Research Article

Effect of laparoscopic salpingectomy on subsequent ovarian response after controlled ovarian hyperstimulation

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Abstract

Background: The effect of salpingectomy on ovarian response is a matter of debate. Due to conflicting data, alternative techniques were developed to perform salpingectomy for treatment of hydrosalpinges in infertile patients. This study aims to evaluate the effect of salpingectomy on ovarian response after stimulation with gonadotropins.

Methods: In a retrospective analysis, one hundred fifty-seven patients with tubal infertility were divided into three groups according to their surgical histories: bilateral salpingectomy (BS group); unilateral salpingectomy (US group); and no history of salpingectomy (NS group). Ovarian response and IVF outcomes were compared between groups by analysis of variance. Prognostic factors for ovarian response were estimated by linear regression models.

Results: In the BS group, the total numbers of oocytes retrieved, and embryos obtained were significantly lower than those in the NS group (p = 0.02). Poor ovarian response was also more frequent in the BS group (p = 0.02). In the US group, follicle development was reduced on the operated side. This effect was more pronounced when salpingectomies were performed for hydrosalpinges than when performed for ectopic pregnancies, and significant decreases were observed in follicle recruitment (p = 0.005) and oocyte retrieval (p = 0.02) on the operated side.

Conclusion: Salpingectomy could have a minor negative effect on ovarian response. This is particularly true with bilateral salpingectomies, in which the ovarian blood supply could be disrupted, with no possible compensation by the contralateral side.

Introduction

Salpingectomy is a common operation, performed for the management of ectopic pregnancy (EP) and, beginning approximately fifteen years ago, in women with hydrosalpinges undergoing *in vitro* fertilization (IVF) [1]. In fact, several reports have indicated that the presence of hydrosalpinges has a detrimental effect on implantation and pregnancy rates [2-9]. Prophylactic salpingectomy in women with large hydrosalpinges has been shown to be beneficial in terms of increased pregnancy and live birth rates after IVF treatment [10-12].

However, salpingectomy is suspected to disrupt ovarian function and to decrease ovarian response to the gonadotropins used in assisted reproductive technology (ART), by reducing the vascular supply to the ovary [13]. While some authors found substantial effects of salpingectomy on ovarian response [13-16], others have not [17-22].

Given these conflicting data and the emergence of alternative techniques to perform salpingectomy for treatment of hydrosalpinges in infertile patients, the question of the effect of salpingectomy on ovarian function is more seriously debated than ever before. This study aimed to investigate the effects of salpingectomy on ovarian response to stimulation and its consequences on IVF outcomes.

Materials and Methods

Patient selection

One hundred fifty-seven patients with tubal infertility, admitted to the IVF center of Bichat Claude Bernard University Hospital (Paris), were enrolled in a prospective cohort study. Inclusion criteria were female patient's age below 40 years at enrollment and tubal infertility as the main etiology indicating standard IVF. Exclusion criteria involved surgical history of oophorectomy or ovarian cystectomy, polycystic ovaries, uterine malformation, and severe male infertility (i.e azoospermia).

Before IVF treatment, all the couples underwent routine fertility screening, in particular a hysterosalpingography, an antral follicle count by pelvic ultrasonography and baseline hormonal tests for ovarian reserve. Data from previous reports of surgical interventions were recorded. The mean follow-up period was 24 months.

Among the 157 patients included, 66 patients had a history of salpingectomy, including bilateral (*BS group*) and unilateral (*US group*) salpingectomy, done mainly by reproductive surgeons of the ob-gyn department. Ninety-one patients with no history of salpingectomy or hydrosalpinges were set as controls (*NS group*).

Ovarian stimulation

All patients were stimulated using one of our standard GnRH agonist or antagonist protocols. Starting recombinant FSH dose was set at 225 ± 75 IU according to patients' age and baseline ovarian reserve. Recombinant human chorionic gonadotropin (rhCG) trigger was administered when at least three mature follicles (more than 17 mm in diameter) were obtained. Follicles between 10 and 16 mm and those equal to or greater than 17 mm were counted in each ovary by ultrasonography on the rhCG day.

