Opportunistic salpingectomy during hysterectomy for benign indications in women at low and high risk for ovarian cancer: a cross-sectional study

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Abstract

Objective

Our study aims to evaluate the role of pathology evaluation of fallopian tubes during hysterectomy for benign indications for the purpose of early detection of serous tubal intraepithelial carcinoma (STIC) in women at high and low risk for ovarian cancer.

Material and methods

This cross-sectional study was conducted at Minia Maternity University Hospital, Egypt, between June 2015 and December 2017. Our study included all women undergoing hysterectomy for benign conditions in the genital tract. Appropriate histories were taken, as well as physical exams, and laboratory and ultrasound evaluations were done prior to scheduling surgery. Abdominal hysterectomies including opportunistic salpingectomies were performed and the whole specimens including the tubal fimbria were sent to the pathology lab for histo-pathological examination.

Results

A total of 526 patients met inclusion criteria for this study. The mean age of the study participants was 49.75±8.95 years, the mean parity was 3.91±1.62 and the mean BMI was 24.21±2.38 Kg/m2. The most common surgical indications for hysterectomy were postmenopausal bleeding (34.6%), a clinically benign adnexal/pelvic mass (31.7%), and menorrhagia (24.7%). The fallopian tubes were found to have either no pathology or benign conditions in 500 out of the 526 patients. Among these patients, 56% had no pathologic abnormality. The most common benign conditions were paratubal cysts (25%), endometriosis (9%), torsion (2%) and hydrosalpinx (1%). STIC was identified in the fallopian tubes of 8 out of 526 patients.

Conclusions

Microscopic examination of the entire fimbriae from all patients regardless of the clinical context represents a novel method of early detection of sporadic tubal carcinoma, a putative precursor to advanced-stage pelvic cancer.

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Introduction

In 2016, an estimated 229,875 women were living with ovarian cancer in the United States, and the number of related deaths was 7.0 per 100,000 women per year.[1] Ovarian cancer was the seventh most common cancer diagnosed among women in the world, and fifth most common cancer diagnosis among women in more developed regions. The world rate was 6.3 per 100,000, and is higher in developed countries and compared to others.[2]

Recent data suggest that intraepithelial carcinoma of the fallopian tube [serous tubal intraepithelial carcinoma (STIC)] is the precursor of high-grade extra-uterine serous carcinoma.[3] Pelvic serous carcinoma is currently the most lethal gynecologic cancer in the United States. The need for early detection is evident as most women present at an advanced stage and survival is poor.[4]

Progress has been made in developing algorithms for identifying and managing patients at high risk for hereditary breast and ovarian cancer (HBOC) syndrome due to BRCA1 or BRCA2 germline mutation[5], however, HBOC accounts for only a minority (10% to 15%) of cases of pelvic serous carcinoma.[6]

The vast majority is sporadic, and effective screening tools for sporadic ovarian cancer remain elusive.[7] A novel approach to early diagnosis is needed. The new paradigm for the pathogenesis of pelvic serous carcinoma may provide an opportunity for early detection.[8] Since it is now recognized that the earliest form of pelvic carcinoma in asymptomatic women with a BRCA mutation typically presents as a noninvasive high-grade STIC, examination of the fimbriae can be viewed as an early detection tool in patients at risk for HBOC who undergo risk-reducing salpingo-oophorectomy (RRS).[9] The diagnosis requires complete and systematic pathologic evaluation of the fallopian tubes using a special protocol for specimen dissection since most STICs in this setting are occult.[10]

The hypothesis of our study is that early cancer detection can also be accomplished in women at low risk for HBOC using similar systematic evaluation of fallopian tubes incidentally removed during surgery for benign indications. Some experts now advocate RRS in low-risk women undergoing tubal sterilization, hysterectomy, or other pelvic surgery for benign indications, so-called opportunistic salpingectomy.[11]

Systematic pathologic evaluation of these low risk fallopian tubes may translate to significant benefits at a population level. Currently, more than 500,000 benign hysterectomies and 600,000 tubal ligations are performed annually in the United States.[12] If these procedures were to include bilateral RRS; the fimbriae could serve as a target for early detection of pelvic cancer.

