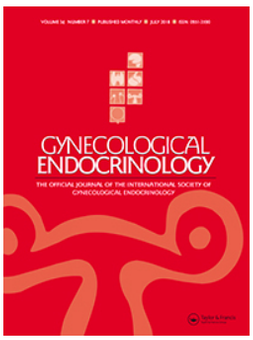

Gynecological Endocrinology

ISSN: 0951-3590 (Print) 1473-0766 (Online) Journal homepage: https://www.tandfonline.com/loi/igye20

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To cite this article: Ilgın Turkcuoglu & Rauf Melekoglu (2018) The long-term effects of endometrioma surgery on ovarian reserve: a prospective case–control study, Gynecological Endocrinology, 34:7, 612-615, DOI: 10.1080/09513590.2017.1419174

To link to this article: https://doi.org/10.1080/09513590.2017.1419174

Published online: 19 Dec 2017.

GYNECOLOGICAL ENDOCRINOLOGY
2018, VOL. 34, NO. 7, 612–615
https://doi.org/10.1080/09513590.2017.1419174

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ENDOMETRIOMA SURGERY AND OVARIAN RESERVE

The long-term effects of endometrioma surgery on ovarian reserve: a prospective case–control study

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ABSTRACT

The objective of this study was to evaluate the long-term effects of endometrioma excision on ovarian reserve. This study evaluated the long-term effects of endometrioma excision on ovarian reserve. A total of 63 women were enrolled in this prospective case–control study; 21 women had histories of endometrioma surgery (study group), 21 women had diagnoses of endometrioma, and 21 healthy age-matched women served as controls. Participants were recruited from the Department of Obstetrics and Gynecology, Inonu University Faculty of Medicine, between January 2007 and January 2016. The mean follow-up duration after endometrioma surgery was 30.4 ± 18.0 months for the study group. The mean follicle-stimulating hormone, luteinizing hormone and estradiol levels were similar among groups, but the anti-Müllerian hormone (AMH) level was significantly lower in the surgery group than in the control group ($p < .001$). The mean AMH level was 42% lower in the endometrioma surgery group than in the endometrioma group and 30% lower in the endometrioma group than in the control group ($p = .080$ and $p = .160$, respectively). Endometrioma has a detrimental effect on ovarian reserve, and decreased ovarian reserve compared with that in healthy fertile subjects without endometrioma is evident shortly after endometrioma excision. However, the endometrioma excision procedure does not significantly decrease the ovarian reserve in the long term.

ARTICLE HISTORY
Received 8 October 2017
Revised 14 December 2017
Accepted 15 December 2017
Published online 19 December 2017

KEYWORDS
Anti-Müllerian hormone; endometrioma; long-term effect

Introduction

Endometriosis is a chronic disease affecting 2 – 10% of the general population and 30 – 50% of infertile women and/or women with pelvic pain. The prevalence of endometriosis and endometriosis-associated infertility has increased over the years [1]. Endometrioma is present in 30 – 40% of endometriosis cases [2,3]. The recommended treatment for endometrioma is surgery, due to the ineffectiveness of medical treatment. Endometrioma excision is superior to ablation with respect to pain relief, a decreased cyst recurrence rate, ruling out of rare cases of malignancy and an increased spontaneous pregnancy rate [4]. The cumulative spontaneous pregnancy rate after endometrioma excision was approximately 50% [5]. However, surgery had no favorable effect on *in vitro* fertilization outcomes for infertile women who underwent endometrioma excision [6,7].

Studies evaluating the effects of endometrioma excision on ovarian reserve have consistently found a significant decrease in the anti-Müllerian hormone (AMH) level shortly after surgery [8–14]. Therefore, endometrioma excision is currently not advisable in nonsymptomatic infertile patients, due to the unfavorable effects on ovarian reserve [15,16]. However, a limited number of studies has documented postsurgical recovery of AMH to a level similar to that measured preoperatively [17–19]. Whether the decrease in AMH level is a persistent or transient effect thus requires further clarification. Current data on the long-term consequences of endometrioma excision in terms of ovarian reserve are insufficient. In this study, we evaluated the long-term effects of endometrioma excision on ovarian reserve.