Oocyte retrieval by ultrasound-guided aspiration was performed by the same reproductive surgeons, thirty-six hours after rHCG, and the number of oocytes retrieved from each ovary was stippled. Insemination or microinjection was performed immediately after, using classical techniques of IVF or ICSI. Forty-eight hours after insemination or microinjection, embryo transfer was performed upon analysis of embryo quality. Progesterone was administered at 400 mg per day intravaginally for luteal phase support.

Poor ovarian response was defined as total oocyte retrieval equal to or less than three. Implantation rate was defined as the number of gestational sacs per embryo transferred per patient. Clinical pregnancy was defined as the presence of an intrauterine gestational sac with fetal cardiac activity at the five-week pelvic ultrasound.

Outcomes

The primary outcome measurement was the total number of oocytes retrieved per cycle. The secondary outcome measurements were the number of follicles recruited between 10 and 16 mm in size and those larger than 16 mm, the peak estradiol level on the day of rHCG, poor ovarian response, number of embryos obtained and clinical pregnancy rate per cycle.

Statistical analysis

Data analysis was performed using SAS software, version 9.1.3 (SAS Institute, Cary, NC, USA). Distribution of quantitative variables was analyzed graphically and by the Shapiro-Wilk normality test. Comparison between quantitative variables was performed by analysis of variance (ANOVA). In cases of significant difference, a specific analysis by Tukey's method (a variant of Student's test) was performed. Comparison between categorical variables was performed by the Chi-square test with 2 degrees of freedom. Non-parametric tests (Wilcoxon) were used in the subgroup analysis. Adjusted odds ratios (ORs) were obtained by means of multivariable linear regression analysis with the number of mature oocytes as the dependent variable. We based the selection criteria for variables on the literature regarding prognostic factors of ovarian response. We tested interaction terms between variables at a significance level of 0.05. The number of cycles was integrated in the statistical analysis.

A power calculation has been conducted at the beginning of recruitment in order to estimate sufficient sample size (44 cycles per group) to achieve adequate power (80%) with 5% type I error.

Informed consent was signed by all the participants, and the study was approved by the local institutional review board (CEERB) under authorization number IRB006477.

Results

The women's mean age was estimated at 32.7 ± 4.6 years old. The average duration of infertility was 3.8 ± 2.9 years. Among the 157 patients included, 25.8% presented with a partner with mild male infertility, 8.4% had a previous history of unilateral tubal surgery, and 6.5% of bilateral tubal surgery. All the patients had normal ovulation and normal basal hormonal tests of ovarian reserve. The clinical characteristics of the three groups studied are summarized in table 1. The mean patients' age and duration of infertility were comparable among groups. Male infertility was observed less frequently in the US group than in the BS and NS groups (10.4% versus 29.4% and 32.9%, respectively; p = 0.01), whereas primary infertility was observed more frequently in the control group than in the BS and US groups (40.7% versus 23.5% and 12.2%, respectively; p = 0.002).

The antral follicles count and basal FSH and AMH were comparable among the groups, while inhibin B was significantly reduced in the BS group (p = 0.04). A history of unilateral tubal repair surgery was less frequently encountered in the NS group (4.4%) versus 11.8% in the BS group and 14.8% in

the US group. In contrast, a history of bilateral tubal surgery was more frequent in the BS group (17.7% versus 6.3% in the US group and 4.4% in the NS group).

Two hundred seventy-one stimulation cycles for IVF were performed, with an average of two cycles per patient (Table 2). The mean interval between salpingectomy, if any, and ovarian stimulation was estimated at 36 months, ranging from 3 to 156 months. Agonist stimulation protocols were the most frequently used in all the groups. The mean duration of stimulation was comparable among the groups. Peak estradiol levels were significantly reduced in the BS group compared to the US and NS groups (1733.9 versus 1905.6 and 2188.0 pg/ml, respectively; p = 0.01). Moreover, the total number of oocytes retrieved was significantly reduced in the BS group, compared to the US and NS groups (7.5 versus 9.5 and 9.8, respectively; p = 0.02). Consequently, the number of oocytes inseminated or microinjected was significantly reduced in the BS group (p = 0.002).

