Two Different Timings of Intrauterine Insemination for Non-Male Infertility

FU-JEN HUANG,^{1,2} SHIUH-YOUNG CHANG,¹ YING-JEN LU,¹ FU-TSAI KUNG,¹ MENG-YIN TSAI,¹ and JICK-FUU WU¹

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Purpose: Our purpose was to assess the simplicity and convenience of treatment scheduled not on weekends, by comparing two different timings of intrauterine insemination (IUI) protocol.

Methods: A prospective observational study of two different protocols of intrauterine insemination was designed. Two hundred and ten infertile couples with normal spermiograms were included in this study. Fifty-eight couples were treated with IUI 26 to 28 h after human chorionic gonadotropin (hCG) injection plus timed intercourse within a 12- to 18-hr period and 147 couples had IUI 36 to 38 hr after hCG injection and timed intercourse within a 12- to 18-hour period. Pregnancy rates were compared with two different protocols of IUI.

Results: The mean age, duration, and causes of infertility and the cycle characteristics following follicular stimulation were similar between the two groups. The cycle characteristics of follicular stimulation in the two treatment groups were not different. There also were no significant differences between the groups in the type of sperm concentration, sperm motility, and the percentage of sperm with normal morphology per insemination. The number of follicles greater than 17 mm per patient was not significantly different between the two groups. The pregnancy rate per cycle also was similar between the two groups in men with lower motile sperm numbers ($<40 \times 10^6$) (23.6% vs. 23.4%) and in men with higher sperm numbers ($\geq 40 \times 10^6$) (25% vs. 24.4%).

Conclusions: The different timing but similar efficacy of these two IUI protocols provides a practical choice to clinicians. The availability of both protocols may avoid unnecessary scheduling of clinical and laboratory work on weekends and holidays in women participating in controlled ovarian hyperstimulation and IUI programs for treatment of non-male infertility.

KEY WORDS: timing of intrauterine insemination; timed intercourse.

INTRODUCTION

Artificial insemination with the husband's semen (AIH) recently has received attention as a treatment for nontubal infertility. Among the various methods of AIH, intrauterine insemination (IUI) with washed sperm has been the most widely used and advocated as a treatment alternative for infertility associated with cervical mucus hostility, antisperm antibodies, endometriosis, and ovulatory disorders, as well as male factor infertility and unexplained infertility (1).

The success rate of IUI has been studied in relation to etiologic categories and other variables, such as age and cycle characteristics by follicular stimulation, with a wide range of results (2,3). Success appears to rely on combined ovarian hyperstimulation with correct timing of IUI using adequate numbers of prepared spermatozoa. Silverberg *et al.* (4) and Matthews *et al.* (5) demonstrated that increasing the total number of motile sperm, by using two IUIs per cycle, resulted in increased pregnancy rates. Several investigators also have observed that the second ejaculate from normozoospermic men increased the total number of motile sperm when added to the first ejaculate (6–9). Luciano *et al.* (10) reported that ultrasound-confirmed follicle rupture occurred on day +1 of the luteinizing hormone (LH) surge in 6%, on day +2 in 72%, and on day +3 in 21%.

Based on these findings, it seems likely that IUI on day +1 after human chorionic gonadotropin (hCG) injection plus timed intercourse could achieve results similar to those obtained with IUI on day +2 after hCG injection in infertile couples with normal spermiograms. In this study, we prospectively tested the hypothesis that the pregnancy rate is similar for these

¹ Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taiwan, Republic of China.

² To whom correspondence should be addressed.

two different timings of IUI after hCG injection. The findings may be used to avoid scheduling work on weekends and holidays.

MATERIALS AND METHODS

Two hundred and ten couples with ovulatory dysfunction, unexplained infertility, and minimal to mild endometriosis were recruited for this study. The study was approved by the Institutional Ethics Committee of our hospital. All women received pre-IUI infertility evaluation of basal serum estradiol (E_2), LH, and follicle-stimulating hormone (FSH) levels, and basal body temperature measurement. The means basal FSH level was less than 12 mIU/ml in all women. Endometriosis was diagnosed visually during laparoscopy according to the American Fertility Society scoring system (11). Ninety-five women received the laparoscopy to diagnose the endometriosis or unexplained infertility. All women in the study had tubal patency, documented by hysterosalpingogram and in some cases also by laparoscopy. Each man had a normal spermiogram (12) on at least two occasions and a negative direct SpermMar IgG test (FertilPro N. V., Belgium). Couples with severe endometriosis, uterine factor, or male factor infertility were excluded. Two hundred and ten couples met the study criteria and gave informed consent to participate in this trial. Only the first treatment cycle of each couple was used in the evaluation of the results.

