The Presence of Hydrosalpinx May Not Adversely Affect the Implantation and Pregnancy Rates in In Vitro Fertilization Treatment¹

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Purpose: To evaluate the effects of hydrosalpinx on the outcome of in vitro fertilization (IVF) treatment, a retrospective study was undertaken at a tertiary referral center for infertility.

Methods: Results of the first IVF treatment cycles in 144 patients from 1 January 1993 to 31 December 1995, who had tubal infertility only and were less than 38 years old, were reviewed. The duration/dosage of hMG used, serum estradiol level on the day of hCG, number of oocytes aspirated and fertilized, number of embryos replaced, implantation rate, clinical pregnancy rate, and pregnancy outcome were compared in patients with and without hydrosalpinx.

Results: The mean implantation rate and clinical pregnancy rate were similar in patients with or without hydrosalpinx. Both groups had similar ovarian responses and fertilization rates. There was no increase in clinical abortion in the hydrosalpinx group but ectopic pregnancies were more common in patients with hydrosalpinx.

Conclusions: The presence of hydrosalpinx did not adversely affect the implantation and pregnancy rates in in vitro fertilization treatment when the results of the first cycle were compared. However, it can lead to a higher incidence of ectopic pregnancies.

KEY WORDS: clinical pregnancy; ectopic pregnancy; hydrosalpinx; implantation; in vitro fertilization/embryo transfer.

INTRODUCTION

In vitro fertilization and embryo transfer (IVF/ET) were first used to treat an infertile woman with severe

tubal damage (1). Tubal infertility remains the most common indication for IVF/ET in many assisted reproduction programs. Fallopian tubes can be damaged by a number of causes, and this can lead to tubal blockage such as proximal obstruction or distal obstruction with or without the formation of hydrosalpinx. It has been assumed for a long time that when the damaged tubes can be bypassed by IVF/ET treatment, the resulting pregnancy rate should approach that of the normal population (2).

IVF/ET treatment in women with tubal infertility is known to be associated with an increased risk of ectopic pregnancy and postaspiration infection (3). Several recent reports (4–8) showed that the presence of hydrosalpinx significantly impaired implantation and the pregnancy rate. The early miscarriage rate was also increased. Some studies (9), however, did not demonstrate any effect.

MATERIALS AND METHODS

To evaluate the effects of hydrosalpinx on the outcome of IVF treatment, a retrospective study of women attending the Assisted Reproduction Unit at the Department of Obstetrics & Gynaecology, Queen Mary Hospital, Hong Kong, for IVF/ET treatment from 1 January 1993 to 31 December 1995 was undertaken.

Couples had to fulfill the following criteria before they were included in this study so as to control for all confounding factors to the greatest extent possible.

- (1) The only cause of infertility was the presence of tuboperitoneal factors. The women had regular

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menstrual cycles and normal FSH levels in the early follicular phase, i.e., <10 IU/L. The men had at least two normal semen analyses according to the WHO criteria (1992).

- (2) The women were less than 38 years old because after that the pregnancy rate is significantly reduced with increasing age.
- (3) The first IVF/ET cycle was used to assess the outcome of this treatment method, as fewer fertile couples, for unknown reasons, might require repeated attempts and will be overrepresented in pooled data of all IVF cycles carried out for tubal infertility within a certain period (8).

Before the couples were enrolled in our IVF program, they underwent a standard protocol of investigations including conventional semen analysis on at least two occasions and hormonal assays of the women (early follicular FSH level on day 2 of the menstrual cycle). Tubal patency was checked by diagnostic laparoscopy and hysteroscopy and a hysterosalpingogram might also have been done before the patient was referred to our program. The presence of hydrosalpinx was confirmed if (a) on laparoscopy the fimbrial end of the tube was occluded with abnormal distention of the ampullary portion of the tube or (b) on hysterosalpingography there was only filling and distention of the ampullary region, and no spillage of dye into the peritoneal cavity through the tube on that side. Some of the cases were confirmed by laparotomy alone. The size of the hydrosalpinx was not recorded.

