<u>**Title**</u>

**Persistence of Fimbrial Tissue on the Ovarian Surface Following Salpingectomy**

<u>**Running title**</u>

Persistent fimbrial tissue on ovarian surface

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**Condensation and short version of title**

**Short title:**

Persistent fimbrial tissue on ovarian surface

**Condensation:**

Residual fimbrial tissue remains on the ovarian surface in a significant proportion of cases

post salpingectomy. This could serve as a site for ovarian carcinogenesis.

**Abstract**

**Background**

Salpingectomy is recommended as a risk-reducing strategy for epithelial tubo-ovarian cancer. The gold standard procedure is complete tubal excision.

**Objective**

To assess the presence of residual fimbrial/tubal tissue on ovarian surfaces following salpingectomy.

**Design**

Prospective analysis of patients undergoing salpingo-oophorectomy +/- hysterectomy for benign indications, early cervical cancer or low risk endometrial cancer at a UK National Health Service Trust. Salpingectomy +/- hysterectomy was performed initially, followed by oophorectomy within the same operation. Separately retrieved tubes and ovaries were serially sectioned and completely examined histologically. The main outcome measure was histologically identified fimbrial/ tubal tissue on ovarian surface. Chi-square/Fisher's exact tests evaluated categorical variables (SPSS-23).

**Results**

25 consecutive cases (mean age= 54.8 years (SD=5.0), comprising 41 adnexae (9= unilateral, 16= bilateral) were analysed. 17 (68.0%), 5 (20.0%) and 3 (12.0%), procedures were performed by consultant gynaecologists, subspecialty/specialist trainees and consultant gynaecological oncologists respectively. 12/25 (48.0%) were laparoscopic and 13/25 (52.0%) involved laparotomy. 4/25 (16.0%, CI: 4.5%, 36.1%) patients or 4/41 (9.8%, CI: 2.7%, 23.1%) adnexae showed residual microscopic fimbrial tissue on the ovarian surface.

Tubes/ ovaries were free of adhesions in 23 cases. Two cases had dense adnexal adhesions but neither had residual fimbrial tissue on the ovary. Residual fimbrial tissue was not

significantly associated with surgical route or experience; (consultant= 3/20 (15%), trainee= 1/5 (20%), p=1.0).

**Conclusion**

Residual fimbrial tissue remains on the ovary following salpingectomy in a significant proportion of cases and could impact the level of risk-reduction obtained.

**Keywords**

High-grade serous carcinoma, ovarian cancer, ovarian surface, prophylactic surgery, residual fimbrial tissue, salpingectomy

**Introduction**

Ovarian cancer (OC), principally its commonest histotypes, high-grade serous ovarian carcinoma (HGSC), is the leading cause of deaths from gynaecological cancers. OC is responsible for 4271 deaths/year in the UK, 42,700 deaths/year in Europe, 14240 deaths/year in the USA and 152,000 deaths/year worldwide.[1, 2] Despite advances in treatment there have been only marginal improvements in survival over the last 20 years.[3] Screening for this disease has not yet been shown to reduce mortality,[4] leading to a drive for exploring newer prevention strategies.

There is increasing evidence that the fallopian tube plays a central role in the origin of HGSC[5-9] and serous tubal intraepithelial carcinoma (STIC) is established as a precursor lesion, present as a continuum with early tubal carcinomas, supporting transition from insitu to invasive cancer.[10] We too have previously seen high-grade serous carcinoma (HGSC) involving fimbrial tissue on the ovarian surface (Figure-1). The growing evidence in favour of tubal origin of epithelial ovarian cancer has led to opportunistic bilateral salpingectomy (OBS) being recommended as an OC prevention strategy for premenopausal women who have completed their family and are undergoing tubal sterilisation or other benign gynaecological surgery.[9] Tubal ligation and hysterectomy itself are associated with a reduction in OC risk.[11] Supporting evidence for salpingectomy also comes from a 35%-42% reduction in OC risk reported on retrospective analysis of Swedish[12] and Danish[13] population based data sets, although in the Swedish study this was limited by lack of control for the contraceptive pill and the number of OC cases in the bilateral salpingectomy subgroups is small. Additionally in high risk women (e.g. *BRCA* carriers) ongoing studies are evaluating the

feasibility of premenopausal early salpingectomy and delayed oophorectomy as an ovarian function preserving two-step method for preventing OC.

