The post-reproductive Fallopian tube: better removed?

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ABSTRACT: Recently, the distal Fallopian tube has attracted considerable attention not only as site of origin for serous cancer in women with BRCA mutations, but also as the anatomical location where the majority of serous ovarian cancers apparently develop. Consequently, the Fallopian tube may be the unique location where early ‘ovarian’ cancers can be found—which would contradict the long-standing impression that the ovaries and the Fallopian tubes are always simultaneously involved. Based on the dismal prognosis associated with ovarian cancer and our inability to screen for early-stage disease, we discuss the rationale for introducing salpinges-hysterectomy as new clinical standard for women in need of hysterectomy and further weigh the arguments for and against bilateral salpingectomy as a sterilization method. There is no known physiological benefit of retaining the post-reproductive Fallopian tube during hysterectomy or sterilization, especially as this does not affect ovarian hormone production. On the other hand, the consequences associated with a surgical menopause provide a rationale for preserving the ovaries in premenopausal women. Prophylactic removal of the Fallopian tubes during hysterectomy or sterilization would rule out any subsequent tubal pathology, such as hydrosalpinx, which is observed in up to 30% of women after hysterectomy. Moreover, this intervention is likely to offer considerable protection against later tumour development, even if the ovaries are retained. Thus, we recommend that any hysterectomy should be combined with salpingectomy. In addition, women over 35 years of age could also be offered bilateral salpingectomy as means of sterilization.

Key words: Fallopian tube / hysterectomy / sterilization / ovarian cancer / cancer prevention

Introduction

Physiologically, the Fallopian tube transports sperm and egg cells and is a frequent site of fertilization. The crucial capture of the egg released from the ovary is accomplished by the fimbriated (distal) end of the Fallopian tube, which ‘floats’ in the pelvis over the ovarian surface and the peritoneum of the pouch of Douglas. However, the Fallopian tube’s propensity to act as a conveyor belt also enables cells and substances from the endometrium, the cervix, the vagina and the Fallopian tube itself to reach the free abdominal cavity (even in retrograde direction). Moreover, the sweeping motions of the fimbriae result in the shedding and spreading of transported ‘goods’ throughout the pouch of Douglas and subsequently the whole abdominal cavity. Accordingly, infections occurring in the Fallopian tube can give rise to pelvic inflammatory diseases. Apart from infection and inflammation (salpingitis), the most frequent clinical problem associated with the Fallopian tube is ectopic pregnancy.

Tumours of the Fallopian tube appear, in contrast, to be rare and are mostly detected by chance. Nevertheless, prophylactic salpingo-oophorectomies in women harbouring germline mutations in BRCA1 or BRCA2 revealed the frequent presence of serous intraepithelial carcinomas originating from the distal end of the Fallopian tube (Piek et al., 2001). This has raised the question whether serous ovarian or peritoneal carcinomas in the absence of proved BRCA1/2 mutations could also be of tubal origin. In line with this hypothesis, serous ovarian cancer was shown to co-exist with serous intraepithelial tubal carcinomas in >50% of all closely examined cases, no matter whether the patients belonged to a defined risk group or were afflicted with sporadic (non-familial) ovarian cancer (Kindelberger et al., 2007). Likewise, a thorough histopathological investigation of Fallopian tubes from women with primary peritoneal carcinomas of the serous subtype revealed the concomitant presence of serous intraepithelial tubal carcinomas in 47% of all cases (Carlson et al., 2008).