Buserelin nasal spray (Hoechst, Frankfurt, Germany), 150 μ g four times a day, was started from day 21 of the menstrual cycle preceding the treatment cycle to downregulate the pituitary before ovarian stimulation. Transvaginal scanning and measurement of serum estradiol level were performed on day 2 of next cycle. Pituitary downregulation was confirmed when there were no ovarian follicles >10 mm in diameter on scanning and the day 2 serum estradiol was <220 pM. Human menopausal gonadotropin (hMG; Pergonal, Serono, Switzerland) was then given, 4 ampoules for the first 2 days and 2 ampoules daily afterward. Monitoring by serum estradiol level was started after 5 days of hMG injections and repeated every 2–3 days. The dosage of hMG was titrated accordingly. Transvaginal ultrasound was performed when the serum estradiol level reached above 3000–4000 pM. hMG injection was discontinued and human chorionic gonadotropin (hCG; Profasi, Serono, Switzerland), 10,000 IU, was administered when the leading follicle reached 18 mm in diameter and there were at least three follicles >15

mm in diameter. Oocyte retrieval under transvaginal ultrasound guidance was performed 38 hr after hCG administration and a maximum of three embryos was replaced into the uterine cavity 48 hr after retrieval. Excess embryos were frozen for subsequent transfer if the woman was not pregnant in that cycle. Cryopreservation of all embryos was considered when the serum estradiol level on the day of ovulatory hCG injection exceeded 30,000 pM.

The luteal phase was supported by hCG injections, 1500 IU on the day of embryo transfer and 6 days after ET. Progesterone suppositories (Cyclogest, 400 mgbid; Cox Pharmaceuticals) were given instead from the day of ET for a week when the serum estradiol level on the day of ovulatory hCG was above 18,000 pM. A urine pregnancy test was done 16 days after ET. If it was positive, ultrasound examination was performed 10–14 days later to confirm intrauterine pregnancy and count the number of gestation sacs present.

The fertilization rate was defined as the proportion of oocytes resulting in the formation of two pronuclei. Clinical pregnancy was defined by the presence of one or more gestation sacs, including ectopic pregnancy or the demonstration of gestational product in the uterine evacuate.

The women's age, the proportion of primary infertility, the duration of infertility, the ovarian response (duration and dosage of hMG used and serum estradiol level on the day of hCG), the number of oocytes aspirated and fertilized, the number of embryos replaced, the implantation rate, and the clinical pregnancy rate were compared between patients with and patients without hydrosalpinx. As most of the data were not normally distributed, they are represented as median (range). Statistical tests were carried out by the Mann–Whitney test, the chi-square test, Fisher's exact test, and the two-tailed Student's *t* test, when appropriate. A *P* value of <0.05 was taken as significant.

RESULTS

Only 144 patients with tubal infertility were identified, and 43 patients (30%) were further complicated by the presence of hydrosalpinx: 18 unilateral and 25 bilateral. The median age of the women was 33 years (range, 20–38 years) and the median duration of infertility was 4.5 years (range, 1–14 years). There were 41 ET cycles in the hydrosalpinx group because two patients had cryopreservation of all embryos for transfer later to reduce the risk of ovarian hyperstimulation

syndrome (serum estradiol level on the day of hCG injection $>30,000$ pM). The nonhydrosalpinx group had 92 transfer cycles, as seven patients had cryopreservation of all embryos and two had an absence of fertilization.

The results are summarized in Table I. The hydrosalpinx group had a significantly longer duration of infertility compared with the nonhydrosalpinx group (5 vs 4 years; $P = 0.02$, χ^2 test). There were no significant differences between these two groups in the woman's age, the proportion of primary infertility, the duration/dosage of hMG used, the serum estradiol level on the day of hCG, the number of oocytes obtained, the median fertilization rate, and the mean number of embryos transferred. The mean implantation rate and clinical pregnancy rate were similar in patients with and without hydrosalpinx. There was no increase in clinical abortion in the hydrosalpinx group. The other significant difference between the two groups was the number of ectopic pregnancy. Three ectopic pregnancies were found in the hydrosalpinx group, whereas there was no ectopic pregnancy in the nonhydrosalpinx group ($P = 0.03$, Fisher's exact test).

DISCUSSION

Aboulghar *et al.* (10) first demonstrated that transvaginal ultrasound needle-guided aspiration of pelvic inflammatory cystic masses before ovulation induction for IVF resulted in a significant increase in the average number of oocytes retrieved and thus the embryos per transfer compared with the control group. However, the difference in the pregnancy rate between the two groups was not statistically significant, probably because of the small sample size. Both Mansour *et al.* (11) and Russell *et al.* (12) reported the therapeutic use of transvaginal ultrasound to aspirate the hydrosalpinges before ovarian stimulation.