Methods

This prospective case–control study was approved by the Ethics Committee of Inonu University Faculty of Medicine (ethical approval no. 2016/71). Verbal and written information was provided to all study participants according to the principles of the Declaration of Helsinki, and written informed consent was obtained from all patients prior to enrollment. The electronic records of patients who underwent laparoscopic excisional ovarian endometrioma surgery with the diagnosis of unilateral or bilateral endometrioma between 2007 and 2016 were analyzed, and 21 patients were enrolled in the endometrioma surgery (ES) group after the inclusion and exclusion criteria were applied. A total of 21 age-matched cases with unilateral or bilateral endometrioma diagnosed by transvaginal ultrasonography who did not undergo endometrioma surgery were enrolled in the study as the first control [endometrioma (E)] group. The second control (C) group consisted of 21 age-matched fertile women with no pelvic pathological finding on transvaginal ultrasonography and no previous diagnosis of endometriosis.

The inclusion criteria were age of 18 – 39 years, no other ovarian surgery except one course of endometrioma surgery for the ES group, application of a standard operation technique by a single surgeon (described below) for the ES group, and follow-up duration >12 months after surgery for the ES group.

The exclusion criteria were previous ovarian surgery (other than one course of endometrioma surgery for the ES group), history of early menopause or premature ovarian failure, history of autoimmune or genetic disease, use of oral contraceptive pills or

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Table 1. Demographic characteristics of the cases.

	C ($n=21$)	E ($n=21$)	ES ($n=21$)	p
Age (years)*	33.4 ± 4.1	30.0 ± 6.3	32.4 ± 6.3	.140
BMI (kg/m^2)*	23.6 ± 2.5	23.4 ± 3.4	26.3 ± 5.6	**.041**
Gravidity*	2.2 ± 1.3	1.1 ± 1.5	1 ± 1.3	**.008**
Parity*	1.9 ± 1.2	0.9 ± 1.2	0.8 ± 1.2	**.011**
Menstrual irregularity**	38.1	19.1	42.9	.223
Smoking rate**	38.1	28.9	0	**.008**
Infertility history**	0	14.3	38.1	**.005**
Mean age of maternal menopause (years)*	51.1 ± 4.7	52.5 ± 6.1	53.3 ± 5.3	.419
Bilaterality rate**	–	38.1	33.3	.747
Endometrioma size (cm)*	–	5.0 ± 2.3	5.4 ± 1.7	.555

*Data are given as mean ± standard deviation.
**Data are presented as percentage.
C: control group; E: endometrioma group; ES: endometrial surgery group.

hormone preparations within 3 months prior to enrollment, history of chemotherapy with ovarian toxicity, history of pelvic radiotherapy, diagnosis of chronic pelvic pain for the C group, diagnosis of infertility for the C group, presence of polycystic ovary syndrome and diagnosis of unexplained infertility.

Operation technique

All endometrioma operations in the ES group were performed by a single physician (I.T.) experienced in endometrioma surgery. The cystectomy procedure was carried out using a stripping technique involving sharp dissection of the ovarian surface to reveal the cleavage plane of the cyst pseudocapsule and removal of the pseudocapsule by blunt dissection and traction from the ovary with two atraumatic graspers. Hemostasis was achieved by bipolar cautery, and cauterization was avoided as much as possible to reduce ovarian damage. The ovarian cortex was left open without suturization. Excised cysts were examined histopathologically and diagnoses were confirmed by pathology.

Evaluation of ovarian reserve and risk factors

All participants underwent transvaginal ultrasonography on the third day of the menstrual cycle. Blood samples were collected by venipuncture on the same day as the ultrasonography assessment for the evaluation of ovarian reserve. Plasma was centrifuged at 2,000 × g for 10 min, then kept frozen at −80 °C until analysis. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2) and AMH levels were then measured in the same reference laboratory.

