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# Stimulated intrauterine insemination in women with unilateral tubal occlusion

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**Objective:** To investigate the value of stimulated intrauterine insemination (IUI) in women with unilateral tubal occlusion.
**Methods:** Superovulation and IUI was performed during 2003-2010 and the medical records were reviewed retrospectively. Thirty-seven infertile women (52 cycles) with unilateral tubal occlusion diagnosed by hysterosalpingography and without other causes of infertility were selected. One-hundred fourteen patients with unexplained infertility served as a control group (182 cycles). The main outcome was the clinical pregnancy rate per cycle.
**Results:** The pregnancy rate per cycle was similar, 17.3% for the unilateral tubal occlusion group and 16.5% for the unexplained infertility group. The rate of miscarriage (11.1% vs. 23.3%) and ectopic pregnancy (11.1% vs. 6.7%) was similar between the two groups. The pregnancy rate was higher in patients with proximal occlusion (25.0%) compared with distal occlusion (13.9%) or unexplained infertility, but not statistically significant.
**Conclusion:** Stimulated IUI can be suggested as the initial treatment option in women with unilateral proximal or distal tubal occlusion.

**Keywords:** Tubal obstruction; Insemination; Pregnancy

## Introduction

Tubal pathology is one of the common causes of infertility and is diagnosed in approximately 30% to 35% of infertile women [1]. A history of pelvic inflammatory disease, septic abortion, ruptured appendix, tubal surgery, or ectopic pregnancy strongly suggests the possibility of tubal damage. Most women with tubal factor infertility have detectable chlamydia antibodies suggesting prior infection [2].

The mechanism responsible for tubal factor infertility obviously involves anatomic abnormalities that prevent the union of sperm and ovum. Proximal tubal obstructions prevent sperm from reaching the distal fallopian tube where fertilization normally occurs. Distal tubal occlusions prevent ovum capture from the adjacent ovary. Whereas proximal tubal obstruction is essentially an all-or-none phenomenon, distal tubal occlusive disease exhibits a spectrum ranging from mild (fimbrial agglutination) to moderate (varying degrees of fimbrial phimosis) to severe (complete obstruction).

Hysterosalpingograpy (HSG) and laparoscopy are the two most common procedures used in the evaluation of mechanical infertility. Images from HSG reveal uterine cavity distortion and the internal architecture of the tubal lumen, neither of which can be evaluated by laparoscopy. Laparoscopy provides detailed information about the pelvic anatomy that HSG cannot, including adhesions, endometriosis, and ovarian pathology. HSG is commonly performed as the first-line approach to assess the anatomy of the uterus and the patency of the fallopian tubes in infertile women [3].

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The treatment of patients with patent tubes or with bilateral tubal occlusion diagnosed by HSG is clear. However, there is no single standard management of patients with unilateral tubal occlusion. There may be several treatment options for these patients including superovulation with intrauterine insemination (IUI), in IVF-ET and laparoscopic surgery [4]. However, information available to date on the pregnancy rate after stimulated IUI in patients with HSG findings of unilateral tubal occlusion is scanty. The purpose of this study is to investigate the value of stimulated IUI in women with unilateral tubal occlusion.

## Methods

### 1. Patients

Among the patients who received stimulated IUI during 2003-2010 at the Seoul National University Bundang Hospital, the study group was selected by the following criteria: 1) age ≤ 38-year-old, 2) unilateral tubal occlusion diagnosed by HSG, and 3) without other causes of infertility. Thirty-seven patients met the criteria. The control group consisted of 114 patients with unexplained infertility during the same period and who met the same inclusion criteria, except for normal findings on HSG. Data were collected retrospectively by chart review for selected patients. Cycle outcomes were compared between the study group (52 cycles) and control group (182 cycles). The main outcome parameter was a clinical pregnancy rate per cycle. The Institutional Review Board of our hospital approved the use of the patients' medical records.

