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Ovarian Response to Gonadotropin Stimulation in Repeated IVF Cycles After Unilateral Salpingectomy

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***Purpose*:** This study aimed to examine ovarian response to gonadotrpoin stimulation after repeated IVF treatment cycles in patients who underwent previous unilateral salpingectomy for tubal pregnancy.

***Methods*:** The study group included 26 patients who underwent unilateral salpingectomy for tubal pregnancy 1–9 years prior to starting IVF treatment. A control group of 52 patients with anatomically intact pelvis was treated during the same time period by ICSI. The two groups were matched for age, number of gonadotropin ampules, and length of stimulation. End point measurements included number of follicles, oocytes, and cleaved embryos in consecutive treatment cycles of each group.

***Results*:** There were 98 cycles in the study group and 154 cycles in the control group. The mean number of follicles, retrieved oocytes, and cleaved embryos were not different in the two groups, and no reductions in these parameters were noted up to 10 cycles of treatment. The mean number of follicles ipsilateral to the operated side was similar to the number of follicles of the contralateral ovary and was not different whether salpingectomy was by laparoscopy or laparotomy.

***Conclusions*:** Unilateral salpingectomy does not affect ipsilateral ovarian response to gonadotropin stimulation even after repeated IVF treatment cycles.

KEY WORDS: Gonadotropins; ovarian stimulation; salpingectomy.

INTRODUCTION

Two recent meta-analyses by Zeyneloglu *et al.* (1) and by Camus *et al.* (2) have suggested an association of a hydrosalpinx and reduced implantation rate and pregnancy loss after in vitro fertilization (IVF) treatment. Hence, salpingectomy under certain circumstances has been proposed as one of the treatment modalities for improving IVF and embryo transfer results in these patients (3). However, a possible adverse effect on ovarian response after salpingectomy due to severance of the common blood supply during the surgical procedure is of important concern (4). Romeu *et al.* (5) noted a significantly lower number of preovulatory follicles in patients after bilateral salpingectomy. Recently, Lass *et al.* (4) reported results of one IVF cycle in 29 patients who had undergone unilateral salpingectomy for tubal pregnancy and found significantly fewer follicles and retrieved oocytes on the operated side but no difference in the overall number of follicles and oocytes as compared with a control group. Other studies did not find a reduction in ovarian function after unilateral or bilateral salpingectomy, but these reports were limited to 1–3 IVF treatment cycles after surgery (6–8).

In this study we have investigated the ovarian response after salpingectomy in patients who underwent between 1 and 10 IVF treatment cycles.

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MATERIALS AND METHODS

From January 1997 to December 2000, there were 837 treatment cycles in 324 women in our unit of assisted reproductive technologies. During that period we identified 26 women who had unilateral salpingectomy for tubal pregnancy sometime before embarking on the IVF treatment. Fourteen salpingectomies were performed by laparotomy and 12 by laparoscopy 1–9 years prior to IVF treatment. No other pelvic surgery had been performed on these patients prior to or during the IVF treatment. Six patients (23.1%) had clinical signs of pelvic inflamatory disease at surgery such as pelvic adhesions (four patients) or a hydrosalpinx contralateral to the ectopic pregnancy (two patients).

Fifty-two women who were treated by intracytoplasmatic sperm injection (ICSI) and had no anatomical pelvic abnormalities served as a control group. Patients with polycystic ovaries imaged by a baseline ultrasound study were not included in the control group. Each patient in the study group was matched with two patients in the control group. Matching was done for age (±1 year), number of gonadotropin ampules (±3 ampules), days of gonadotropin administration (±1 day). Patients in both groups received ovarian stimulation using a long downregulation protocol by Buserilin (Suprefact nasal, Aventis Pharma, Netanya, Israel) as the GnRH-agonist and urinary gonadotropins. The treatment was monitored by serum estradiol concentrations measurments obtained 14 h after gonadotropin administration and by transvaginal ultrasonography assessment of follicular growth every 2–3 days. Human chorionic gonadotropin (hCG) trigger (5000–10000 IU) was administered when at least two follicles attained a mean diameter of 17–20 mm. Follicular number was counted for each ovary by ultrasonography on the hCG day. The number of oocytes was summed up for both ovaries. Fertilization was confirmed 18 h after IVF/ICSI, and embryos were transferred 2 or 3 days after fertilization. The main outcome measures in the study were number of follicles, number of oocytes, and number of cleaved embryos in consecutive treatment cycles in the study and control groups.

