

# Comparison of Pregnancy Rate in Simultaneous Human Chorionic Gonadotropin Administration with Intrauterine Insemination Vs. Standard Intrauterine Insemination

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## Abstract

**Objective:** Artificial insemination (AI) has been used to treat infertile couples for approximately 200 years. Time interval between administration of Human Chorionic Gonadotropin (HCG) and intrauterine insemination (IUI) is one of controversial subjects in AI. Fertility rate is in the highest level on the day before ovulation. The aim of study is to compare pregnancy rate in standard IUI versus simultaneous HCG administration with IUI.

**Materials and Methods:** In a randomized, controlled clinical trial, 141 women 20-35 years selected for IUI among patients referring to infertility clinic of Al-Zahra hospital in Tabriz, Iran in 2013. They were entered into study in two groups of simultaneous (n=71) and standard (n=70). After ovulation stimulation by clomiphene and human menopausal gonadotropin (HMG) and creating up to 3 dominant follicles in each patient, a single dose of HCG was administered; thereafter, IUI was done in the simultaneous group instantly and 34-40 hours following HCG injection in the standard group.

**Results:** In the standard and simultaneous groups, mean pregnancy rate per patient was 25.7% and 21.1% respectively (p=0.52) and pregnancy rate per IUI cycle was 16.4% and 15.3% respectively (p=0.82) that was not significantly different. Furthermore, between two groups in terms of age, the number of mature follicles, and endometrial thickness, there was no significant difference.

**Conclusion:** Although difference in pregnancy rate between two groups was not statistically significant, simultaneous HCG with IUI is a comfort method for patients due to less cost and fewer patient's referrals to clinic.

**Keywords:** HCG, HMG, IUI, Pregnancy

## Introduction

Artificial insemination (AI) that is the most common treatments of infertility has been used to treat infertile couples for approximately 200 years (1). In this method, in a stimulated ovulation cycle or normal cycle, prepared semen fluid is inseminated into uterus. One of the most common indications of IUI is associated with male factor (2). IUI is the accepted treatment in men with severe hypospadias, retrograde ejaculation, sexual impotence, and sexual dysfunction. Moreover, it is applicable to overcome the oligospermia, asthenozoospermia, low semen volume, and sperm antibodies (2). Although higher number of spermatozoa does not increase the likelihood of success of IUI, IUI success will be very low with less than one million motile sperm. Probably successful IUI is associated with increased total number of motile spermatozoa beyond a threshold of approximately 10 million (3,4). In addition to male factors, ovulatory dysfunction, uterus cervical factors and idiopathic infertility are also other indications for IUI (5). In natural cycles and stimulated cycles by clomiphene, the most practical and reliable method for timing of IUI is the urine LH monitoring

that nearly begins 3 days before the expected day of ovulation. Thereafter, insemination is done the day after the LH surge (6). Alternatively, the HCG instead of daily monitoring of urinary LH is injected after the growth and dominance of follicles that results in ovulation in about 34-40 hours after the injection. In standard IUI, IUI was done within 34-40 hours after HCG injection. Normal sperm can survive in the female reproductive tract at least 3 days with maintaining power of fertilization with oocyte while oocyte can be successfully fertilized only up to 12-24 hours after releasing (1). In normal fertile couples, intercourse nearly a day before ovulation or on the day of ovulation increased the fertilization rate. Pregnancy rate drops off significantly (may be to zero) the day after ovulation. According to many references, presence of sperm in the genital tract the day before fertilization increases fertilization rate to the highest rate close to 30 percent (1,3). One of the major problems in IUI cycles is premature LH elevation and releasing of oocytes before the time set for IUI and opportunity loss for sperm entering into the female reproductive tract and fertilization (6). Some similar studies showed increased rate of pregnancy

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in simultaneous IUI with HCG injection.

With regard to high prevalence of infertility in Iran and broad social effects of this problem, the frequent use of IUI treatment for couples experiencing infertility, the limitations of conducted studies and lack of similar studies in Iran, we decided to evaluate the time of HCG injection on therapeutic outcome (pregnancy rate) in a randomized clinical trial.