While the hypothesis that serous ovarian and peritoneal carcinomas (pelvic serous carcinomas) originate from the Fallopian tube is clearly supported by the simultaneous presence of serous tubal intraepithelial carcinomas in patients at high risk for ovarian cancer or with sporadic or familial ovarian cancer (Przybycin et al., 2010), additional evidence was provided by molecular geneticists who found characteristic mutations in p53 (‘p53 signatures’) in more than half of the investigated tubal tissues, irrespective of specific genetic risk factors (Marquez et al., 2005; Tone et al., 2008). Similarly, serous tubal intraepithelial carcinomas were found to share deregulations of oncogenic
pathways as well as alterations in p53 and in DNA repair genes with later stage pelvic serous carcinomas (Kindelberger et al., 2007). Even completely benign Fallopian tubes already showed microscopic lesions that likely precede histologically detectable serous tubal intraepithelial carcinomas and may thus contain the earliest precursor cells for a subsequent epithelial malignancy. Knowledge regarding the prevalence of p53 signatures and serous tubal intraepithelial carcinomas in apparently normal Fallopian tubes is scarce as tissues from patients with no known ovarian cancer risk are rarely assessed according to the SEE-FIM protocol (Medeiros et al., 2006). (SEE-FIM describes the procedure for Sectioning and Extensively Examining the Fimbria.) Available data are summarized in Table I. In line with this concept, a recent study has shown that transformed secretory epithelial cells from human Fallopian tubes can establish high-grade Müllerian carcinomas in mice (Kast et al., 2011).

Anatomically, the presumed tubal origin of pelvic serous carcinomas becomes all the more plausible as these intraepithelial carcinomas preferentially manifest at the fimbriated end of the Fallopian tube, which connects the ovarian and peritoneal surface epithelium. Of note, even microscopic lesions can shed malignant cells into the abdominal cavity, as evidenced by positive pelvic washings from patients whose carcinomas were completely confined to the Fallopian tube (Manchanda et al., 2011). Thus, the traditional assumption that serous carcinomas with extensive spread to the peritoneum, omentum and further abdominal organs are mostly of ovarian origin must be questioned. Notwithstanding these considerations, even those pelvic serous carcinomas that show only minimal involvement of the ovaries still tend to be classified as ovarian cancers.

Importantly, this re-consideration of pelvic cancer aetiology is more than a scholarly issue for onomatologists. Instead, an appreciation of the concept that the relatively frequent serous ovarian carcinomas likely originate from the fimbriated end of the Fallopian tube should have immediate consequences for prevention and therapy. Thus, also gynaecologists who have not specialized in oncology are now confronted with the question of whether the Fallopian tube should be removed during a hysterectomy or sterilization, while the contribution of an additional concomitant oophorectomy might also be reconsidered.

### Table I

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Median age (years)</th>
<th>p53 signature</th>
<th>STIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semmel et al. (2009)</td>
<td>1</td>
<td>69</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Shaw et al. (2009)</td>
<td>64</td>
<td>49</td>
<td>12 (19%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Lee et al. (2007)</td>
<td>58</td>
<td>59</td>
<td>19 (33%)</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

n.d., not determined.

None of these patients harboured BRCA1/2 mutations or had a family history of ovarian cancer. All fimbriae were histologically assessed according to the SEE-FIM ([Sectioning and Extensively Examining the Fimbria] protocol (Medeiros et al., 2006)).

### Hysterectomy and simultaneous oophorectomy

Among women of reproductive age, hysterectomy is (in developed countries) the second most frequently performed surgical intervention, superseded only by Caesarean section. In the USA, this amounts to roughly 600 000 hysterectomies per year. About 20 million women in the USA have undergone hysterectomy and about one-third of all 60-year-old women have had a hysterectomy (Whiteman et al., 2008). In 1999, simultaneous removal of the ovaries and Fallopian tubes was performed in 55% of hysterectomies, while back in 1965 these adnexes were only removed in 25% of all cases: the tendency to perform an additional salpingo-oophorectomy has thus more than doubled. Recent figures from the Agency of Healthcare Research and Quality (http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5105a1.htm; 5 August 2011, date last accessed) indicate that an additional salpingo-oophorectomy along with hysterectomy was performed in 50% of American women aged 40–44 years and in 78% of between 45 and 64 years. In absolute numbers, this means that every year about 300 000 US women with hysterectomy have undergone a prophylactic salpingo-oophorectomy, whereas another 300 000 US women with hysterectomy have retained their ovaries and Fallopian tubes.