Statistics

With our sample size of 26 patients in the study group we assumed a difference of three follicles and three retrieved oocytes compared with the control group to be clinically significant, giving a power of 70%. Differences between groups were analyzed by Student's *t* test. Values were considered significantly different if P was < 0.05 with the use of a two-tailed test.

RESULTS

Ninety-eight cycles were considered in the study group and 154 cycles in the control group. The age range of the patients at the start of IVF treatment in the study and control groups was the same, 19–42 years. In 20 patients of the study group (76.9%) the time that had passed between the first and the last treatment cycles was 0–24 months; for 6 patients (23.1%) it was 24–48 months.

As shown in Table I, 12/26 patients in the study group (46.2%) had four or more treatment cycles. The mean ± SD age of the patients in the study and control groups at the start of the treatment and at the last treatment cycle was not different ($P > 0.1$). The duration of gonadotropin treatment and number of gonadotropin ampoules used per cycle was comparable in the study and control groups.

No difference was found between study and control groups in the following outcome measures

Table I. Baseline Characteristics and Stimulation Results of Patients in Study and Control Groups

	Study	Control	Statistical significance
Patients	26	52	
No. of treatment cycles	98	154	
No. of patients			
1–3 cycles	14	38	
4–6 cycles	9	11	
7–10 cycles	3	3	
Age at first cycle	32.1 ± 4.1	32.0 ± 5.1	ns
Age at last cycle	33.4 ± 4.5	36.5 ± 5.1	ns
Days of gonadotropin treatment	11.6 ± 3.1	10.8 ± 2.5	ns
No. of gonadotropin ampoules	30.1 ± 9.3	30.6 ± 9.1	ns
No. of follicles (two ovaries)	12.3 ± 6.4	13.1 ± 6.2	ns
Follicles ≥15 mm (two ovaries)	8.0 ± 5.1	8.1 ± 5.6	ns
hCG day estradiol (pMol/L)	5189 ± 3310	5631 ± 3512	ns
No. of oocytes (two ovaries)	8.6 ± 5.3	8.4 ± 4.9	ns
No. of cleaved embryos	5.5 ± 3.4	4.0 ± 2.3	ns

Note. Mean ± SD values were calculated as mean of individual mean. ns = not significant ($P > 0.1$) between study and control groups. pMol/L = picomol per liter.

investigated: mean number of follicles in both ovaries, mean number of follicles ≥15 mm in both ovaries, hCG day estradiol levels, mean number of oocytes retrieved from both ovaries and mean number of cleaved embryos (Table I). Importantly, the mean number of follicles on hCG day in the ovary on the side of salpingectomy was not different from that on the intact side 6.3 ± 3.2 and 6.2 ± 3.1, respectively ($P > 0.1$). Likewise, the mean number of follicles ≥15 mm was comparable between operated and intact sides 3.5 ± 2.3 and 4.2 ± 3.1, respectively ($P > 0.1$).

Analysis of the results according to the surgical procedure revealed that the mean number of follicles developing in the ovary ipsilateral to the removed tube did not differ whether the surgical procedure was a laparoscopy 7.3 ± 3.0 or a laparotomy 6.4 ± 2.3 ($P > 0.1$). Likewise, the total number of oocytes retrieved and number of cleaved embryos in patients who underwent laparoscopy, 8.8 ± 4.9 and 5.6 ± 3.5, respectively, was not different from those in patients who had a laparotomy, 8.6 ± 4.3 and 5.5 ± 4.0, respectively.

Figure 1 shows that no difference could be found in the number of developing follicles between the ovary ipsilateral and contralateral to the removed tube in consecutive treatment cycles and up to the 10th cycle.

Table II shows the mean number of follicles in both ovaries, mean number of oocytes retrieved, and mean number of cleaved embryos for each ordinal cycle in the study and control groups. It is of note that not only during the first 3 cycles but even from the 4th to the 10th cycle (34 cycles in the study group and 38 cycles in the control group) no statistical difference could be found in these parameters between the two groups. Furthermore, no reduction in these measurements was noted among each group from the first to the last treatment cycle.

