

# Time-limited hydrotubation combined with clomiphene citrate treatment for unexplained infertility

**O.E. Yapca, I.B. Delibas, I. Karaca, Y. Kumtepe, S. Kadanali**

*Ataturk University, Faculty of Medicine, Department of Obstetrics and Gynaecology, Erzurum (Turkey)*

## Summary

**Purpose:** To evaluate time-limited hydrotubation combined with clomiphene citrate as treatment for unexplained infertility. **Materials and Methods:** In this unblinded, randomized controlled trial of patients who had unexplained infertility, 40 patients were treated with time-limited hydrotubation (saline, 20 ml; flushed within 20 to 30 seconds) and clomiphene citrate (total, 70 cycles) and 40 patients were treated with clomiphene citrate alone (total, 74 cycles). All women underwent an ovulation induction protocol with clomiphene citrate (100 mg/d orally for five days, from day 3 to day 7 of the cycle). Hydrotubation was performed after detection of the dominant follicle. **Results:** There were 15 pregnancies in the 80 patients (19%) (total, 144 stimulated cycles; 10% pregnancies per cycle). The frequency of clinical pregnancy per cycle was significantly greater in patients who were treated with hydrotubation and clomiphene citrate (nine pregnancies per cycle [13%]) than those treated with clomiphene citrate alone (two pregnancies per cycle [3%]; odds ratio, 5.3; 95% confidence interval, 1.1 to 25.5;  $p \leq 0.05$ ). The frequency of pregnancy per patient (total, clinical, or chemical) was similar for the two treatment groups. The frequency of live birth or abortion per cycle or patient was similar between the two treatment groups. **Conclusion:** Time-limited hydrotubation and clomiphene citrate may increase the frequency of clinical pregnancy per cycle in women who have unexplained infertility.

**Key words:** Obstetrics; Fallopian tubes; Ultrasonography; Conception; Pregnancy.

## Introduction

Unexplained infertility is a common cause of infertility [1]. Although there is no consensus about which tests are essential for diagnosing unexplained infertility, it has been recommended that all basic tests for infertility should be normal including laboratory assessment of ovulation, tests of anatomic structure of the uterine cavity and fallopian tubes, and semen analysis [2-4]. Therefore, unexplained infertility is a diagnosis of exclusion.

Tests for fallopian tube patency are important in the evaluation of infertility but are sensitive only for gross defects. It may be difficult to detect subtle anatomic or functional problems of the fallopian tubes that may have negative effects on fertility [5-8].

The tubal lumen caliber and course of the fallopian tube may contribute to infertility. The intramural tubal lumen caliber may be narrow (0.1 mm) [9]. The fallopian tubes are tortuous in most patients, but the intramural segment of the fallopian tube may be straight in most patients [10, 11]. In addition, hormonal changes associated with the menstrual cycle have effects on physiologic activities of the fallopian tubes. During the estrogen dominant phase of the menstrual cycle, transisthmic flow may decrease and contractions of tubular musculature may increase [12, 13]. During the proliferative phase of the menstrual cycle, the cilia beat less frequently than they do after ovulation and the proportion of ciliated cells decreases along the tube [14, 15].

Patients who have multiple tubal tortuosities and who have laparoscopy may have a higher incidence of conception, possibly because tubal insufflation may alleviate tubal obstruction. A higher incidence of conception may occur after laparoscopy because of removal of minor obstruction such as fine intraluminal adhesions or thickened mucous plugs [16]. Amorphous material may form a cast in the tubal lumen in 33% women who have segmental tubal resection because of proximal tubal obstruction [17].

There is a need for effective techniques to address the subtle functional and anatomic tubal problems that may prevent pregnancy. Hydrotubation is a technique in which a liquid mixture or saline solution (aqueous or oil-soluble medium) is flushed through the cervix into the uterine cavity and fallopian tubes. Although it is unknown whether hydrotubation increases fertility, hydrotubation may improve the frequency of pregnancy because it may mechanically dislodge dense material in the tubes [18]. Previous studies have used different volumes and contents of saline solution, but the duration of flushing (not time-limited) has not been described quantitatively [19-23].