Poor ovarian response was more frequently observed in the BS group than in the US and NS groups (21.7% versus 9.5% and 6.9%, respectively; p = 0.02). The number of embryos obtained was significantly reduced in the BS group (p = 0.04), but the implantation rate, pregnancy rate per cycle and live birth rates were comparable among the groups.

Subgroup analysis of unilateral salpingectomy population

A subgroup analysis of the US population revealed that the mean number of follicles (10 to 16 mm) recruited on the day of rhCG administration was lower on the salpingectomy side compared to the contralateral side (6.8 versus 8.2, respectively; p = 0.007). After stratification based on the etiology of salpingectomy (i.e., ectopic pregnancy or hydrosalpinx), we observed a significant decrease on the salpingectomy side compared to the contralateral side in the number of follicles recruited (p = 0.005) and in the number of mature follicles (p = 0.03) on the day of rhCG administration only when the salpingectomy was performed for hydrosalpinges. Similarly, we observed a significant decrease in the number of oocytes retrieved from the salpingectomy side (mean difference of 2.07; p = 0.02) when tubal surgery was indicated for hydrosalpinges (Table 3).

Multiple regression analysis

We included previous covariates, in addition to other relevant confounders, in a linear regression model with the number of oocytes as the outcome variable (Table 4). In the bilateral salpingectomy group, the number of mature oocytes retrieved remained reduced by 2.08 (p = 0.01), compared to that of the control group. No interaction was noticed

Table 1: Clinical characteristics of the study population (n = 157) according to specific groups.

	Bilateral Salpingectomy	Unilateral Salpingectomy	No Salpingectomy	p
Age (years)	32.3 ± 3.4	32.7 ± 5.1	32.7 ± 4.5	0.94
Duration of infertility (years)	3.6 ± 3.1	3.4 ± 2.8	4.2 ± 2.9	0.33
Associated moderate male infertility, n (%)	5 (29.4%)[a]	5 (10.4%)[b]	30 (32.9%)[a]	0.01
Primary infertility, n (%)	4 (23.5%)[a]	6 (12.2%)[b]	37 (40.7%)[a]	0.002
FSH (IU/L)	7.2 ± 2.9	7.0 ± 2.2	7.0 ± 1.9	0.89
AMH (ng/mL)	2.6 ± 1.8	3.1 ± 2.6	2.9 ± 2.2	0.52
Inhibin B (pg/mL)	45.0 ± 22.7[a]	56.9 ± 23.0[b]	50.9 ± 23.6[b]	0.04
Antral follicle count (AFC)	11.0 ± 4.2	11.0 ± 3.9	12.0 ± 5.1	0.31
History of tubal repair surgery				0.04
- unilateral, n (%)	2 (11.8%)[a]	7 (14.6%)[a]	4 (4.4%)[b]	
- bilateral, n (%)	3 (17.7%)[a]	3 (6.3%)[b]	4 (4.4%)[b]	

Note: Values are shown as means ± Standard Deviations or number (percentage).
[a,b]significant difference between the groups selected (ANOVA or Chi-square).

Table 2: Comparison of stimulation cycles and outcomes of the study population (n = 157) according to specific groups.

