

## Different Timing of Intrauterine Insemination and Pregnancy Outcome in Patients with Unexplained Infertility: A Randomized Controlled Study

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### ABSTRACT

**Background:** In this era of rapid advancements in assisted reproductive technologies, intrauterine insemination (IUI) is still widely offered to subfertile couples, as a cheaper and less invasive treatment option before proceeding to IVF.

**Objective:** To determine the most suitable timing of hCG administration prior to intrauterine insemination for optimizing pregnancy outcome and success rate.

**Patients and methods:** A randomized controlled study conducted in Obstetrics and Gynecology Department, Sohag University from 30 June 2018 to 30 June 2019 and included couples with unexplained infertility. A total of 110 patients were recruited in our study, 30 patients dropped out; where 20 patients were due to inadequate stimulation, bad endometrium or more than 3 follicles were present, 6 patients did not show up for folliculometry after being given treatment and 4 patients did not show up for the procedure after being given the hCG trigger.

**Results:** This study showed an improved pregnancy rate when IUI was performed with a time interval of 24–36 h (13 case with positive pregnancy test).

**Conclusion:** IUI after ovulation induction can be done any time between 24 and 48 h after hCG injection without significant differences in pregnancy rates.

**Keywords:** Intrauterine Insemination, Ovarian induction, Unexplained Infertility.

### INTRODUCTION

In this era of rapid advancements in assisted reproductive technologies, intrauterine insemination (IUI) is still widely offered to subfertile couples, as a cheaper and less invasive treatment option before proceeding to IVF<sup>(1)</sup>. IUI is superior to timed intercourse because in IUI, motile spermatozoa, which are morphologically normal, are concentrated in small volumes and placed directly into the uterus, close to the released oocyte<sup>(2)</sup>.

There are various factors affect the success rate of IUI including female age, types of ovarian stimulation, the optimal procedures for sperm preparation, insemination method, and timing of insemination in regards to (hCG) injection to yield the best pregnancy outcome<sup>(3)</sup>. One of the most debated issues is the timing of insemination in relation to (hCG) injection to yield the best pregnancy outcome. Although insemination at 34–38h after (hCG) injection is most prevalently used, the clinical evidence for this time is scarce, there is no difference in simultaneous use of (hCG) injection compared to cycles in which IUI is performed after 34–36 hours following hCG injection<sup>(4)</sup>.

Järvelä *et al.*<sup>(5)</sup> reported that pregnancy rate was higher when hCG was administrated after the IUI than when hCG was administrated at 24–32 hours before insemination. On the other hand, in a randomized study by Aydin *et al.*<sup>(6)</sup> they compared the clinical pregnancy rate between IUIs with simultaneous hCG injection and IUIs performed at 34–36 h after hCG injection; they

found no difference in clinical pregnancy rate between the two groups. There is no 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<sup>(7)</sup>. There is insufficient evidence to determine whether there is any difference in safety and effectiveness between different methods of synchronization of ovulation and insemination, more researches are needed<sup>(8)</sup>.

We aimed in this study to determine the most suitable timing of hCG administration prior to intrauterine insemination for optimizing pregnancy outcome and success rate.

### SUBJECTS AND METHODS

A randomized controlled study conducted in Obstetrics and Gynecology Department, Sohag University from 30 June 2018 to 30 June 2019 and included couples with unexplained infertility.

A total of 110 patients were recruited in our study, 30 patients dropped out; where 20 patients were due to inadequate stimulation, bad endometrium or more than 3 follicles were present, 6 patients did not show up for folliculometry after being given treatment and 4 patients did not show up for the procedure after being given the hCG trigger.

Patients were divided randomly according to the time intervals between hCG injection and IUI into four groups, each group 20 patient: group (1); Patients



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undergone IUI 24 h after hCG administration, group (2); Patients undergone IUI 36 h after hCG administration, group (3); Patients undergone IUI 48 h after hCG administration, group (4); Patients undergone simultaneous use of IUI and hCG administration.

Inclusion criteria included normal semen parameters or mild impaired according to WHO (9), normal transvaginal ultrasound performed in the early follicular phase of cycle, ovulatory midluteal serum progesterone level, bilateral patent tubes, normal early follicular phase hormone assay.

Exclusion criteria included women with endometriosis, uterine abnormality, poor ovarian reserve, non-ovulatory cycle, severe semen parameters impairment according to WHO (9).

All women had the following: Complete history taking, physical examination and investigations included; ovulation was confirmed with follicular monitoring by TVS, tubal patency was confirmed by hysterosalpingography or laparoscopy, male factor infertility was excluded by semen analysis according to WHO criteria (9).