The present authors hypothesized that treatment with time-limited hydrotubation may be a useful empirical method to improve the frequency of pregnancy for women with unexplained infertility. The beneficial effects of hydrotubation in previous studies (that had no time limitation during the procedure) may have been associated with the

Revised manuscript accepted for publication November 25, 2013

mechanical force of flushing and pharmacologic effects of different agents added to the hydrotubation solution. In the present study, the authors evaluated the mechanical effect of hydrotubation with saline alone in a time-limited fashion. When the ejection velocity may reach a maximum value, hydrotubation may be more effective because of higher mechanical force.

## Materials and Methods

### Subjects

This was an unblinded, randomized controlled trial comparing the efficacy of time-limited hydrotubation and clomiphene citrate or clomiphene citrate alone on the frequency of pregnancy in women who were diagnosed with unexplained infertility. The study was performed in accordance with the Code of Ethics of the Declaration of Helsinki [24]. The study protocol was approved by the Ataturk University Medical Faculty Ethical Committee (registered approval number 2009/3-06).

Participants were recruited from 116 consecutive couples undergoing infertility counseling at the Infertility and Assisted Reproduction Unit, Department of Obstetrics and Gynaecology, Ataturk University from May 2009 to April 2010. A complete infertility investigation had been performed before referral to the Assisted Reproduction Unit. Women were included in the study when they had unexplained infertility and (1)  $\geq$  two years (two to five years) unprotected sexual intercourse, (2)  $\geq$  two semen analyses from their partner that were normal, (3) age 18 to 35 years, (4) confirmation of bilateral tubal patency by hysterosalpingogram or diagnostic laparoscopy, (5) confirmation of normal uterine cavity by hysteroscopy or ultrasonography, (6) serum follicle stimulating hormone level  $< 10$  IU/L and serum estradiol level  $< 75$  pg/ml at day 3 (menstrual cycle), and (7) regular menstrual cycles during the previous six months.

Exclusion criteria were (1) a history of ovarian and/or adnexal surgery, (2) presence of major medical or pelvic organic diseases or endocrine conditions such as thyroid disease or hyperprolactinemia, (3) use of hormonal medication within the previous six months before the first study visit, (4) women with body mass index  $> 30$  kg/m<sup>2</sup>, (5) women with ovarian or tubal abnormalities, and (6) subjects with male factor infertility.

There were 20 couples that did not satisfy the inclusion criteria. In the 96 eligible couples, 80 couples accepted inclusion into the study and gave informed consent for ovulation induction with or without hydrotubation. Subjects were randomized for treatment using sequentially numbered opaque sealed envelopes that were given to a nurse who was not involved in the study and who assigned women to two study groups: (1) hydrotubation and clomiphene citrate (40 patients) and clomiphene citrate alone (40 patients).

### Treatment and evaluation

All patients had ovulation induction with clomiphene citrate 100 mg/d orally for five days, from day 3 to day 7 of the menstrual cycle. After spontaneous bleeding, endometrial thickness and follicle measurements were performed on day 3 and 12 of the cycle with a transvaginal ultrasonography unit that was equipped with a five to seven MHz endovaginal probe. Ultrasonographic examinations were repeated on days 13 and 14 when the leading follicle diameter was  $< 18$  mm on day 12. After one or two follicles with diameter  $\geq 18$  mm were detected on ultrasonography, the couples were advised to have sexual intercourse on alternate days for one week. If  $\geq$  three mature follicles ( $\geq 18$  mm) devel-

oped, the intervention was cancelled and the couples were advised to avoid sexual intercourse for the subsequent two weeks. Ovulation was monitored by midluteal phase serum progesterone or by ultrasonography. Endometrial thickness was measured on the day that the dominant follicle was detected.