Some centres have changed clinical protocols to incorporate OBS into practice.[14] Recent guidelines from the American Congress of Obstetricians and Gynecologists (ACOG)[15] and Society of Gynecologic Oncology (SGO)[16] recommend OBS be considered as an OC prevention strategy whilst also highlighting the need and importance for further trials to confirm the validity and benefit of this approach. We found that around 30% of UK clinicians are currently undertaking this procedure, while 89% would support a prospective trial.[17] Prospective data on the level of reduction in OC risk following salpingectomy are lacking. Additionally, the presence of residual tubal tissue on the ovarian surface following salpingectomy has not been prospectively evaluated. This could have potential implications for the level of risk reduction. We present data which prospectively reports on the presence of residual microscopic fimbrial tissue on the ovarian surface following salpingectomy.

**Methods:**

Patients

Patients undergoing salpingo-oophorectomy +/- hysterectomy (laparoscopic or laparotomy) for benign indications, early cervical cancer or low-risk endometrial cancer were included. Patients with other pelvic malignancy, previous bilateral salpingectomy or bilateral oophorectomy were excluded.

Salpingectomy Procedure

The surgical procedure was undertaken in two steps within the same operation. Salpingectomy with or without hysterectomy (as indicated) was performed initially. This was

followed by bilateral oophorectomy as a second step within the same operation. Thus overall each patient had the same planned elective surgical procedure. The ovaries and tubes removed were sent in separately labelled pots: right tube, left tube, right ovary and left ovary. In some specimens, fallopian tubes remained attached to the uterus. Intra-operative findings were documented using a customised form (supplementary table-1). Procedures were undertaken by consultant gynaecologists, consultant gynaecological oncologists and specialist or subspecialty trainees in gynaecological oncology.

Histopathological examination of fallopian tubes and ovaries:

Histological assessment was undertaken by a team of two gynaecological pathologists at the Royal London Hospital (NS and AF). Fallopian tubes were serially sectioned according to SEE-FIM protocol (Sectioning and Extensively Examining the FIMbriated end of the fallopian tube).[18] This protocol entails lengthwise sectioning of the fimbriated portion of the tube to maximize exposure of the tubal plicae with maximum serial sectioning of no more than 2-3mm apart. The ovaries were also serially sectioned in their entirety and examined for presence of any remnant tubal tissue. The uterus where removed was assessed in accordance with routine histological protocol and the surgical indication. Histological slides stained with hematoxylin and eosin (H&E) were reviewed by both gynaecological pathologists. Confirmation and agreement by both pathologists was obtained in cases where fimbrial tissues were identified.

Consecutive patients fulfilling the inclusion criteria within the Barts Health Cancer Network were identified between 1st October 2015 and 5th January 2016. This was done through close liaison between gynaecological oncology team, benign gynaecology consultants linked to the cancer network, administrative assistants as well as review of the online surgical diary

at Royal London Hospital. Of the 39 consecutive cases identified, 25 were finally suitable for analysis. 14 were excluded for the following reasons: (a) protocol deviation, with all specimens sent to the pathology lab in error in the same single pot (n=4); (b) planned case not performed as patient not fit on the day (n=4); (c) case not deemed suitable by operating surgeon due to significant adnexal pathology and surgical difficulty (n=6).

This project was approved by the Clinical Effectiveness Unit (CEU) and Research and Development (R&D) team at Royal London Hospital, Barts Health NHS Trust (UK) as a clinical effectiveness audit (Project ID=5855). Permission for data analysis and submission for publication was given. This project was not funded through any grant. It is supported by the Department of Gynaecological Oncology, Royal London Hospital, London, UK and Barts Cancer Institute, Queen Mary University, London, UK.

Assuming a null hypothesis or gold standard of '1'% specimens having residual tubal tissue, for a power of 80% and α=0.05, the sample size for identifying 10% specimens with residual tubal tissue is 25. Baseline characteristics were described using descriptive statistics. Chi-square/Fisher's exact and Mann-Whitney tests were used to evaluate differences between categorical and continuous variables respectively. Statistical analyses were performed on SPSS version 23 (IBM Corp 2010 Armonk, NY).

