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## Fallopian tube: Its role in infertility and gynecological oncology

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**Core tip:** Disorders of the fallopian tube play a major role in infertility. These disorders include congenital anomalies, inflammation and different other causes of tubal obstruction. Recently several studies suggested a role for the fallopian tube in the development of ovarian carcinoma, mainly high grade serous carcinoma. This article reviews the role of the fallopian tube in infertility and gynaecological oncology.

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### Abstract

Disorders of the fallopian tube play a very important role in both infertility and gynaecological oncology. Tubal factor infertility is considered among the leading causes of female factor infertility. Many tubal disorders are related to infertility including congenital anomalies, acute and chronic inflammatory diseases, endometriosis and other pathologies that result in partial or total fallopian tube obstruction. In the field of gynaecological oncology, ovarian surface epithelial tumors remain one of the most fatal malignancies in women worldwide carrying the worst prognosis among female genital malignancies. For decades, the cell of origin of epithelial tumors has remained controversial and was largely believed to be surface ovarian epithelium. Recently several studies suggested that there is a major role of the fallopian tube in the development of ovarian surface epithelial tumors, mainly high grade serous carcinoma and other tumour types. In this article we review the role of the fallopian tube in both infertility and gynaecological oncology.

### INTRODUCTION

The fallopian tube plays an important role in problems related to infertility<sup>[1]</sup> and is only recently recognized to play the leading role in the pathogenesis of pelvic (non-uterine) serous carcinomas<sup>[2]</sup>.

### THE FALLOPIAN TUBE AND INFERTILITY

Infertility is defined as couple's failure to conceive after 1 year of regular, unprotected intercourse<sup>[3]</sup>. Tubal factor infertility is among the leading causes of female factor infertility accounting for 7%-9.8% of all female factor infertilities. Tubal disease directly causes 36% and 85% of all cases of female factor infertility in developed and developing nations respectively<sup>[4]</sup>.

The fallopian tubes must be patent with normal anatomic relation to the adjacent ovary to allow the capture

of an ovum, provide a suitable environment for fertilization, and transport the fertilized ovum to the endometrial cavity for implantation<sup>[3]</sup>. Transport of gametes and embryos is achieved by complex interaction between myosalpinx contractions, ciliary activity and the flow of tubal secretions<sup>[5]</sup>. This complex movement also aims at stirring of the tubal contents to ensure mixing of gametes and embryos with tubal secretions<sup>[6]</sup>. The fallopian tube itself acts as a sperm storage site as the endosalpinx provides a favorable environment for sperms. Sperm-endosalpingeal contact preserves the viability of sperms increasing the chance for successful fertilization<sup>[1]</sup>.

Tubal factor infertility may result from complete blockage of the distal end of the fallopian tube (hydrosalpinx) as a sequelae of sexually transmitted disease (STD), surgical intervention or other intra-abdominal conditions, non-gynecological abdomino-pelvic infection, endometriosis, or a congenital anomaly. Proximal obstruction may result from salpingitis isthmica nodosa (SIN) or other inflammatory conditions, or it may be idiopathic. Peritubal adhesions or damage to the lining of the tube can impair tubal mobility, oocyte pickup, and/or sperm and embryo transport<sup>[7]</sup>.

## CONGENITAL ANOMALIES AND GENETIC DISORDERS

Congenital müllerian duct abnormalities are considered fairly common and have been estimated to be present in 1 in 500-700 women, yet complete absence of fallopian tube is a very rare condition that is usually unilateral and asymptomatic<sup>[8,9]</sup>. Absence or loss of patency of segments of the fallopian tube (atresia, hypoplasia, or interruption)<sup>[10]</sup>, and ampullary atresia<sup>[11]</sup> were also described. These may be unilateral or bilateral, and can occur with or in conjunction with uterine anomalies, such as uni or bi-cornuate uterus<sup>[10]</sup>.