### 2. Superovulation and IUI

Drugs used for ovarian stimulation included clomiphene citrate (CC) (Clomiphene, Young-Poong, Seoul, Korea), letrozole (Femara, Novartis, Basel, Switzerland), and gonadotropins. Gonadotropins included recombinant FSH (Gonal F, Merck Serono, Geneva, Switzerland), highly purified urinary FSH (Metrodin, Merck Serono), hMG (Menogon, Ferring, Copenhagen, Denmark; Pergonal, Merck Serono; IVF-M, LG life science, Seoul, Korea), or HP-hMG (Menopur, Ferring).

Ovarian stimulation was performed by CC alone (15 cycles), letrozole alone (3 cycles), CC+FSH (55 cycles), CC+hMG (56 cycles), CC+FSH+hMG (38 cycles), letrozole+FSH (10 cycles), letrozole+hMG (24 cycles), letrozole+FSH+hMG (3 cycles), FSH alone (24 cycles), hMG alone (3 cycles), and FSH+hMG (3 cycles). Among them, pituitary suppression was made by GnRH antagonist in 5 cycles and GnRH agonist in 1 cycle. Distribution of the ovarian stimulation regimen was similar between the two groups.

Ovarian stimulation started on the 3rd day of menstruation, after basal ultrasound examination and hormonal assay. Letrozole (2.5 mg/day) or CC (50 to 100 mg/day) was administered for five consec-

utive days starting from day 3 to 5. The starting dose of gonadotropin was 75 or 150 IU according to the status of the patients, including age, hormonal status, number of cycles, and response in the previous cycle, and was administered every day or every other day from day 3 to 7. Follicular development was monitored by ultrasound and by serum estradiol levels. A single intramuscular injection of 5,000 to 10,000 IU urinary hCG (Profasi, Merck Serono) or 250 μg recombinant hCG (Ovidrel, Merck Serono) was performed if at least one follicle ≥ 18 mm. A single IUI was performed 36 to 40 hours later. If an LH surge was assumed by positive urine LH test on the triggering day, IUI was performed the day after hCG injection. Sperm preparation was performed by the density gradient method (Sperm gradient kits, Cook Medical, Brisbane, Australia). Sperm parameters were recorded as prepreparation values.

A serum β-hCG test was performed 15 to 20 days after hCG administration. In pregnancy cycles, transvaginal ultrasound was performed 4 to 5 weeks after hCG administration. Clinical pregnancy was defined as the presence of a gestational sac on ultrasonography. Miscarriage was defined as the loss of a pregnancy before the 12th week of gestation.

### 3. Statistical analysis

The SPSS Ver. 17.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. The Student's $t$-test was used for analysis of continuous data and the chi-squared test was used for analysis of categorical data. Differences were considered statistically significant if the $p$-value $< 0.05$.

## Results

There were no differences in clinical parameters including women's age, body mass index, and infertility duration between the two groups (Table 1). However, previous history of ectopic pregnancy and abdominopelvic surgery was significantly higher in patients with uni-

**Table 1.** Patient's basic clinical characteristics

| Characteristics | Unilateral tubal occlusion (n=37) | Unexplained infertility (n=114) | $p$-value |
|---|---|---|---|
| Patient's age (yr) | 32.6±3.2 | 32.3±2.9 | NS |
| Husband's age (yr) | 35.7±4.1 | 36.0±4.1 | NS |
| Body mass index (kg/m²) | 21.9±3.6 | 21.4±2.8 | NS |
| Primary infertility (%) | 51.4 | 67.5 | NS |
| Infertility duration (yr) | 2.8±1.6 | 2.9±1.8 | NS |
| Previous ectopic pregnancy | 6 (16.2) | 4 (3.5) | 0.007 |
| Previous abdominopelvic surgery | 16 (43.2) | 6 (5.3) | <0.001 |

Values are presented as mean ± standard deviation or number (%).
NS, not significant.

lateral tubal occlusion than those with unexplained infertility. Previous ectopic (tubal) pregnancy was treated by salpingectomy in all of the six patients with unilateral tubal occlusion. In the unexplained group, three tubal pregnancies and one cervical pregnancy were noted; the tubal pregnancies were treated by laparoscopic salpingostomy (n=1), or local (n=1) or systemic (n=1) injection of methotrexate. The one cervical pregnancy was treated by cervical curettage. In all of these four patients, the subsequent HSG was normal. Previous abdomino-pelvic surgery included salpingectomy (n=7), myomectomy (n=3), oophorectomy (n=3), ovarian cystectomy (n=2), cesarean section (n=1), peritonitis (n=1), salpingoophorectomy (n=1), cesarean section+ovarian cystectomy (n=1), myomectomy+salpingectomy (n=1), salpingostomy (n=1), and appendectomy (n=1).