Andersen *et al.* (4) and Strandell *et al.* (6) retrospectively showed that the presence of hydrosalpinx in IVF/ET was associated with a significant reduction in the implantation and pregnancy rates and a significant increase in early pregnancy loss. Similar findings were also reported by Kassabji *et al.* (5), Vandromme *et al.* (7), and Fleming and Hull (8). A similar trend was also demonstrated in frozen-thawed embryo transfer cycles (6). In contrast to those shown by Aboulghar *et*

Table I. Summary of Results Between Patients with and Patients Without Hydrosalpinx in the First IVF Treatment Cycle

	With hydrosalpinx (<i>n</i> = 43)	Without hydrosalpinx (<i>n</i> = 101)	<i>P</i> value
Age (yr) ^a	32.0 (20–36)	33.0 (25–38)	0.10 ^b
1°/2° infertility	27/16	59/42	0.62 ^c
Duration of infertility (yr) ^a	5.0 (2–13)	4.0 (1–14)	0.02 ^{b,d}
hMG duration (days) ^a	10.0 (7–20)	10.0 (7–21)	0.74 ^b
hMG dosage (ampoules) ^a	26.0 (20–88)	26.0 (18–156)	0.14 ^b
E ₂ on day of hCG (pM), mean (SE)	8183 (1136)	8217 (605)	0.98 ^e
Oocytes			
Total	401	1058	
Median (range)	7 (3–27)	8 (1–41)	0.26 ^b
Embryos			
Total	290	758	
Median (range)	6 (1–19)	7 (0–27)	0.63 ^b
Median fertilization rate (%)	78	75	0.65 ^b
Transfer cycle	41	92	
Embryos transferred			
Total	117	263	
Mean $\pm$ SE	2.72 $\pm$ 0.12	2.60 $\pm$ 0.10	0.93 ^e
Clinical pregnancy (per ET%)	9 (22.0)	11 (12.0)	0.14 ^c
Clinical abortion	1	5	0.67 ^f
Ectopic pregnancy	3	0	0.03 ^{d,f}
Ongoing pregnancy	5	6	0.31 ^f
No. of gestational sacs	9	20	0.50 ^c
Mean implantation rate (%)	7.3	7.3	0.99 ^e
Babies delivered	6	9	0.26 ^c

^a Data are median (range).

^b Mann–Whitney test.

^c Chi-square test.

^d Statistically significant.

^e Two-tailed Student's *t* test.

^f Fisher's exact test.

al. (10), the numbers of oocytes retrieved and embryos transferred in the above studies were not found to be reduced in the presence of hydrosalpinx.

In this study, hydrosalpinx was diagnosed mainly by laparoscopy with or without hysterosalpingogram and was found to be present in 30% of patients who had a tuboperitoneal problem as the only identifiable cause of infertility. This figure was similar to that reported by Fleming and Hull (8). Both hydrosalpinx and nonhydrosalpinx groups had similar ovarian responses and fertilization rates. The hydrosalpinx group had a longer duration of infertility but there was no statistically significant difference in the implantation and clinical pregnancy rates between these two groups.

Therefore, this study did not demonstrate a negative effect of hydrosalpinx on IVF outcome, in contrast to other recent studies, which in general showed a 50% reduction in the implantation and pregnancy rates. The results of the first IVF cycle were compared in the present study to control the confounding variables. This may partly explain the difference in IVF outcome because those patients with poor prognostic factors might require repeated attempts and were overrepresented in the pooled data. Sharara *et al.* (9) could not confirm a negative effect of hydrosalpinx on IVF outcome when antibiotic treatment (doxycycline, 100 mg bid for 10 days) was given prior to the IVF cycle to patients with elevated titers of *Chlamydia trachomatis* IgG antibody. Chlamydial antibody was not checked in our assisted reproduction program.