The use of diethylstilbestrol (DES) during pregnancy was discontinued decades ago, but surgical specimens from patients who were born during the DES era may still be examined today, showing substantial developmental damage to the fallopian tubes. Fetal exposure to DES results in shortened, sacculated, and convoluted fallopian tubes. The fimbriae are constricted, and the os is pinpoint. The mucosa may be absent and if present, the plicae do not develop<sup>[1]</sup>.

Tubal dysfunction may also be caused by the immotile cilia of Kartagener's syndrome<sup>[5]</sup>, including about one half of the patients with primary ciliary dyskinesia (PCD). The latter is an autosomal recessive condition with estimated incidence of 0.5-1 in 30000 live births, causing dysfunctional motility of cilia and impaired mucociliary clearance, resulting in many clinical manifestations including recurrent sinopulmonary disease, laterality defects and infertility<sup>[12]</sup>.

## INFLAMMATORY DISEASES

Salpingitis causes tubal occlusion, peritubal adhesion

and fimbrial damage, all of which can lead to reproductive failure<sup>[13,14]</sup>. Microorganisms and the host's immune response may result in scar tissue formation, altering the activity of tubal cilia, resulting in the partial or complete destruction of cilia with alteration of the composition and viscosity of the tubal secretions<sup>[15]</sup>. The inflammation in the tube may extend to adjacent tissues, including the ovary, forming a tubo-ovarian abscess<sup>[16]</sup>.

Three major types of salpingitis are recognized: acute, chronic, and granulomatous/histiocytic<sup>[1]</sup>.

Acute salpingitis (other than physiologic salpingitis, occurring at time of menses or puerperium)<sup>[1,16]</sup> is the pathologic correlate of the clinical entity, pelvic inflammatory disease (PID), which occurs in young, sexually active women in the reproductive age<sup>[1]</sup>. Acute salpingitis may be caused by an ascending infection, following invasive procedures (such as curettage or the insertion of intrauterine devices)<sup>[17]</sup>, or secondary to STD by Chlamydia, *N. gonorrhoeae* or *Mycoplasma*<sup>[16]</sup>. Seminal fluid acts as a vehicle through which microbes are transferred to the upper genital tract. Some microorganisms have the ability to attach to the surface of spermatozoa, whilst others are obligate intracellular parasites within the spermatozoa<sup>[15]</sup>. Other non-sexually transmitted pathogens (*e.g.*, *E. coli*, *streptococci*, *staphylococci*, *coliform bacilli*, and *anaerobes*) may reach the tubes *via* the blood stream or lymphatics, especially after an abortion or pregnancy<sup>[16]</sup>. The response of the mucosa of the fallopian tube to microorganisms is not uniform. For example, *E. coli* cause swelling of the ciliary tips with adhesions between shortened and swollen cilia and cause shortened microvilli in non-ciliated cells. *N. gonorrhoeae* causes invagination in ciliated cells and loss of microvilli in non-ciliated cells<sup>[15]</sup>.

Chlamydia trachomatis (a Gram-negative bacterium) is the most common organism of STDs worldwide<sup>[18]</sup>, it can be isolated from a large portion of women with tubal factor infertility and elevated anti-C trachomatis antibodies can be detected in more than 70% of women with tubal occlusion. Yet, the exact pathogenesis of C trachomatis-induced tubal damage is still unknown with no available effective vaccines<sup>[19,20]</sup>. The primary site of chlamydial infections is the columnar endocervical epithelial cells<sup>[20]</sup>. It has been hypothesized that the host immune response by C trachomatis infection is responsible for the damage rather than the infection itself<sup>[21,22]</sup>. The protective host immune response is induced by production of antibodies against chlamydial major outer membrane protein (MOMP). This was supported by the recent findings that immunization with a native MOMP induces protection<sup>[22]</sup>. However, antibodies against chlamydial heat shock protein (HSP) 60 are associated with pathologies, which may provide an explanation for the observation that whole chlamydial organism-based vaccines is associated with exacerbated pathology. Chlamydial infection leads to tubal ciliated epithelial destruction with subsequent tubal infertility and ectopic pregnancy *via* production of cytokines, including interleukin (IL)-1, which has a toxic effect on ciliated tubal cells<sup>[15]</sup>. Chlamydia can enter a dormant, per-

sistent state, where, in the absence of a productive infection, there is still a low level of immune stimulation from antigen recognition. This low level stimulation is believed to cause chronic inflammatory cell infiltration<sup>[20]</sup>.

