The Impact of Salpingectomy on Anti-Mullerian Hormone Levels and Ovarian Response of In Vitro Fertilization Patients

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ABSTRACT: **Background:** Laparoscopic salpingectomy is strongly related to successful in vitro fertilization (IVF) treatments.

Objectives: To compare the ovarian reserve, including anti-mullerian hormone (AMH) levels, in patients who underwent salpingectomy before IVF to IVF patients who had not been salpingectomized.

Methods: In this retrospective study, medical records of women who were treated by the IVF unit at our institute were reviewed. We retrieved demographic data, surgical details, and data regarding the ovarian reserve. Details of 35 patients who were treated by IVF after salpingectomy were compared to 70 IVF patients with no history of salpingectomy treatment. Nine women underwent IVF treatment before and after having salpingectomy, and their details were included in both groups.

Results: The levels of AMH, follicular stimulating hormone (FSH), estradiol, and progesterone were not significantly different in the groups. The antral follicular count (AFC), number of oocytes retrieved, amount of gonadotropin administered for ovarian stimulation, and number of embryos transferred (ET) were also not significantly different.

Conclusions: Salpingectomy does not seem to affect ovarian reserve in IVF patients.

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KEY WORDS: anti-mullerian hormone, assisted reproductive technology, infertility, ovarian function, salpingectomy

Laparoscopic salpingectomy is strongly related to successful in vitro fertilization (IVF) treatments. Prophylactic salpingectomy for women with tubal-factor infertility, before the initiation of IVF treatment, was considered a standard of care [1,2]. Consequently, prophylactic salpingectomy is performed in almost 20% of women who are candidates for IVF treatments [3]. In addition, patients who are surgically treated for ectopic pregnancy might need to undergo IVF treatments for future reproduction, especially if both fallopian tubes have been removed. Although it is considered a simple and safe procedure with a low rate of complications, the close anatomical association of the vascular and nervous supply to the fallopian tubes and ovaries constitutes the rationale for the risk of impaired ovarian function after salpingectomy [4,5].

Research findings on the effect of salpingectomy on ovarian reserve are not entirely conclusive. While studies regarding ovarian reserve and response to stimulation present no significant differences between salpingectomized and non-salpingectomized patients [6-10], only a few investigate the AMH levels, and these results are controversial [4,11-13]. Therefore, in this study we sought to determine the effect of salpingectomy on the ovarian reserve, including anti-mullerian hormone (AMH) levels, in IVF patients.

PATIENTS AND METHODS

In this retrospective, single center study, we reviewed the files of all patients who underwent laparoscopy, and included only those who had complete salpingectomy, with no additional procedures, between January 2009 and December 2016 (salpingectomy group). Cases of salpingostomy, tubal ligation, or partial salpingectomy were also excluded. Cases in which the histopathology result was not benign were also excluded. From the patients who met the inclusion criteria, we retrieved data for those who were treated at the Wolfson Medical Center IVF unit after December 2016. For the control group, we selected a larger group of IVF patients who had not undergone salpingectomy before initiating IVF treatment. The ratio of experimental group to control group was 1:2. Background data included age, BMI, chronic diseases, smoking history, infertility duration, and cause of infertility. The women in the control group were matched to those in the salpingectomy group by age, body mass index (BMI), and the cause of infertility. Surgical details included the indication for salpingectomy and whether the procedure included the removal of both fallopian tubes or only one. Laparoscopic salpingectomy was performed as a prophylactic procedure for patients with hydrosalpinx before initiating IVF treatment or as a surgical treatment for ectopic pregnancy when indicated.

OVARIAN FUNCTION AND RESPONSE ASSESSMENT

Antral follicle count (AFC) and serum concentrations of AMH and FSH on menstrual cycle day 3 were measured no more

than three cycles before the initiation of IVF treatment. AFC was obtained by performing trans-vaginal ultrasound. Estradiol and progesterone levels were measured on the day of human chorionic gonadotropin (hCG) administration.