**Study Protocol:**

- Ovulation induction: Ovulation stimulation was given to all the patients in form of aromatase inhibitor (AI) 5 mg, (Femara; Novartis Pharma Services, Switzerland) beginning on day 3 of the cycle and the transvaginal sonography (TVS) was used to monitor follicular growth every 2 days until the dominant follicle reached or exceed approximately 18 mm.

- Triggering: Ovulation was triggered by injecting of highly purified hCG 10,000 IU (Choriomon 5000 IU IBSA institut Biochimique SA Switzerland) intramuscularly.
- IUI: IUI was performed after preparation (swim up technique) with a disposable 1 ml soft IUI catheter which was inserted through the cervix near the uterine fundus under aseptic condition. After insemination patients remained in supine position for 10-15 min.

**Ethical approval:**

Before the beginning of the study and in accordance with the local regulation followed, the protocol and all corresponding documents were declared for Ethical and **Research approval by Faculty of Medicine, Sohag University, Egypt.** Every patient signed an informed written consent for acceptance of the operation.

**Statistical analysis**

Data was analyzed using IBM SPSS Statistics for Windows version 20. Quantitative data were expressed as means ± standard deviation, and median. Qualitative data were expressed as number and percentage. The data were tested for normality using Shapiro-Wilk test. The nonparametric Kruskal–Wallis test was used for data which wasn't normally distributed. Chi-square ( $\chi^2$ ) test was used for comparison regarding qualitative variables. A 5% level was chosen as a level of significance in all statistical tests used in the study.

**RESULTS**

There was statistically significant difference between studied groups as regard concentration (Table 1).

**Table (1): Comparison of basic semen characteristics between the study groups**

Variables	Group 1 (N.= 20)	Group 2 (N.= 20)	Group 3 (N.= 20)	Group 4 (N.= 20)	P-value
<b>Concentration (mil/ml)</b>					
<b>Mean± S.D.</b>	41.25 ± 20.88	57.3 ± 25.15	41.25 ± 29.32	34 ± 15.56	
<b>Median</b>	37.5	56	29	32	0.01*
<b>Progressive motility (%)</b>					
<b>Mean± S.D.</b>	41.2 ± 12.59	35.7 ± 11.06	34.4 ± 8.97	33 ± 11.95	
<b>Median</b>	35	35	33.5	30	0.11
<b>Morphology (%)</b>					
<b>Mean± S.D.</b>	25.5 ± 16.32	23.45 ± 17.39	34.65 ± 25.72	27.95 ± 18.74	
<b>Median</b>	19	20	22.5	21	0.67

\*: P-value is statistically significant

Table 2 showed that there was no statistical significant difference between studied groups as regard pelvic ultrasound at time of hCG injection (mm).

**Table (2): Comparison between the study groups regarding pelvic ultrasound at time of hCG injection**

	Group 1 (N.= 20)	Group 2 (N.= 20)	Group 3 (N.= 20)	Group 4 (N.= 20)	P-value
<b>Dominant follicle size (mm)</b>					
<b>Mean± S.D.</b>	19.95 ± 1.15	19.6 ± 1.27	19.65 ± 0.99	19.9 ± 1.17	0.769
<b>Median</b>	20	20	20	20	
<b>Endometrial thickness (mm)</b>					
<b>Mean± S.D.</b>	8.95 ± 0.69	8.8 ± 0.79	8.75 ± 0.79	8.95 ± 0.76	0.731
<b>Median</b>	9	9	9	9	

**Table 3** showed that there was no statistical significant difference (p-value > 0.05) between studied groups as regard pregnancy. The final numbers of patients which have an ongoing pregnancy are 15 because one patient in group 2 aborted after 2 months of pregnancy.

**Table (3): Comparison between the study groups regarding pregnancy**

Variables	Group 1 (N.= 20)	Group 2 (N.= 20)	Group 3 (N.= 20)	Group 4 (N.= 20)	P-value
<b>Positive Chemical pregnancy</b>	5 (25%)	8 (40%)	3 (15%)	2 (10%)	0.111
<b>Positive Clinical pregnancy</b>	5 (25%)	7 (35%)	3 (15%)	1 (5%)	0.1
<b>Ongoing pregnancy</b>	5 (25%)	6 (30%)	3 (15%)	1 (5%)	0.09

## DISCUSSION

Intrauterine insemination with ovarian stimulation has been used over the years, as a treatment for mild male factor, anovulation and unexplained infertility<sup>(10)</sup>. Regimens vary between centers and also between clinicians. Hence the correct timing of insemination to improve pregnancy is a debated issue<sup>(11)</sup>. There are some important factors affecting the outcome of IUI. These factors include female age, tube malfunction, duration of infertility, endometrial thickness, number of mature follicles, various techniques of semen preparation, sperm motility and concentration<sup>(12)</sup>.