Follicular stimulation was initiated with FSH (75 IU; Metrodin, Serono Laboratories Inc., Randolph, MA) in 66 couples at a standard dose of 2 ampoules/day, and with hMG (75 IU FSH + 75 IU LH; Pergonal, Serono Laboratories Inc., Randolph, MA) in 112 couples at a standard dose of 2 ampoules/day. The doses were adjusted on day 7 of stimulation. Thirty-two couples received both (CC) and human menopausal gonadotropin (hMG). In these patients, 100 mg/day of CC from day 3 to day 7 of the menstrual cycle, combined with 2 ampoules/day of hMG starting from day 3, was administered. A dose of hCG (Pregnyl, N.V. Organon/Oss, Holland), usually 10,000 IU, was administered intramuscularly when ultrasound revealed the follicle expected to be 17 mm.

Intrauterine insemination was performed with two protocols after hCG administration depending on whether the IUI would occur on the weekend or not. Briefly, the first group of patients was scheduled to undergo IUI 26 to 28 hr after hCG injection (10 AM injection) on a Thursday or Friday when the criteria

of follicular growth were expected to be reached. However, the second group of patients, which were IUI cohort patients serving as controls, received IUI 36 to 38 hr after hCG injection (10 PM injection). All patients were instructed to have intercourse between 12 to 18 hr after insemination according to our standard IUI programs (13). Luteal phase hormonal support was achieved with micronized progesterone 400 mg/day until 10 weeks of gestational age if the patient conceived. Qualitative serum β -hCG test was performed no earlier than 14 days after ovulation for those women who had not started menstruating. Transvaginal sonography was performed 5 weeks after ovulation to document fetal viability in all patients with positive β -hCG results. Clinical pregnancy was defined as either an ectopic pregnancy, intrauterine pregnancy with fetal cardiac activity, or chorionic villi identified in case of abortion.

The semen was prepared using a modified Percoll gradient method as previously described (14). Semen analysis was done before and after preparation. Two couples in the first group and three from the second group were excluded from further analysis due to poor response to follicular stimulation or failure to have timed intercourse after IUI. Women from 205 couples who fulfilled the criteria were inseminated with 0.5 to 1 ml of prepared semen. A TDT catheter (Laboratories, C.C.D., Paris, France) was used for insemination.

All statistical analyses were performed using the SAS statistical package (SAS Inc. 1988, SAS User's Manual, North Carolina). Differences in the pregnancy rates of the two groups were compared using the Mantel-Haenszel χ^2 test. For comparison of the means, Student's t test was performed where appropriate. For comparison of the differences in stimulation regimens and causes of infertility, χ^2 test was per-

Table I. Characteristics of Patients Undergoing Artificial Insemination

	Day 1 IUI ^a and intercourse	Day 2 IUI and intercourse
No. of patients	58	147
Age ($\pm$ SEM)	31.5 ($\pm$ 4.1)	31.8 ($\pm$ 4.3) ^b
Years of infertility ($\pm$ SEM)	4.5 $\pm$ 2.6	4.1 $\pm$ 2.2 ^a
Cause of infertility		
Endometriosis (%)	19 (32.8)	47 (31.9) ^c
Ovulatory dysfunction (%)	31 (53.5)	79 (53.8) ^c
Unexplained (%)	8 (13.7)	21 (14.3) ^c

^a IUI, Intrauterine insemination.

^b $P > 0.05$, by comparing two protocols, Student's t test.

^c $P > 0.05$, by comparing two protocols, χ^2 test.

formed as appropriate. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

The two groups had similar background characteristics, in terms of mean age of the female patients, duration of infertility, and the percentage of various diagnostic–etiologic categories including endometriosis, ovulation dysfunction, or unexplained infertility (all *P* > 0.05) (in Table I). The cycle characteristics of follicular stimulation in the two treatment groups were shown in Table II. There were no significant differences between the groups in the type of ovarian stimulation used (hMG, FSH, or CC/hMG), serum levels of E₂ on the day of hCG administration, sperm concentration, sperm motility, and the percentage of sperm with normal morphology per insemination (all *P* > 0.05). The number of follicles greater than 17 mm per patient was not significantly different between the two groups.

The overall pregnancy rate per cycle was similar between the two groups. We also assessed the effects of different timings of IUI after hCG injection between patients inseminated with $<40 \times 10^6$ or $\geq 40 \times 10^6$ sperm, based on the results of a previous report regarding the distribution of pregnancy rates after IUI according to total motile sperm inseminated (13). The pregnancy rate per cycle also was found to be similar between the two groups in patients with a lower number of motile sperm ($<40 \times 10^6$) (23.6% vs. 23.4%) and in patients with a higher number of sperm ($\geq 40 \times 10^6$) (25% vs. 24.4%) (in Table III).

