cases also by laparoscopy. Early follicular phase hormone assay (basal FSH, LH, estradiol (E2), prolactine (PRL), and thyroid stimulating hormone (TSH)) measurements were made on Day 3 of the cycle. Couples with endometriosis, uterine or tubal factor, poor ovarian reserve, and male infertility were excluded. Patients were classified into two groups according to their infertility diagnosis: unexplained ($n = 78$) and PCOS ($n = 35$). A couple was considered to have unexplained infertility when the results of semen analysis, hormonal assay, hysterosalpingography, and/or laparoscopy were normal.[8]

Controlled ovarian hyperstimulation was initiated with 37.5−150 IU of pure FSH or human menopausal gonadotropin (hMG) starting on Day 2 or Day 3 of the cycle. Transvaginal USG was performed with serum E2 levels starting on Day 6 for the follicular development. A dose of 10,000 IU urinary hCG or 250 μg recombinant hCG was administered when at least one follicle of $\geq$ 18 mm was seen on transvaginal ultrasonography.

Patients were divided randomly into two groups at the time of hCG administration. Patients in Group 1 ($n = 38$; 33.6%) underwent IUI 24 hours after hCG administration. Group 2 ($n = 75$; 66.4%) underwent IUI 36 hours after hCG administration. All patients were instructed to have intercourse when the dominant follicle reached a diameter of approximately 16 mm and 12 hours after insemination. Following the transfer, the patients received 200 mg/day vaginal progesterone supplementation for luteal support until 12 weeks of gestational age if the patient conceived. Qualitative serum β-hCG test was performed 14 days after insemination if menstruation had not started. A clinical pregnancy was defined as the presence of a gestational sac with accompanying fetal cardiac activity by ultrasound at least 4 weeks after insemination. The demographic features, infertility types, dominant follicle number, endometrial thickness on hCG day, timing of intrauterine insemination, and clinical pregnancy rates of the patients have been evaluated. Statistical analysis was performed as follows: normal distribution of data was evaluated using the Kolmogorov−Smirnov test. The continuous variables were presented as means ± standard deviation and compared using the independent samples t test. The nonparametric variables and data without normal distribution were tested using the Mann−Whitney U test, and correlation analysis was performed using Spearman's correlation test. The comparison of categorical values was made utilizing Fisher's exact test or Chi-square test. A p value < 0.05 were considered statistically significant.