In chronic salpingitis, the tubal fimbriae adhere to the ovary and adjacent tissues with subsequent obliteration of the ostium, leading to a hydrosalpinx or pyosalpinx. Hydrosalpinx is typically bilateral, but it may be unilateral. Late stages of chronic salpingitis may result in fibrous obliteration of the whole tubal lumen<sup>[16]</sup>.

Granulomatous and histiocytic salpingitis may result from infection by different organisms (*e.g.*, *Mycobacterium tuberculosis*, *Schistosoma*, *Oxyuris vermicularis*, *Actinomyces*, *Coccidioides immitis*) or as part of a systemic granulomatous disease (*e.g.*, sarcoidosis and Crohn's disease)<sup>[17]</sup>. It may also be induced by local non-infectious causes, including foreign bodies introduced for diagnostic or therapeutic purposes (*e.g.*, lubricant jellies, mineral oil, powder or lipiodol)<sup>[1,16,17]</sup>.

The commonest cause of granulomatous salpingitis is infection with *Mycobacterium tuberculosis*; predominantly affecting females below the age of 40 years, with peak age between 21-30 years. Tubal involvement occurs in 80%-90% of women with genital tuberculosis and is usually bilateral (90% of the cases)<sup>[23,24]</sup>. Tuberculous salpingitis is uncommon in the western world yet prevalent in developing countries<sup>[24]</sup>, accounting for much less than 1% of cases in the United States, while representing nearly 40% of cases in India<sup>[1]</sup>.

Female genital tuberculosis occurs secondary to primary disease elsewhere in the body. The spread is usually hematogenous or *via* the lymphatic route<sup>[24]</sup>. Sexual transmission of the disease is also documented but direct spread from other intraperitoneal foci is very rare<sup>[23]</sup>. Tuberculosis may cause minimal tubal damage and lead to ectopic pregnancy. However, extensive damage to the tubes can lead to tubal blockage in 60% of cases. Peritubal adhesions and tubo-ovarian masses have been found in 47.2% of cases<sup>[24]</sup>. As the tubercles enlarge and coalesce, they may erode through the mucosa and discharge their contents into the tubal lumen, leading to progressive scarring, with plica distortion and agglutination. Calcification can occur in areas of fibrosis<sup>[1,16,17]</sup>.

Female genital schistosomiasis was described for the first time in a young Egyptian woman more than 100 years ago<sup>[25]</sup>. Tubal schistosomiasis may be one of the common causes of granulomatous salpingitis worldwide; yet it is rare in the United States<sup>[1,16]</sup>. More than 207 million people, representing 85% of those who live in Africa, are infected with schistosomiasis<sup>[26]</sup>. In Africa, the fallopian tube is involved by schistosomiasis in 22% of all infected women<sup>[1,2]</sup>, with 7% presenting by infertility. The cervix, fallopian tubes and vagina are the most common gynecological sites to be affected. Blood vessel anastomoses between the pelvic organs are probably responsible for "spill-over" of eggs into the genital tract<sup>[27]</sup>. Gross findings appear to be related to fibrosis surrounding the eggs, producing a nodular or fibrotic tube<sup>[1,16]</sup>.

Fungal infection rarely can cause tubo-ovarian abscesses or granulomatous salpingitis. Responsible organisms include *Blastomyces dermatitidis*, *Coccidioides immitis*, *Candida*, and *Aspergillus* reaching the fallopian tube by hematogenous spread or in the course of disseminated disease<sup>[1,16]</sup>. Pseudo-xanthomatous salpingitis (referred to as "pigmentosis tubae") is associated with endometriosis, yet it also might result from salpingitis with associated hemorrhage<sup>[1,16,17]</sup>. A granulomatous reaction may also be encountered in small to medium size arteries in patients with giant-cell arteritis<sup>[16]</sup>.