### Materials and Methods

This randomized controlled clinical trial was conducted on 141 infertile women 20-35 years of age with normal ovarian reserve tests and normal Hysterosalpingography (HSG) in simultaneous and standard groups in 2013 at the infertility research center of Al-Zahra hospital in Tabriz, Iran.

#### Inclusion criteria

- At least one year of infertility
- Infertility cause of male factor, decreased ovulation in patients [e.g. patients with polycystic ovary syndrome (PCO)]
- Unexplained infertility
- Mild endometriosis

#### Exclusion criteria

- Severe Endometriosis
- Mullerian anomalies such as bicornuate uterus and uterine septum
- Uterus fallopian tube blockage
- Severe impairment of sperm parameters

Patients were randomly entered into simultaneous and standard groups. Patients referred to clinic on days 1-5 of the menstrual cycle for visit and trans-vaginal ultrasound. In the cases of normal ultrasound (lack of cysts and lack of cystic follicles >15 mm in the ovary), ovulation stimulation began with administration of clomiphene and HMG. 100 mg of clomiphene was administered from 3-5 days of the menstrual cycle for 5 days. HMG with the number of 2-4 within 6 to 10 days of the menstrual cycle was administered at 4-6 pm. Patients on days 11 to 13 of menstrual cycle were again assessed by transvaginal ultrasound and in whoever the maximum total of 3 dominant follicles were observed in both ovaries, in the standard group a single dose of HCG (5000 unit) was administered at 8-9 pm of that day and IUI was performed 34-40 hours later (2 days later at 8 to 11 am). However, in the simultaneous group 20 min later a single dose of HCG 5,000 U was administered and then IUI was performed simultaneously. Sample preparation method for liquid semen was similar in both groups and was performed by swim up method. Vaginal progesterone 400 mg was administered every night (beginning at night after IUI) for 16 days in order to support luteal phase; on day 17, pregnancy test (B-HCG serum) was performed that with positive pregnancy test, progesterone suppository was continued up to 14 gestational weeks. Two groups were similar in terms of infertility cause and the number of dominant follicles. In this study, the pregnancy rate was

considered as the primary outcome. Treatment cycles were repeatable up to 6 times in each patient.

Variables examined included age of patients and their spouses, type of infertility, cause of infertility, tests such as follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, prolactin and thyroid stimulating hormone (TSH), HSG result, laparoscopy history, history of previous IUI cycle and the type and the number of previous IUI and their results, the previous history of follicular dimension and the number of follicles, a history of previous abortion or ectopic pregnancy. To statistically assess, descriptive statistical methods (frequency, percentage, mean  $\pm$  SD) were used. In order to compare qualitative results, chi-square test and for quantitative comparison between two groups, independent t-test were used. To assess the individual role of each factor independently in the incidence of the main outcome, multivariate logistic regression was used. Study results were analyzed using SPSS 17 statistical software. P value less than 0.05 in this study was considered statistically significant.

### Results

In this randomized controlled clinical trial, 141 women with a history of at least one year of infertility related to mild male factor (at least ten million of motile sperm), reduced ovulation in patients with PCOS, mild endometriosis and unexplained infertility were examined. 70 patients were in IUI standard group and 71 patients in the group of simultaneous HCG with IUI.

#### Basic findings

The mean age of patients was  $27.24 \pm 3.71$  years (range 20 to 35). The mean age of the patients' spouses was  $32.12 \pm 5.36$  years (range 18 to 43 years). Average duration of infertility was  $4.95 \pm 3.07$  years (range 1 to 23 years), (Figure 1).

#### Laboratory findings

Average level of FSH:  $6.9 \pm 3.15$  mIU/l, Range 1.7 to 16.2. Average level of LH:  $10.77 \pm 7.45$  mIU/l, range 1.5 to 25. Average level of Estradiol:  $115.84 \pm 91.72$  pg/ml, range 0.68 to 542. Average level of Prolactin:  $267.53 \pm 232.74$  mIU/ml, range 2.64 to 1668. Average level of TSH:  $2.35 \pm 1.72$  micIU/l, range 0.5 to 11.38.