Therefore, our study aims to evaluate

the role of the evaluation of fallopian tubes removed during hysterectomy for benign indications in early detection of STIC in women at high and low risk for ovarian cancer

Materials and methods

This was a cross-sectional study conducted at Minia Maternity University Hospital, Egypt between June 2015 and December 2017. The Institutional Ethical Review Board approved the study protocol. Our study included all women undergoing hysterectomies for benign conditions in the genital tract.

We excluded women with intraoperative findings of any malignancy and those with tubal specimens that did not contain fimbriae.

We obtained a written informed consent from all women before participationand after discussing the nature of the study. Patients were recruited from the outpatient gynecology clinic. First, the participating women were enrolled in the screening phase of the study. This phase included taking histories, clinical examinations, ultrasound evaluations and full laboratory investigations. After clinical evaluation and consent, abdominal hysterectomies, including opportunistic salpingectomy, were performed and whole specimens including the tubal fimbria were sent to the pathology lab for histo-pathological examination.

Our protocol is similar to those described by others, including the so-called SEE-FIM protocol.[10] In brief; tubes were fixed in formalin before slicing at 3-mm intervals. The fimbriae were sliced parallel to the length of the

plicae, and the non-fimbriated portion of the tube was sliced in cross-sections. All tissue slices were submitted for microscopic examination with a single hematoxylin and eosin (H&E)-stained slide prepared from each tissue block.

Our protocol also included standardization of diagnostic criteria. Malignancy of the fallopian tube mucosa was classified as STIC or invasive tubal carcinoma. A diagnosis of STIC required the presence of unequivocal morphologic and immune-histochemical criteria.

Criteria for STIC include:

- cellular crowding

- stratification

- loss of polarity

- nuclear enlargement

- hyperchromasia

- atypical nuclear contours

- mitoses

- loss of cilia

Invasive carcinoma is diagnosed when:

- Tumor cells form a confluent solid or papillary mass or

- Present below the basement membrane, growing into the submucosal connective tissue.

Results:

Among the population that had been admitted to our center during the period

of the study, a total of 526 patients met inclusion criteria for this study (516 patients were low risk and 10 patients were high risk for ovarian cancer). The mean age of the study participants was 49.75±8.95 years, the mean parity was 3.91±1.62 and the mean BMI was 24.21±2.38 Kg/m2. The most common surgical indications for hysterectomy were postmenopausal bleeding (34.6%), a clinically benign adnexal/pelvic mass (31.7%), and menorrhagia (24.7%).

Table1. Main pathologic diagnoses in uterus or ovary

Diagnosis	Number of patients
In uterus	
Leiomyoma	171
Adenomyosis	125
Endometrial hyperplasia with atypia	16
Endometrial hyperplasia without atypia	121
Atrophic endometritis	40
No major pathologic abnormality	75
In ovary	
Benign serous cyst	147
No major pathologic abnormality	208
Endometriosis	47
Benign mucinous cystadenoma	42
Mature teratoma	10
Functional cysts	40
Fibroma	10
Ovarian abscess	5
Torsion	10
Occult high-grade serous carcinoma	2
Granulosa cell tumor	3
Brenner tumor	1
Borderline mucinous ovarian tumor	1

The most common surgical procedures performed for patients were bilateral salpingo-oophorectomy with hysterectomy (31.7%), bilateral salpingectomy with unilateral oophorectomy and hysterectomy (19.5%), and bilateral salpingectomy with hysterectomy (15%).

