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Original Research

# Persistent tubal epithelium in ovaries after salpingectomy

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**Summary**

The aim of this study is to evaluate the presence of residual tubal tissue and endosalpingiosis on the ovarian surface after salpingectomy. A total of 105 ovarian tissues of 54 patients who underwent abdominal total hysterectomy with bilateral or unilateral salpingo-oophorectomy for benign indications between January 2019 and December 2019 were included in the study. Salpingectomy was performed prior to oophorectomy in all patients. The adhesion grade score was calculated for each case. Persistent tubal epithelium was found in 16 (29.6%) of the patients. There was a significant difference in adhesion scores between the persistent tubal epithelium -negative and persistent tubal epithelium -positive patients ($p$ = 0.041). In conclusion, permanent tubal epithelium may remain in the ovaries after salpingectomy. Persistent tubal epithelium is more common in cases with intra-abdominal adhesions. Opportunistic and risk-reducing salpingectomy is effective to prevent ovarian cancer, although it is not a definitive solution.

*Key words*: Endosalpingiosis; Epithelial ovarian cancer; Persistent tubal epithelium; Salpingectomy.

## Introduction

Traditionally, the majority of pelvic serous cancers are thought to originate from the ovary, while the presence of a serous precursor in the Fallopian tube epithelium has dramatically changed this view in recent years. The current evidence indicates that epithelial ovarian cancers originate from three potential sites: ovary, tuba, and Müllerian epithelial regions [1-3]. According to the theory of tubal carcinogenesis, opportunistic/protective salpingectomy prevents the development of epithelial ovarian cancer [4]. The American College of Obstetricians and Gynecologist (ACOG) and Society of Gynecologic Oncology (SGO) recommend that opportunistic salpingectomy should be considered in gynecologic operations for benign reasons [5].

In recent years, histological relationship between endosalpingiosis and pelvic serous neoplasia has attracted increasing attention [6]. However, much remain unknown regarding the role of endosalpingiosis in the pathogenesis of ovarian cancer development and there is still a need for prospective data on the extent to which risk-reducing salpingectomy provides protection in ovarian/peritoneal serous cancers [5]. In the present study, we aimed to evaluate the presence of residual tubal tissue and endosalpingiosis on the ovarian surface after salpingectomy.

## Materials and Methods

### *Study design and study population*

This single-center, prospective study was conducted at Dokuz Eylul University, Faculty of Medicine, Department of Obstetrics and Gynecology between January 2019 and December 2019. All patients were informed about the nature of the study and a written informed consent was obtained. The study protocol was approved by the local Ethics Committee (No. 2019/04-27). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Throughout the study period, a total of 165 patients who underwent total abdominal/ laparoscopic hysterectomy with bilateral or unilateral salpingectomy for benign indications such as uterine fibroids, uterine prolapse, abnormal uterine bleeding (non-cancerous), or endometrial polyps were screened. Those having primary or metastatic genital malignancy, benign or malignant adnexal masses, or previous salpingectomy were excluded from the study. A total of 57 patients met the inclusion criteria and gave consent for oophorectomy were included. However, three of them were excluded from the study for the following reasons: a borderline ovarian tumor (n = 2), Grade 1 endometrial carcinoma (n = 1) in the final pathological examination. Finally, 105 ovarian tissues of a total of 54 patients were included. Data including baseline demographic and clinical characteristics of the patients were recorded.

### *Surgical technique*

In all patients, laparotomy was performed under general anesthesia by a single surgical team. The operation was initiated by clamping both the ovarian ligament. The peritoneum was opened parallel to the infundibulopelvic ligament and the infundibulopelvic ligament was ligated once the ureters were reached. After dissecting the adhesions between the tuba uterina and ovary, the adhesion grade score was determined upon the agreement of both surgeons (Table 1).



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Table 1. — *Adhesion grade score*

| Adhesion grade score* | |
|---|---|
| 0 | No adhesions |
| 1 | Filmy adhesions, blunt dissection |
| 2 | Strong adhesions, sharp dissection |
| 3 | Very strong vascularized adhesions, sharp dissection, damage hardly preventable |

*Coccolini, F., et al. (2013) [22]. "Peritoneal adhesion index (PAI): proposal of a score for the "ignored iceberg" of medicine and surgery." World Journal of Emergency Surgery. https://doi.org/10.1186/1749-7922-8-6.

The salpingectomy was completed by cutting the tuba uterina from the mesosalpinx and at the level of the cornua. Following gross examination, the ovaries were separated from the uterus. Both surgeons confirmed that there was no visible residue of tuba uterine on the ovary. All specimens including right ovary, left ovary, right tuba, and left tuba were marked separately and sent for histopathological examination.

