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Original Research

Previous ovarian surgery increases the risk of tubal factor infertility

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Summary

Aim: Previous ovarian surgery for endometriosis results in decreased ovarian reserve and poor response to treatment in women with infertility. However, the impact of previous overall ovarian surgery on the incidence of infertility is unclear. Therefore the authors investigated impact of previous ovarian surgery on infertility incidence. *Materials and Methods:* This is a case-control study using retrospectively collected data in women who received infertility treatment (cases) or delivered babies (controls) at a tertiary center between 2003 and 2012. *Results:* The frequency of previous ovarian surgery was similar in both groups ($p > 0.05$) but it was higher in women with tubal infertility than their matched controls ($p < 0.05$). Also, the frequency of previous reproductive organ surgery was higher in the case group and in women with tubal or unexplained infertility ($p < 0.05$). *Conclusion:* Previous ovarian surgery is not associated with entire infertility, but may increase tubal factor infertility through adhesion formation and damage to adjacent tubes.

Key Words: Ovary; Surgery; Infertility; Ovarian reserve; Endometriosis.

Introduction

Ovarian surgery is one of the most common surgeries in women. There is a 5% to 10% lifetime risk for women undergoing surgery due to suspected ovarian tumor [1]. Moreover, about two-thirds of ovarian tumors are diagnosed during the reproductive years [2]. In numerous studies, ovarian surgery showed to potentially impair fertility. Specifically, ovarian surgery reduces ovarian reserve. For example, a meta-analysis and a cross-sectional study demonstrated a significant decline in serum anti-Müllerian hormone (AMH) levels after ovarian surgery for endometrioma [3, 4]. However, to date, it remains unclear whether ovarian surgery impairs the pregnancy rate.

Previous studies reported that women with previous ovarian surgery for endometrioma had fewer retrieved oocytes after hyperstimulation than those without surgery [5, 6]. Conversely, other studies showed contradicting results. One study reported a similar follicular response to hyperstimulation between women who underwent unilateral ovarian cystectomy for endometrioma and those with normal ovary [7]. Moreover, a retrospective study including infertile women showed that clinical pregnancy rate of women with previous ovarian surgery for endometrioma was similar to that of women without previous surgery [8]. Furthermore, in another study, postcystectomy ovaries showed a reduced follicular response during natural and CC-stimulated cycles in women under the age of 35 years. However, it was also shown that postcystectomy ovaries produced a comparable number of follicles as normal ovaries when stimulated with gonadotropins [7]. In other words, cystectomy alone does not reduce the pregnancy rate. Most studies examining the effect of ovarian surgery on fertility included only women with infertility. Therefore, the result of such studies cannot be completely applicable to women without infertility. It is still unclear whether previous ovarian surgery is a risk factor for infertility. To the best of the present authors' knowledge, there has not been a study addressing the association of previous ovarian surgery and infertility to date. Therefore, the authors planned to investigate, as the primary objective, the association between previous ovarian surgery and infertility by comparing the frequency of previous ovarian surgery in women with infertility with those without infertility. The secondary objective was to evaluate the association between previous surgery of reproductive organs (ovary, tubes, and uterus) and infertility.

Materials and Methods

Upon obtaining approval from the Institutional Review Board, with the requirement of informed consent waived, clinical data of

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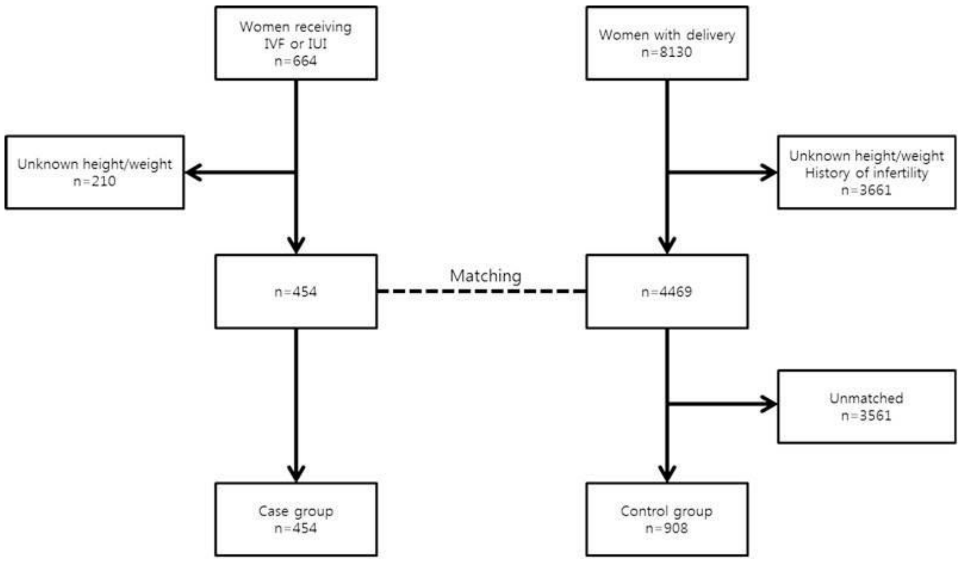

