# Comparison of Single Versus Double Intrauterine Insemination

Kazım Gezginç*, Hüseyin Görkemli, Çetin Çelik, Rengin Karatayli,
M. Nedim Çiçek, M. Cengiz Çolakoglu

*Department of Obstetrics and Gynecology, Medical Faculty of Meram, Selcuk University, Konya, Turkey.*

## SUMMARY

**Objective:** To compare the outcomes of single versus double intrauterine insemination.

**Materials and Methods:** This prospective randomized study was carried out in 100 infertile patients. One intrauterine insemination was applied 36 hours after human chorionic gonadotropin (hCG) injection to 50 patients in the first group. To 50 patients in the second group, two intrauterine inseminations were applied, of which the first was applied 24 hours after and the second 48 hours after the hCG injection.

**Results:** In the first group, pregnancies were detected in eight patients (pregnancy rate per patient was 16%, pregnancy rate per cycle was 10.6%). In the second group, pregnancies were detected in five patients (pregnancy rate per patient was 10%, pregnancy rate per cycle was 6.4%). There was no statistically significant difference between the two groups ($p > 0.05$).

**Conclusion:** Single intrauterine insemination can be considered to be more reasonable than double intrauterine insemination treatment, taking into consideration the economic cost and the psychologic trauma to the patients. However, further studies with larger sample sizes are needed in order to reveal any actual differences between the two methods. [*Taiwan J Obstet Gynecol* 2008;47(1):57–61]

**Key Words:** double, intrauterine insemination, pregnancy rate, single

## Introduction

Since *in vitro* fertilization (IVF) technology, including sperm preparation techniques, has been developed in recent years, intrauterine insemination (IUI) appears to be gaining popularity. It has also been accepted as a more economical method when compared with other assisted reproductive techniques.

Currently, the most popular areas for the application of IUI in infertility treatment are unexplained infertility and moderately severe male infertility [1]. When spontaneous pregnancy rates are compared with timed postcoital pregnancy rates, IUI is found to significantly increase the pregnancy rates in unexplained and moderately severe male infertility cases [2]. Also, the cumulative pregnancy rate following three sequential cycles of IUI was found to be similar to that with IVF, and was also reported to be economically beneficial. According to meta-analysis results, single cycle IUI application, together with ovarian stimulation, resulted in pregnancy in 16.4% of cases [3,4].

IUI in appropriate patients is a highly satisfactory treatment modality, taking into account its good results and low cost.

## Materials and Methods

This was a prospective randomized study carried out in 100 infertile patients. The patients were divided into two groups. To achieve randomization, the patients who were admitted during the first and third weeks of every month were included in the first group, while patients who were admitted during the second and fourth weeks of every month were included in the second group. IUI had not been performed on these patients before, and this was their first admission. In our study, the patients

*Correspondence to:* Dr Kazım Gezginç, Department of Obstetrics and Gynecology, Medical Faculty of Meram, Selcuk University, Akyokuş 42080, Konya, Turkey.
E-mail: kazimgezginc@hotmail.com
Accepted: August 29, 2007

who wanted to have children and had not succeeded in getting pregnant, despite a regular sexual life for 1 year, were accepted as infertile and were included in the study.

In all patients included in the study, an anamnesis was taken; age, the type and duration of infertility, basal follicle-stimulating hormone (FSH), luteinizing hormone (LH) and estradiol ($E_2$) levels on the third day of the menstrual cycle, basal ultrasonography on the third day of the menstrual cycle, spermiogram problems, systemic diseases that could be associated with infertility (such as hypothyroidism, hyperthyroidism and polycystic ovarian syndrome) were all recorded and considered.

Patients with a minimum sperm count of 10 million/$cm^3$, motility criteria of ≥ 40%, i.e. sum of progressive motility (3+) and (4+), and a normal sperm ratio according to Kruger's strict criteria of ≥ 10% were included in the IUI program. The body mass indices (BMIs; BMI = weight [kg]/height $[m]^2$) of all patients were calculated.