Removal of the ovaries during hysterectomy is, indeed, a matter of debate (Hickey et al., 2010; Vitos et al., 2011). According to large case-control studies, oophorectomy and the resulting surgical menopause increase the long-term risk for cardiovascular, psychosexual and cognitive dysfunctions (Falkeborn et al., 2000; Rocca et al., 2007; Rivera et al., 2009). Moreover, a prospective study by Parker et al. (2009a) showed that oophorectomy along with hysterectomy lowers the risk for ovarian cancer, whereas the incidence of fatal and non-fatal coronary heart diseases increased. As only one in 1500 women aged 50 years and one in 400–600 women aged 60–70 years develop ovarian cancer in the course of one year (National Cancer Institute, 2004), ovarian cancer remains a relatively rare disease, responsible for 16 000 fatalities per year in the USA. Heart disease, in contrast, is a major killer causing 490 000 deaths among American women annually (Parker et al., 2007). Thus, an overall significant negative association of the effect of oophorectomy with mortality (all causes) was found. Moreover, none of the groups (or age groups) displayed a positive correlation between oophorectomy and increased survival (Parker et al., 2009a). In contrast, a recent study by Jacoby et al. (2011) failed to detect a significant increase in cardiovascular events after bilateral oophorectomy performed at the time of hysterectomy. However, while both the (Parker et al., 2007; Jacoby et al., 2011) studies investigated large sample sizes, follow-up times were considerably different, i.e. patients in the National Health Service study in the UK were followed for 24 years (Parker et al., 2009a), whereas data from the Women’s Health Initiative study (Jacoby et al., 2011) were evaluated for just 8 years after oophorectomy—which obviously limits the information content regarding the long-term effects on women’s health (Arnold and Colditz, 2011). Accordingly, a prophylactic bilateral oophorectomy may do more harm than good. The removal of the ovaries at the time of hysterectomy should thus be approached with great caution (Parker et al., 2009b), especially in premenopausal women.
This is reflected by a guideline from the American College of Obstetricians and Gynaecologists (ACOG), which recommends conservation of the ovaries, at least for premenopausal women with no known genetic risk for ovarian cancer (ACOG, Practice bulletin No. 89; 2008). Moreover, even for women at a high risk of developing cancer, the idea of performing risk-reducing bilateral salpingectomy followed by bilateral oophorectomy after the onset of the menopause appears somewhat plausible (Leblanc et al., 2011), even though this approach still has to be investigated (Greene et al., 2011).

For patients who are at a low risk for ovarian cancer, the surgeon will sometimes have to decide in the operating theatre, while performing the hysterectomy, whether the ovaries should be removed or retained: as long as the ovaries appear ‘normal’, they should probably be retained; if they look suspicious, they should better be removed. While this is admittedly a very rough guide, as ovaries that appear normal are not necessarily histologically normal/benign, macroscopically visible pathological alterations have often been detected already sonographically. Thus, the surgeon can often discover ovarian pathology at a pre-operative stage (Shwyader, 2008).

Interestingly, some degree of cancer protection is also achieved by hysterectomy alone. Women who had undergone hysterectomy while retaining their ovaries and Fallopian tubes showed a 36% lower risk of developing ovarian cancer during the next 15 years (Chiariaino et al., 2005). Tubal ligation likewise reduced the ovarian cancer risk by 34–40%, as evidenced by case–control studies and subsequent meta-analyses (Green et al., 1997; Cibula et al., 2011). While the reasons for these reduced rates of ovarian cancer both after hysterectomy and after tubal ligation are not clear, both hysterectomy and tubal ligation interfere with the upward movement of endometrioid cells from the uterus and with the transport of potentially carcinogenic substances from the vagina towards the fimbriated end of the Fallopian tube, and further into the pelvis, ovarian surface epithelium or peritoneum (Cibula et al., 2011). In addition, these interventions reduce the risk of chronic infections in the pelvis, which might also promote ovarian carcinogenesis (Ness et al., 2003; Carvalho and Carvalho, 2008). A further explanation has been offered suggesting that protective anti-mucin 1 (MUC1) antibodies might be induced by the release of MUC1 into the bloodstream during tubal ligation (Pinheiro et al., 2010). Thus, while there are obviously a few different causes for the development of serous pelvic cancers, there may be just as many protective mechanisms at work in individual patients.

