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RESEARCH ARTICLE

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A retrospective analysis of ovarian response to gonadotropins after laparoscopic unilateral or bilateral salpingectomy for hydrosalpinges

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Abstract

Background and Aims: We compared the effects of unilateral and bilateral salpingectomy for hydrosalpinx on ovarian function, oocyte retrieval, and embryogenesis.

Methods: We retrospectively examined the hospital records of 109 women with unilateral hydrosalpinx and 57 women with bilateral hydrosalpinges who had undergone in vitro fertilization (IVF) treatment (280 oocyte retrieval cycles) between January 2011 and December 2018. We compared age at oocyte retrieval, level of anti-Müllerian hormone (AMH) measured within 1 year of oocyte retrieval, duration of infertility, number of previous IVF treatments, level of follicle stimulating hormone, total gonadotropin dose, number of oocytes retrieved, fertilization rate, blastocyst formation rate, and peak serum estrogen concentration. This study was approved by the institutional review board.

Results: Of the women with unilateral hydrosalpinx, no significant differences were observed in ovarian response, rate of fertilization or rate of blastocyst production between the 21 women (24 cycles) who had undergone unilateral salpingectomy and the 88 women (146 cycles) who had not. Of the women with bilateral hydrosalpinges, the 13 (24 cycles) who had undergone bilateral salpingectomy had slightly lower AMH levels and significantly fewer oocytes retrieved (5.5 ± 3.9 vs 8.3 ± 5.5; P = .0068) than the 44 women (86 cycles) who had not had a salpingectomy. Women who had undergone bilateral salpingectomy also had significantly lower peak serum estrogen concentrations than those who had not undergone salpingectomy (1876.1 ± 765.9 vs 2489.5 ± 1551.4; P = .009).

Conclusion: In women with hydrosalpinx, bilateral salpingectomy may reduce ovarian function and response to gonadotropins, especially the number of oocytes retrieved. Unilateral salpingectomy does not have these effects.

KEYWORDS

anti-Müllerian hormone, bilateral salpingectomy, hydrosalpinx, in vitro fertilization, ovarian function, unilateral salpingectomy

1 | INTRODUCTION

Several studies have indicated that prophylactic salpingectomy is beneficial for women with hydrosalpinx in terms of increasing pregnancy and live birth rates after in vitro fertilization (IVF).[1-6] However, the effect of salpingectomy for hydrosalpinx on ovarian function has been debated, with previous studies showing a variety of results.[2,4,5,7-12] Some authors have reported that unilateral and bilateral salpingectomy can influence ovarian function.[7-12] To obtain more data, we conducted a retrospective study comparing the effects of unilateral and bilateral salpingectomy for hydrosalpinx on ovarian function, oocyte retrieval, and embryogenesis.

2 | MATERIALS AND METHODS

We searched the hospital records of our institution between January 2011 and December 2018 and identified 166 women (aged 25-45 years) diagnosed with unilateral or bilateral hydrosalpinges who underwent IVF (280 oocyte retrieval cycles). Of these, 109 (170 cycles) had unilateral hydrosalpinx and 57 (110 cycles) had bilateral hydrosalpinges. The women with hydrosalpinx were divided into two groups based on whether or not they had undergone salpingectomy for their hydrosalpinx. In this study, the salpingectomies were all performed using laparoscopic surgery.

We excluded women whose partners required testicular biopsy for intracytoplasmic sperm injection (ICSI) and women with fertilization failure due to immature embryos because of advanced polycystic ovary syndrome. Informed consent was obtained from all participants for the use of their data for publication.

We compared patients' age at oocyte retrieval, level of anti-Müllerian hormone (AMH) measured within 1 year of oocyte retrieval, duration of infertility, number of previous IVF treatments, and basal level of follicle stimulating hormone (FSH) on the third to fifth day of menstruation. The same AMH assay was used for all women. AMH, FSH, and estradiol were measured using a cobas automated chemiluminescence immunoassay analyzer with appropriate reagent kits (cobas 8000; Roche in vitro Diagnostics).

Ovarian response was assessed by calculating the total gonadotropin dose, number of oocytes retrieved, fertilization rate, blastocyst formation rate, and peak serum estrogen (E2) concentration on the day of trigger administration.