### *Histopathological examination*

Histopathological examination was performed by two pathologists experienced in gynecopathology. Ovaries were cut at 2-mm intervals. Hematoxylin & eosin (H&E)-stained pathology sections were examined with a light microscope ($\times$200). All specimens were analyzed for the presence or absence of tubal epithelium. The tubal epithelium, which is visible in a section taken from the ovary after salpingectomy, may belong to the existing endosalpingiosis foci or residue of a normal Fallopian tube epithelium. As it is not always possible to separate these two conditions using immunohistochemistry, they were named as persistent tubal epithelium (PTE) in our pathology report. Figure 1 shows a micrograph of endosalpingiosis in ovary H&E stains.

### *Statistical analysis*

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 24.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean $\pm$ standard deviation (SD), median (min-max) or number and frequency, where applicable. Normally distributed variables were compared using the Student *t*-test, while non-normally distributed variables were compared using the Mann-Whitney U test. The chi-square and Fisher's exact tests were used to analyze data. A $p$ value of $< 0.05$ was considered statistically significant.

## Results

A total of 105 ovarian tissues of 54 patients were analyzed for histological presence of tubal fimbrial tissue on the ovary. Of the patients, the mean age was 51.31 $\pm$ 8.52 (range 42 to 78) years. Thirty-one (57%) of the patients were in the premenopausal period and 23 (43%) of the patients were in the postmenopausal period.

Table 2. — *Indication for surgery*

| **Indication** | n / N (%) |
|---|---|
| Uterine fibroids | 23 / 54 (42.6%) |
| Abnormal vaginal bleeding | 17 / 54 (31.6%) |
| Chronic pelvic pain | 8 / 54 (14.6%) |
| Endometrial polyp | 4 / 54 (7.4%) |
| Uterine prolapse | 2 / 54 (3.7%) |

*Data are given in number and total number (percentage), unless otherwise stated.*

Indications for the operations are summarized in Table 2. Of the patients, 51 (94.4%) had bilateral and three (5.6%) had unilateral salpingo-oophorectomy.

According to the histopathological examination, PTE was observed in 20 ovarian tissues in 16 (29.6%) patients. The PTE was unilateral in 12 (75%) cases (8 right ovary/4 left ovary) and bilateral in four (25%) cases.

There was no statistically significant difference in the age, gravidity, parity, previous history of abdominal surgery, and menopausal status between the patients with and without PTE ($p > 0.05$) (Table 3).

Adhesion scores of the PTE-positive and PTE-negative patients are presented in Table 4. Four (%100) patients with bilateral PTE had adhesion. The rate of PTE was significantly higher in the patients with adhesion ($p = 0.04$).

## Discussion

Epithelial ovarian cancer is one of the leading causes of mortality among gynecologic malignancies worldwide [5]. High-grade serous cancers constitute 70% of all ovarian cancers and its high prevalence is associated with challenges regarding screening and early diagnosis [5-8]. However, in parallel with the recent developments in the pathogenesis of the disease, the importance of primary prevention strategies in disease prevention has increased.

It has been well documented that most high-grade serous cancers originate from serous tubal intraepithelial cancer (STIC) at the tubal fimbrial end and can implant on the ovarian surface [3, 9]. Review of the pathology literature has long drawn attention to the relationship between endosalpingiosis and borderline and low-grade serous cancers. Tubal etiology has been shown to play a central role in the