**<u>Results</u>**

Forty-one adnexae (9 unilateral and 16 bilateral) from 25 patients were analysed for histological presence of tubal fimbrial tissue on the ovary. The mean age of patients was 54.8 years (SD=5.0, range 45-64). Table-1 describes the indications for surgery. A summary of all the cases, including procedure undertaken, age, presence of intra-operative adhesions

and fimbrial tissue on the ovary at histology, is given in Table-2. Twelve (48.0%) and 13 (52.0%) cases were carried out by laparoscopy and laparotomy respectively. All patients undergoing hysterectomy had hysterectomy with salpingectomy (tubes attached to the uterus) followed by oophorectomy as a two-step procedure. Consultant gynaecologists, subspecialty or specialist trainees and consultant gynaecological oncologists performed 17/25 (68.0%), 5/25 (20.0%) and 3/25 (12.0%) procedures respectively. Cases were randomly allocated depending on surgical list availability. The final histology following surgery was reported as benign in 19/25 (76%) cases and malignant in 6/25 (24%) cases (Table-2). No intra- or post-operative complications (based on Dindo-Clavien classification)[19] occurred. The mean blood loss for our study population was 230mls (SD=168.3). The mean duration of hospital stay was 2.2 days (SD=1.0).

Residual microscopic fimbrial tissue was found on the ipsilateral ovarian surface in four of 25 patients (16.0%, CI: 4.5%,36.1%) or 4/41 (9.8%, CI: 2.7%,23.1%) adnexae removed. This is illustrated in Figure-2. An objective measurement to quantify the residual fimbrial tissue in the four cases showed, the tissue measured (a) 3mm x 2mm x 1mm; (b) 2mm x 2mm x 2mm; (c) 4mm x 2.5mm x 2 mm; (d) 3mm x 2mm x 1.5 mm in the four cases respectively. All four cases occurred in women undergoing abdominal hysterectomy. There were two cases (one adnexa in each case) where dense adhesions were encountered intra-operatively. In one case fimbriae were densely adherent to the right ovary, with 2/3 of its fimbrial portion enclosed in adhesions. The other had involvement of the whole tube including the fimbrial portion being densely adherent to the ovary. However, in both cases the tubes were surgically separated from the ovaries and neither ovary showed any residual fimbrial tissue on the ovarian surface. Intraoperatively, there were no adhesions between the tube and

ovary in any of the other 23 patients. The fimbriae lay completely separately and were not found to touch the ovary (no fimbria ovarica seen) in any of these 23 patients.

The presence of fimbrial tissue was not significantly affected by the route of surgery (laparoscopic/ laparotomy) or experience of the surgeon. Although all fours cases with residual fimbrial tissue were performed by laparotomy, this association is not statistically significant (p=0.096) and given small numbers we feel it is probably due to chance. We don't think this relates to surgical technique. One of these four was performed by a specialist trainee (1/5) under direct supervision and three (3/20) by experienced consultant gynaecologists (p=1.0).

**Comment**

**Main Findings**

We found that 16% women or 10% adnexae had fimbrial tissue implants on the ipsilateral ovarian surface despite salpingectomy. Moreover these did not occur in cases with adhesions or any form of adherence of fimbriae/tube to the ovary. The ovaries lay completely separate and well away from the fallopian tubes in these cases. While surgical removal of an adherent tube (either due to adhesions or fimbria ovarica) may result in residual tubal/fimbrial tissue on the ovarian surface, these findings of implants on non-adherent ovaries in a considerable proportion of women were completely unexpected. This could represent a potential site for ovarian carcinogenesis. To the best of our knowledge this is the first prospective series evaluating the presence of residual fimbrial tissue which may remain after salpingectomy. We searched Medline and Embase databases using free text and thesaurus-based search terms:

Salpingectomy, fimbria, fimbriae, fimbrial tissue, residual tubal tissue, ovary surface, tubal implants, fimbrial implants, uterine tubal mucosa, salpingectomy and ovary.  We used three strategies:

1.  (('Salpingectomy') AND ('fimbria' OR 'fimbriae' OR 'residual fimbrial tissue' OR 'residual tubal tissue' OR 'ovary surface'))

2.  (('tubal implants' OR 'fimbrial implants' OR 'uterine tubal mucosa') AND ('salpingectomy'))

3.  (('tubal implants' OR 'fimbrial implants' OR 'uterine tubal mucosa') AND ('ovary'))

Details of the search strategy are given in supplementary table-2. Overall 125 abstracts were reviewed by two co-authors. No reports describing the presence of fimbrial tissue post salpingectomy were identified.