#### Findings associated with infertility and previous treatments

Cause of infertility in 104 patients (73.8%) was primary and in 37 patients (26.2%) was secondary (Figure 2 and 3). Infertility in 79 patients (56%) was due to anovulation, in 40 patients (28.4%) idiopathic and in 22 patients (15.6%) due to the male factor. In the HSG, the uterus was normal in all patients. Both uterine tubes were not closed simultaneously in any patient. In 7 patients (5%), right fallopian tube was closed and in 5 patients (3.5%) left fallopian tube was closed. None of the patients had history of open surgery. 17 patients (12.1%) had a previous history

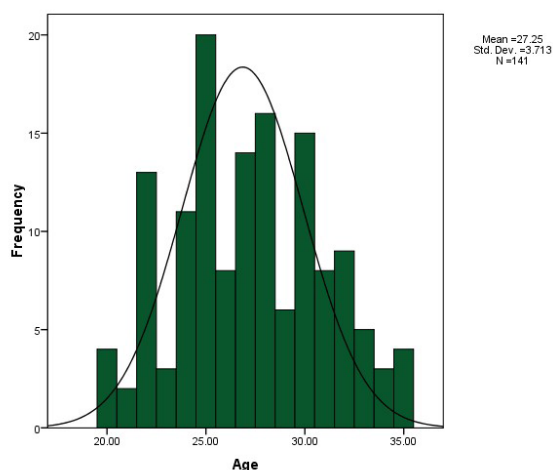


Figure 1. The age distribution of patients.

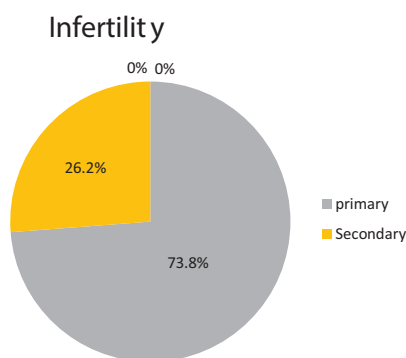


Figure 2. Infertility type (primary or secondary) in the patients.

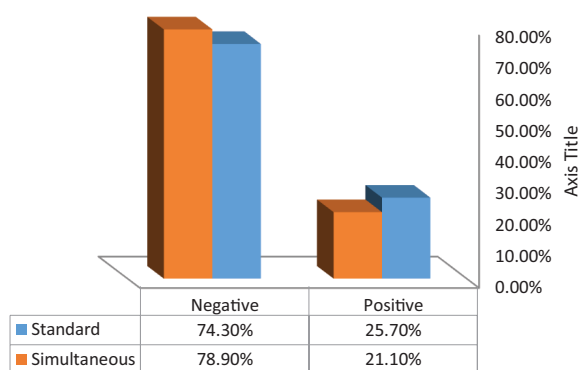


Figure 3. Comparison the pregnancy rate between two groups of simultaneous and standard.

of laparoscopy. 48 patients (34%) had a history of previous failed IUI cycle that all of the cases were standard. The mean number of previous IUI cycles was  $1.68 \pm 1.16$ . The total number of IUI cycles was 220. 6 patients (4.2%) were with history of ectopic pregnancy, 5 patients (3.5%) with PCO history, and 16 patients (11.35%) with abortion history. The overall pregnancy rate per patient was 23.4%.

Every change has been shown in Tables 1 and 2.

### Sonographic findings

The mean endometrial thickness in patients was  $7.46 \pm 1.72$  mm (range 4 to 13 mm). Average size of follicles on right and left side was  $17.7 \pm 3.74$  and  $14.95 \pm 4.77$  mm respectively. The mean number of follicles on left and right side was  $2.28 \pm 0.51$  and  $2.22 \pm 0.49$ , respectively. Every change has been shown in Tables 1 and 2.

According to the results of tables, just fertility type and the number of follicles (more than one mature follicle) between two groups were significantly different. The history of previous IUI cycles, the number of IUI cycles, and the number of follicles (more than one mature follicle) were significant differences between two groups of positive and negative pregnancy (Table 2).

All the significantly different parameters between two groups were entered into logistic regression to determine independent antipant factors for pregnancy incidence. Finally, none of these variables was antipant factors for estimation of pregnancy incidence.