## ENDOMETRIOSIS

Endometriosis affects 5%-10% of the general female population of reproductive age<sup>[28]</sup>, including 50%-60% of women and teenage girls with pelvic pain<sup>[29]</sup>. About 30%-50% of women with endometriosis are infertile<sup>[30]</sup>. Infertile women are 6-8 times more likely to have endometriosis than fertile women. Of infertile women 25%-50% have endometriosis<sup>[8,29]</sup>. Tubal endometriosis is identified in approximately 10% of fallopian tubes, most commonly involving the distal end<sup>[31]</sup>. Normally, endometrial tissue can be found within the mucosa of intramural and isthmus segments of the fallopian tube, referred to as endometrial colonization<sup>[1]</sup>. Endometriosis of the tube can be found within the lumen (focal replacement of tubal epithelium by uterine mucosa)<sup>[17]</sup>; or myosalpinx or on the serosa. Occasionally, tubal endometriosis may produce a mass simulating a tumor (polypoid endometriosis). Post-salpingectomy endometriosis is an apparently common form of endometriosis that occurs in the tip of the proximal stump of the fallopian tube years after tubal ligation<sup>[1]</sup>.

Despite extensive research, several mechanisms have been proposed to explain endometriosis-related tubal factor infertility with no consensus reached to date<sup>[32]</sup>. The most popular hypothesis involves retrograde menstruation into the peritoneal cavity<sup>[33]</sup>. The retrograde menstruation of non-sterile menstrual blood into the peritoneal cavity provides a route for microbial transport. The menstrual debris may also promote continued survival and persistence of these microorganisms in the upper genital tract. These microorganisms may replicate causing tubal damage and the microflora stimulate chemotaxis of macrophages and the subsequent secretion of secondary inflammatory mediators identified in this condition<sup>[15]</sup>.

Other mechanisms include: (1) associated pelvic inflammation causing adhesions and scar formation with subsequent impaired ovarian oocyte release or capture as well as impairment of tubal transport due to physical obstruction<sup>[15,30]</sup> in advanced stages of endometriosis<sup>[33]</sup>; (2) associated increased volume of peritoneal fluid<sup>[30]</sup>, that contains increased numbers of macrophages and their secreted products (*e.g.*, growth factors, cytokines, and angiogenic factors) affecting various aspects of reproduction<sup>[33]</sup>. Also a macromolecular ovum capture inhibitor, causing formation of a membrane over the fimbrial cilia,

has been detected in the peritoneal fluid from women with endometriosis<sup>[15]</sup>; (3) Recently, endometriosis has been proposed to be an autoimmune disease because of the presence of a variety of autoantibodies against endometrium, ovary and sperm, these autoantibodies can be an important risk factor in endometriosis-associated infertility<sup>[34]</sup>; (4) Other theories are altered hormonal and cell-mediated function due to increased IgG and IgA antibodies and lymphocytes in the endometrium of women with endometriosis leading to alteration of endometrial receptivity and embryo implantation; and (5) associated endocrine and ovulatory disorders (*e.g.*, longer follicular phase with possibly lower serum estradiol levels and lower LH-dependent progesterone secretion during the luteal phase of the cycle)<sup>[30]</sup>.

SIN or “adenomyosis” of the fallopian tube is a pseudo-infiltrative lesion consisting of diverticula of tubal epithelium in the isthmus. It occurs in women between the ages of 25 and 60 years (average, 30 years)<sup>[1]</sup>. The incidence of SIN in healthy, fertile women ranges from 0.6% to 11%<sup>[31]</sup>. It is bilateral in approximately 85% of cases<sup>[17]</sup>. It is accompanied by infertility in approximately one-half of patients<sup>[17]</sup> by interfering with upward sperm migration<sup>[31]</sup>. It may be difficult to distinguish SIN from tubal endometriosis in some cases<sup>[1]</sup>.