DISCUSSION

In this study, couples who performed intercourse 12 to 18 hr after IUI had similar pregnancy rate in the group who received early IUI and timed intercourse (IUI, 26 to 28 hr after hCG; effect of pooling, 38 to 46 hr after hCG) and routine IUI and timed intercourse (IUI, 36 to 38 hr after hCG; effect of pooling, 48 to 56 hr after hCG). A possible explanation for the similar pregnancy rate following two different timings of IUI after hCG injection may be the fact that ovulation occurs in a broad range of time to ovulation time after hCG administration. The time to ovulation after intramuscular hCG injection ranged from <36 hr to >48 hr, according to the findings in a previous clomiphene–hCG intrauterine insemination study (15). Andersen *et al.* (16) also demonstrated that the time interval from hCG administration to the first follicular rupture ranged from 34 to 46 hr. In several studies, the total number of motile sperm in the second ejaculate from normozoospermic men has been shown to be 32.9% the number of the first ejaculate within a 1- to 4-hr period (6), 42.9% to 53.1% within a 24-hr period (7,8), and 48% within a 96-hr period (9). Double inseminations at 24-hr intervals also have been shown to be more successful than a single insemination after gonadotropin-induced superovulation, possibly due to a significantly greater number of spermatozoa inseminated (4,5). In our previous study, patients receiving intrauterine insemination combined with timed intercourse achieved better pregnancy rates than those who received intrauterine insemination only (13). These studies may explain the efficacy of sperm pooling in the uterus following timed intercourse in our study,

Table II. Cycle Characteristics During Follicular Stimulation

	Day 1 IUI and intercourse	Day 2 IUI and intercourse
No. of patients	58	147
Stimulation regimen		
Receiving hMG ^a (%)	31 (53.5)	79 (53.7) ^b
Receiving pure FSH (%)	20 (34.4)	44 (29.2) ^b
Receiving CC/hMG (%)	7 (12.1)	24 (16.4)
Number of follicles (≥ 17 mm) per cycle ($\pm$ SEM)	2.5 $\pm$ 0.5	2.6 $\pm$ 0.6 ^c
E2 level on day of hCG (pg/ml) ($\pm$ SEM)	1081 $\pm$ 551	1028 $\pm$ 541 ^c
Sperm parameters per insemination		
Sperm concentration ($\times 10^6$ /ml) ($\pm$ SEM)	33.6 $\pm$ 14.7	34.3 $\pm$ 20.2 ^c
Motility (%) ($\pm$ SEM)	86.9 $\pm$ 5.9	84.3 $\pm$ 7.3 ^c
Normal morphology (%) ($\pm$ SEM)	64.8 $\pm$ 12.3	62.6 $\pm$ 10.1 ^c

^a Abbreviations: IUI, intrauterine insemination; hMG, human menopausal hormone; FSH, follicle-stimulating hormone; CC, clomiphene; E₂, estradiol.

^b *P* > 0.05, by comparing two protocols, χ^2 test.

^c *P* > 0.05, by comparing two protocols, Student's *t*-test.

Table III. Effect of Intrauterine Insemination Combined with Timed Intercourse on Pregnancy Rate by Inseminated Total Motile Sperm Count

	Day 1 IUI ^a and intercourse	Day 2 IUI and intercourse
Cycles No.	58 (14) ^b	147 (35)
Overall pregnancy rate <40 × 10 ⁶ total motile sperm inseminated	0.241	0.238 ^c
No. of cycles	38 (9) ^b	98 (23)
Pregnancy rate	0.236	0.234 ^c
≥40 × 10 ⁶ total motile sperm inseminated		
No. of cycles	20 (5) ^b	49 (12)
Pregnancy rate	0.250	0.244 ^c

^a IUI, Intrauterine insemination.^b Values in parentheses are numbers of pregnancies.^c $P > 0.05$, by comparing two protocols, χ^2 test.

which showed similar pregnancy rate despite different timing of IUI.

Although there is a trend toward better conception rates with increasing total motile sperm count in some studies (17–19), Berg *et al.* (20) showed that IUI performed with a considerably higher number of motile sperm does not lead to a significant increase in pregnancy rates for populations with cervical factor infertility or mild endometriosis. In our previous study, insemination with a considerably higher number of motile sperm also was not associated with better pregnancy rates for populations with ovulatory dysfunction, endometriosis, or unexplained infertility (13). In the present study, the timed intercourse (38 to 46 hr after hCG) may increase the sperm pooling in the uterus in the first group to achieve the similar pregnancy rates as the second group, although IUI was performed earlier than the widely used schedule (36 to 38 hr after hCG). In the second group, the sperm pooling in the uterus (48 to 56 hr after hCG) was not associated with better pregnancy rates, possibly due to the maximal effect of sperm number on the pregnancy rates. These results may avoid unnecessary scheduling of work on weekends or holidays. Karacan *et al.* (21) also showed that there was no deleterious effect when Sunday services were not offered.

Our present results demonstrate that intrauterine insemination 26 to 28 hr following hCG injection and timed intercourse achieved a pregnancy outcome similar to that of the widely used schedule (36 to 38 hr after hCG injection). These two protocols also may provide a practical choice for performing IUI for treatment of non-male infertility and also may be used

to avoid scheduling clinical and laboratory work on weekends and holidays.

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