### Discussion

Fertilization is possible in time close to ovulation. However, the number of days before and after ovulation is not clear definitely. Therefore, numerous studies were performed in order to determine timing of normal intercourse and also to evaluate the procedure of assisted reproductive techniques. In this study, 141 women with a history of at least one year of infertility is entered into a randomized controlled study and then standard IUI and simultaneous HCG injection with IUI were compared. The mean age of patients in standard and simultaneous groups in our study was  $(27.78 \pm 3.64)$  and  $(26.92 \pm 3.72)$  years respectively ( $p = 0.26$ ). Age of spouses was nearly similar and about 32 years ( $p = 0.28$ ). Patients had no significant difference in terms of duration of fertility ( $5.11 \pm 3.47$ ) years in the standard and  $(4.6 \pm 1.88)$  years in the simultaneous group, ( $p = 0.47$ ). The other parameters that influence the probability of pregnancy incidence, including infertility cause; anovulation in (55.7% of standard, and 56.3% of simultaneous group), history of previous laparoscopy (85.7% in standard and 90.1% in simultaneous group), history of previous IUI (40% in standard and 28.2% in simultaneous group), the median number of previous IUI cycles ( $1.75 \pm 1.3$  in standard and  $1.57 \pm 0.69$  in simultaneous groups) were nearly similar in both groups.

Moreover, there were no differences in endometrial thickness, size and number of follicles on left and right side between two groups. There was a significant difference just in two cases. The first case was infertility type (primary or secondary) that primary infertility was higher in patients of simultaneous group (85.7% vs. 66.7%,  $p = 0.009$ ) and second case was the number of patients with more than one follicle in their ovaries that was in the standard group much higher than in the simultaneous group ( $p = 0.04$ ). In a study conducted by Ilkkay et al. in Finland, simultaneous IUI with HCG injection was compared with

**Table 1.** Comparison of results between simultaneous and standard groups.

Groups	Standard intrauterine insemination	Simultaneous HCG administration with intrauterine insemination	P-value
Age of patient	27.78 ±3.64	26.92±3.72	0.26
Age of patient's spouse	32.08±5.13	31.29±4.85	0.35
Infertility Length (year)	5.11±3.47	4.6±1.88	0.47
Infertility type (primary)	44 (66.7%)	60 (85.7%)	0.009*
<b>Infertility cause</b>			
Male factor	11 (15.7%)	11 (15.5%)	0.99
Anovulation	39 (55.7%)	40 (56.3%)	
Idiopathic	20 (28.6%)	20 (28.2%)	
Laparoscopy history	60 (85.7%)	64 (90.1%)	0.42
History of previous IUI	28 (40%)	20 (28.2%)	0.13
The mean number of previous IUI cycle	1.75±1.4	1.57±0.69	0.62
The number of follicles (more than one mature follicle)	46 (65.7%)	34 (47.9%)	0.04*
Endometrial thickness (mm)	7.89±1.81	7.36±1.49	0.51
Diameter of right side ovary follicle(mm)	18.01±3.57	17.42±3.9	0.35
Diameter of left side ovary follicle (mm)	15.37±4.75	14.54±4.79	0.34
Positive pregnancy test per patient	18 (25.7%)	15 (21.1%)	0.52
Positive pregnancy test per menstrual cycle	18 (16.4%)	20 (15.3%)	0.82

\*P value less than 0.05 was considered statistically significant.