DISCUSSION

Recent meta-analyses have suggested an association between hydrosalpinx and reduced implantation rate and pregnancy loss after IVF treatment (1,2). During the past few years there is an ongoing debate concerning the possible adverse effect of unilateral or bilateral hydrosalpings on IVF/ICSI success (9,10). Some consensus seems to emerge from recent studies concerning indications for salpingectomy while planning IVF/ICSI treatment in patients with a hydrosalpinx (11). A hydrosalpinx visible by ultrasonography at oocytes retrieval, especially if previous IVF cycles failed, may be accepted as a valid indication for salpingectomy (3). A relevant question may however be asked: Does salpingectomy have a deleterious impact on ovarian performance in subsequent IVF/ICSI cycles?

In our study the mean number of follicles developed in the ovary ipsilateral or contralateral to the removed tube was similar, 6.3 ± 3.2 and 6.2 ± 3.1, respectively. Moreover, no difference in follicular number was noted between the two ovaries even after repeated cycles. The above two findings taken together, and the finding that the mean follicular number and mean number of oocytes retrieved was not different in the study group and control group (Table I) suggests by

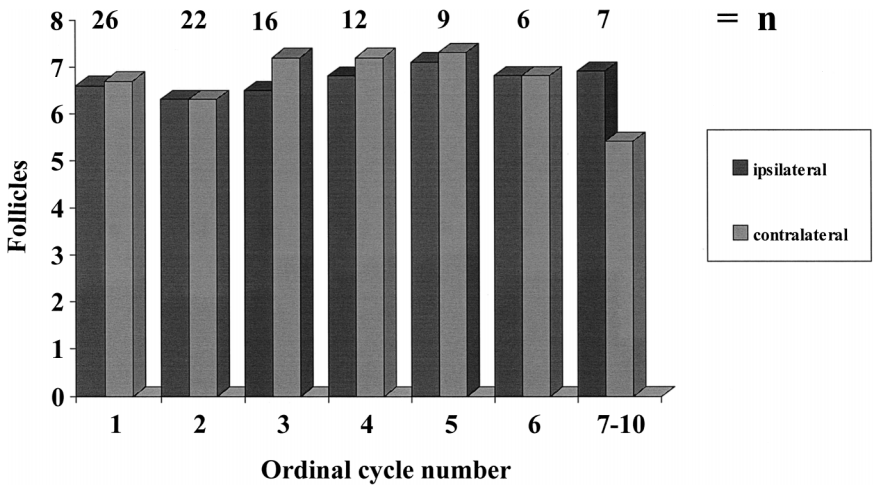

Fig. 1. Comparison of follicular number on hCG day in ovary ipsilateral (black bars) and contralateral (grey bars) to salpingectomy. n is the number of treatment cycles in each ordinal cycle number from 1 to 10.

Table II. Follicles, Oocytes, and Cleaved Embryos by Ordinal Cycle Number in Study and Control Groups

Ordinal cycle number	1	2	3	4	5	6	7–10	Statistical significance
No. of cycles study (98)	26	22	16	12	9	6	7	
No. of cycles control (154)	53	37	26	15	10	6	7	
No. of follicles								
Study	12.8 ± 4.1	12.4 ± 3.9	13.5 ± 4.5	14.0 ± 5.1	14.4 ± 4.7	13.6 ± 4.7	12.3 ± 4.1	ns
Control	13.1 ± 4.2	14.0 ± 4.8	12.6 ± 5.0	13.8 ± 4.6	12.2 ± 3.8	10.8 ± 3.5	12.4 ± 3.8	
No. of oocytes								
Study	9.1 ± 2.9	9.2 ± 2.8	8.7 ± 4.0	9.1 ± 3.7	7.4 ± 3.3	9.4 ± 3.2	5.1 ± 2.5	ns
Control	7.8 ± 2.4	8.0 ± 2.5	8.3 ± 3.5	8.0 ± 2.7	7.9 ± 4.1	10.2 ± 3.1	9.3 ± 3.1	
No. of embryos								
Study	5.5 ± 2.4	6.1 ± 3.1	5.0 ± 2.1	5.3 ± 2.0	4.4 ± 1.9	7.8 ± 2.9	4.1 ± 2.2	ns
Control	4.4 ± 1.8	4.4 ± 2.2	3.4 ± 1.8	7.3 ± 3.1	4.8 ± 2.5	4.4 ± 2.1	5.6 ± 2.9	