For women who are at a high genetic risk of developing ovarian cancer (most likely owing to mutations in BRCA1/2), prevention surgery might also consist of an initial removal of the Fallopian tube only (salpingectomy) while the ovaries might be retained until the onset of the biological menopause (Greene et al., 2011). However, while this approach should minimize the adverse effects of a surgical menopause, combined salpingo-oophorectomy was also found to reduce the risk of breast cancer in pre-menopausal BRCA mutation carriers significantly (Greene and Mai, 2009). Thus, a decision to retain the ovaries in such high-risk patients should only be made after a thorough consultation comprising a careful assessment and discussion of the respective risks. Currently, there are rationales for either decision—and there are no clinical data describing the protective effect of salpingectomy alone in women at a high risk for both ovarian and breast cancer.

### The retained Fallopian tube after hysterectomy or sterilization

After hysterectomy, the Fallopian tubes can no longer fulfill their previous physiological function. Thus, sparing the Fallopian tubes during hysterectomy comprises no known benefits. Accordingly, none of the textbooks for gynaecological surgery provides a plausible reason for not removing the remnants of Fallopian tubes concomitant to hysterectomy. As the blood supply of the ovaries is secured via the infundibulopelvic ligament, it is not affected when hysterectomy is combined with salpingectomy. Also the hormone profile is not altered by salpingectomy, even months later (Dar et al., 2000; Sezik et al., 2007; Ghezzi et al., 2009). To the best of our knowledge, long-term effects, such as the timing of menopause, have not been analysed systematically after hysterectomy combined with salpingectomy. Thus, all presumed negative effects are still speculative. The blind-ended remnants of the Fallopian tubes may instead give rise to multiple complications, the most frequent (35.5%) being hydroosalpinx (Morse, 2002; Repasy et al., 2009), which requires revision surgery in 7.8% of patients (Morse et al., 2006). Further possible problems originating from retained Fallopian tube remnants are summarized in Fig. 1 (compare, Pacenza and Salsano, 2001; Basu and Ward, 2007; Singla, 2007; Ghezzi et al., 2009; Timor-Tritsch et al., 2010; Rezvani and Shaaban, 2011). Thus, bilateral salpingectomy concomitant with hysterectomy is widely recommended to avoid subsequent tubal pathology (Morse et al., 2006).

Sterilization is the most frequently applied contraceptive method worldwide. According to the United Nations statistics on worldwide contraceptive use (http://www.un.org/esa/population/publications/contraceptiveuse2005/2005_World_Contraceptive_files/WallChart_WCU2005.pdf; 5 August 2011, date last accessed), about 200 million women of reproductive age are sterilized. While about 8.1% of the 15- to 49-year-old women in developed countries who are married or in a relationship have undergone tubal sterilization, this applies to 22.3% of women of reproductive age in less-developed countries. Tubal sterilization is normally avoided during pregnancy but it can be performed during Caesarean section, and after childbirth or induced abortion. While surgical techniques vary worldwide and depend on the available equipment and the experience of the respective health-care team (Lawrie et al., 2011), most surgeons target the narrowest and most uniform calibre portion of the extramural Fallopian tube, i.e. the 2–3 cm long isthmic portion. This part is either resected (e.g. during a Caesarean section) or, in most cases, laparoscopically coagulated. The fimbriated end of the Fallopian tube thus remains mostly unaffected. With regard to the outcome, the most effective contraception is achieved by complete salpingectomy (Bartz and Greenberg, 2008).