	Bilateral Salpingectomy	Unilateral Salpingectomy	No Salpingectomy	p
Number of stimulation cycles	47	79	145	
Interval between surgery and IVF, (months)	38.6 ± 46.7	45.1 ± 39.4	32.8 ± 30.4	0.18
Fertilization technique: IVF, n (%)	24 (51.1)	53 (67.1)	77 (53.5)	0.09
Stimulation protocol: Agonist, n (%)	41 (87.2%)	73 (92.4%)	134 (92.4%)	0.37
Duration of stimulation (days)	10.0 ± 2.4	10.1 ± 1.6	10.2 ± 1.5	0.79
Total dose of FSH used (IU)	2155.1 ± 776.7	2230.9 ± 783.1	2373.3 ± 696.8	0.16
Peak estradiol level (pg/mL) *	1733.9 ± 989[a]	1905.6 ± 1038	2188.0 ± 1025[b]	0.01
Follicles > 16 mm *	5.0 ± 2.5	5.7 ± 3.6	6.1 ± 4.0	0.34
Total oocytes retrieved	7.5 ± 4.5[a]	9.5 ± 5.4	9.8 ± 4.9[b]	0.02
Oocytes inseminated or microinjected	5.9 ± 4.0[a]	8.5 ± 5.1[b]	8.8 ± 5.0[b]	0.002
Poor ovarian response: ≤ 3 oocytes, n (%)	10 (21.7)[a]	7 (9.5)[b]	10 (6.9)[b]	0.02
Number of embryos obtained	3.5 ± 3.0[a]	5.0 ± 3.8	5.0 ± 3.2[b]	0.04
Number of embryos transferred	1.7 ± 1.1	1.7 ± 1.1	1.8 ± 1.0	0.60
Pregnancy rate per cycle	8 (17.8)	22 (29.7)	45 (31.3)	0.20
Live birth rate	3 (6.7)	14 (19.2)	22 (15.3)	0.30

*on the day of hCG administration; [a,b]significant difference between the groups selected (ANOVA or Chi-square).

Table 3: Comparison of ovarian response on the operated side and the non-operated side in the Unilateral Salpingectomy group, according to the etiology of salpingectomy.

Unilateral Salpingectomy group	Salpingectomy for ectopic pregnancy n = 49 (62%)				Salpingectomy for hydrosalpinges n = 30 (38%)			
	Salpingectomy side	Contra-lateral side	Δ	p	Salpingectomy side	Contra-lateral side	Δ	p
Day 3 AFC*	5.7 ± 2.9	5.7 ± 3.2	-0.03	0.6	5.1 ± 1.8	5.6 ± 1.4	-0.52	0.6
Follicles (10-16 mm)**	6.9 ± 3.7	7.8 ± 3.9	-0.85	0.19	6.6 ± 3.3	9.0 ± 3.8	-2.38	0.005
Follicles (>16 mm)**	2.9 ± 2.5	2.6 ± 2.2	+0.24	0.59	2.3 ± 2.0	3.7 ± 2.4	-1.39	0.03
Oocytes retrieved	4.7 ± 3.2	4.9 ± 3.7	-0.18	0.71	3.1 ± 2.8	5.2 ± 2.5	-2.07	0.02

*Antral follicle count, **on the day of hCG administration.

Table 4: Multiple regression model for the number of mature oocytes retrieved (N = 238; R^2 = 18%).

Variable	Number of mature oocytes retrieved		
	β coefficient*	95% confidence interval	p value
No salpingectomy (ref**)	0.00	-	-
Unilateral salpingectomy	-0.77	-2.07 to 0.52	0.24
Bilateral salpingectomy	-2.08	-3.71 to 0.46	0.01

* Adjusted for woman's age, interval between surgery and stimulation, etiology of salpingectomy, previous abdominal surgeries, type of infertility, ovarian reserve, stimulation protocol and duration, and total FSH dose used.
** Reference class.

between the etiology of salpingectomy and interval between salpingectomy and ovarian stimulation.

Discussion

This study showed a significant decrease in peak estradiol levels, in the number of oocytes retrieved and fertilized, and in the number of embryos obtained after BS, compared to the US and NS groups. Poor ovarian response was also more frequent in the BS group despite comparable mean basal characteristics. These results suggest an alteration in ovarian response after bilateral salpingectomy. A decrease in the number of follicles recruited was also observed from the ovary on which salpingectomy was performed, compared to the contralateral side in the US group, which highlights that salpingectomy could be a causal factor in this alteration in ovarian response. In addition, the absence of a history of ovarian surgery in the studied population reinforces the suspected role of salpingectomy.

However, the non-randomized design of this study might have caused some limitations regarding the consistency of the selected groups. In addition to some differences in surgical histories and types of infertility, starting doses of FSH were selected according to the patients' ovarian reserve (antral follicle count and AMH levels). However, the duration of stimulation and total dose of FSH used were comparable among groups, and primary infertility was more frequent in the control group.