Note. ns = not significant ($P > 0.1$) between study and control groups and between each ordinal cycle and all others for follicular number, oocytes retrieved, and cleaved embryo in both study and control groups.

inference that the oocyte yield from each ovary was very close although only the total number of oocytes from both ovaries was counted.

Our control group comprised healthy women of couples who were referred for ICSI. In these women increased ovarian response to gonadotropins may be expected. However the lack of difference in mean follicular number and mean number of oocyte retrieved between the study and control groups suggests a reasonable case—control match. This may be due, in part, to the exclusion of patients with polycystic ovaries from the control group.

We are aware that assuming a difference of three follicles or three retrieved oocytes between the study group and control group (26 and 52 patients, respectively) is yielding a power of 70% to the statistics. However, for clinical significant difference of two follicles or two retrieved oocytes to give a power of 80%, a study group of 80 patients and a control group of 160 patients are needed.

Our results are consonant with other studies suggesting an undistinguished ovarian function after salpingectomy. Contrary to previous studies which examined ovarian response for only one to three cycles (3,6–8,12), we have studied up to 10 treatment cycles in our patients and did not observe a reduction in the mean number of follicles, oocytes, and cleaved embryos throughout the cycles. Verhulst *et al.* (6) examined 26 patients after bilateral salpingectomy in 67 cycles (2.6 cycles/patient) and compared them with a control group of 134 patients with intact pelvises. They observed a similar number of oocytes retrieved and a similar pregnancy rate/embryo transfer. Their conclusion was that bilateral salpingectomy had no detrimental effect on ovarian performance in IVF treatment. Ejdrup Bredkjaer *et al.* (12) evaluated 139 patients after salpingectomy for hydrosalpinx (21% unilateral and 79% bilateral) and observed a high implantation rate as well as a normal live birth rate for three cycles subsequent to surgical treatment. Strandell *et al.* (3) assessed in a prospective study the effect of a planned surgical removal of a hydrosalpinx (unilateral or bilateral) on IVF results. They found that the mean number of retrieved oocytes was 10.2,10.9, and 10.7 in patients with zero, one, or two tubes left in place demonstrating the preserved function of the ovary/ies on the operated side at least for one IVF cycle after surgery. Dar *et al.* (7) investigated ovarian response to stimulation in IVF in 26 patients who had salpingectomy for ectopic pregnancy by comparing cycles before and after the surgical procedure. They did not find a difference in the number of oocytes retrieved from the operated side before or after surgery and not from either ovary after salpingectomy. Embryonic quality was comparable before and after surgery. They conclude that laparoscopic salpingectomy does not abate ovarian response in the IVF cycle that follow the procedure. A recent study by Strandell *et al.* (8), which is related to a previous study (3), comparing ovarian function before and after unilateral or bilateral prophylactic salpingectomies prior to IVF, confirmed preservation of ovarian response to gonadotropins for at least two cycles after the operation.

The mechanism in which salpingectomy might cause reduced ovarian response is not clear. Animal studies have revealed fewer ovulations on the side of microsurgical fimbriectomy, in rats (13) and surgical division of the anatomical blood vessels between the ovary and the fimbria in rabbits (14).

Studies from the 1980s before the routine use of operative laparoscopy, reported adverse effects on

ovarian function following salpingectomy. Removal of the Fallopian tubes may have a detrimental effect on the ovarian arterial supply. The medial tubal artery, which is most important for supply of blood to the tube, has its origin at the same point as the median ovarian artery. Salpingectomy, not properly performed close to the tube, may disrupt the normal blood flow to the ovary. This may have a negative impact on steroid production and further follicular development. In our study we had an opportunity to compare ovarian function after salpingectomy by either laparotomy or laparoscopy in a small group of patients and no difference was found in the number of oocytes retrieved and embryos cleaved between patients operated by these two procedures.This is a sample size too small for any conclusions. We shall surely be able to learn more on ovarian function after laparoscopic salpingectomy in the future, since it is becoming the most frequent procedure for this purpose. In this respect the study by Strandel *et al.* (3) referred to above is supportive since after about 100 laparoscopic salpingectomies ovarian function was shown to be preserved.