In the patients who were randomized for treatment with hydrotubation and clomiphene citrate, time-limited hydrotubation was performed once per treatment cycle after detection of the dominant follicle ( $\geq 18$  mm). A sterile vaginal speculum was inserted into the vagina, and the vagina and cervix were cleansed with sterile saline (ten ml). A pediatric Foley catheter (8 French) was introduced into the cervical canal and pushed beyond the cervical os into the uterine cavity (2.5 cm). The balloon was insufflated with saline (three ml) to obstruct the cervical canal. Saline solution (20 ml) was flushed into the uterine cavity and tubes, and the time of flushing was limited to 20 to 30 seconds (mean, 26). In patients who reported abdominal pain or discomfort during flushing, the ejection velocity of saline was decreased.

Six patients in the study group and four patients in the control group, who had no pregnancy after the first cycle, refused treatment in the second menstrual cycle. All women were followed until it was evident that pregnancy was unsuccessful or pregnancy was confirmed successful by serum  $\beta$ -human chorionic gonadotropin level ( $>20$  IU/L). Patients with positive  $\beta$ -human chorionic gonadotropin level were further followed for presence of an intrauterine gestational sac, yolk sac, and fetal pole on ultrasonography by a radiologist who was blinded to the study. Chemical pregnancy was diagnosed if serum  $\beta$ -human chorionic gonadotropin level was  $>20$  IU/L, and it did not rise to the level of  $> 1,500$  IU/L and no intrauterine gestational sac with double line signal was detected in transvaginal ultrasonography in control examinations. Clinical pregnancy was diagnosed if fetal pole was detected within the gestational sac. The authors used the term abortion for clinical pregnancies. Chemical pregnancies were not included in abortion rate. A maximum of two treatment cycles per patient were planned. The primary outcome measure was frequency of pregnancy per cycle.

### Data analysis

Data analysis was performed with statistical software (Statistical Package for Social Sciences, version 11.5). Normality was evaluated with Shapiro-Wilk test. Results were reported as median (range, minimum to maximum) or number (percent). Comparisons between groups were made with Mann-Whitney test for continuous data and Fisher exact test or Yates or Pearson  $\chi^2$  test (chi-square test) for categorical data. Odds ratios with 95% confidence intervals were calculated for frequency of pregnancy. Statistical significance was defined by  $p \leq 0.05$ .

## Results

The study groups were similar in age, body mass index, duration of infertility, frequency of previous unsuccessful assisted reproduction treatment, number of cycles, and number of follicles  $\geq 18$  mm (Table 1). Median endometrial thickness was significantly greater in the patients who were treated with hydrotubation and clomiphene than those treated with clomiphene citrate alone (Table 1).

There were 15 pregnancies that occurred in the 80 patients (19%) (total, 144 stimulated cycles; 10% pregnancies per cycle) (Table 2). In four patients who had hydrotubation and clomiphene citrate and two patients who

Table 1. — *Clinical characteristics of patients who were treated for unexplained infertility.\**

	Hydrotubation and clomiphene citrate	Clomiphene citrate alone	$p \leq \dagger$
No. patients	40	40	
No. cycles	70	74	
Age (y)	22.5 (19 to 32)	24 (18 to 32)	NS
Body mass index (kg/m <sup>2</sup> )	23.8 (22.4 to 27.3)	24 (22.4 to 26.4)	NS
Duration of infertility (y)	3.3 (2 to 5.8)	3.5 (2.1 to 5.7)	NS
Patients who had previous unsuccessful assisted reproduction treatment	16 (40)	17 (43)	NS
No. cycles	2 (1 to 2)	2 (1 to 2)	NS
No. follicles per cycle ≥ 18 mm	1 (1 to 2)	1 (1 to 2)	NS
Endometrial thickness (mm)	8 (6 to 11)	7 (5 to 10)	0.02

\* Data reported as number, median (range, minimum to maximum), or number (%)  
 † NS, not significant ( $p > 0.05$ )

had clomiphene citrate alone, pregnancy occurred in the first cycle. The frequency of clinical pregnancy per cycle was significantly greater in patients who were treated with hydrotubation and clomiphene citrate than those treated with clomiphene citrate alone (Table 2). The frequency of total or chemical pregnancy per cycle was similar for the two treatment groups (Table 2).