Our research showed that all study groups had comparable age, female BMI denoting comparable ovarian response to stimulation, endometrial thickness, the mean diameter of the dominant follicle before ovulation trigger and semen parameters were all above accepted levels. All these variables were nullified. This allowed us to comment on the duration between ovulation trigger and IUI procedure as a factor affecting pregnancy rate. The overall chemical pregnancy rate reported in this study was 22% and the clinical pregnancy rate was 20%.

The present study showed no significant difference in pregnancy outcomes between the four groups. Also there was no relationship between the average mature follicle size and clinical pregnancy outcomes. **Yumusak et al.**<sup>(11)</sup> compared the clinical pregnancy rates of patients with polycystic ovary syndrome (PCOS) and unexplained infertility according to the timing of single IUI procedures. To homogenize the study groups, they excluded other possible causes of infertility. Clinical

pregnancy rates per cycle were 22.9% in the PCOS group and 26.9% in the unexplained group. However, IUI procedures performed 24 hours following hCG trigger day were found to be related to better cycle outcomes among patients with unexplained infertility, unlike PCOS patients.

Another study by **Elsersy et al.**<sup>(13)</sup> compared the clinical pregnancy rate of patients of unexplained infertility according to different timing of single IUI. The clinical pregnancy rate in patients in group 1 who received IUI 24 hours after hCG triggering was 22.4% while the clinical pregnancy rate in patients who received IUI 36 hours after hCG triggering was 16%, which indicated favorable outcomes in group 1. However, both gave acceptable results. **Robb et al.**<sup>(14)</sup> showed no significant difference in pregnancy outcomes between IUIs performed at 24 versus 36 h after hCG with 182 clomiphene citrate/IUI cycles in 90 women. However, the small numbers, low overall pregnancy rates and inclusion of various causes of female infertility diagnosis, including poor ovarian reserve, anovulatory, unexplained, anatomic, male factor are the possible weaknesses of the retrospective study. Also, in a prospective randomized controlled study, **Blockeel et al.**<sup>(15)</sup> demonstrated that significantly higher clinical pregnancy rates per IUI cycle were observed in patients undergoing IUI 1 day after the LH rise, when compared with patients undergoing IUI 2 days after the LH rise in natural cycles. This proves the clinical importance of IUI timing on pregnancy rates among subfertile patients.

The main problem for PCOS patients is anovulation. Accordingly, for PCOS patients, IUI timing is not as important as for patients with unexplained infertility. This result can be a reflection of higher quality of oocytes in the later hCG day trigger cycles than in earlier hCG day trigger cycles. Perhaps clinicians trigger the preovulatory follicles earlier than physiologically needed, which decreases the fertility potential of an originally competent oocyte. A study by **AboulGheit** <sup>(16)</sup> allocated 125 couples undergoing IUI cycles into 3 groups; each performing IUI at a different interval from hCG at 24, 36 and 48 h, the author found no significant difference in pregnancy outcomes between the three groups. The rate of positive hCG was 14.3% in the 24-h group, 17% in the 34-h group and 21.4% in the 40-h group. Though not statistically significant, there is a trend toward a higher pregnancy rate in couples in the 40-h group. **Claman et al.** <sup>(17)</sup> decided to randomly compare treatment cycles assigned to a short (32–34-hour) or a long (38–40-hour) interval between hCG and IUI after superovulation therapy. The short and long hCG–IUI interval treatment groups were comparable with respect to age and diagnosis. They found no difference in pregnancy rates regardless of whether male factor was a part of the infertility problem. They found no difference between pregnancy rates whether IUI was performed after a short (32–34-hour) or a long (38–40-hour) interval after hCG injection (OR = 0.673, 95% CI 0.297–1.518).

In conclusion our study demonstrates that IUI can be timed to occur anywhere between 24 and 48 hours after hCG injection but preferable at time between 24–36 h.

## CONCLUSION

IUI after ovulation induction can be done any time between 24 and 48 hr after hCG injection, but earlier IUI procedures 24–36 hour from hCG injection have favorable clinical pregnancy rates. This flexibility in the hCG–IUI time interval makes IUI more convenient for both the infertile patient and the clinic staff.

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