Depending on the time that has elapsed since sterilization, the proximal segment of the Fallopian tube can show histological alterations, such as luminal dilatation, plical attenuation or chronic inflammation, characterized by infiltrates and pseudopolyp formation, while plical thickening is frequently observed in the distal segment. Possible resulting problems are summarized in Fig. 1. All these aberrations are related to the observed loss of function and indicate that microsurgical reanastomotic procedures are unlikely to be successful (Stock, 1983).

The vast majority of women who decide to undergo sterilization will remain comfortable with this decision for the rest of their lives.
However, an adequate pre-sterilization counselling is absolutely mandatory especially because this has been shown to correlate with post-sterilization satisfaction (Lawrence et al., 2011). Still, a small proportion of sterilized women will later feel regret and 1–3% ask for a reversal procedure (Chi and Jones, 1994). Common reasons for revising the previous decision for sterilization include altered family structures, a new partner or the death of a child. The most important parameter leading to a regret of sterilization is, however, an early age at the time of the sterilization. The cumulative likelihood of expressing regret within the 14 years following sterilization was 20% for women ≤ 30 years but only 6% for women > 30 years of age (Petersen et al., 2008). In contrast, for women who were over 35 years old when sterilized, the cumulative risk for regret was below 2% over the next 14 years (Schmidt et al., 2000; Bartz and Greenberg, 2008). In those cases where a refertilization was requested, the interval between the two interventions was, on average, 6 years (Schepens et al., 2011).

For women who wish to become pregnant again despite having undergone sterilization, two options remain: surgical re-anastomosis or IVF. Surgical refertilization opens up all possibilities for natural conception and allows the conception of several singleton pregnancies. It may, however, take a long time until the refertilized woman becomes pregnant, which means that this method is less suited to older women. In addition, the rate of ectopic pregnancies is rather high in re-anastomized tubes (Schepens et al., 2011). Boeckxstaens et al. (2007) analysed delivery rates after IVF treatment or surgical reversal and found that for patients aged ≥ 37 years a cumulative delivery rate of 51.4% was achieved after IVF compared with 36.6 % after reversal. While prospective randomized studies on this topic are still lacking (Yossry et al., 2006), most gynaecologists would probably recommend that women who have been sterilized who wish to become refertilized in an advanced age (around 40 years) should undergo IVF treatment, as this method generally takes the least time for pregnancy to be achieved. To summarize, women who wish to undergo sterilization once they are at least 35 years old and have completed their family are unlikely to change their mind. For those 1–2% of women who request refertilization in order to have further children, this wish normally arises after about 6 years. As these women are then 40 years of age (or even older), the method of choice would be IVF as pregnancy may thus be achieved within a relatively short period of time. Accordingly, bilateral salpingectomy appears to be a suitable approach to sterilization for older women (> 35 years of age) who are unlikely to require functioning Fallopian tubes during later life. While this decision should, of course, be left to the individual patient, salpingectomy could eliminate significant health hazards that would have to be tolerated if the post-reproductive Fallopian tubes were retained in spite of sterilization.

**Risk-reducing salpingectomy during salpinges-hysterectomy and sterilization**

A considerable body of evidence indicates that pelvic serous cancers (cancers of the ovary, peritoneum or Fallopian tube) originate from the fimbriated end of the Fallopian tube. Thus, whenever a hysterectomy is indicated, a combined salpinges-hysterectomy should be performed. For the patient, there are no known disadvantages associated with simultaneous salpingectomy and hysterectomy. Advantages are the likely avoidance of consecutive tubal pathology (see Fig. 1) that might otherwise require additional surgery and, most likely, a reduced risk of developing a pelvic serous cancer.