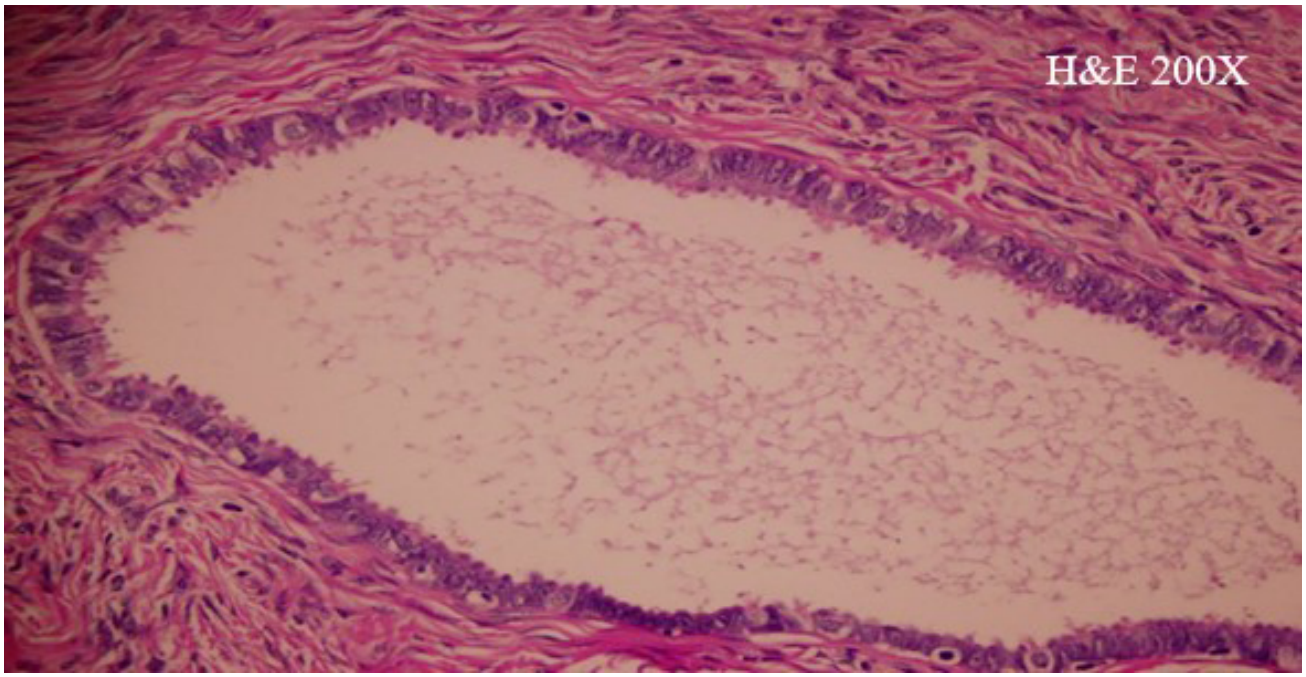



Figure 1. — Micrograph showing endosalpingiosis in ovary H&E stains.

Table 3. — *Baseline demographic and clinical characteristics of patients*

| | **PTE-positive (n = 16)** | **PTE-negative (n = 38)** | ***p* value** |
|---|---|---|---|
| Age, year | 51.25 ± 8.61 | 51.34 ± 8.60 | 0.879 |
| Gravidity | 2.50 ± 1.50 | 2.89 ± 2.11 | 0.497 |
| Parity | 2.12 ± 1.45 | 2.00 ± 1.41 | 0.767 |
| Previous history of abdominal surgery | 3/16 (18.8%) | 16/38 (42.1%) | 0.128 |
| Menopausal status (Pre-/post-) | 7/9 (77.7%) | 14/24 (58.3%) | 0.235 |

*Data are given in mean ± standard deviation or number and total number (percentage), unless otherwise stated. PTE: persistent tubal epithelium.*

Table 4. — *Adhesion scores of the PTE-positive and PTE-negative patients*

| | **No Adhesion *(Adhesion grade score: 0)*** **n (%)** | **Adhesion (*Adhesion grade score: > 0)*** **n (%)** | **Total** | |
|---|---|---|---|---|
| PTE-negative n (%) | 35 (64.8%) | 3 (5.6%) | 38 (70.4%) | |
| PTE-positive n (%) | 11 (20.4%) | 5 (9.3%) | 16 (29.6%) | $p = 0.041$ |
| Total | 46 (85.2%) | 8 (14.8%) | 54 (100%) | |

*Data are given in number and percentage, unless otherwise stated. PTE: persistent tubal epithelium.*

development of high- and low-grade serous ovarian cancers [9]. There is a growing number of evidence regarding its precursor role in the opportunistic bilateral salpingectomy (BS) as an ovarian cancer prevention strategy [4, 9, 10]. In high-risk women including carriers of the breast cancer gene (BRCA) mutation, a two-stage approach for the prevention of ovarian cancer is recommended and has been widely adapted: early salpingectomy in the early premenopausal state, followed by subsequent oophorectomy. The ACOG and SGO also recommend that opportunistic salpingectomy can be considered to prevent ovarian cancer [5, 11-13].