**Strengths and Limitations**

Our paper has several advantages, such as the prospective nature of this work, use of a serial sectioning histopathological protocol with strict pathological review by two experienced pathologists, as well as inclusion of both laparoscopic and laparotomy based surgical approaches. We excluded cases with benign or malignant adnexal pathology which may have the propensity to increase false positive findings. All our cases included macroscopic normally looking tubes and ovaries. A limitation is the small number of cases in our series. Additionally, four cases were excluded due to error in transport of histological specimens. However this series has sufficient power to detect a ≥10% incidence of residual fimbrial tissue, a level found in this study.

**Interpretation / Meaning:**

These findings are of crucial if not of critical importance as well as hypothesis generating. We suggest that clumps of fimbrial tissue may be shed from the fimbrial end of the tubes, some of which implant on the ovarian surface. However, it is also possible that fimbrial tissue adheres to the ovarian surface over repeated ovulatory episodes, and then may become detached from the tube. We hypothesise that this residual tissue may also undergo malignant transformation (just like fimbria present in the tube) following geno-toxic injury over a period of time. The presence of STIC/invasive lesions in the tubal tissue of women with OC reported in various series varies from 11-60%.[20-30] Our findings support the possible tubal origin of OC despite absence of STIC lesions in the tube as malignant transformation could have started in the fimbrial implants on the ovarian surface without involving the rest of the tube. It could also explain a recent finding of some STICs being genomically different to co-existent serous OC and thus metastasize.[31] It also corroborates the hypothesis that OC may arise in cortical inclusion cysts, as the fimbrial tissue found on the surface of the ovary, could get incorporated into these cysts and undergo subsequent malignant transformation.[32] Alternatively, the ovarian surface in conjunction with the fimbrial implant may rupture during ovulation and subsequently predispose fimbriae to malignant transformation. Ovarian surface epithelium at junction areas may contain a novel stem cell niche that is responsible for surface epithelium regeneration and subsequently prone to malignant transformation.[33]

We speculate that these fimbrial tissues may also be shed and implant on the peritoneal surface (just as on the ovary) but currently there is no conclusive histological evidence to support this possibility. However, if true, this could explain the occurrence of primary peritoneal cancer in low-risk women as well as in 4% *BRCA1/BRCA2* carriers despite bilateral

salpingo-oophorectomy.[34] It may also explain the presence of malignant peritoneal cytology found in some women at risk-reducing surgery without a co-existent invasive cancer/STIC lesion.[34]

The tubo-peritoneal junction (TPJ) has been suggested as a likely site for origin of serous OC, with STICs found at and in the immediate vicinity of the TPJ.[35] Transitional metaplasia is found in up to 26% of TPJs and it has been proposed that adnexal peritoneum, Fallopian tube epithelium and ovarian surface epithelium (OSE) should be viewed as a continuous unit[36]. Our data indicate another potential site for STICs which lies outside the TPJ, but within fimbriae shed on the ovarian surface. We found fimbrial implants in both pre-menopausal and post-menopausal women. However, a number of questions remain unanswered, including the precise mechanism and timing of shedding of fimbrial tissue as well as the duration for which this tissue may persist on the ovarian surface, and the lead time to malignant transformation after implantation on the ovary. We do not know if these fimbriae are shed due to hormonal or cell non-autonomous mechanisms occurring predominantly in the pre-menopausal period with fimbrial tissue subsequently remaining on the ovaries in postmenopausal women or whether this is an active process that also occurs after the menopause. These issues need to be addressed through future research. According to the tubal hypothesis it is fimbrial tissue which is the main cell of origin of HGSC. However, not all HGSC arise within the tube.[37] Recent genomic analysis of co-existent STIC and serous OC cases indicated STICs were precursors in only 50% cases.[31] Our findings thus may also help explain why salpingectomy prevents only a proportion of epithelial OC and will not prevent all cases. The issue of undertaking OBS in routine practice or within the context of a well-designed trial has been widely debated.[38] Early salpingectomy has also