A further opportunity for risk-reducing salpingectomy is a prophylactic salpingectomy during sterilization. Bilateral salpingectomy does not only eliminate the risk of subsequent hydrosalpinx: further advantages over conventional methods, such as fimbriectomy, partial salpingectomy, banding or coagulation, include the absolute prevention of intrauterine pregnancies and the almost complete elimination of tubal pregnancies. Moreover, as recent pathological and molecular findings show that the fimbriated end of the Fallopian tube can give rise to pelvic serous carcinomas, bilateral salpingectomy as a means of sterilization would offer protection against these tumours and further provide the opportunity to assess, in an ethical manner, the
‘weight’ of bilateral salpingectomy as a risk-reducing procedure (i.e. in patients who have their wish for sterilization fulfilled in an optimal way by this elective intervention).

Simultaneous removal of the Fallopian tubes during hysterectomy or a bilateral salpingectomy for sterilization requires only a minimal extension of the surgical procedure. Likewise, laparoscopic salpingectomies do not pose any challenges to a gynaecological surgeon. Considering the enormous feasibility of the intervention, a campaign to promote prophylactic salpingectomy during hysterectomy or tubal ligation has already been launched in British Columbia, Canada (Blank, 2011). Moreover, gynaecologists might also strive to teach the details of the procedure to their general surgery colleagues who could then perform preventive salpingectomy in conjunction with operations where they have access to the Fallopian tubes in women of post-reproductive age.

Open questions related to prophylactic bilateral salpingectomy

Recent findings suggest that most malignant serous ‘ovarian’ carcinomas originate from the distal Fallopian tube, which calls for a reassessment of preventive strategies. However, a small proportion of serous cancers as well as endometrioid, clear cell, mucinous carcinomas are still thought to arise from ovarian surface epithelium (Chene et al., 2009; Kurman and Shih le, 2010). Accordingly, a qualified recommendation for future preventive surgery will need to consider the relative proportion of all Müllerian-derived carcinomas originating from the Fallopian tube or the ovaries. Thus, the prevalence of serous tubal intraepithelial carcinomas and p53 signatures in the female population undergoing hysterectomy for benign indications—the vast majority of patients in whom a preventive measure may be undertaken—must now be investigated. Based on our current knowledge, we propose that bilateral salpingectomy can reduce the risk of developing a serous pelvic carcinoma. Consequently, prospective studies that assess the future risk of epithelial ovarian cancer after simple hysterectomy, or hysterectomy plus bilateral salpingectomy, are badly needed. Moreover, as salpingectomy only might also be sufficient to prevent a still unknown proportion of the histologically different ovarian and tubal malignancies, bilateral salpingectomy might also be considered in women who do not want to conceive in the future and who are undergoing abdominal surgery for non-gynaecological indications.

Conclusion

Until recently, the scientific discourse regarding the aetiology and prevention of ovarian cancer focused on the ovary while the Fallopian tube was largely forgotten (Dietl and Wischhusen, 2011). The Fallopian tube was mainly regarded as an accessory appendage to the ovaries. Now, awareness is growing that the Fallopian tube requires due attention by both pathologists and gynaecological surgeons. Accordingly, the Fallopian tube should also be considered as a distinct anatomical entity that can be separated from the ovary. During a hysterectomy or tubal ligation, surgeons should thus strive to remove the Fallopian tubes when pregnancy is no longer desired. Such a bilateral salpingectomy has no known physiological side effects but is likely to reduce the risk for pelvic carcinomas. The additional removal of the ovaries during hysterectomy should, in contrast, be carefully assessed for the individual patient as the resulting surgical menopause has immediate effects. Such an approach would embrace all new insights related to the origin of ovarian cancer and translate our current knowledge into procedures that may be most appropriate for many patients. Nevertheless, rigorous studies investigating the prophylactic effect of bilateral salpingectomy alone are clearly warranted before the recent scientific findings can be fully applied in clinical practice.

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Prophylactic salpingectomy for cancer prevention?


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