Patients included in the study were divided into two groups. In the first group of 50 patients, we applied single IUI 36 hours after 10,000 IU of human chorionic gonadotropin (hCG) (Pregnyl, Organon, Istanbul, Turkey) administration, following ovulation induction. In the second group of 50 patients, we applied two IUIs at 24 and 48 hours after 10,000-IU hCG injection, following ovulation induction.

For ovulation induction, our first choice was clomiphene citrate, but some patients who were resistant to clomiphene citrate were induced with gonadotropins. The ratio of patients induced with each method was similar in the two groups. During ovulation induction with clomiphene citrate (Klomen, Koçak, Istanbul, Turkey), we started the drug on the fifth day of the menstrual cycle with the minimum dose (50 mg/day) for 5 days. In patients not responding to this dose, we increased the dosage by 50 mg in each cycle, up to 150 mg/day. Recombinant FSH (Gonal-F, Serono, Istanbul, Turkey) was used for ovulation induction in the gonadotropin group.

Ovulation induction was initiated on the third day of the menstrual cycle with 75 IU/day of recombinant FSH and was continued by increasing the dose until an 18-mm follicle was detected.

All patients were followed up by folliculometry. Ovulation was triggered by 10,000 IU of hCG when the follicular diameter, measured by ultrasonography, reached 18–22 mm in patients treated with either clomiphene citrate or gonadotropins.

The semen sample needed for insemination was prepared by swim-up technique. In the first group, insemination was carried out 36 hours after hCG administration; whereas in the second group, two inseminations were carried out at 24 and 48 hours after hCG administration. Insemination was performed in the lithotomy position via an IUI catheter (Gynetics Medical Products N.V., Hamont-Achel, Belgium) after the vagina and the cervix had been washed with isotonic solution. During the procedure, the cervix was not held with a grasper unless definitely necessary. After the procedure, the patients rested on the treatment table for up to 30–40 minutes.

All patients were tested for serum β-hCG levels on the fourteenth day following the predicted ovulation day. Clinical pregnancy was detected by the demonstration of fetal cardiac activity by transvaginal ultrasonography.

The statistical significance of the results was evaluated using the SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) for Windows software. The data were defined by mean and standard deviation. Comparisons of data were carried out using Chi-squared tests and Fisher's exact test. Statistical significance was accepted at $p < 0.05$.

## Results

One hundred patients, 50 in the first group and 50 in the second group, were included in the study. There was no statistically significant difference between the two groups according to age, the duration of infertility or body mass indices ($p > 0.05$). When both groups were evaluated for hormone levels, there were no statistically significant differences in FSH, LH or $E_2$ ($p > 0.05$). The ages, mean FSH, LH and $E_2$ levels, body

**Table 1.** Patient age, duration of infertility, body mass index, mean follicle-stimulating hormone (FSH), luteinizing hormone (LH) and estradiol ($E_2$) levels in both groups

| | Group 1 | Group 2 | *p* |
|---|---|---|---|
| Age (yr) | 29.22 ± 3.73 | 29.96 ± 4.67 | NS |
| Duration of infertility (yr) | 4.72 ± 3.27 | 4.26 ± 2.08 | NS |
| Body mass index ($kg/m^2$) | 26.10 ± 2.85 | 25.02 ± 1.82 | NS |
| FSH (mIU/mL) | 5.40 ± 2.26 | 5.18 ± 2.08 | NS |
| LH (mIU/mL) | 4.54 ± 2.23 | 4.82 ± 2.54 | NS |
| $E_2$ (pg/mL) | 40.04 ± 15.46 | 42.04 ± 15.87 | NS |

*NS = not significant ($p > 0.05$).*

**Table 2.** Types of infertility and the reasons in both groups

| Types of infertility and the reasons | Group 1, *n* (%) | Group 2, *n* (%) | *p* |
|---|---|---|---|
| Female factors | 35 (70) | 30 (60) | NS |
| Anovulation | 16 (32) | 9 (18) | NS |
| Endometriosis | 6 (12) | 7 (14) | NS |
| Unexplained | 13 (26) | 14 (28) | NS |
| Male factors | 15 (30) | 20 (40) | NS |
| Oligospermia | 12 (24) | 15 (30) | NS |
| Oligoasthenospermia | 3 (6) | 5 (10) | NS |

