The Effect of Hydrosalpinges on IVF-ET Outcome

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Purpose: Our purpose was to determine if the presence of a hydrosalpinx effects the outcome of in vitro fertilization (IVF)–embryo transfer.

Methods: We performed a retrospective analysis of IVF cycle stimulation sheets.

Results: A total of 1000 patients with tubal factor infertility was analyzed. There were 60 hydrosalpinx patients who underwent 116 initiated cycles with 106 embryo transfers, compared to 940 control patients undergoing 1428 initiated cycles with 1150 embryo transfers. Both groups had a similar response to ovarian stimulation, number of oocytes retrieved, and number of embryos transferred. The hydrosalpinx group had a significantly higher preclinical loss rate ($22/59 = 37\%$ vs $80/566 = 14\%$; $P = 0.001$), a significantly lower implantation rate ($55/352 = 16\%$ vs $795/3795 = 21\%$; $P = 0.013$), a trend toward a reduced delivery rate per transfer ($28/106 = 26\%$ vs $387/1150 = 34\%$; $P = 0.066$), a significantly higher ectopic pregnancy rate ($5/59 = 8\%$ vs $16/566 = 3\%$; $P = 0.04$), and a similar spontaneous abortion rate ($9/37 = 24\%$ vs $99/486 = 20\%$; $P = 0.28$) compared to the control tubal factor group.

Conclusions: This study demonstrates a decrease in implantation rates and an increase in preclinical miscarriages and ectopic pregnancies in patients with hydrosalpinges compared to tubal-factor patients without sonographic evidence of dilated fallopian tubes.

KEY WORDS: hydrosalpinx; in vitro fertilization; ectopic pregnancy; implantation.

INTRODUCTION

Although in vitro fertilization–embryo transfer (IVF-ET) was initially developed to overcome intractable

tubal disease or the absence of fallopian tubes (1), it has evolved into a therapeutic modality for almost all forms of infertility. Consequently, the number of assisted reproductive centers has greatly increased since the late 1970s and early 1980s, with approximately 250 centers initiating almost 40,000 cycles according to 1994 data from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology (2). With this rapidly expanding experience, it has become evident that a number of factors are involved in determining a couple's chance of success undergoing IVF-ET. Some of these factors include the age and ovarian reserve of the female patient (3) as well as the associated infertility factor(s) (4). Recently, a number of retrospective studies (5–13) have suggested that tubal-factor infertility is not a single entity, and the subgroup of patients with hydrosalpinges has a worse prognosis. Some have even suggested that extirpation of the diseased tubes may improve implantation and pregnancy rates (8,13). Therefore, the purpose of this study was to assess the significance of a hydrosalpinx noted on a baseline ultrasound at the initiation of an IVF-ET cycle on reproductive outcome.

MATERIALS AND METHODS

A computer search of patients under the age of 40 undergoing IVF at The Center for Reproductive Medicine and Infertility, The New York Hospital–Cornell Medical Center, between January 1989 to December 1995 for the primary diagnosis of tubal-factor infertility was conducted. One thousand patients met these criteria. The stimulation sheets of these patients were reviewed, and 60 patients were noted to have a unilateral or bilateral cystic structure consistent with a hydrosalpinx on their baseline transvaginal ultrasound in all cycles. Seven of these patients were noted to have bilateral cystic structures. A hydrosal-

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pinx was defined sonographically as a tubular-shaped anechoic structure separate from the ovary (14). Ultrasounds were performed by the physicians of The Center for Reproductive Medicine and Infertility utilizing the above criteria. The control group then consisted of all the tubal-factor infertility patients without sonographic evidence of a hydrosalpinx.

The procedure for our assisted reproductive program has been described previously (3,15). Briefly, a variety of controlled ovarian stimulation protocols (long and short leuprolide acetate plus gonadotropins and clomiphene citrate plus gonadotropins) was implemented based on the patient's previous response to ovarian stimulation, age, and day 3 hormonal status. Follicular maturation was monitored by estradiol levels and transvaginal ultrasounds on a regular basis. Human chorionic gonadotropin (hCG; 5000–10,000 IU) was administered when at least two follicles reached a mean diameter of ≥ 17 mm, followed by transvaginal oocyte retrieval 35 hr later. Conventional in vitro insemination or microsurgical insemination occurred based on appropriate indications (15). Preembryos were then transferred transcervically back to the patient 72 hr after retrieval.