The basal serum hormonal levels and partner's semen parameters in the IUI cycles did not differ between the two groups (Table 2). The pregnancy rate per cycle, pregnancy rate per patient (24.3% vs. 26.3%), and the rate of miscarriage and ectopic pregnancy were also similar.

The number of patients (cycles) with a proximal and distal obstruction was 13 (16) and 24 (36), respectively. There were 5 patients (6 cycles) with hydrosalpinx among the patients with distal tubal occlusion; a pregnancy was achieved in one cycle but ended in miscarriage

**Table 2.** IUI cycle outcomes

| Clinical parameters | Unilateral tubal occlusion (n=52) | Unexplained infertility (n=182) |
|---|---|---|
| Basal serum LH (mIU/mL) | 3.6±1.0 | 4.6±1.7 |
| Basal serum FSH (mIU/mL) | 7.0±2.7 | 6.3±1.8 |
| Basal serum estradiol (pg/mL) | 37.8±28.7 | 28.2±11.1 |
| Basal serum AMH (ng/mL) | 4.1±2.4 | 2.9±1.7 |
| Semen volume (mL) | 3.0±1.6 | 2.6±1.4 |
| Sperm concentration (×10$^6$/mL) | 281.3±289.3 | 261.2±301.8 |
| Sperm motility (%) | 60.3±26.3 | 57.0±24.1 |
| Stimulation regimen | | |
| CC | 4 | 11 |
| Letrozole | 0 | 3 |
| CC+gonadotropins | 41 | 110 |
| Letrozole+gonadotropins | 4 | 31 |
| Gonadotropins only | 3 | 27 |
| Total dose of gonadotropin (IU) | 445.8±250.7 | 532.9±328.2 |
| Number of previous IUI cycles | 1.83±0.64 | 1.52±0.78 |
| Number of follicle (≥16 mm) | 2.9±1.4 | 2.8±1.5 |
| Leading follicle size (mm) | 20.7±2.2 | 20.7±2.3 |
| EM thickness (mm) | 8.1±1.8 | 8.9±2.2 |
| Clinical pregnancy | 9 (17.3) | 30 (16.5) |
| Clinical abortion | 1 (11.1) | 7 (23.3) |
| Multiple pregnancy | 0 (0) | 3 (10) |
| Ectopic pregnancy | 1 (11.1) | 2 (6.7) |

Values are presented as mean ± standard deviation or number (%).
All variables are not statistically different between the two groups.
IUI, intrauterine insemination; AMH, anti-Müllerian hormone; CC, clomiphene citrate; EM, endometrial.

at the 7th gestational week. The mean number of follicles was 2.0 ± 1.1 and the mean diameter of the leading follicle was 19.1 ± 2.1 mm in the site of the patent tube at the triggering day. The pregnancy rate was lower in the patients with distal occlusion (13.9%) compared with proximal occlusion (25.0%) or unexplained infertility (16.5%), but was not statistically significant.

## Discussion

In the present study, the pregnancy rate was better in patients with proximal occlusion (25.0%) than in those with distal occlusion (13.9%) or unexplained infertility (16.5%). Therefore, stimulated IUI can be suggested as the initial treatment option in women with unilateral proximal tubal occlusion. Our results also indicate that stimulated IUI can be suggested as the first-line option in women with unilateral distal tubal occlusion because the pregnancy rate was similar to those with unexplained infertility. In another report with a similar design, the cumulative pregnancy rate in women with unilateral mid or distal tubal occlusion (19%) was lower than in those with unilateral proximal tubal occlusion (38.2%) and was significantly lower than in those with unexplained infertility (42.6%) [4]. Thus, in that study the authors concluded that patients with unilateral distal tubal occlusion on HSG should be referred for laparoscopic assessment or IVF. However, we propose that stimulated IUI should be recommended as the first-line option in women with unilateral proximal or distal tubal occlusion.