Similar to this study, Fleming and Hull (8) evaluated the first cycle of embryo transfer after IVF and found that the presence of a hydrosalpinx halved the implantation rate. Other factors, e.g., the size of the hydrosalpinx, may affect the IVF outcome. Large hydrosalpinges were associated with the poorest outcome (6), but this was not supported by Andersen *et al.* (13). Tubal infertility is a heterogeneous group and includes patients with different grades of tubal damage resulting from different causes. High-grade tubal damage was found to be associated with a low success rate in an IVF program (14). Tuberculosis is relatively more common in Asian countries and its presence in the genital tract is associated with a lower clinical pregnancy rate per cycle compared with other tubal factor patients (15). Tuberculosis usually leads to tubal damage without the formation of hydrosalpinx and may lower the implantation rate of the group without hydrosalpinx in our population. The size of the hydrosalpinx and the extent and causes of tubal damage

were not recorded in detail. This may also lead to the different outcome in different studies.

Although the exact mechanisms remain speculative, there are several possible explanations suggested for the reported adverse effects of hydrosalpinx. As ovarian responses evidenced by the numbers of oocytes collected and thus embryos transferred are similar in patients with and without hydrosalpinx, the reduced implantation and pregnancy rates in the hydrosalpinx group suggest that the uterine environment may be rendered hostile to the embryos transferred. Fluid accumulation in the uterine cavity due to passage of some fluid from the hydrosalpinges can occasionally be recorded during transvaginal ultrasound monitoring for IVF cycles in patients with hydrosalpinges (11, 13). Even the presence of tiny amounts of fluid inside the uterine cavity may be harmful, as the ultramicroscopic pinopodes on the luminal surface of the endometrial epithelial cells are believed to have the function of extracting fluid from the microenvironment of the embryo to facilitate contact and implantation (16). The fluid may contain microorganisms, debris, toxins, cytokines, or prostaglandins, which can exert a detrimental effect on the receptivity of the endometrium (6) or on the developing embryos inside the uterus.

Another proposed mechanism is that the endometrium is also damaged at the same time that the tubes are acutely inflamed and damaged. This may have a permanent negative effect on implantation in the endometrium (6). Alteration in integrin expression has been reported (Lessey BA, Castelbaum AJ, Riben M, abstract). Endometrial biopsies obtained from asymptomatic women at risk of chlamydial infection showed evidence of chronic endometritis and were positive for *C. trachomatis* (17).

Mean levels of estradiol cytosolic and nuclear receptors and cytosolic progesterone receptors of a hydrosalpinx were found to be significantly lower than those of a normal fallopian tube (18). The decrease in the steroid receptor population of hydrosalpinx has been considered one of the factors leading to the poor intra-uterine pregnancy rate after salpingoneostomy. It is still not known whether the reduction in steroid receptors in hydrosalpinx will be associated with a similar reduction in the endometrium, and this may contribute to the negative effect of hydrosalpinx on IVF outcome.

It seems important to study the direct causes by which hydrosalpinx affects the implantation process, as the best treatment for IVF patients with hydrosalpinx has not yet been resolved. Because of the reported negative effects on success, various treatment options have been proposed. Transvaginal ultrasound has been

used to aspirate the hydrosalpinx prior to IVF cycles (10–12), but fluid could still be recollected after aspiration in the uterine cavity during treatment, complicating the embryo transfer procedure. Surgical treatments for hydrosalpinx result in a poor fertility outcome in natural conception, but they may help the prevention of fluid collection in the uterine cavity if they are performed before IVF cycles. Distal salpingostomy before IVF cycles may be useful as well but it may provide only temporary drainage of the hydrosalpinx. Two recent studies (5,19) reported that excision of hydrosalpinx significantly increased the pregnancy potential after IVF to rates comparable with those in women without hydrosalpinx.

It has been suggested that surgical excision of the tubes can be offered to those patients with hydrosalpinx prior to their first IVF cycle to optimize the chance of success (19). The results of this study could not support this approach as patients with or without hydrosalpinx had similar implantation and pregnancy rates in their first treatment cycle. Ectopic pregnancy was shown to be more common in patients with hydrosalpinx in the present study. The routine removal of both tubes before IVF treatment, however, was not shown to eliminate the occurrence of ectopic pregnancy (20).

We conclude that the presence of hydrosalpinx may not adversely affect the implantation and pregnancy rates in in vitro fertilization treatment but it can lead to a higher incidence of ectopic pregnancies. Further studies are needed to elucidate the exact mechanisms by which hydrosalpinx may impair the implantation and pregnancy rates and to find out the best treatment for IVF patients with hydrosalpinx, especially in those new cases prior to the first treatment cycle.

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