The main pathologic findings in hysterectomy specimens were summarized in **(Table 1)**. The ovarian pathologic findings were also mentioned in Table 1. All cases were benign except in three patients. The first presented with a clinically suspected adnexal mass and was found to have ovarian high-grade serous carcinoma. The second patient presented with a clinically benign ovarian cyst was found to have a borderline mucinous tumor. The third patient, who had a family history of breast carcinoma, was found to have ovarian high-grade serous carcinoma and STIC of the ipsilateral fallopian tube.

Table 2. Fallopian tube histopathology

Diagnosis	Number of patients
STIC	8
Atypical mucosal proliferation	15
Invasive carcinoma	3
No pathologic abnormality	298
Tubal endometriosis	47
Paratubal cysts	136
Tubo-ovarian abscess	4
Hydrosalpinx/chronic salpingitis	5
Torsion	10

The fallopian tubes were found to have either no pathology or benign conditions in 500 out of the 526 patients **(Table 2).** Among these patients, 56% had no pathologic abnormality. The most common benign conditions were paratubal cysts (25%), endometriosis (9%), torsion (2%) and hydrosalpinx

(1%). STIC was identified in the fallopian tubes of 8 out of 526 patients (one in the high risk group represented 10% of cases and seven in the low risk group represented 1.3% of cases). Five patients were suspected to have benign ovarian cysts, and one patient presented with ovarian high-grade serous carcinoma. The ovaries of the last two patients showed no pathological abnormalities **(Figure 1)**.

The fallopian tubes were grossly normal in six patients and contained cysts in the other two patients. STIC was confined to the fimbriae in five patients, involved both the fimbriae and non-fimbriated tube in two patients, and involved only the non-fimbriated tube in one patient. STIC was multifocal in all patients except three. The linear span of the mucosa involved by STIC ranged from 1 to 5mm. Seven STICs had a flat growth pattern, and one grew in an exophytic, tufted, micropapillary pattern **(Table 3).**

The ovary of the eighth patient with STIC contained occult high-grade serous carcinoma. This 47-year-old patient had a family history of breast cancer (high risk) and a long-standing history of pelvic pain from a fibroid uterus and endometriosis.

Fifteen of 526 patients had an abnormal mucosal proliferation of the fallopian tube but failed to meet full criteria for a diagnosis of STIC. There were proliferations with mild atypia of

unknown clinical significance of the sort that Vang and colleagues designate as "normal/reactive in their classification system.[13]

The most common surgical indication was an adnexal cyst. Except in the case of four patients with marked adhesions, both tubes were removed.The gross appearance of the tubes was normal in 11 patients; while cysts and surface adhesions were grossly visible in the tubes of 4 patients. The ovarian pathology was benign in all patients. These mucosal proliferations involved unilateral fimbriae in nine patients, bilateral fimbriae in fivepatients, and a non-fimbriated tube in one patient. The linear span of these proliferations was <1mm in all cases. None of these 15 patients underwent surgical staging, received adjuvant therapy, or were referred for genetic risk assessment.