The frequency of pregnancy per patient (total, clinical, or chemical) was similar for the two treatment groups (Table 3). The frequency of live birth or abortion per cycle or per patient was similar between the two groups (Tables 2 and 3). No multiple pregnancy occurred in either treatment group. In the patients who were treated with hydrotubation and clomiphene citrate, four patients (10%) experienced discomfort that began during hydrotubation and persisted approximately for 20 minutes. Vital signs were normal during and after hydrotubation, and there were no other complications. There was one patient in each group who developed mild ovarian hyperstimulation syndrome that resolved spontaneously without hospitalization. There was no ectopic pregnancy in either group.

## Discussion

The present study showed a significantly greater frequency of clinical pregnancy per cycle in patients who were treated with time-limited hydrotubation and clomiphene citrate than those treated with clomiphene citrate alone. Hydrotubation may increase the frequency of pregnancy by improving subtle problems of the fallopian tubes that may cause unexplained infertility [18]. The frequency of total pregnancy, chemical pregnancy, or live birth (per cycle or per patient) was not significantly altered by hydrotubation.

In a previous study, the frequency of pregnancy was not improved by hydrotubation with a large volume of saline

Table 2. — *Frequency of pregnancy per cycle in patients who were treated for unexplained infertility.\**

Variable	Hydrotubation and clomiphene citrate	Clomiphene citrate alone	95% Odds Ratio	Confidence Interval	$p \leq \dagger$
No. cycles	70	74			
Pregnancy per cycle					
Total	11 (16)	4 (5)	3.3	(1.0 to 10.8)	NS
Clinical	9 (13)	2 (3)	5.3	(1.1 to 25.5)	0.05
Chemical	2 (3)	2 (3)	1.1	(0.2 to 7.7)	NS
Live birth	8 (11)	2 (3)	4.7	(1.0 to 22.7)	NS
Abortion	1 (0)	0 (0)	-	-	NS

\* Data reported as number (%); † NS, not significant ( $p > 0.05$ )

Table 3. — *Frequency of pregnancy per patient in patients who were treated for unexplained infertility.\**

Variable	Hydrotubation and clomiphene citrate	Clomiphene citrate alone	95% Odds Ratio	Confidence Interval	$p \leq \dagger$
No. patients	40	40			
Pregnancy per patient					
Total	11 (27.5)	4 (10)	3.4	(1.0 to 11.9)	NS
Clinical	9 (22.4)	2 (5)	5.5	(1.1 to 27.4)	NS
Chemical	2 (5)	2 (5)	1.0	(0.1 to 7.5)	NS
First cycle	4 (10)	2 (5)	2.1	(0.4 to 12.2)	NS
Live birth	8 (20)	2 (5)	4.8	(0.9 to 24.0)	NS
Abortion	1 (0)	0 (0)	-	-	NS

\* Data reported as number (%); † NS, not significant ( $p > 0.05$ )