Ultrasonographic assessment

Transvaginal ultrasonography was performed by a single experienced gynecologist in all cases with a transvaginal 7.5-MHz probe (Voluson E6; GE Medical Systems, Milwaukee, WI). Ovarian volume was calculated as length × width × height × 0.523 [19]. The cyst-free ovarian volume was calculated for the E group by subtracting the cyst volume from the total ovarian volume. Each participant's average ovarian volume was calculated using the formula: right ovarian volume + left ovarian volume/2.

Hormonal assays

Serum FSH, LH and E_2 levels were measured using enzyme-linked fluorescence assays (Abnova, Taipei, Taiwan) according to the manufacturer's instructions.

Statistical analyses

Power analysis indicated that at least 21 individuals should be included in each group if the greatest between-group difference in the AMH level was 1.0 ng/mL [standard deviation (SD), 0.7 ng/mL], the type-I error was 0.05 and the type-II error was 0.20 [20].

The data were analyzed using the Statistical Package for Social Sciences (version 20.0; SPSS Inc., Chicago, IL). Data are given as means ± SDs and percentages. The characteristics of cases were compared using one-way analysis of variance (ANOVA) and Pearson's chi-squared test. When one-way ANOVA revealed a significant difference, the Bonferroni *post hoc* test was applied to identify the group contributing to the difference. A linear regression analysis model was applied to analyze the effects of the independent factors age, surgery, bilaterality of endometrioma, endometrioma size, and smoking status on the AMH level. p values $<.05$ were considered to be statistically significant.

Results

The mean follow-up duration after endometrioma surgery was 30.4 ± 18.0 months for the ES group. The mean ages of the C, ES and E groups were similar (33.4 ± 4.1 years, 32.4 ± 6.3 years and 30.0 ± 6.3 years, respectively; $p=.140$). The body mass index (BMI) differed significantly among groups ($p=.041$; Table 1). The menstrual irregularity rate and mean age of maternal menopause were similar among groups. No patient in the ES group smoked, and the smoking rate was similar in the C and E groups. The rate of bilateral endometrioma and the mean endometrioma size at initial diagnosis were similar in the ES and E groups (Table 1). Regarding ovarian reserve tests, the total antral follicle count in both ovaries was similar among groups. However, the average ovarian volume was significantly smaller in the ES group than in the C group (Table 2). The mean FSH, LH and E_2 levels on day 3 of the menstrual cycle were similar among groups. However, the mean AMH level was significantly lower in the ES group than in the C group ($p<.001$). The mean AMH level was 42% lower in the ES group than in the E group, and 30% lower in the E group than in the C group. However, these differences were not significant ($p=.080$ and $p=.160$, respectively).

The rate of decreased ovarian reserve (DOR) was significantly higher in the E group than in the C group (38.1% vs. 9.5%, $p=.03$) and in the ES group than in the C group (57.1% vs. 9.5%, $p=.001$). However, this rate did not differ significantly between the E and ES groups ($p=.217$; Table 2).

Table 2. Ovarian reserve parameters of the cases.

	C (a) ($n=21$)	E (b) ($n=21$)	ES (c) ($n=21$)	p	p a *vs.* b	p a *vs.* c	p b *vs.* c
Average ovarian volume (cm^3)*	6.1 ± 1.7	5.5 ± 1.4	4.5 ± 1.1	.002	ns	.012	ns
Total antral follicle count*	8.8 ± 3.3	7.4 ± 3.5	7.0 ± 3.2	.224	ns	ns	ns
Day 3 FSH*	9.7 ± 7.8	10.2 ± 10.7	14.7 ± 17.6	.377	ns	ns	ns
Day 3 LH*	5.5 ± 2.8	6.3 ± 3.9	9.2 ± 8.6	.103	ns	ns	ns
Day 3 E_2*	44.7 ± 19.8	41.7 ± 20.3	59.8 ± 34.2	.058	ns	ns	ns
AMH*	2.7 ± 1.4	1.9 ± 1.4	1.1 ± 0.7	<.001	ns	<.001	ns
DOR % (ratio)**	2 (9.5)	8 (38.1)	12 (57.1)	.005	.030	.001	.217

*Data are given as mean ± standard deviation.
**Data are presented as percentage.
AMH: anti-Müllerian hormone; C: control group; DOR: decreased ovarian reserve; E: endometrioma group; E_2: estradiol; ES: endometrial surgery group; FSH: follicle-stimulating hormone; LH: luteinizing hormonens: non-significant.