Three of 526 patients had invasive carcinoma of the fallopian tube (all of them were from the low risk group) **(Table 4).** The tumor was present below the basement membrane, growing into the submucosal connective tissue **(Figure 2)**. Postmenopausal bleeding was the most common surgical indication. Both tubes were removed in all three patients. The ovarian pathology was benign in all except one patient, who showed occult high-grade serous carcinoma.
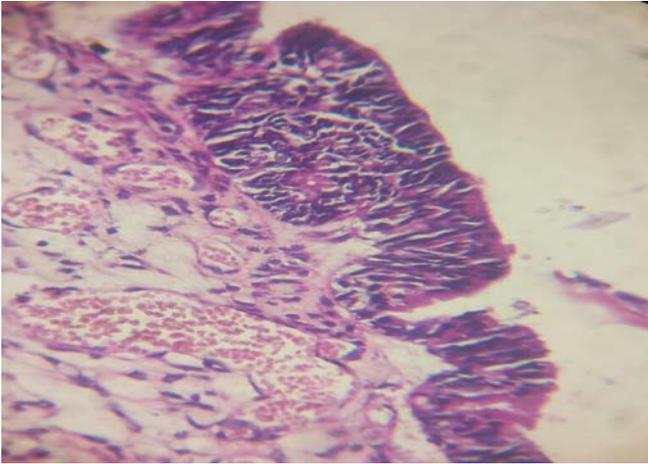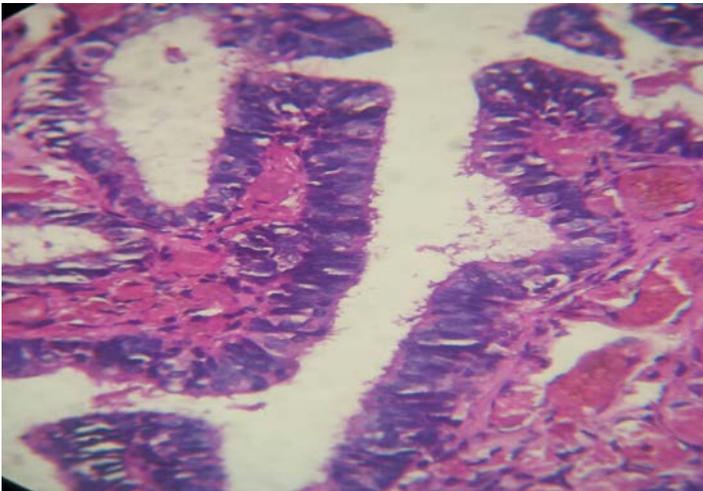
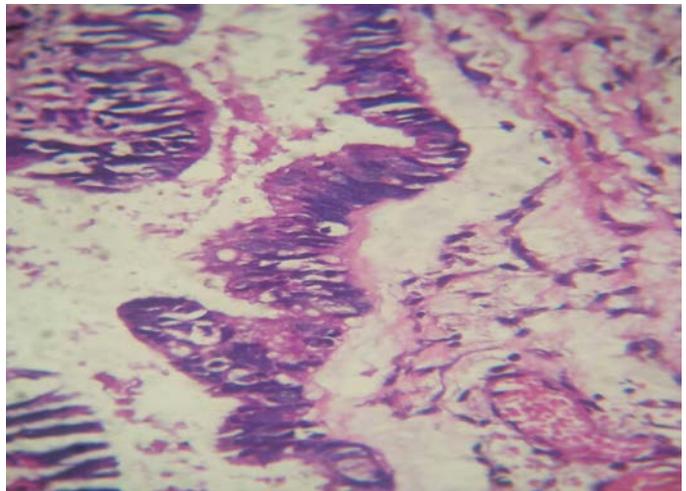(a)   (b)
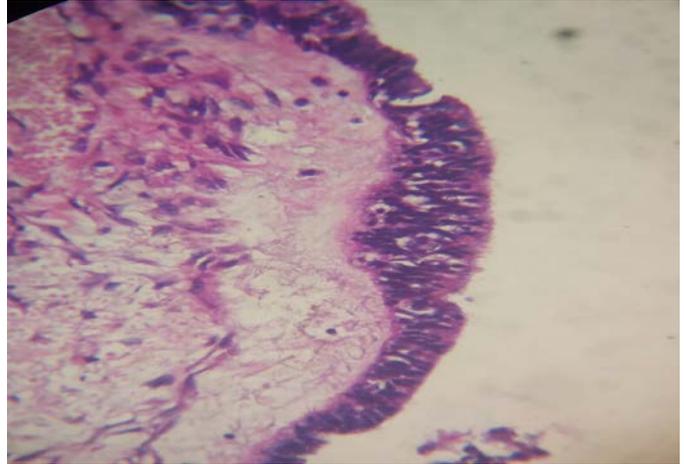
(c)   (d)