(50 ml) performed one day before intrauterine insemination [19]. However, hydrotubation with a solution that included an antibiotic, hyaluronidase, and a steroid (10 to 30 ml), performed during the proliferative phase of the menstrual cycle for three consecutive days, was associated with a high frequency of subsequent pregnancy (62.5% within three months) in patients who had unexplained infertility and normal hysterosalpingogram [20]. Possible explanations for this finding include a mechanical effect of hydrotubation, plug weakening by hyaluronidase, treatment of undiagnosed infection with antibiotics, and anti-inflammatory effects of steroids [20]. In addition, perturbation with dilute lidocaine in a balanced salt solution (10 to 20 ml), one day before intrauterine insemination, resulted in significant improvement in frequency of pregnancy (14.9% vs 3.2%) in women diagnosed with unexplained infertility, possibly because of the effect of lidocaine to reduce sperm phagocytosis [21, 25]. However, another study of hydrotubation with low dose lidocaine in saline (20 ml) or saline alone, one day before intrauterine insemination, showed similar clinical frequency of pregnancy with or without lidocaine (17.4% vs 11.2%) in patients with unexplained infertility [22]. A review of 11 randomized trials showed that

tubal flushing with oil soluble medium versus no intervention was associated with a significant increase in the frequency of pregnancy [23]. The beneficial effects of hydrotubation in women with unexplained infertility may be attributed to the mechanical force of flushing or pharmacologic effects of the various agents added to the hydrotubation solution.

The duration of flushing may be another important factor that may differ between the studies about hydrotubation. In previous studies, the flushing technique had not been standardized and was described qualitatively (slowly or steadily). The present study investigated time-limited hydrotubation (20 to 30 seconds) on frequency of pregnancy in women with unexplained infertility. Adequate mechanical force may be required to dislodge debris in the fallopian tubes, and this may necessitate sufficient flow velocity of saline in the tubes within a limited time. However, high flow velocity may cause intolerable adverse effects such as abdominal pain. Future study may define the maximum flow velocity that may be tolerated during hydrotubation.

## Conclusion

Time-limited hydrotubation and clomiphene citrate may increase the frequency of clinical pregnancy per cycle in women who have unexplained infertility. Hydrotubation was well tolerated and there were no complications. Limitations of the present study include the small sample size, which may have limited the potential to demonstrate other significant differences in results between the two treatment groups. The present study provides justification for future larger randomized trials to further investigate time-limited hydrotubation in women with unexplained infertility and to define the optimal volume and ejection velocity of solution during the procedure.