## ECTOPIC PREGNANCY

Ectopic pregnancy is defined as a pregnancy occurring outside the uterus or in an abnormal site within the uterus; 95%-99% arise in the fallopian tube<sup>[35]</sup>. The vast majority (80%) occur in the ampulla, with the isthmus (10%) and infundibulum (5%) being less common sites<sup>[31]</sup>. About 25% of tubal pregnancies have ruptured by the time of diagnosis<sup>[1]</sup>. This may impair/destroy tubal function with partial occlusion or luminal adhesions<sup>[36]</sup>. The usual treatment for tubal pregnancy is salpingectomy, yet segmental tubal resection may be appropriate in selected cases<sup>[17]</sup>. Retention of fertility after an ectopic pregnancy depends on how that pregnancy was managed and on the presence or absence of known risk factors<sup>[37]</sup>. Improvements in management of ectopic pregnancies have enhanced efforts towards preserving subsequent fertility; a principal goal of conservative treatment. However, conservative treatments are likely to increase the recurrence rate of ectopic pregnancy as the conserved tube is usually a damaged tube<sup>[38]</sup>.

## THE FALLOPIAN TUBE AND GYNECOLOGICAL ONCOLOGY

Primary fallopian tube adenocarcinoma is rare, accounting for less than 0.2% of cancer diagnoses among women annually<sup>[39]</sup>. Tubal carcinoma represents 0.7%-1.5% of gynecologic invasive malignancies<sup>[1]</sup> with an incidence of 0.41 per 100000 women in the United States<sup>[40]</sup>. In England and Wales, 40 cases of primary tubal adenocarcinoma are registered annually<sup>[41]</sup>.

On the other hand, ovarian cancer is the 6<sup>th</sup> most common cancer in women worldwide and the 7<sup>th</sup> most common cause of cancer death<sup>[42]</sup> with an age-adjusted incidence rate 12.7 per 100000 women per year. This is based on cases diagnosed in 2005-2009 from 18 SEER geographic areas<sup>[43]</sup>. In Western countries, ovarian carcinoma is the 5<sup>th</sup> most common malignancy ranking 4<sup>th</sup> in cancer mortality, accounting for 4% of cancer in women and is the most frequent cause of death due to gynecological cancer. In United States women, ovarian cancer ranks 9<sup>th</sup> in incidence and 5<sup>th</sup> in mortality, accounting for 3% of cancers and 5% of cancer deaths. Serous carcinoma is the most common type of the ovarian epithelial malignancies, accounting for approximately 80% of cases<sup>[44]</sup>.

Ovarian cancer has one of the highest death-to-incidence ratios<sup>[2,45]</sup> and is considered the most lethal of gynecologic malignancies<sup>[44]</sup>. The age-adjusted death rate is 8.2 per 100000 women per year in the United States<sup>[43]</sup>.

A prerequisite for the success of early detection of any disease is the clear understanding of its natural history<sup>[46]</sup>. The high ovarian cancer related death rates have been attributed to the unavailability of effective screening tools, the absence of early symptoms in many patients, and the typical presentation at advanced stages when prognosis is poor<sup>[2,47]</sup>. One of the greatest obstacles to the detection of early-stage ovarian cancer was the poor understanding of its histogenesis and pathogenesis<sup>[2]</sup>.

Until recently, the incessant ovulation theory has been the most accepted theory of ovarian carcinogenesis. According to this theory, constant ovulation-induced damage and repair of the ovarian surface epithelium (OSE) results in malignant transformation<sup>[48]</sup>. Ovarian carcinoma was also traditionally thought to originate from the OSE or ovarian epithelial inclusions (OEI)<sup>[2,49]</sup>. Hence, investigative efforts for early detection were centred on the ovary for decades. However, all have not been successful<sup>[2,50]</sup>, as they failed to identify a convincing precursor in the ovary<sup>[49]</sup>. This was greatly reflected on the overall survival for women with ovarian cancer, which has not changed in any fundamental manner over the last 50 years<sup>[43]</sup>.