Figure 1. — Flow diagram of patients included in the study of the 664 women who underwent infertility treatment; 210 with unknown height or weight were excluded. Of the 8,130 women who delivered babies, 3,661 with a history of infertility or unknown height or weight before pregnancy were excluded. Through propensity score matching, 454 and 908 women were selected as the case and control groups, respectively.

women who received infertility treatment or delivered babies at the present institute between 2003 and 2012 were collected from medical records. The authors identified 664 women who underwent infertility treatment and 8,130 women who delivered babies.

Infertility treatment was defined as IVF or intrauterine insemination (IUI). The collected variables were as follows: year of infertility treatment or delivery, age, height, weight, history ofendometriosis, ectopic pregnancy, and previous surgery. In women who underwent infertility treatment, the type of infertility was investigated. In women who delivered babies, history of infertility and weight before pregnancy were obtained. Previous surgery was classified into ovarian, reproductive organs, and other. Ovarian surgery was defined as the manipulation of ovarian tissue, except for bilateral oophorectomy.

Surgery of reproductive organs was defined as the transperitoneal manipulation of ovarian, tubal or uterine tissue, except for cesarean section, tubal ligation/reversal, bilateral oophorectomy, bilateral salpingectomy, and diagnostic surgery. Therefore, women with previous ovarian surgery were always considered as women with previous reproductive organ surgery.

The type of infertility was classified into male, decreased ovarian reserve, ovulatory, pelvic, tubal, uterine, and unexplained factor. When there were multiple causes of infertility, the presumed main cause of infertility was used for classification. Of the 664 women who underwent infertility treatment, 210 with unknown height or weight were excluded. Of the 8,130 women who delivered babies, 3,661 with a history of infertility or unknown height or weight before pregnancy were excluded. Through propensity score matching, 454 and 908 women were selected as the case and control groups, respectively (Figure 1).

Propensity score calculation and matching were performed using Matchlt package in R version 2.15.0 (R Development Core Team (2012) R: A language and environment for statistical computing, reference index version 2.15.0. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org). The year of infertility treatment or delivery, age, height, weight, and history of endometriosis and ecopic pregnancy were used to calculate the propensity score.

The ratio between the two groups was 1:2, and the nearest matching was performed. Characteristics of the case group were compared with those of the control group. Chi-square or Fisher's exact test was used for categorical variables. Student's *t*-test was used for continuous variables. If there was a significant difference in any variable between the case and control groups, the ratio for matching was planned to be reduced to 1:1. When the difference was not corrected, despite the reduction of ratio, conditional logistic regression analysis, including the variable with a difference, was planned to compare the frequency of previous ovarian surgery or reproductive organ surgery between women with infertility and those without infertility. Except for propensity score calculation and matching, all analyses were performed using SPSS version 20.0.0 . Null hypotheses of no difference were rejected for *p*-values of less than 0.05.

Table 1. — *Characteristics of patients.*

	Case (n=452)		Control (n=904)	
Year, n (%)				
2003	5	(1.1)	24	(2.7)
2004	22	(4.9)	47	(5.2)
2005	27	(6.0)	67	(7.4)
2006	40	(8.8)	74	(8.2)
2007	84	(18.6)	143	(15.8)
2008	50	(11.1)	116	(12.8)
2009	62	(13.7)	79	(8.7)
2010	74	(16.4)	128	(14.2)
2011	67	(14.8)	154	(17.0)
2012	21	(4.6)	72	(8.0)
Age, mean±SD, yr		34±4		34±4
Height, mean±SD, cm		160±5		160±5
Weight, mean±SD, kg		57±8		56±11
Endometriosis, n (%)	41	(9.1)	76	(8.4)
Ectopic pregnancy, n (%)	4	(0.9)	7	(0.8)

Data are expressed as mean± standard deviation or absolute numbers (%). SD, standard deviation.

Table 2. — *Frequency of previous ovarian surgery.*

Type of infertility	n	Case Surgery	%	n	Control Surgery	%
All	452	54	11.9	904	90	10.0
Male	55	3	5.5	110	5	4.5
Decreased ovarian reserve	25	2	8.0	50	11	22.0
Ovulatory	22	1	4.5	44	1	2.3
Pelvic	41	20	48.8	82	39	47.6
*Tubal	107	18	16.8	214	13	6.1
Uterine	23	0	0	46	6	13.0
Unexplained	179	10	5.6	358	15	4.2

*$p < 0.05$

Results

The year of infertility treatment or delivery was well-balanced between the case group and control group. In both groups, the mean age was 34 years and the mean height was 160 cm. The mean body weight of the case group was 57 kg, and that of the control group was 56 kg. History of endometriosis was present in 9.1% of the case group and in 8.4% of the control groups. History of ectopic pregnancy was positive in 0.9% of case group and 0.8% of control group. None of the characteristics was statistically different between the two groups (Table 1).