been proposed as an alternative initial step (with a delayed oophorectomy in the menopause as a second step) for high risk women who want to avoid detrimental consequences of premature menopause[17]. Premature menopause itself is associated with a 3.03% increase in cardiovascular mortality, sexual dysfunction and osteoporosis.[39] A recent systematic review highlights the limited and low-quality of available evidence on level of OC-risk reduction and ovarian function associated with salpingectomy, with the large retrospective studies being limited by indication and detection bias.[40] There has been lack of clarity on a number of issues, namely the level of risk reduction, the long-term impact of salpingectomy on ovarian function or onset of premature menopause and the issues of cost-effectiveness of this approach.

Our results suggest fimbrial tissue persists on the ovarian surface despite salpingectomy. This could play a role in ovarian carcinogenesis and be one of the reasons why salpingectomy does not prevent all epithelial OC.  These data further highlight the importance and need for well-designed prospective trials/research to define more precisely the level of benefit of reduction in ovarian cancer risk obtained from salpingectomy as a surgical prevention strategy. This is required for both the low and high risk populations. This is essential to understand the balance of risks and harms of this intervention so that women can make properly informed decisions on whether or not to undergo this procedure.

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**Table 1. Indication for surgery**

| Indication | *n* (%) |
|---|---|
| | |

| | |
|---|---|
| Menorrhagia | 8/25 (32.0) |
| Pelvic mass | 2/25 (8.0) |
| Ovarian cyst | 4/25 (16.0) |
| Pelvic pain | 1/25 (4.0) |
| Postmenopausal bleeding | 4/25 (16.0) |
| *Others | 6/25 (24.0) |

*2 cases of confirmed cervical cancer (case number 14 and 21 see table-2), 3 cases of complex atypical

hyperplasia (case number 11, 23 and 25 see table -2), 1 case of risk-reducing salpingo-oophorectomy for BRCA

2 (case number 24 see table-2)

1    **Table 2- Summary of all surgical cases**

| Case No. | Age | Menopausal status | Indication for surgery/ Preoperative diagnosis | Procedure undertaken | Final Pathology | Stage (if malignant) | Adnexae included in analysis | Intraoperative adhesions | Residual fimbrial tissue on ovarian surface |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 52 | Pre-menopausal | Menorrhagia | Laparotomy TAHBSO | Benign leiomyoma | n/a | Both | No | Yes (left) |
| 2 | 50 | Pre-menopausal | Menorrhagia | Laparotomy subtotal hysterectomy + BSO | Benign leiomyoma | n/a | Both | No | No |
| 3 | 56 | Post-menopausal | Right ovarian cyst (benign) | Laparoscopic BSO | Simple serous cyst right ovary | n/a | Left | No | No |
| 4 | 52 | Pre-menopausal | Menorrhagia | Laparotomy TAHBSO | Benign leiomyoma | n/a | Both | No | Yes (left) |

| 5 | 53 | Pre-menopausal | Pelvic pain, fibroid uterus | Laparotomy TAHBSO | Leiomyomata | n/a | Both | No | No |
|---|----|----------------|------------------------------|--------------------|-------------|-----|------|-----|-----|
| 6 | 59 | Post-menopausal | Left ovarian mass (benign) | Laparoscopic BSO | Left ovarian fibroma | n/a | Right | No | No |
| 7 | 52 | Pre-menopausal | Menorrhagia | Laparotomy TAHBSO | Benign leiomyoma | n/a | Both | No | No |
| 8 | 63 | Post-menopausal | Benign endometrial biopsy but persistent PMB | Laparotomy TAHBSO | High grade mixed undifferentiated and endometriod carcinoma with LVSI (unexpected finding) | Ib | Both | No | No |
| 9 | 55 | Post-menopausal | Benign endometrial biopsy but persistent PMB | TLHBSO | Grade 1 endometriod endometrial carcinoma with MELF pattern (unexpected finding) | 2 | Right | No | No |
| 10 | 50 | Pre-menopausal | Menorrhagia | Laparotomy TAHBSO | Adenomyosis, leiomyomata, non-atypical hyperplasia | n/a | Left | No | No |
| 11 | 54 | Post- | Complex atypical | TLHBSO | Adenomyosis. Right ovarian | n/a | Both | Yes (dense | No |