**Table 2.** Comparison of results between two groups of positive pregnancy test and negative pregnancy test

Groups	Positive pregnancy	Negative pregnancy	P-value
Age of patient	27.84 ±3.96	27.06±3.63	0.29
Age of patient's spouse	33.45±5.73	32.14±4.64	0.11
Infertility Length (year)	5.35±4.93	4.74±2.19	0.34
Infertility type (primary)	24 (72.7%)	80 (77.7%)	0.56
<b>Infertility cause</b>			
Male factor	6 (18.2%)	16 (14.8%)	0.57
Anovulation	20 (60.6%)	59 (54.6%)	
Idiopathic	7 (21.2%)	33 (30.6%)	
Laparoscopy history	3 (9.1%)	14 (13%)	0.55
History of previous IUI	8 (24.2%)	40 (37%)	0.04*
The mean number of previous IUI cycle	1.88±1.53	1.41±0.71	0.03*
The number of follicles (more than one mature follicle)	14 (42.4%)	65 (60.1%)	0.01*
Endometrial thickness (mm)	7.71±1.56	7.39±1.76	0.36
Diameter of right side ovary follicle (mm)	18.18±2.66	17.56±4.02	0.41
Diameter of left side ovary follicle (mm)	14.66±4.8	15.11±4.78	0.48
<b>Treatment group</b>			
Standard	18 (54.5%)	52 (48.1%)	0.52
Simultaneous IUI with HCG injection	15 (45.5%)	56 (51.9%)	

standard method of IUI that has been reported increased rate of pregnancy from 10.9% to 19.6% in simultaneous group (7). Another similar assessment in a clinical trial by Aydin et al. (8) was performed on 220 couples in 2013 with male factor infertility or unknown causes. The patients were classified into two groups standard IUI (n= 106) and simultaneous IUI with HCG (n= 96). There were no significant differences in patients in both groups in terms of demographic characteristics and cycles. According to the results of transvaginal ultrasound in both standard and simultaneous IUI groups, clinical pregnancy rate was

9.4% and 12.2% respectively. The differences between two groups were not statistically significant (p= 0.52). However, more clinical trials were recommended for further clarification of these effects. In another study in India, Syed Monajatur Rahman et al. did IUI 24 hours after HCG injection. Results were similar in both groups. However, they have concluded in order to determine the right time of HCG injection, further studies should be done with larger samples (9).

Similar to our study in the study of Järvelä et al. (7) age of the patients was nearly similar in both groups about 29

years. The study also showed no difference between two groups in the number of follicles. Despite our study, there was follicles number more than 1 in 50% of the patients of two groups. The main cause of infertility in 50% of patients in the study remained unknown. Both groups had unexplained infertility. In the studies of Aydin et al. (8), Rahman et al. (9) and Robb et al. (10), there was no significant difference between the initial and demographic characteristics of the two groups.

Mostafa et al. (11) examined factors such as the patient's age, endometrial thickness, size and the number of follicles and initial test results that were similar to our study. In the standard and simultaneous groups of our study, pregnancy rate per patient were 26.6% and 21.3% ( $p=0.54$ ) respectively and pregnancy rate per IUI cycle were 16.15% and 15.2% ( $p=0.87$ ) respectively. In survey conducted in our study, like other studies (7,8-11), although there was no significant difference in pregnancy test between two groups, pregnancy rate in both groups was slightly higher than the previous studies (10). In the study of Järvelä et al. (7) pregnancy rate based on urine test was reported 10% and 19.6% in both standard and simultaneous respectively while this value was about 15% in both groups in our study. In the study of Aydin et al. (8), although pregnancy was clinically evaluated, reported statistics were lower than our study (9.4% and 12.2%). Statistics of Mostafa et al. (11) were 8% and 10% in the standard group and simultaneous group respectively. Despite the differences in the overall statistics of pregnancy rate that it also seems pregnancy in standard IUI to be fewer than simultaneous IUI, it has not been observed in any of these studies (7,8,11). The only study similar to our study is the study of Rahman et al. in India (9); in this study the pregnancy rate was reported about 30%. Although the methods used in this study were different from our study, with regard to epidemiologic similarities it can be probably confirmed that this difference is due to changes in the geographic, nutritional and genetic factors.

### Conclusion

Finally, between two groups examined in our study, no significant difference was found in pregnancy rate. There were no advantages over using standard IUI than simultaneous IUI. Until further studies, IUI standard as the gold standard method is used. In simultaneous IUI, in addition to theoretical advantages mentioned in the study, patient referrals to physician decreased that caused patient comfort and reduction of treatment cost, so this method can be used as an alternative for patients.

### Ethical issues

The study was approved by the ethic committee of Tabriz University of Medical Sciences.

### Conflict of interests

Authors declare that there is no any conflict of interests.

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