*NS = not significant ($p > 0.05$).*

**Table 3.** Outcomes of intrauterine insemination in patients from both groups

| | Group 1 | Group 2 | Total | *p* |
|---|---|---|---|---|
| Pregnancy (+) | 8 | 5 | 13 | |
| Pregnancy (−) | 42 | 45 | 87 | NS |
| Total | 50 | 50 | 100 | |

*NS = not significant ($p > 0.05$).*

mass indices and durations of infertility for patients in both groups are shown in Table 1.

In 35 patients in the first group, we detected female factor infertility (70%), whilst in the remaining 15 cases, there was male factor infertility (30%). In the second group, 30 patients demonstrated female factor infertility (60%) and the remaining 20 patients male factor infertility (40%). Table 2 details the types of infertility and their causes. When both groups were compared for the type of infertility and the causes, there was no statistically significant difference between them with univariate analysis ($p > 0.05$).

Ovulation induction was performed with clomiphene citrate in 58 of the patients included in the study (58%), whilst gonadotropins were used for the remaining 42 patients (42%). In the first group, 29 patients were induced with clomiphene citrate (58%), and 21 patients were induced with gonadotropins (42%); in the second group, ovulation was induced with clomiphene citrate in 29 patients (58%), and with gonadotropins in 21 patients (42%). In our study, there was no statistically significant difference according to the agents used for ovulation induction ($p > 0.05$).

Seventy-five cycles and 78 cycles of ovulation induction were carried out in the first and second groups, respectively. No patient in either group had more than two cycles of ovulation induction, and there was no statistically significant difference between the two groups in the number of cycles of ovulation induction performed ($p > 0.05$). When we look at the results after IUI performed following ovulation induction, eight pregnancies were detected in the first group (pregnancy rate per patient, 16%; per cycle, 10%); no pregnancy was detected in the remaining 42 patients (84%). Five pregnancies were detected in the second group (pregnancy rate per patient, 10%; per cycle, 6.4%); no pregnancy occurred in the remaining 45 patients (90%). There was no statistically significant difference ($p > 0.05$) in pregnancy rates between the different insemination procedures. The results of the procedures are shown in Table 3.

## Discussion

Five basic tests were defined for the investigation of infertile couples in the American Fertility Society 1992 and World Health Organization (WHO) 1993 meetings: semen analysis, the evaluation of ovulation, the evaluation of the patency of the uterus and the tubes, the postcoital test, and laparoscopy [5,6]. In evaluating infertile couples in this study, we checked spermiograms, ovulation, basal FSH, LH and $E_2$ levels on the third day of the menstrual cycle, basal ultrasonography on the third day of menses, hysterosalpingography, and laparoscopy, when necessary. Among the basic tests for the evaluation of infertile couples, only the postcoital test was not performed in our study. The postcoital test was not performed because of the unknown effects of this test on prognosis in large and controlled studies, and because IUI was already planned for these patients.

In the treatment of infertility, expectant management or active treatment modalities, or sometimes both, can be used. Expectant management is offered especially for young patients who have experienced a short duration of unexplained infertility; in 60% of these cases, pregnancies develop within 2 years [7].

Among the active treatment modalities, IUI appears to be an alternative method which, together with the development of sperm preparation techniques, parallels developments in assisted reproductive technology within the last 20 years. Currently, in most clinics, patients without tubal infertility are taken into an IVF program after a few trials of IUI. Compared with the low pregnancy rates reported previously, the currently reported pregnancy rates are high. Both the increase in the sperm concentration and the increase in the number of oocytes as a result of superovulation play a role in this success.

Freundl [8] offered assisted reproductive techniques to patients who failed to become pregnant after four cycles of treatment with IUI. In this study, a maximum of two cycles of IUI was performed in the patients.