| | | menopausal | hyperplasia on endometrial biopsy | | endometriosis and benign serous adenofibroma | | | adhesion right fimbriae & ovary) | |
|---|---|---|---|---|---|---|---|---|---|
| 12 | 55 | Post-menopausal | Right ovarian mass (benign) | Laparotomy TAHBSO | Fibroma - right ovary, serous cystadenomas and adenofibroma - left ovary + benign paratubal cysts bilaterally. | n/a | Right | No | No |
| 13 | 61 | Post-menopausal | Right ovarian mass (benign) | Laparoscopic BSO | Hilar cell hyperplasia - left ovary, mature cystic teratoma - right ovary and tube | n/a | Left | No | No |
| 14 | 45 | Pre-menopausal | Adenocarcinoma of cervix | Laparoscopic radical hysterectomy + BSO | Viloglandular adenocarcinoma of cervix with LVSI | 1b1 | Both | No | No |
| 15 | 64 | Post-menopausal | Left ovarian cyst | Laparoscopic BSO | Benign serous cyst – left ovary | n/a | Right | No | No |
| 16 | 50 | Pre- | Menorrhagia | LAVH + BSO | Adenomyosis | n/a | Both | No | No |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | menopausal | | | | | | | |
| 17 | 55 | Post-menopausal | Benign endometrial biopsy but persistent PMB | Laparotomy TAHBSO | Grade 3 endometriod endometrial carcinoma with LVSI | 2 | Both | No | Yes (left) |
| 18 | 55 | Post-menopausal | Left ovarian mass (benign) | Laparotomy TAHBSO | Dermoid - left ovary | n/a | Right | No | No |
| 19 | 62 | Post-menopausal | Grade 1 endometrioid endometrial cancer (stage 1A on MRI) | Laparotomy TAHBSO | Grade 1 endometriod endometrial carcinoma with focal LVSI | 1b | Both | No | Yes (left) |
| 20 | 52 | Pre-menopausal | Menorrhagia | Laparotomy TAHBSO | Benign leiomyoma | n/a | Both | No | No |
| 21 | 59 | Post-menopausal | Grade 1 squamous cell carcinoma of | Laparoscopic radical hysterectomy | Well differentiated squamous cell carcinoma of cervix | 1b1 | Both | No | No |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | cervix | and BSO | | | | | |
| 22 | 56 | Pre-menopausal | Menorrhagia | Laparotomy TAHBSO | Adenomyosis, benign leiomyomata | n/a | Right | No | No |
| 23 | 55 | Post-menopausal | Complex atypical hyperplasia on endometrial biopsy | TLHBSO | Atypical hyperplasia | n/a | Both | No | No |
| 24 | 45 | Pre-menopausal | Risk-reducing surgery for BRCA 2 mutation | Laparoscopic BSO | Benign ovaries and tubes | n/a | Both | Yes (dense adhesion left tube/fimbriae and ovary) | No |
| 25 | 59 | Post-menopausal | Complex atypical hyperplasia on endometrial biopsy | LAVH + BSO | Atypical hyperplasia | n/a | Both | No | No |

2

3    TAHBSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy, TLHBSO = total laparoscopic hysterectomy and bilateral salpingo-oophorectomy, LAVH/BSO

4    = laparoscopic assisted vaginal hysterectomy and salpingo-oophorectomy, BSO = bilateral salpingo-oophorectomy, LVSI = Lymphovascular space invasion, MELF =

5    microcystic elongated and fragmented, PMB = postmenopausal bleeding

6

**Figure caption and legends**

Figure-1: high grade serous carcinoma in fimbria adherent to ovarian surface

*High grade serous carcinoma (red arrow) in one of the fimbria (black arrows) adherent to the surface of the ovary.*

Figure-2: Fimbrial tissue implant on ovarian surface

*Fimbria (black arrows) adherent to the surface of the ovary.*