Furthermore, how aging affects the prevalence of endosalpingiosis still remains to be elucidated. In our study, the mean age was 51.31 ± 8.52 years. Similarly, in the study of Gan *et al.* [5] the mean age was 54.8 ± 5.0 years and 44% of the patients were premenopausal women. In addition, we evaluated 105 ovarian tissues in 54 pre- and postmenopausal women and detected PTE in 20 ovarian tissues separately. No evidence of tubal carcinoma or STIC, ovarian serous or other neoplasia was observed in any of the cases. If these patients underwent salpingectomy to pro-

tect their ovaries for risk reduction, the etiological factor of ovarian carcinogenesis would be present in 20 ovarian tissues in 16 patients. If we consider tubal carcinogenesis as a potential precursor for serous ovarian cancers, risk-reducing salpingectomy is unable to demonstrate the expected protective effect in all patients. Therefore, one can speculate that the PTE on the ovaries may continue to constitute a potential role for ovarian carcinogenesis.

In the current study, the rate PTE was found to be significantly higher on the ovarian tissues of the patients who had pelvic adhesions during the operation, compared to those without pelvic adhesions. In addition, four patients with bilateral PTE had adhesions. Adhesions observed in these cases were thought to be secondary to pelvic infection. Inflammatory processes may cause epithelial proliferation and hyperplasia in the tubal mucosa [4, 6]. As a result of this tubal proliferation spilling from the distal end, implantation on the ovaries and pelvic peritoneum may become easier.

In a recent study, Wong *et al.* [14] examined the completeness of salpingectomy for ovarian cancer risk reduction and found residual salpingeal tissues in 5.6% of ovaries following salpingectomy. Of the ovaries with residual salpingeal tissues, there was no significant difference in level of surgeon (attending versus resident) or type of surgery (minimally invasive versus laparotomy). The authors concluded that salpingectomy was effective to remove salpingeal tissue from ovaries, supporting the use of prophylactic salpingectomy for ovarian cancer risk reduction in clinical practice. In another study, Ayres *et al.* [15] investigated the possible direct attachment of the fimbria to the ovary in surgically removed tubal and ovary specimens and reported the rate of PTE as 15%. Previous studies have demonstrated that the prevalence of endosalpingiosis varies between 3.5 and 12.5% [4]. In their prospective study, Gan *et al.* [5] reported that 16% of women or 10% of adnexae evaluated separately had fimrial tissue implants after ipsilateral salpingectomy. The relatively high rate of PTE (22%) in our study can be attributed to the concurrent evaluation of the tubular epithelium and endosalpingiosis and careful histopathological examination. Also, these results indicate the role of endosalpingiosis in the development of ovarian and pelvic serous neoplasia without tubal STIC.

About 30 to 40% of high-grade serous cancers have been shown to be associated with STIC at the 1/3 tubal distal end [16]. Retrospective studies reported that opportunistic salpingectomy could reduce the risk of serous carcinoma by 50% in high-risk patients (BRCA1 and BRCA2 carriers) [17, 18]. Another problem is the potential of tumor development of ovarian and adjacent peritoneum, which is the other major origin of these tumors. It is known that 50% of women carry a TP53 gene mutation containing at least one epithelial structure of the cytotoxic ovulation fluid [19, 20].

Risk-reducing BS substantially reduces the risk of cancer development by eliminating the precursor neoplasms in high-risk women. The most important problem at this stage is that whether there is a precursor escape before risk-reducing salpingectomy or the presence of ongoing endosalpingiosis and preneoplastic lesions which may develop in the secondary Müllerian system. Therefore, one of the most important strategies to prevent ovarian cancer after risk-reducing salpingectomy appears to be the effective and widespread use of tests specifically developed for cancer susceptibility genes and germ-line mutations [7, 21]. We believe that future studies investigating the role of PTE on the ovarian and pelvic peritoneal surfaces without tubal invasive carcinoma or STIC in the neoplastic process would provide a further contribution to this topic.

Nonetheless, there are some limitations to the present study including the lack of high-risk cases (BRCA1 and BRCA2) for the development of ovarian cancer, and cases with previous salpingectomy or tubal ligation. In such cases, ovarian tissue does not provide information about the presence of ectopic tubal epithelium and endosalpingiosis. However, these subjects would be investigated in our future studies.

In conclusion, fimbrial tissue may persist on the ovarian surface following salpingectomy, indicating that salpingectomy does not prevent all epithelial ovarian cancers. Further studies are warranted to gain a better understanding of the benefit of risk-reducing salpingectomy to prevent ovarian cancer and to translate our current knowledge into the practice which may be the most appropriate for the patients.

## Ethics approval and consent to participate

All patients were informed about the nature of the study and a written informed consent was obtained. The study protocol was approved by the Ethics Committee for Non-Invasive Clinical Research of Dokuz Eylul University, Faculty of Medicine (No. 2019/04-27). The study was conducted in accordance with the principles of the Declaration of Helsinki.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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