Over the last several years, based on combined morphological and molecular data, a dualistic model for the pathogenesis of ovarian carcinoma has emerged<sup>[50,51]</sup>. The dualistic model divides ovarian epithelial tumors into two categories: Type I and Type II<sup>[1]</sup>. Type I tumors are generally low-grade; including low grade serous carcinoma (LG-SC), low-grade endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma and malignant Brenner tumor. These tumors usually present at low stage and behave in a relatively indolent fashion<sup>[49]</sup>. In contrast, type II tumors are high-grade, highly aggressive and present in advanced stage. They have been said to arise “*de novo*”. They include high-grade serous carcinoma, high-grade endometrioid carcinoma, malignant mesodermal mixed tumour and undifferentiated carcinoma<sup>[1,49]</sup>.

It is now believed that the fallopian tube may be the origin of ovarian carcinoma, rather than the ovarian surface epithelium, traditionally regarded as the origin of ovarian carcinoma<sup>[17]</sup>.



## ROLE OF THE FALLOPIAN TUBE IN TYPE I OVARIAN SURFACE EPITHELIAL TUMORS

Low grade serous carcinoma is thought to evolve in a stepwise fashion from ovarian surface epithelial inclusions (OEIs)/serous cystadenomas to serous borderline tumors to invasive carcinoma<sup>[2,49,52]</sup>, although they can be *de novo*<sup>[53]</sup>.

The fallopian tube plays a central role in various components of this stepwise sequence<sup>[54]</sup> as it is proposed that the majority of OEIs are derived from the fallopian tube epithelial cells. These cells are capable of implanting on the ovarian surface<sup>[2]</sup> at the time of ovulation when the surface ovarian epithelium is ruptured<sup>[55]</sup>.

This idea is supported by the following evidence: (1) Epithelial cells from tubal mucosa are easily shed after flushing the fallopian tube<sup>[55]</sup>; (2) Most (78%) of the OEIs and serous cystadenomas display morphological features and immunophenotype of tubal type epithelium (calretinin-/PAX8+/tubulin+)<sup>[2,50]</sup>; (3) Fallopian-derived OEIs may represent intra-ovarian endosalpingiosis; and (4) There is evidence against mesothelial origin of OEIs with müllerian metaplasia including, scarceness of hybrid or intermediate type of OEIs with both mesothelial and tubal phenotypes. In addition, studies show mesothelium-derived OEIs are not capable of growing into tumour masses with low cellular proliferative activity, compared to fallopian-derived OEIs that showed high proliferative activity and immunophenotype that are similar or almost identical to ovarian serous tumors<sup>[2,50]</sup>.

## ROLE OF THE FALLOPIAN TUBE IN TYPE II OVARIAN SURFACE EPITHELIAL TUMORS

Accumulating evidence suggests that the fallopian tube epithelium, predominantly in the fimbrial region<sup>[1,49]</sup>, is the source of a significant proportion of high-grade serous carcinomas<sup>[49]</sup>. This is based on identification of epithelial atypia, carcinoma *in situ*, and small high-grade serous tubal carcinomas in risk-reducing salpingo-oophorectomy (RRSO) specimens from women with BRCA mutations<sup>[1,56]</sup>.

Mutation of TP53 is a hallmark of high-grade pelvic serous carcinoma<sup>[57]</sup>. The identification of TP53 mutations in Serous Tubal Intra-epithelial Carcinomas (STICs) provides support for the tubal origin of high-grade serous carcinomas<sup>[1,49]</sup>. More recently it has been found that there are short stretches of morphologically normal tubal epithelium that are immunohistochemically positive for p53, and that have a Ki-67 proliferation index higher than normal tubal epithelium but lower than STICs. A minimum of 12 tubal secretory epithelial cells that are p53 positive has been proposed as a definition for a "p53 signature," which is a candidate for a STIC precursor. p53 signatures are also found in the general population. TP53 mutations have been found in a majority of p53 signatures<sup>[1,49]</sup>.