Figure 1.STIC was confined to the non-fimbriated portion of the tube in case (a, b) and confined to the fimbriae in case(c, d)

Table 3. Analysis of STIC cases

Case Number	Age	Surgical Indication	Initial Surgery	Gross Pathology in Tubes	Ovarian Diagnosis	Location of STIC	Focality of STIC	Growth Pattern of STIC	Size of Tumor (mm)	Clinical Risk for HBOC
1	67	Adnexal mass	TAH-BSO	None	Serous cystadenoma	Unilateral fimbriae	Single focus	Flat	1	Low risk
2	57	Postmenopausal bleeding	TAH-BSO	None	Mucinous cystadenoma	Unilateral fimbriae	Single focus	Flat	1.5	Low risk
3	70	Postmenopausal bleeding	TAH-BSO	Tubal cyst	No major pathology	Unilateral non-fimbriated tube	Two foci	Flat	4	Low risk
4	40	Adnexal mass	USO	None	Mature teratoma	Unilateral fimbriae	Single focus	Flat	1.5	Low risk
5	59	Adnexal mass	TAH-BSO	None	Serous cystadenoma	Mostly in non-fimbriated tube	Multiple foci	Flat	3	Low risk
6	52	Postmenopausal bleeding	TAH-BSO	None	No major pathology	Unilateral fimbriae	Multiple foci	Flat	2	Low risk
7	47	Pelvic mass	TAH-BSO	Tubal cyst	Ovarian high-grade serous carcinoma	Unilateral fimbriae	Multiple foci	Flat and micropapillary	5	High risk
9	61	Adnexal mass	TAH-BSO	None	Serous cystadenoma	Mostly in non-fimbriated tube	Two foci	Flat	2.5	Low risk

TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; USO, unilateral salpingo-oophorectomy

Discussion

The standard of care for pathologic evaluation of grossly normal fallopian tubes removed for benign indications in women who are not at high risk for HBOC has been a single representative tissue section per tube.[14,15] Until recently; the fimbriae have been largely ignored in low-risk patients from a diagnostic perspective. It is now established that it is the fimbriated end of the tube that is most likely to harbor an occult cancer in high-risk patients.[10, 16, 17]

Some authors are suggesting that the standard of care should be redefined such that the fimbriae are evaluated routinely in low as well as in high risk patients to detect occult tubal cancer.[18] Pathologists outside of academic practices may have also begun to extrapolate sampling protocols from high-risk patients to low-risk patients and may be directing attention to the fimbriae. However, the benefits, limitations, costs, and clinical management implications have not been fully studied in a prospective manner.

Table 4. Analysis of invasive carcinoma cases

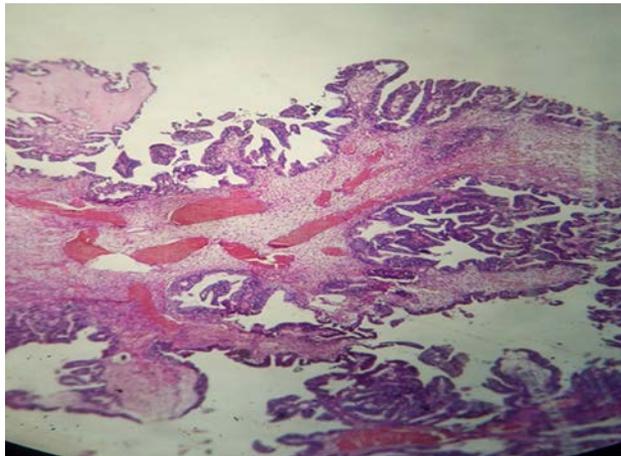| Case	Age	Surgical Indication	Initial Surgery	Gross pathology in tubes	Ovarian Diagnosis	Clinical Risk for HBOC
1	58	Postmenopausal bleeding	TAH-BSO	None	Occult high-grade serous carcinoma	Low risk
2	60	Postmenopausal bleeding	TAH-BSO	None	No major pathologic abnormality	Low Risk
3	47	Adnexal mass	TAH-BSO	None	Serous cystadenoma	Low Risk

Figure 2. Invasive tubal carcinoma

Our study demonstrates that the presence of tubal carcinoma would have gone undetected in the specimens of 7 of 516 low-risk women and 1 of 10 high risk women had the current standard of care for tissue sampling been used. Thus, systematic examination of the fallopian tube fimbriae in low and high risk women will indeed identify cases of early-stage tubal cancer that would otherwise have not been recognized.