IVF TREATMENTS

Ovarian stimulation was conducted according to long or short protocol, according to the physician's decision.

Down regulation of the pituitary was achieved by gonadotropin-releasing hormone (GnRH) agonist (Triptorelin, Ipsen Pharma Biotech, Signes, France). It was initiated at the midluteal phase of the previous menstrual cycle, according to the long protocol, and on the third day of menstruation, in the short protocol. Down regulation lasted until the day of hCG injection in both protocols. Controlled ovarian stimulation was achieved by daily sub-cutaneous injection of FSH (Gonal-F, Merk Serono, Geneva, Switzerland). The gonadotropins dose (75–450 IU/day) was adjusted according to ultrasonography results and serum estradiol levels.

When two follicles reached 17 mm in diameter, intramuscular injection of 250 mg of hCG (Ovitrel, Merk Serono) was administered. Oocytes were retrieved under transvaginal ultrasonography guidance within 34–36 hours of hCG injection.

STATISTICAL ANALYSIS

Every patient had between 1 and 8 cycles of ovum pick-up. For each patient, the number of oocyte retrieved, total gonadotropins used, and hormone levels were calculated as the average of all cycles. The number of ET was also calculated as the average of all procedures when more than one transfer had been performed.

Details of the salpingectomy group were compared to those of the control group.

A self-control comparison was also performed, but only for patients who underwent IVF treatments before and after salpingectomy.

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA). Continuous data were compared by Student's *t*-test, and categorical data were compared by chi-square test or by Fisher's exact test, as appropriate. $P < 0.05$ was considered statistically significant

The research protocol was approved by the institutional review board at Wolfson Medical Center before the study began. The study approval number is 0221-16-WOMC.

Informed consent was not needed because of retrospective nature of the study, which was fully based on data analysis.

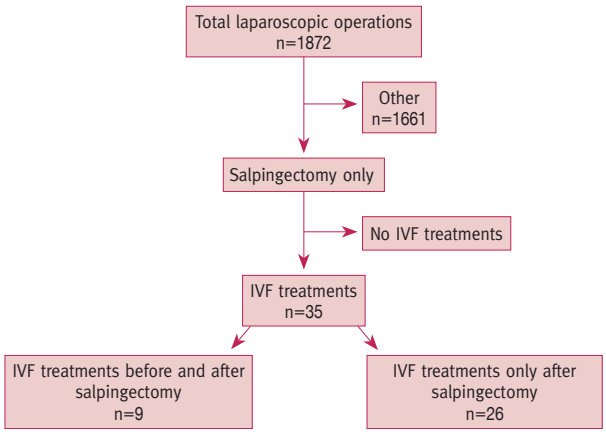
RESULTS

A total of 1872 patients underwent laparoscopy during the study period, including 211 patients (11.3%) who underwent complete bilateral or unilateral salpingectomy, with no additional procedure. Thirty five of the 211 patients who underwent complete salpingectomy underwent IVF treatments at our institute at a later state. These patients were defined as the salpingectomy group and were compared with 70 other IVF patients who did not undergo salpingectomy. The latter group comprised the control group. Nine of the 35 women underwent IVF treatment both before and after salpingectomy. Their data were included in both groups. Figure 1 presents the selection of the salpingectomy group cases.

Demographic and background data, including mean age, BMI, chronic diseases, and smoking history, were not significantly different in the groups. Infertility duration and the rate of tubal factor as the cause for infertility were also similar in the groups. Table 1 presents demographic and background characteristics for both groups.

AMH levels of the salpingectomy group were not significantly different from those of the control group (2 ± 1.6 vs. 1.4 ± 2, respectively; $P = 0.1$). Similar results were observed when other ovarian reserve and response parameters were compared, including FSH levels, AFC, estradiol and progesterone levels, total amount of gonadotropins used for ovarian stimulation, and the number of oocytes retrieved and embryos transferred.