A positive pregnancy was defined by a β -hCG level >5 mIU/ml (first IRP, 75/537) 10 days post embryo transfer on two separate occasions. Biochemical pregnancies were defined as a positive pregnancy test without evidence of fetal heart activity or a gestational sac. Clinical pregnancies included only those patients with a gestational sac and fetal heartbeat visualized on ultrasound. Implantation rate was defined as the number of sacs with a fetal heartbeat by cycle day 49 divided by the number of embryos transferred. Spontaneous abortion rate included those losses occurring before 20 weeks' gestational age.

The study and control groups were compared with regard to age, ovarian stimulation response, number of oocytes retrieved and fertilized, and preembryos

transferred as well as clinical outcome. Student's *t* test was used for the comparison of means and the binomial proportions test was used to compare rates. A *P* value <0.05 was considered significant.

RESULTS

The hydrosalpinx patients tended to be younger than the nonhydrosalpinx patients (34 ± 3.0 vs 35 ± 3.4 ; $P = 0.01$). The 60 hydrosalpinx patients underwent 116 initiated cycles with 106 embryo transfers, compared to 940 control patients undergoing 1428 initiated cycles with 1150 embryo transfers. Both groups had a similar response to ovarian stimulation as demonstrated by estradiol level on the day of hCG (control, 1340 ± 832 pg/ml, vs hydrosalpinx, 1358 ± 730 pg/ml). There was also no significant difference between the control and the hydrosalpinx groups in the mean number of oocytes retrieved (10.4 ± 6.5 vs 10.8 ± 5.7) and fertilized (7.0 ± 4.8 vs 6.8 ± 4.1) and the mean number of preembryos transferred (3.3 ± 0.9 vs 3.3 ± 1) (Table I). Microsurgical insemination was performed on 107 of 1428 (7.49%) of the control patients, compared to none of the hydrosalpinx patients.

The clinical outcomes are shown in Table II. There were 566 positive pregnancies in the control group, of which 486 had a documented gestational sac with fetal cardiac activity noted on transvaginal ultrasound. The hydrosalpinx study group contained 59 positive pregnancies, with 37 clinical pregnancies. The preclinical loss rate was significantly higher in the hydrosalpinx patients compared to the control tubal factor group ($22/59 = 37\%$ vs $80/566 = 14\%$; $P = 0.001$). The implantation rate of the hydrosalpinx patients was significantly lower than that of the control group ($55/352 = 16\%$ vs $795/3795 = 21\%$; $P = 0.013$). Although not statistically significant, there was a trend toward

Table I. Comparison of Control and Hydrosalpinx IVF Cycles

	Control	Hydrosalpinx	<i>P</i> values ^a
No. patients	940	60	
Age	35 ± 3.4	34 ± 3.0	0.01
No. cycles	1428	116	
No. transfers	1150	106	
No. oocytes	10.4 ± 6.5	10.8 ± 5.7	NS
No. fertilized	7.0 ± 4.8	6.8 ± 4.1	NS
Peak estradiol	$1304 \text{ pg/ml} \pm 832$	$1358 \text{ pg/ml} \pm 730$	NS
No. embryos transferred	3795	352	
Mean No. embryos transferred	3.3 ± 0.9	3.3 ± 1.0	NS

^a Student's *t* test.

Table II. Clinical Outcome of the Control and Hydrosalpinx Groups

	Control	Hydrosalpinx	P value ^a
Pregnancies	566	59	
Clinical pregnancies	486	37	
Preclinical loss rate	0.14	0.37	0.001
Ectopics	16	5	
Deliveries	387	28	
No. sacs	795	55	
Implantation rate	0.21	0.16	0.013
Deliveries/transfer	0.34	0.26	0.066
Abortion rate	0.20	0.24	0.28
Ectopic rate	0.03	0.08	0.04

^a Binomial proportions test.

a reduced delivery rate per transfer in the hydrosalpinx patients ($28/106 = 26\%$ vs $387/1150 = 34\%$; $P = 0.066$). Also, there was a significantly higher ectopic pregnancy rate in the hydrosalpinx group compared to the control group ($5/59 = 8\%$ vs $16/566 = 3\%$; $P = 0.04$). The spontaneous abortion rate was similar between the two groups (hydrosalpinx $9/37 = 24\%$ vs control $99/486 = 20\%$; $P = 0.28$)

DISCUSSION

With the increasing prevalence of pelvic infections (16), tubal-factor infertility represents one of the most common etiologies for patients presenting for infertility and assisted reproductive therapy. Counseling patients with regard to their prognosis of a live birth after IVF-ET depends on many factors including age, ovarian reserve, infertility factors (3, 4), and center specific success rates. Our retrospective study suggests that patients with tubal-factor infertility represent a heterogeneous group and those with dilated tubes at the onset of their IVF cycle have a significant reduction of implantation rates and an increased rate of preclinical abortions and ectopic pregnancies.