Proximal occlusion is sometimes just a false reading in which the tube is actually open on subsequent testing. Tubal spasm, temporary mucous plugging, and underfilling of the tube may cause a false-positive by HSG when proximal obstruction is demonstrated. The false-positive rate for proximal tubal obstruction may be as high as 15% [5]. Consequently, confirmation of proximal occlusion by repeat HSG or laparoscopic chromopertubation should be considered. Proximal tubal occlusion can be corrected at the time of initial HSG. In one report, a second HSG yielded bilateral tubal patency in 60% of patients who were diagnosed with proximal tubal obstruction [6]. None of the patients diagnosed with proximal tubal occlusion by HSG in our study group underwent repeat HSG or laparoscopy for confirmation, but it is possible that they might not truly have had tubal occlusion. Therefore, the false positive reading on HSG of proximal tubal occlusion could be a reason for the higher pregnancy rate in our study.

Traditionally, laparoscopy was the final diagnostic procedure of any infertility investigation. However, laparoscopy can be omitted in women with normal HSG or suspected unilateral distal tubal pathology on HSG, since it was not shown to change the original treatment plan indicated by HSG in the majority of the patients. However, lapa-

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roscopy should be recommended in cases with suspected bilateral tubal occlusion on HSG, since it altered the original treatment plan in a third of the patients from IVF to induction of ovulation with IUI [7].

Therapies that directly correct tubal factor infertility are entirely surgical. As success rates for assisted reproductive technology continue to improve, the indications for surgical approaches in the treatment of tubal factor infertility have become increasingly limited. Still, many of the principles underlying surgical management remain important. Microsurgical tubocornual anastomosis is the primary surgical approach, with postsurgical ongoing pregnancy rates averaging 47.4% in five reported series involving 175 patients [8-12]. Previous studies demonstrated that laparoscopic salpingectomy of tubal occlusion improves IVF pregnancy rates in women with hydrosalpinges. Selective salpingography performed under fluoroscopy can also be used. If selective salpingography fails to recreate tubal patency, proximal tubal cannulation can be performed using a guidewire under radiologic guidance [13].

The value of surgical correction or tubal cannulation in unilateral tubal factor infertility has mainly been investigated as part of the overall approach to tubal or pelvic factor infertility. A meta-analysis of surgical techniques for treating proximal tubal pathology reported that in cases of sterilization reversal, bilateral microsurgical anastomosis was associated with higher total and ongoing pregnancy rates than macrosurgery. However, in cases of proximal tubal obstruction, pregnancy rates after transcervical tubal cannulation were similar to those achieved after microsurgery [12].

In younger women with mild distal tubal occlusive disease, laparoscopic surgery may be viewed as an alternative to IVF, but when the disease is severe or pregnancy does not occur during the first postoperative year, IVF is the logical choice. For older women with any significant degree of distal tubal disease, IVF is generally the first and best option because cycle fecundability after distal tubal surgery is low (1% to 2%), time is limited, and IVF is both more efficient and more effective [14].

In patients with unilateral tubal occlusion on HSG, the choice of management is still vague. The physician should choose one of the following strategies: 1) further evaluation of the pelvis with laparoscopy, 2) repeating HSG with or without catheterization, 3) attempting to achieve pregnancy with ovarian stimulation and IUI through one patent tube, 4) referring the couple for IVF. Except for stimulated IUI, all the other treatment options have been investigated in the literature.

In conclusion, stimulated IUI can be suggested as the initial treatment in women with unilateral proximal or distal tubal occlusion. Because it was a small retrospective study and multiple types of stimulation were lumped together with no differentiation of the various types of stimulation, further prospective randomized studies are needed to verify our findings.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

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