Table 3. Independent predictors of low AMH level in endometrioma cases.

	p
Age	.029
Surgery	.001
Bilaterality	.629
Endometrioma size	.109
Smoking status	.622

We also compared the DOR rate between bilateral and unilateral endometrioma cases, but found no significant difference. In the E group, the DOR rate was 37.5% for bilateral endometrioma cases and 38.5% for unilateral endometrioma cases ($p=.965$). In the ES group, the DOR rate was 71.4% for bilateral surgery cases and 50% for unilateral surgery cases ($p=.350$).

Linear regression analysis revealed significant negative effects of increased age and a history of endometrioma surgery on the AMH level. The bilaterality of endometrioma, endometrioma size, and smoking status had no significant effect on the AMH level (Table 3).

Discussion

The current study, with the longest follow-up period to date, revealed a significantly lower AMH level and significantly higher DOR rate in the ES group compared with fertile, healthy women without endometrioma. The DOR rate was significantly higher in the E group than in healthy subjects, but was similar between the ES and E groups.

Prior to this study, the longest follow-up period after excisional endometrioma surgery was 12 months [13,21–23]. Vignali et al. [21] and Sugita et al. [22] detected recovery of the AMH level to the preoperative value 12 months after endometrioma excision with the stripping technique and bipolar electrocoagulation, although a significant decrease was present at months 1−6 following surgery. Ding et al. [13] and Shao et al. [23] analyzed bilateral and unilateral endometrioma cases separately. In contrast to the other two studies, hemostasis was achieved by suturing rather than electrocoagulation. Ding et al. [13] found recovery to preoperative AMH levels at 6 and 12 months after surgery; however, Shao et al. [23] detected a continuous decline in AMH levels at 6 and 12 months after surgery, which was significant in the bilateral endometrioma group but not in the unilateral endometrioma group. In the early postoperative period, a sharp decline in the AMH level may occur due to the unintentional removal of the ovarian cortex and the loss of follicles growing on the stripped cyst wall. Another possible mechanism is thermal damage to the healthy ovarian cortex and its vasculature caused by electrocoagulation and surgery-related local inflammation. A later increase in the AMH level may be due to follicular rearrangement and the partial replacement of the growing follicles from the follicular pool.

Although recovery of the AMH level was detected in these studies, the AMH level did not increase and remained significantly lower than the preoperative level at 12 months after surgery in some patients [19,22]. Therefore, several risk factors may increase the probability of persistent ovarian damage in some patients with endometrioma. Endometrioma diameter >7 cm, presurgical serum AMH level, and endometrioma bilaterality have been correlated with the post-surgical AMH level [24,25]. However, the correlations of bilaterality and endometrioma size with decreased AMH levels disappeared 12 months after surgery [8,21,22]. In the current study, we detected no relationship between the serum AMH level and bilaterality or endometrioma size over the long-term follow-up period. The correlation between bilaterality or endometrioma size and a decreased AMH level shortly after surgery may reflect the unintentional excision of a larger volume of healthy ovarian cortex. However, the relationship seems to disappear over time, likely due to compensatory follicular rearrangement and recruitment.

Several studies have revealed lower AMH levels in cases with endometrioma than in control subjects without endometrioma [26–28]. In the current study, the mean AMH level of the E group was 30%, lower than that of healthy fertile subjects without endometrioma; however, this difference was not significant. Nevertheless, the DOR rate was significantly higher in patients with endometrioma than in those without endometrioma.

In conclusion, endometrioma has a detrimental effect on ovarian reserve, and DOR becomes more prominent after endometrioma excision in comparison with healthy fertile subjects without endometrioma. However, endometrioma excision did not significantly decrease individual patients' ovarian reserves in the long term. The decision to undergo surgery should be made cautiously, especially in patients of advanced age.

Acknowledgements

We received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Disclosure statement

The authors have no conflict of interest.

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