Data from the literature regarding this subject have been conflicting. Several studies have not found a significant decrease in ovarian response after salpingectomy [17,18,20-23]. However, most of these studies did not differentiate between unilateral and bilateral salpingectomy and did not mention whether previous adnexal surgeries were performed, and few studies have included large sample sizes, have been sufficiently well-designed, and have discussed salpingectomy indications; Meng, et al. [16] found a significant decrease in the number of oocytes retrieved and significant increases in the dose of gonadotropins and in the duration of stimulation in patients who underwent bilateral salpingectomy, compared to patients without salpingectomy. Furthermore, the authors observed a significant decrease in the number of oocytes retrieved on the salpingectomy side, compared to the contralateral side. We found similar results and further quantified the effects of bilateral salpingectomy on the reduction of mature oocytes at retrieval. This alteration observed in ovarian response after salpingectomy is rather quantitative than qualitative as pregnancy and live birth rates did not differ between groups.

In the subgroup analysis of unilateral salpingectomy, the etiology of salpingectomy was of the utmost importance because ovarian response was significantly reduced after surgery for hydrosalpinges, but this was not the case after surgery for ectopic pregnancies. These results suggest that salpingectomy for hydrosalpinges is potentially more harmful than salpingectomy for ectopic pregnancy regarding future ovarian response to hyperstimulation. Even though we did not have the exact etiology of hydrosalpinx, several hypotheses might explain these findings. In ectopic pregnancy situations, the mesosalpinx usually presents important neovascularization, increasing the arterial blood supply not only to the tube but also to the ovary. This neovascularization would protect against the potential damage induced by salpingectomy. In contrast, chronic pelvic inflammatory disease, which is a frequent source of hydrosalpinges, would also affect the ovary through adhesions and/or blood supply alteration. These effects might be emphasized by salpingectomy, thus decreasing ovarian response to stimulation.

Therefore, indications for bilateral salpingectomy for hydrosalpinges should be carefully considered. Indeed, surgical treatment of hydrosalpinges is recommended prior to IVF, especially when hydrosalpinges are visible on ultrasound [10], but salpingectomy should be only bilateral if the hydrosalpinges are bilateral [11]. To improve pregnancy rates in patients with hydrosalpinges without risking a decrease in ovarian response, alternatives to salpingectomy were proposed, such as neosalpingostomy and proximal tubal occlusion, yielding similar IVF outcomes [11,19,24].

Many studies have attributed the decrease in ovarian response after salpingectomy to surgical damage to the ovarian blood supply in the mesosalpinx [25-28]. However, this observation might not only be the result of injury to the tubal arcade. Because of numerous anatomical variations in the tubo-ovarian arterial network, the entire ovarian blood supply could be injured after salpingectomy [29]. In fact, Doppler studies have shown a decrease in ovarian blood flow after salpingectomy [13]. Therefore, a minimally invasive surgery is crucial, specifically avoiding cauterization with old generation energies that have strong lateral thermic effects. Data from recent reviews highlighted this potential impair in ovarian response to hyperstimulation during IVF [30], even though it appears that salpingectomy is unlikely to have a substantial adverse impact on pregnancy outcome [31].

In conclusion, bilateral salpingectomy could have a negative effect on ovarian response, when compared with unilateral US or no surgery. It is rather a quantitative effect, limited to 2.1 mature oocytes. It is most likely "etiology-dependent" effect, mainly observed after salpingectomy for hydrosalpinges than for ectopic pregnancy. Good tubal scoring for prognosis could help in making surgical decisions, and alternatives to salpingectomy should be discussed in cases of altered ovarian reserve or if technical difficulties are encountered. Ultimately, even if unilateral salpingectomy does not seem to have a significant effect on ovarian response, it remains to be demonstrated whether this lack of difference is due to a real contralateral offsetting effect or to the potential adjustment of ovarian stimulation by the clinician.

Ethics

Subjects have given their written informed consent.

The study protocol has been approved by the research institute's committee on human research.

Author's contributions

CY: statistical analysis, patient recruitment, revision; AB: revision and writing; CC: data collection and writing; ALM: patient recruitment; SF: patient recruitment

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