## References

- [1] [No authors listed]: "Infertility revisited: the state of the art today and tomorrow. The ESHRE Capri Workshop. European Society for Human Reproduction and Embryology". *Hum. Reprod.*, 1996, 11, 1779.
- [2] Fatum M., Laufer N., Simon A.: "Investigation of the infertile couple: should diagnostic laparoscopy be performed after normal hysterosalpingography in treating infertility suspected to be of unknown origin?" *Hum. Reprod.*, 2002, 17, 1.
- [3] Badawy A., Khiary M., Ragab A., Hassan M., Sherif L.: "Laparoscopy - or not - for management of unexplained infertility". *J. Obstet. Gynaecol.*, 2010, 30, 712.
- [4] Hatasaka H.: "New perspectives for unexplained infertility". *Clin. Obstet. Gynecol.*, 2011, 54, 727.
- [5] Khan K.S., Chien P.F.: "Evaluation of a clinical test. I: assessment of reliability". *BJOG*, 2001, 108, 562.
- [6] Chien P.F., Khan K.S.: "Evaluation of a clinical test. II: Assessment of validity". *BJOG*, 2001, 108, 568.
- [7] Gubbini G., Tabanelli C., Orlandi C., Bazzocchi G., Lanfranchi As-suero G.: "A method for evaluating human tubal motility in vivo: a new approach for infertility investigation". *Acta Eur. Fertil.*, 1991, 22, 315.
- [8] Mastrianni L. Jr.: "The fallopian tube and reproductive health". *J. Pediatr. Adolesc. Gynecol.*, 1999, 12, 121.
- [9] Rocker I.: "The anatomy of the utero-tubal junction area". *Proc. R. Soc. Med.*, 1964, 57, 707.
- [10] Sweeney W.J.: "The interstitial portion of the uterine tube-its gross anatomy, course and length". *Obstet. Gynecol.*, 1962, 19, 3.
- [11] Lisa J.R., Gioia J.D., Rubin I.C.: "Observations on the interstitial portion of the fallopian tube". *Surg. Gynecol. Obstet.*, 1954, 92, 159.
- [12] Ström C., Dahlström A., Lindblom B., Ahlman H.: "Effects of intraluminal administration of adrenoceptor agonists on transisthmic flow in the rabbit oviduct". *Biol. Reprod.*, 1983, 29, 295.
- [13] Korenaga M., Kadota T.: "Changes in mechanical properties of the circular muscle of the isthmus of the human fallopian tube in relation to hormonal domination and postovulatory time". *Fertil. Steril.*, 1981, 36, 343.
- [14] Lyons R.A., Djahanbakhch O., Mahmood T., Saridogan E., Sattar S., Sheaff M.T., et al.: "Fallopian tube ciliary beat frequency in relation to the stage of menstrual cycle and anatomical site". *Hum. Reprod.*, 2002, 17, 584.
- [15] Crow J., Amso N.N., Lewin J., Shaw R.W.: "Morphology and ultra-structure of fallopian tube epithelium at different stages of the menstrual cycle and menopause". *Hum. Reprod.*, 1994, 9, 2224.
- [16] Leeton J., Selwood T.: "The tortuous tube: pregnancy rate following laparoscopy and hydrotubation". *Aust. N. Z. J. Obstet. Gynaecol.*, 1978, 18, 259.
- [17] Sulak P.J., Letterie G.S., Coddington C.C., Hayslip C.C., Woodward J.E., Klein T.A.: "Histology of proximal tubal occlusion". *Fertil. Steril.*, 1987, 48, 437.
- [18] Rasmussen F., Lindequist S., Larsen C., Justesen P.: "Therapeutic effect of hysterosalpingography: oil- versus water-soluble contrast media - a randomized prospective study". *Radiology*, 1991, 179, 75.
- [19] Aboulghar M.A., Mourad L.M., Al-Inany H.G., Aboulghar M.M., Mansour R.T., Serour G.A.: "Prospective randomized study for hydrotubation versus no hydrotubation before intrauterine insemination in unexplained infertility". *Reprod. Biomed. Online*, 2010, 20, 543.
- [20] Saini P., Kumar A.: "Pretreatment with hydrotubation in infertility management improves pregnancy rates". *International Congress Series*, 2004, 1271, 11.
- [21] Edelstam G.A., Andersson E., Rådestad A., Flam F., Gottlieb C.: "The effect of lignocaine on sperm phagocytosis in the peritoneal fluid from women with or without endometriosis". *Hum. Reprod.*, 1998, 13, 1353.
- [22] Morad A.W., Abdelhamid A.A.: "Prospective randomized study for hydrotubation with or without lidocaine before intrauterine insemination in unexplained infertility". *Middle East Fertility Society Journal*, 2012, 17, 250.
- [23] Johnson N., Vandekerckhove P., Watson A., Lilford R., Harada T., Hughes E.: "Tubal flushing for subfertility". *Cochrane Database Syst. Rev.*, 2005, 2, CD003718.
- [24] World Medical Association: "Declaration of Helsinki: ethical principles for medical research involving human subjects". 59<sup>th</sup> WMA General Assembly, Seoul, October 2008. Available at: <http://www.wma.net/en/30publications/10policies/b3/> Accessed August 17, 2012.
- [25] Edelstam G., Sjösten A., Bjuresten K., Ek I., Wänggren K., Spira J.: "A new rapid and effective method for treatment of unexplained infertility". *Hum. Reprod.*, 2008, 23, 852.

Address reprint requests to:  
I. BAHRI DELIBAS, M.D.  
Yeni mahalle, Namik Kemal Caddesi  
Gokkusagi apt. C blok, No: 4  
Osmançik, Corum (Turkey)  
e-mail: delibashi@hotmail.com