Our findings cannot be directly translated to estimate the incidence of STIC in the general population of women at low or high risk for high-grade pelvic serous carcinoma because of the study design limitations. These limitations include the small sample size, the exclusion of women with any form of malignancy in the female genital tract and the restriction of the high-risk population to those who have elevated HBOC risk. The clinical significance of STIC in low-risk patients is unknown. The follow-up time in our study is too limited to draw any conclusions about behavior; however, at least three of our patients had concurrent invasive tubal carcinoma, and one of them had occult ovarian cancer. Thus, the possibility of concurrent advanced-stage occult cancer should be considered in low as well as high risk patients found to have STIC. If STIC is neglected in low-risk patients, it can subsequently progress to advanced-stage pelvic cancer.

Since the development of STIC is also likely related to patient age, it may be reasonable to propose enhanced tissue sampling strategies as a function of

patient age.

In our study, all the patients with STIC were over the age of 40, which may represent a minimum age for defining concern for STIC in low and high-risk women. In our study most of the STIC cases presented with a grossly cystic ovary (either an epithelial cystic neoplasm or cystic teratoma), so whether ovarian findings should also guide concern for occult STIC should be considered.

The main source of STIC is the fimbria (five of eight cases STIC and 14 of 15 cases atypical mucosal proliferation), so we propose that it is reasonable to examine the entire fimbriae but only a representative section of the non-fimbriated tube. It is conceivable that this protocol may miss a rare case in which STIC is restricted to the unsampled non-fimbriated tube without involving the fimbriae. The small sample size and the low number of cases of STIC may not be statistically adequate to comment on how rare such a case might be in low-risk patients.

In our study, one patient with atypical mucosa in the fimbriae was found to have a STIC in the non-fimbriated tube. Thus, any atypia in the fimbriae requires examination of all remaining tissue from the non-fimbriated portions of both fallopian tubes. When the dissection of the tube is carefully performed at slice intervals no thicker than 2 or 3 mm, there is no need to examine more than a single H&E stained slide per tissue block. In addition, automatic deeper levels are not needed when these dissection conditions are practiced.[17]

It is worth considering that a pathologic diagnosis of unknown clinical or genetic significance may provoke concern and/or anxiety in the clinician and/or patient since appropriate management remains to be defined. This is one of the potential negative effects of increasing surveillance for STIC in low-risk patients, since a subset of patients will be found to have STIC. The potential for overdiagnosis of STIC is similarly undesirable. The risks for overdiagnosis or underdiagnosis of atypical findings remain unknown. As pathologists are being guided to direct more attention to the fallopian tubes, familiarity with diagnostic criteria becomes paramount.

Conclusions

We propose that our results support changing the standard of care for sampling unremarkable fallopian tubes in all patients especially those who are at low risk for HBOC.

Our protocol recommends microscopic examination of the entire fimbriae from all patients regardless of the clinical context. This represents a novel method for early detection of sporadic tubal carcinoma, a putative precursor to advanced-stage pelvic cancer. As there is an increase in opportunistic salpingectomy in women undergoing benign pelvic surgeries such as hysterectomy, examination of the tubal fimbria as mentioned previously may help in identifying the earliest stage of tubal carcinoma, especially in low risk patients.

Further studies are also needed to detect the long term behavior of STIC and the behavior of various forms of atypical mucosal proliferations in low-risk patients.

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