Figure 1. Selection of salpingectomy group cases



IVF = in vitro fertilization

Table 1. Background and demographic characteristics

	Control (n=70)	Salpingectomy (n=35)	*P* value
Age, years, mean ± SD	34.3 ± 3	34.2 ± 5	0.9
BMI, kg/m², mean ± SD	24.1 ± 6.3	25.2 ± 5.6	0.4
Diseases, n (%)	12 (17.1)	7 (20)	0.8
Smoking history, n (%)	6 (8.5)	3 (8.6)	1.0
Infertility, years, mean ± SD	2.9 ± 2.3	3.1 ± 2	0.7
Infertility-tubal factor, n (%)	44 (62)	22 (62)	1.0

BMI = body mass index, SD = standard deviation

An additional comparison of women with only tubal factor infertility failed to demonstrate significant difference between AMH levels (1.7 ± 1.8 vs. 1.3 ± 2.1, respectively; $P = 0.4$).

Fourteen patients (40%) of the salpingectomy group underwent surgery for an ectopic pregnancy, and the other 21 (60%) underwent salpingectomy due to hydrosalpinx. When comparing AMH levels in patients who underwent extrauterine pregnancy (EUP)-indicated salpingectomy to those who underwent hydrosalpinx-indicated salpingectomy, no significant difference was demonstrated (2 ± 2.4 vs. 1.4 ± 2, respectively; $P = 0.4$). Another comparison between 14 women (40%) who underwent bilateral salpingectomy and 21 women (60%) who underwent unilateral salpingectomy, did not reveal significant difference in AMH levels (1.8 ± 2.4 vs. 1.4 ± 2, respectively; $P = 0.4$). Table 2 presents the ovarian assessment.

We also performed a self-controlled analysis: a subgroup analysis of nine patients who underwent IVF treatment before and after salpingectomy. This analysis did not reveal significant differences between the ovarian parameters before and after salpingectomy. Table 3 presents the self-controlled ovarian assessment.

DISCUSSION

In this study, AMH levels were not significantly different in the groups. The other ovarian reserve and response parameters also did not differ. Moreover, significant difference was not observed when only cases of tubal factor infertility were compared, nor when the same women were compared to themselves, before and after salpingectomy (self-controlled analysis).

Research regarding the effect of salpingectomy on AMH levels is scant, and it is even less common when studying IVF patients. Two studies [4,12] observed negative effects of salpingectomy on AMH levels of IVF patients, while a third study contradicted these results [11]. Like Ni et al [11], we also demonstrate that AMH levels of salpingectomized patients are not significantly different from non-salpingectomized patients. This contradiction can be explained in several ways. First, the median duration between surgery and post-salpingectomy AMH measurements in our study was 12 months, while in other studies, it was only a few months. It has already been suggested that AMH levels temporarily decrease after ovarian surgeries, and return to normal after recovery [14]. Second, in our department tubal resection is performed at the level of the posterior tubal margin, carefully sparing the mesosalpinx, and much attention is given when coagulating, in order to use the lowest amount of energy needed.

Orvieto and colleagues [6] studied the ovarian response of the same patients before and after salpingectomy but did not measure AMH levels. To the best of our knowledge, the research conducted by Venturella and collaborators [15] is the only study that evaluates AMH before and after salpingectomy in the same cohort of patients, although it has minor relevance to IVF patients since it included only fertile women who had reached their reproductive goals, aged 35–50 years. Hence, to the best of our knowledge, our study is the first to compare AMH levels in IVF patients before and after salpingectomy. Although the number of patients is too small to suggest protocol changes, the findings are nonetheless important to emphasize that AMH levels do not significantly differ.