The study by Kang et al [9] supported the importance of the female age in the success of IUI and reported the fertility rate of 20% in women aged 35 years and younger, 12% in patients aged 35 to 40 years and 6% in patients aged 40 years and older. In our study, the mean age of the patients in the first group was 28.76 ± 4.49 years (range, 22–38 years) and in the second group, this was 28.44 ± 5.53 years (range, 19–38 years).

Collins et al [10] emphasized the importance of the duration of infertility on the prognosis and reported that the cumulative pregnancy rate decreased by 2% each year in patients 25 years old or older, with infertility duration of 3 years or longer. In this study, the mean duration of infertility was 4.76 ± 3.84 years (range, 2–18 years) in the first group and 3.74 ± 2.68 years (range, 1–11 years) in the second group.

Another factor affecting the prognosis of infertility treatment is body mass index. The range of body mass indices that is accepted as normal and that is not known to affect ovulatory function is 20–25 [11]. Wittemer et al [12] reported that the chance of pregnancy decreased when the body mass index was below 20 or above 25.

Several reports in the literature demonstrate an increase in pregnancy rates due to IUI following ovulation induction by clomiphene citrate or gonadotropins [13–15].

According to the WHO criteria, the lowest normal sperm count is accepted to be 20 million/cm$^3$. In some studies, the sperm count was found to be below 20 million/cm$^3$ in more than 25% of fertile males [16].

Delepine et al [17] reported that the sperm count was a factor in the IUI success and that the highest pregnancy rates were observed in patients in which 5–10 million/cm$^3$ of spermatozoa were inseminated. In this study, the patients with a minimum sperm count of 10 million/cm$^3$, motility criteria of ≥ 40%, i.e. the sum of (3+) and (4+), and normal sperm ratio according to Kruger's strict criteria of ≥ 10% were included in the IUI program.

The timing of insemination is also important in IUI treatment. Deaton et al [18] induced patients with clomiphene citrate, and performed IUI according to urinary LH monitoring in one group and according to ultrasonographic monitoring and hCG administration in the second group. When the two groups were compared for pregnancy rates, there was no statistically significant difference. In our study, ultrasonographic monitoring and hCG administration was used for the timing of IUI.

Ragni et al [19] induced cycles with clomiphene citrate or gonadotropins, and applied IUI 34 hours after hCG administration in the first group, two IUIs 12 and 34 hours after hCG administration in the second group and two IUIs 34 and 60 hours after hCG administration in the third group. The pregnancy rate was found to be 14.4% per patient and 8.3% per cycle in the first group, and 30.4% per patient and 6.7% per cycle in the second group.

Silverberg et al [20] reported that the fertility rate was higher when insemination was done 18 and 42 hours after hCG administration following ovulation induction, when compared with a single insemination performed 34 hours after hCG administration.

In their ovulation induction cycles, Matilsky et al [21] applied single IUI 24 hours after hCG administration in the first group and two IUIs 24 and 48 hours after hCG administration in the second group. The pregnancy rate was 9.7% per patient and 5% per cycle in the first group and 37.9% per patient and 17.9% per cycle in the second group.

Cantineau et al [22] reported that double IUI had no advantage over single IUI. Zeyneloğlu [23] reported that double IUI has been suggested to increase efficiency, but recent studies have not confirmed this finding. Alborzi et al [24] reported that amongst patients undergoing controlled ovarian hyperstimulation with IUI, the results of single and double IUI did not differ statistically.

When we looked at the results of IUI after ovulation induction in this study, fetal cardiac activity was detected in eight patients (16%) in the first group, while in the remaining 42 patients (84%), pregnancy was not achieved. In the second group, 5 patients (10%) showed fetal cardiac activity, but in the remaining 45 patients (90%), pregnancy was not achieved. Timing and number of IUIs had no statistically significant effect on pregnancy ($p > 0.05$).

In conclusion, a single IUI application can be more desirable than double insemination, taking into account the cost and psychologic trauma caused to the couples both during sperm donation and applications of repeated IUIs. However, further studies with larger sample sizes are needed in order to reveal any actual differences between the two methods.

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