All women underwent a standard stimulation protocol using pituitary downregulation with a gonadotropin-releasing hormone (GnRH) agonist (buserelin acetate; Buserecure, Fuji Pharma Japan) or a GnRH antagonist (cetrorelix acetate; Merck Biopharma Co., Ltd.). The initial dose of human menopausal gonadotropin (Ferring; Ferring Pharmaceuticals Co., Ltd.) or recombinant FSH (GONAL-f; Merck Biopharma Co., Ltd) was individualized according to the women's age, FSH level, AMH level, and antral follicle count on the third day of menstruation, determined by transvaginal sonography. Gonadotropin therapy (150-300 IU/day, total dose ≥1500 IU) was started on the third day, and the dose was adjusted according to the ultrasound findings and serum E2 level. Transvaginal ultrasonography was routinely performed on the eighth and 10th day of ovarian stimulation and every 2 days thereafter. When at least three follicles reached a mean diameter ≥18 mm, human chorionic gonadotrophin (HCG 5000 IU; Fuji Pharma Japan) was administered using the long and short protocols and buserelin acetate was used as a trigger in the protocol using cetrorelix acetate. Ultrasound-guided transvaginal oocyte retrieval was performed 35 to 36 hours after trigger administration.

To assess blastocyst quality, we classified blastocyst morphology according to the Gardner score.[13]

The oocytes were inseminated three to 5 hours later using conventional insemination procedures or ICSI, depending on the semen parameters. Collected semen samples were centrifuged using two Percoll solutions (90% and 45%) for 20 minutes at 300*g* and then centrifuged in washing buffer for 5 minutes at 300*g*. Pelleted sperm were resuspended in Universal IVF Medium (Origio Japan). Prepared semen with sperm concentrations $<5 \times 10^6$/mL or number of motile sperm $<5 \times 10^6$/mL was selected for ICSI, and semen with higher sperm counts was used for conventional IVF.

TABLE 1 Background and ovarian response, rate of fertilization, and rate of blastocyst production in women with unilateral hydrosalpinx

Unilateral hydrosalpinx	With no surgery	After salpingectomy	*P* value
OPU cycles (no. of women)	146 (88)	24 (21)	
Age (y)	36.2 ± 4.4	35.1 ± 4.0	.25
AMH (ng/mL)	3.3 ± 2.5	3.5 ± 1.9	.65
Infertility period (m.)	27.5 ± 27.7	30.5 ± 20.0	.52
Number of OPU treatment	3.4 ± 4.1	2.7 ± 2.1	.20
Basic FSH level	7.9 ± 5.9	8.3 ± 8.6	.83
Total amount of Gn. (U)	3012.7 ± 1208.3	2857 ± 871.8	.45
No. of oocytes retrieved	7.9 ± 5.4	8.0 ± 5.0	.93
Rate of fertilization (%)	65.9 (759/1152)	67.7 (130/192)	.62
Rate of blastocyst production (%)	57.7 (314/544)	60.0 (60/99)	.59
Peak E2 level (pg/mL)	2336.3 ± 1573.4	2857.3 ± 871.8	.02

Abbreviations: AMH, anti-Müllerian hormone; E2, estrogen; FSH, follicle stimulating hormone; No., number; OPU, oocyte pick up.

TABLE 2 Background and ovarian response, rate of fertilization, and rate of blastocyst production in women with bilateral hydrosalpinges

Bilateral hydrosalpinx	With no surgery	After salpingectomy	*P* value
OPU cycles (no. of women)	86(44)	24(13)	
Age (y)	35.9 ± 4.7	36.7 ± 4.6	.46
AMH (ng/mL)	3.4 ± 3.1	2.8 ± 2.2	.28
Infertility period (m.)	17.8 ± 22.3	18.7 ± 17.4	.83
Number of OPU treatment	3.5 ± 2.5	5.6 ± 5.0	.05
Basic FSH level	6.6 ± 3.8	7.1 ± 4.8	.63
Total amount of Gn. (U)	2786.9 ± 939.6	3259 ± 1851	.23
No. of oocytes retrieved	8.3 ± 5.5	5.5 ± 3.9	.0068
Rate of fertilization (%)	71.0(506/703)	67.7(90/133)	.31
Rate of blastocyst production (%)	58.6(224/382)	48.7(37/76)	.11
Peak E2 level (pg/mL)	2489.5 ± 1551.4	1876.1 ± 765.9	.009

Abbreviations: AMH, anti-Müllerian hormone; E2, estrogen; FSH, follicle stimulating hormone; No., number; OPU, oocyte pick up.

The diagnosis of hydrosalpinx was confirmed by hysterosalpingography, magnetic resonance imaging, transvaginal ultrasonography, and the laparoscopic surgery report.