The fact that salpingectomy is free from negative effects on other ovarian reserve and response markers has already been demonstrated in previous studies [2,6,8], and it also correlates with our finding that AMH levels do not change before and after salpingectomy. Two systematic literature reviews [17,18] support our results that salpingectomy has no negative effects

Table 2. Ovarian assessment

	Control (n=70)*	Salpingectomy (n=35)*	*P* value
AMH (ng/ml)	2 ± 1.6	1.4 ± 2	0.1
FSH (IU/L)	7.5 ± 2.5	8.3 ± 4.9	0.26
AFC	14.6 ± 9.8	12.5 ± 5.6	0.24
Estradiol (pmol/L)	1993 ± 1292	1788 ± 1500	0.5
Progesterone (nmol/L)	0.9 ± 0.7	0.9 ± 0.5	1.0
Total gonadotropins (IU)	2835 ± 1247	3245 ± 1588	0.1
Oocytes retrieved	8.2 ± 6.9	7.1 ± 3.8	0.4
Embryo transferred	2.1 ± 0.5	2 ± 0.7	0.4
Tubal factor only			
AMH (ng/ml)	**(n=44)** 1.7 ± 1.8	**(n=22)** 1.3 ± 2.1	0.4
Salpingectomy indication			
AMH (ng/ml)	**EUP (n=14)** 2 ± 2.4	**Hydrosalpinx (n=21)** 1.4 ± 2	0.4
Unilateral vs. bilateral salpingectomy			
	Bilateral (n=14) 1.8 ± 2.4	**Unilateral (n=21)** 1.5 ± 2	0.65

*Mean ± SD

AFC = antral follicular count, AMH = anti-mullerian hormone, FSH = follicular stimulating hormone

Table 3. Self-control ovarian assessment, n=9

	Before salpingectomy	After salpingectomy	*P* value
AMH (ng/ml)	0.9 ± 0.8	1.4 ± 1.7	0.49
FSH (IU/L)	8.0 ± 2.2	4.5 ± 4.5	0.09
AFC	16 ± 18.3	11.5 ± 7.4	0.55
Estradiol (pmol/L)	2326 ± 772	2094 ± 753	0.57
Progesterone (nmol/L)	0.9 ± 0.2	0.8 ± 0.4	0.1
Total gonadotropins (IU)	3406 ± 1621	4487 ± 2312	0.3
Oocytes retrieved	8.6 ± 4.9	5.8 ± 5.1	0.3
Embryo transferred	2.6 ± 1.3	2.3 ± 0.8	0.6

AFC = antral follicular count, AMH = anti-mullerian hormone, FSH = follicular stimulating hormone

on ovarian reserve markers and on ovarian response to ovarian stimulation protocols. Notwithstanding, they mention that data are scarce and further research is due regarding this topic.

Like the results Pereira and co-authors [16], we found no differences between the EUP-indicated salpingectomy and the hydrosalpinx-indicated salpingectomy regarding postoperative AMH levels.

Our study has two limitations. First, it is a retrospective study, and second, the small number of patients limit its strength, even though it is not significantly smaller than other studies.

The study also has several strengths. To the best of our knowledge, it is the first to compare AMH levels in the same IVF patients before and after salpingectomy. Second, since the study was conducted in a single center study, the uniform and standardized surgical and fertility treatments revalidate the results.

CONCLUSIONS

Salpingectomy does not affect the ovarian response or the ovarian reserve, including AMH levels, among IVF patients. Prospective, as well as larger studies are necessary to confirm these results.

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Capsule

Neutrophils induce antibody-dependent cellular cytotoxicity via a special mechanism

Antibody-dependent cellular cytotoxicity is an important process by which cancer cells can be targeted and killed. Immune cells, such as T and NK (natural killer) cells, express Fc receptors that recognize cancer cells coated with antibodies. They then release cytotoxic granules that result in apoptosis. **Matlung** and co-authors showed that neutrophils induce antibody-dependent cellular cytotoxicity via a completely different mechanism. This process entails trogocytosis-induced lysis of tumor cells, which the authors term "trogoptosis." They found that neutrophils endocytose cytoplasmic fragments of target cells induces cancer cell necroptosis. In addition to direct killing, this mechanism may be important for the release of cancer neoantigens and damage-associated molecular patterns, which further activate and direct the immune response to tumors.

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Eitan Israeli

"To acquire knowledge, one must study; but to acquire wisdom, one must observe"

Marilyn vos Savant, (b. 1946), American magazine columnist