The frequency of previous ovarian surgery in the case group was not different from that in the control group (11.9% *vs.* 10.0%, $p > 0.05$). However, the frequency of previous ovarian surgery was higher in women with tubal infertility than in their matched controls (16.8% *vs.* 6.1%, $p < 0.05$). In the other types of infertility, the frequency of previous ovarian surgery was similar between the two groups (Table 2).

The frequency of previous surgery to reproductive organs was higher in the case group than in the control group (21.9% *vs.* 13.3%, $p < 0.05$). The frequency of previous surgery to reproductive organs was higher in women with tubal or unexplained infertility than in their matched controls (34.6% *vs.* 13.1%, $p < 0.05$ for tubal infertility; 14.5% *vs.* 7.0%, $p < 0.05$ for unexplained infertility). However, in the other types of infertility, the frequency of previous reproductive organ surgery was similar between the two groups (Table 3).

Discussion

The present study suggests that previous ovarian surgery does not appear to increase the risk of whole infertility, but may increase the risk of some types of infertility. To the best of the present authors' knowledge, there has not been any study addressing whether the fertility rate of women with previous ovarian surgery is lower than those without previous surgery.

A previously published review stated that there are no data available on the fecundity of women with a single ovary [9]. The best available data regarding fertility following ovarian surgery was pregnancy outcome of women with ovarian neoplasms who received fertility-sparing surgeries. A systematic review reported that 48% of women succeeded in achieving after fertility-sparing surgeries for borderline ovarian tumors [10]. However, these efforts were limited because they lacked a control group.

Previous studies on the impact of ovarian surgery to infertility have focused on decreased ovarian reserve. Many studies showed a significant decline in the serum AMH levels after ovarian surgery [3, 4]. Some studies reported poor IVF outcome after ovarian surgery, and suggested that a decreased ovarian reserve was the cause of poor outcome [5, 6]. A previous study reported that experienced laparoscopists could minimize the destruction of ovarian tissue during surgery and increase live-born rate after surgery for endometrioma in women with infertility; they insisted that ovarian hemostasis should be performed with sutures rather than electrocautery to minimize the thermal damage and preserve the ovarian reserve [11]. However, the findings of the present study suggest that we should focus more on the prevention of adhesion and tubal damage than the preservation of ovarian reserve. According to a paper on endometrioma and pregnancy rates, the resulting conception rate was not affected by the size or location of ovarian endometrioma, but on the tubal condition [12]. Specifically, the frequency of previous ovarian surgery in women with infertility due to decreased ovarian reserve was similar to their matched controls. However, the frequency of previous ovarian surgery in women with infertility possibly due to adhesion formation and damage to tubes was higher than their matched controls. The deterioration of ovarian reserve after ovarian surgery could be the concern for women with infertility, but it seemed not to be a major problem in women without infertility. Conflicting reports regarding the IVF outcome after ovarian surgery [5-9] also supported the present hypothesis, which was that the deterioration of ovarian reserve by ovarian surgery might decrease fertility only in women with marginal ovarian reserve.

The present study showed that previous surgery to reproductive organs is associated with infertility. However, the results should be interpreted cautiously. The association did not prove that previous surgery to reproductive or-

Table 3. — *Frequency of previous surgery to reproductive organs.*

Type of infertility	Case n	Case surgery	Case %	Control n	Control surgery	Control %
*All	452	99	21.9	904	120	13.3
Male	55	4	7.3	110	6	5.5
Decreased ovarian reserve	25	5	20.0	50	11	22.0
Ovulatory	22	1	4.5	44	2	4.5
Pelvic	41	22	53.7	82	42	51.2
*Tubal	107	37	34.6	214	28	13.1
Uterine	23	4	17.4	46	6	13.0
*Unexplained	179	26	14.5	358	25	7.0

*$p < 0.05$.

gans caused infertility. It is possible that previous reproductive organ surgery is not the cause, but rather a consequence of infertility. Given the limitations of retrospectively designed studies, it is not known whether the purpose of the surgery was to solve the cause of infertility. However, the hypothesis that adhesion and tubal damage from previous surgery to reproductive organs would increase infertility can be explained by both the association of previous ovarian surgery with tubal infertility and that of previous reproductive organ surgery with tubal or unexplained infertility. Most gynecological surgeries are associated with a risk of pelvic adhesions and subfertility. Low-quality evidence suggests that barrier agents, including oxidized regenerated cellulose and expanded polytetrafluoroethylene, may all be more effective than no treatment in reducing the incidence of adhesion formation following pelvic surgery. However, there was no evidence on the effects of barrier agents used during pelvic surgery on fertility outcomes in women of reproductive age in a previous systemic review [13]. Another study suggests the relationship between adhesion and FSH, and infertility was unclear [14]. This suggests that location of adhesion is important, not adhesion itself, causing infertility. This result supports the present authors' assumptions. Moreover, this study suggests that unilateral ovarian surgery alone can induce bilateral tubal dysfunction.