Other molecular evidence strongly supporting the

theory of fallopian tube origin of high-grade serous are: (1) lack of convincing definitive precursors of high-grade serous carcinoma in the ovary; (2) in RRSO specimens, occult carcinomas are more common in the fallopian tube than in the ovary; (3) STICs are associated, almost exclusively, with high-grade serous carcinoma, and not other histological types; (4) a high frequency of identical TP53 mutations in STICs/p53 signatures and synchronous ovarian/peritoneal high-grade serous carcinomas; (5) the finding of fallopian tube epithelial dysplasia in isolation exhibiting aneusomy for multiple chromosomes; (6) significant differences in telomere lengths between STICs and their paired concurrent ovarian/peritoneal high-grade serous carcinomas (if STICs merely represented metastases of ovarian/peritoneal carcinomas, they would be expected to have telomeres of similar lengths); (7) gene expression profiles of tubal and ovarian serous carcinomas are similar; and (8) gene expression patterns of ovarian serous carcinomas are more similar to those of normal tubal mucosa compared with normal ovarian epithelium<sup>[1]</sup>.

Junctions between the different types of epithelia are often hot spots for carcinogenesis. Their role in neoplasia in certain locations, *e.g.*, cervical squamo-columnar, gastro-esophageal, and ano-rectal junctions is well recognized. Given the mounting evidence implicating the fimbria as the site of origin of ovarian serous carcinoma, the fallopian Tube-Peritoneal Junction (TPJ) is considered a potential site of ovarian carcinogenesis. This junction is defined as the junction of the columnar epithelium of the fallopian tube and the mesothelium of the tubal serosa<sup>[1]</sup>.

In a recent study TPJ was found to be highly tortuous with tongues of mesothelium extending from the infundibular peritoneal-fimbrial junction at the outer edges of the fimbriae, onto the fimbrial plicae to join the tubal epithelium at various points along and between fimbrial plicae and plica tips<sup>[58]</sup>. Transitional metaplasia occurs at the TPJ<sup>[59-61]</sup>, and is reported in several studies<sup>[59,62]</sup>. It is likely that the transitional metaplasia is a normal event in the TPJ, analogous to squamous metaplasia in the cervical transformation zone<sup>[58]</sup>, and may be analogously a site of tumour origin.

The origin of serous neoplasms at the TPJ could also explain the rare detection of stage I high-grade serous carcinoma. In addition, the extensive lymph-vascular system normally found at this junction with almost direct contact to the basement membrane of the tubal epithelium may explain the early spread of a minimally invasive tubal carcinoma throughout the abdominal cavity due to easy and rapid access into this system when the primary tumour is still of microscopic size<sup>[58]</sup>.

Among ovarian surface epithelial tumors, the origin of intestinal-type mucinous ovarian and Brenner tumors is even more confusing than that of serous tumors as they lack a Mullerian phenotype. The recent suggestion that mucinous and Brenner tumors may arise from transitional metaplasia<sup>[61]</sup> indicates that the TPJ may be involved in carcinogenesis of a wide variety of ovarian neoplasms.

In view of the potential importance of the TPJ in ovarian, tubal, and pelvic neoplasia, a recent protocol for exami-

nation of the fallopian tubes has been proposed, designated the SEE-FIM protocol<sup>[63]</sup>. The goal of this protocol is to insure complete examination of the ovarian surface and tubal mucosa with maximum exposure of the fimbriae<sup>[63]</sup>.

In summary, serous tumors develop from the fallopian tube, endometrioid, and clear cell tumors arise from fallopian tube endometriosis and mucinous, and Brenner tumors develop from transitional-type epithelium located at the TPJ<sup>[58]</sup>.

Although the data suggesting that EOC arises in extra-ovarian sites and involves the ovaries secondarily is compelling, serous neoplasms (low- and high-grade) involve the ovaries and other pelvic and abdominal organs, much more extensively than the fallopian tubes. Similarly, although endometrioid and clear cell carcinomas develop from endometriosis that frequently occurs in multiple sites in the pelvis, these neoplasms are almost always confined to the ovaries. It is likely that the propensity for growth in the ovary is multifactorial, but the precise reasons for this are unknown<sup>[58]</sup>.

So the fallopian tube appears to be a strong player both in infertility and gynaecological neoplasia. This highlights the importance of thorough fallopian tube status investigation in the course of assessment of women presenting with either infertility or gynaecological tumors.

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