Our results, showing preserved ovarian response after salpingectomy in patients with several IVF treatment cycles is encouraging. Admittedly the number of such cycles was limited (Table II) and this issue should be investigated in larger studies. Nevertheless, in patients with a damaged ovary or missing ovary (not an uncommon situation in women with severe pelvic disease) and in patients with known or suspected reduced ovarian reserve (age), proximal tubal clamping rather than salpingectomy should be considered for improving IVF results with the existence of a significant hydrosalpinx.

REFERENCES

1. Zeyneloglu HB, Arici A, Olive DL: Adverse effects of hydrosalpinx on pregnancy rates after in vitro fertilization–embryo transfer. Fertil Steril 1998;70(3):492–499
2. Camus E, Poncelet C, Goffinet F, Wainer B, Merlet F, Nisad I, Philippe HJ: Pregnancy rates after in-vitro fertilization in cases of tubal infertility with and without hydrosalpinx: A meta-analysis of published comparative studies. Hum Reprd 1999;14(5):1243–1249
3. Strandell A, Lindhard A, Valderstrom U, Thorborn J, Janson PO, Hamberger L: Hydrosalpinx and IVF outcome: A prospective, randomized multicenter trial in Scandinavia on salpingectomy prior to IVF. Hum Reprod 1999;14(11):2762–2769
4. Lass A, Ellenbogen A, Croucher C, Trew G, Margara R, Becattini C, Winston RML: Effect of salpingectomy on ovarian response to superovulation in an in vitro fertilization–embryo tranfer program. Fertil Steril 1998;70(6):1035–1038
5. Romeu A, Steingold K, Jones D, Acosta AA: Significance of bilateral salpingectomy in the outcome of IVF-ET (Abstract p159) Paper presented at fifth World Congress on In Vitro Fertilization and Embryo Transfer, April 5–10, 1987, Norfolk, VA
6. Verhulst G, Vandersteen N, Van Steirteghem AC, Devroey P: Bilateral salpingectomy does not compromise ovarian stimulation in an in-vitro fertilization/embryo transfer program. Hum Reprod 1994;9(4):624–628
7. Dar P, Sachs GS, Strassburger D, Bukovsky I, Arieli S: Ovarian function before and after salpingectomy in artificial reproductive technology patients. Hum Reprod 2000;15(1): 142–144
8. Strandell A, Lindhard A, Waldenstrom U, Thorburn J: Prophylactic salpingectomy does not impair the ovarian response in IVF treatment. Hum Reprod 2001;16(6):1135–1139
9. Lass A: What effect does hydrosalpinx have on assisted reproduction? What is the preferred treatment for hydrosalpinges? The ovary's perspective. Hum Reprod 1999;14(7):1674–1677
10. Puttemans P, Campo R, Gordts S, Brosens I: Hydrosalpinx and ART. Hydrosalpinx–functional surgery or salpingectomy? Hum Reprod 2000;15(7):1427–1430
11. Strandell A, Linhard A: Hydrosalpinx and ART: Salpingectomy prior to IVF can be recommended to a well-defined subgroup of patients. Hum Reprod 2000;15(10):2072–2074
12. Ejdrup Bredkjaer H, Ziebe S, Hamid B, Zhou Y, Loft A, Linhard A, Nyboe Andersen A: Delivery rates after in-vitro fertilization following bilateral salpingectomy due to hydrosalpinges: A case control study. Hum Reprod 1999;14(1):101–105
13. Beyth Y, Winston RML: Ovum capture and fertility following microsurgical fimbriectomy in the rabbit. Fertil Steril 1981;35(2):464–466
14. McComb P, Delbeke L: Decreasing the number of ovulations in the rabbit with surgical division of the blood vessels between the fallopian tube and ovary. J Reprod Med 1984;29(5):827–829