The present study has several limitations. Bias cannot be completely eliminated due to its retrospective design, although the authors controlled key variables, such as endometriosis and ectopic pregnancy, as well as using propensity score matching to best minimize bias. The variables were collected retrospectively from medical records, resulting in possible information bias. Some variables, such as the presence of uterine myoma, were not obtained. Compared to the case group, a higher number of women with unknown height or weight was excluded in the control group. Further studies are needed to determine whether there is a difference in the incidence of tubal factor infertility depending on the use and type of adhesion barrier.

Conclusion

Previous ovarian surgery does not seem to increase the risk of whole infertility, but may increase the risk of tubal factor infertility through adhesion formation and tubal damages. Hence, it is important to make an effort to prevent adhesion and tubal damage in women with reproductive age receiving pelvic surgeries.

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References

[1] National Institutes of Health Consensus Development Conference Statement.: "Ovarian cancer: screening, treatment, and follow-up". *Gynecol. Oncol.,* 1994, *55*, S4.
[2] Hillard P.J.A.: "Benign Diseases of the Female Reproductive Tract". *In:* Berek J.S., (ed). *Berek & Novak's Gynecology*. Philadelphia: Lippincott Williams & Wilkins, a Wolters Kluwer Business,2012.
[3] Raffi F., Metwally M., Amer S.: "The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis". *J. Clin. Endocrinol. Metab.,* 2012, *97*, 3146.
[4] Streuli I., de Ziegler D., Gayet V., Santulli P., Bijaoui G., de Mouzon J., Chapron C.: "In women with endometriosis anti-Mullerian hor- mone levels are decreased only in those with previous endometrioma surgery". *Hum. Reprod.,* 2012, *27*, 3294.
[5] Geber S., Ferreira D.P., Spyer Prates L.F., Sales L., Sampaio M.: "Ef- fects of previous ovarian surgery for endometriosis on the outcome of assisted reproduction treatment". *Reprod. Biomed. Online,* 2002, *5*, 162.
[6] Ho H.Y., Lee R.K., Hwu Y.M., Lin M.H., Su J.T., Tsai Y.C.: "Poor response of ovaries with endometrioma previously treated with cys- tectomy to controlled ovarian hyperstimulation". *J. Assist. Reprod. Genet.,* 2002, *19*, 507.
[7] Loh F.H., Tan A.T., Kumar J., Ng S.C.: "Ovarian response after la- paroscopic ovarian cystectomy for endometriotic cysts in 132 mon- itored cycles". *Fertil. Steril.,* 1999, *72*, 316.
[8] Wong B.C., Gillman N.C., Oehninger S., Gibbons W.E., Stadtmauer L.A.: "Results of in vitro fertilization in patients with endometriomas: is surgical removal beneficial?". *Am. J. Obstet. Gynecol.,* 2004, *191*, 597.

[9] Lass A.: "The fertility potential of women with a single ovary". *Hum. Reprod, Update,* 1999, *5*, 546.
[10] Swanton A., Bankhead C.R., Kehoe S.: "Pregnancy rates after conservative treatment for borderline ovarian tumours: a systematic review". *Eur. J. Obstet. Gynecol. Reprod. Biol.,* 2007, *135*, 3.
[11] Yu H.T., Huang H.Y., Soong Y.K., Lee C.L., Chao A., Wang C.J.: "Laparoscopic ovarian cystectomy of endometriomas: surgeons' ex- perience may affect ovarian reserve and live-born rate in infertile pa- tients with in vitro fertilization-intracytoplasmic sperm injection". *Eur. J. Obstet. Gynecol. Reprod. Biol.,* 2010, *152*, 172.
[12] Fujishita A, Khan KN, Masuzaki H, Ishimaru T:. "Influence of pelvic endometriosis and ovarian endometrioma on fertility". *Gynecol. Obstet. Invest.,* 2002, *53*, 40.
[13] Ahmad G., O'Flynn H., Hindocha A., Watson A.: "Barrier agents for adhesion prevention after gynaecological surgery". *Cochrane Database Syst Rev.*, 2015, *4*, CD000475
[14] Bowman M.C., Cooke I.D., Lenton E.A.: "Investigation of impaired ovarian function as a contributing factor to infertility in women with pelvic adhesions". *Hum. Reprod. (Oxford),* 1993, 8, 1654.

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