Results are presented as the mean ± SD. Differences between groups were tested using the unpaired Student's *t* test or chi-square test, with $P < .01$ considered significant.

3 | ETHICS STATEMENT

This study was approved by the Hanabusa women's clinic ethical committee/institutional review board (reference number 2020-01) on February 17, 2020 with ethical principles that have their origin in the Declaration of Helsinki. All women in this study have signed informed consents before the study.

4 | RESULTS

Of the 109 women with unilateral hydrosalpinx, 88 did not undergo unilateral salpingectomy and had a total of 146 oocyte retrieval cycles; 21 women underwent unilateral salpingectomy and had 24 oocyte retrieved cycles. These two groups showed no significant differences in clinical characteristics, such as age, AMH level, infertility period, number of previous IVF treatments and basal FSH level. In addition, there was no significant difference in the number of oocytes retrieved (Table 1).

Of the 57 women with bilateral hydrosalpinges, 44 did not undergo bilateral salpingectomy and had 86 oocyte retrieval cycles, whereas 13 women underwent bilateral salpingectomy and had 24 oocyte retrieval cycles. There were no significant differences in most clinical characteristics between women who had undergone bilateral salpingectomy and those who had not. AMH level was lower in women who had undergone salpingectomy than those who had not, but this difference was not significant. However, significantly fewer oocytes were retrieved for IVF in women who had undergone salpingectomy than in those who had not (5.5 ± 3.9 vs 8.3 ± 3.8; $P = .0068$). Also, the peak of E2 was significantly lower in women who had undergone salpingectomy than in those who had not, even though similar amounts of gonadotropin were used for the stimulation in both groups (1876.1 ± 765.9 vs 2489.5 ± 1551.4; $P = .009$; Table 2).

5 | DISCUSSION

This study suggests that unilateral salpingectomy for hydrosalpinx does not affect ovarian response to gonadotropins or the number of oocytes retrieved for IVF, but bilateral salpingectomy for hydrosalpinx might reduce these responses.

Several studies have shown that salpingectomy is associated with a decrease in AMH, an increase in FSH, and a decrease in oocyte collection in women undergoing IVF, indicating that ovarian function is diminished by salpingectomy.[7,10,12] However, some reports have shown that tubal surgery has no significant impact, or a deleterious effect, on ovarian reserve or responsiveness.[8,9,11] Additionally, it is well known that hydrosalpinx impairs embryo transfer, implantation rate, and might cause miscarriage[14-18] Therefore, most previous reports suggest that the hydrosalpinx should be removed before embryo transfer to improve the outcome of embryo transfer.[1-6]

AMH is a glycoprotein dimer primarily secreted by granulocytes of prenatal follicles and small antral follicles. The level of AMH remains relatively constant throughout the menstrual cycle. It is correlated with the number of follicles and the ovarian reserve, and predicts the response to controlled ovarian stimulation. For these reasons, AMH is used to evaluate changes in the ovarian reserve after salpingectomy.[19-24]

To improve outcomes of embryo transfer sequential to oocyte retrieval, fertility specialists need to identify when a woman with hydrosalpinx should have a salpingectomy.

Our study showed that in women with unilateral hydrosalpinx, salpingectomy did not affect AMH level or oocyte retrieval compared to women who had not had salpingectomy. This suggests that careful timing of unilateral salpingectomy for hydrosalpinx is unnecessary,

because unilateral salpingectomy would not diminish ovarian function or affect the number of oocytes retrieved. In women requiring unilateral salpingectomy for hydrosalpinx, similar numbers of oocytes would be retrieved after the procedure as before.

By contrast, our study showed that in women with bilateral hydrosalpinges, significantly fewer oocytes were retrieved from those who had undergone bilateral salpingectomy than from those who had not. It also showed that the peak of E2 level after bilateral salpingectomy was significantly smaller than that in women who had not had a salpingectomy, even though the average total amount of gonadotropin used for stimulation was almost the same in both groups.

Together, these findings suggest that bilateral, but not unilateral, salpingectomy might be associated with reduced ovarian sensitivity to gonadotropin. Moreover, AMH level in women after bilateral salpingectomy was lower than that in women with no bilateral salpingectomy, although the difference was not significant. AMH level, number of oocytes retrieved and peak E2 level are all markers of ovarian reserve. In our study, two markers (number of oocytes retrieved and peak E2 level) of ovarian reserve were significantly decreased, and AMH level was slightly (but not significantly) lower, in women who had undergone bilateral salpingectomy than in those who had not. Cumulative evidence suggests that serum AMH level strongly predicts ovarian reserve,[19-24] so further discussion for a full evaluation of ovarian reserve is warranted after salpingectomy for hydrosalpinx.