Our study is consistent with the growing body of literature suggesting that the presence of a hydrosalpinx has a significantly negative impact on IVF-ET implantation and/or delivery rates (5–13). The majority of previously published reports have identified their hydrosalpinx population based on hysterosalpingogram or operative assessment (laparoscopy or laparotomy) (5,6,8–13) prior to the initiation of the IVF-ET treatment cycle. In our study we have included only those patients with sonographic evidence of unilateral or bilaterally dilated tubes on their baseline ultrasound proximate to ovarian stimulation and compared their

outcome to that of tubal-factor patients without these sonographic findings. Since other, more sensitive methods of detecting hydrosalpinges (hysterosalpingogram or laparoscopy) were not specifically used in this study, the overall number of patients with hydrosalpinges is probably underreported. The hydrosalpinx patients had a significantly reduced implantation rate and a trend toward a reduced delivery rate compared to the control group. This is similar to a study in 1994 which included 62 patients treated in 104 cycles with a dilated tube(s) on cycle day 2 compared to 741 tubal-factor patients without sonographic evidence of a dilated tube(s) who had 1190 oocyte retrievals. They also noted a significant reduction in implantation, pregnancy, and delivery rates in the hydrosalpinx patients (7).

In addition to a reduction in the implantation efficiency, we noted an increase in extrauterine pregnancies occurring in the hydrosalpinx patients compared to the control tubal-factor patients. This was not surprising, since a previous study published by our group in 1994 demonstrated that 85.7% of all ectopic pregnancies resulting from IVF-ET were in patients with tubal disease (17). Although an early study by Martinez and Trounson (18) could not identify specific risk factors associated with the occurrence of ectopic pregnancies in patients undergoing IVF-ET, other studies (19,20) have demonstrated a significant increase in ectopic pregnancy related to preexisting tubal pathology.

A number of observations and in vitro studies have provided theories in an attempt to explain the mechanism by which hydrosalpinges may cause a negative impact on IVF-ET outcome. Case reports have demonstrated that during ovulation induction hydrosalpinges can enlarge, with the ensuing accumulation of fluid in the uterine cavity (21,22,23). Concerns that this fluid may hinder implantation have resulted in both transcervical uterine aspiration (22) and transvaginal hydrosalpinx drainage prior to ET (23). The composition of this fluid has been shown to contain low levels of protein and bicarbonate, which may alter embryo growth (24). Meyer *et al.* (25) demonstrated that patients with hydrosalpinges had a decreased expression of $\alpha\beta 3$ integrin, which may cause a decrease in endometrial receptivity. Also, recent in vitro experiments culturing murine embryos in hydrosalpinx fluid have demonstrated increased fragmentation and degeneration and decreased rates of blastulation, consistent with a direct toxic effect on embryogenesis (26,27).

We have also demonstrated a preclinical loss rate in the tubal infertility patients with a hydrosalpinx that is more than twice that of tubal infertility patients

without hydrosalpinges. A recent report has demonstrated that women with hydrosalpinges have a higher incidence of antibodies to chlamydial heat shock protein (HSP) 10 compared to tubal-factor infertility patients without hydrosalpinges (28). Since HSPs are expressed in the early developing embryo, and antibodies to this protein have been correlated with a negative impact on IVF outcome (29), this may be one mechanism to explain the increased preclinical loss rate.

This study demonstrates a decrease in implantation rates and an increase in preclinical miscarriages and ectopic pregnancies in patients with hydrosalpinges compared to tubal-factor patients without sonographic evidence of dilated fallopian tubes. Although some retrospective studies (8,13) have suggested that removal of dilated fallopian tubes improved subsequent IVF success, these studies are inherently difficult in determining causation. Patients currently are counseled as to the potential deleterious effect that a hydrosalpinx may have on IVF outcome. In those patients with repeat failures of IVF success, without an identifiable cause, a salpingectomy is recommended. This therapeutic dilemma awaits a prospective randomized study to assess accurately the impact of hydrosalpinges on IVF outcome.

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