These results might mean that fertility specialists would have to change the management of salpingectomy depending on whether the woman has unilateral or bilateral hydrosalpinx. The women after bilateral salpingectomy would retrieve smaller number of oocytes than the women who did not have salpingectomy even with the same stimulation.

Several authors have reported a significant decrease in the ipsilateral ovarian response after salpingectomy.[7,10,12] This is reflected by the reduced quantity of developing follicles during stimulation for IVF, or significantly fewer follicles and retrieved oocytes on the salpingectomized side, compared with patients who have not undergone salpingectomy.[7,10,12] There have also been several reports that salpingectomy has a detrimental effect on ovarian blood supply.[12,25-28] Salpingectomy carries the risk of reducing ovarian vascularity and consequently ovarian function because the medial tubal artery has its origin at the same point as the median ovarian artery. Also, the close anatomical association of the vascular supply to the fallopian tubes and ovaries constitutes the rationale risk of impairing ovary. Surgeons who are not aware of fertility issues may perform overly rough procedures, or inappropriately use electrosurgery (monopolar or bipolar diathermy) or an ultrasonic scalpel (which uses ultrasonic vibrations up to 55 KHz) to cut and coagulate the vessels in the mesosalpinx. The use of endoscopic automatic stapling devices would further risk diminishing the blood supply.[25-28] Women with unilateral or bilateral hydrosalpinges may experience a temporary reduction in their ovarian blood supply after salpingectomy, according to previous reports.[12,25-28] However, ipsilateral ovarian function after unilateral salpingectomy might be compensated through the blood supply from the ovarian artery and ascending branch of the uterine artery. We suggest there may be a stepwise compensation in ovarian blood supply in such cases. Indeed, Xu-ping Ye et al reported a stepwise trend in the sensitivity to gonadotropin and the number and quality of embryos retrieved between women who had undergone salpingectomy (unilateral or bilateral) and those who had not. Their report showed a stepwise trend in oocyte retrieval, with fewer oocytes retrieved from women who had undergone bilateral salpingectomy than those who had undergone unilateral salpingectomy, and most oocytes being retrieved from women who had not undergone any tubal surgery.[7] With unilateral salpingectomy, blood supply compensation might be better and faster than with bilateral salpingectomy, so ovarian function might be restored more quickly and fully after unilateral salpingectomy than after bilateral salpingectomy.

Our study suggests that the ovarian response to gonadotropins, and the number of oocytes retrieved in IVF, is not affected by unilateral salpingectomy for hydrosalpinx but is reduced by bilateral salpingectomy. Therefore, fertility specialists should manage fertility treatment according to whether the woman has unilateral hydrosalpinx (with unaffected contralateral ovarian function and fallopian tube) or bilateral hydrosalpinges.

Our study has some limitations. First, the group without salpingectomy included women who were unable to undergo this surgery for various reasons; for example, the extensive and strong adhesions caused by previous surgery (for uterine fibroma or ovarian tumor), inflammatory diseases such as pelvic infection, or frozen pelvis due to endometriosis, were expected to prohibit successful salpingectomy. Second, the number of patients in our study was relatively small. A large-scale prospective randomized controlled study is needed to confirm whether unilateral or bilateral salpingectomy for hydrosalpinx affects ovarian function and oocyte retrieval for IVF.

6 | CONCLUSION

Ovarian function was adequate for IVF after unilateral salpingectomy for unilateral hydrosalpinx, but bilateral salpingectomy for bilateral hydrosalpinges might reduce ovarian function and impair the number of oocytes retrieved. A large-scale prospective randomized controlled study is needed to evaluate the effects of salpingectomy on ovarian function, and to determine the most appropriate treatment for unilateral and bilateral hydrosalpinges in women who are undergoing IVF.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Conceptualization: Yuri Mizusawa
Formal Analysis: Yuri Mizusawa
Writing - review and editing: Yuri Mizusawa
Writing - original draft: Yuri Mizusawa

Methodology: Yuri Mizusawa

Investigation: Yuri Mizusawa, Yukiko Matsumoto, Shoji Kokeguchi, Masahide Shiotani

All authors have read and approved the final version of the manuscript.

Yuri Mizusawa had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The corresponding author confirm that manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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