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REVIEW

Functional Morphology of the Human Uterine Tubes in the 21st Century: Anatomical Novelties and Their Possible Clinical Applications

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Summary
The uterine tube (UT) pathologies account for 25-35 % of female factor infertility. Although these peculiar organs were first studied several hundred years ago, they have become overlooked and neglected mainly due to the successes of reproductive medicine. Nevertheless, reproductive medicine still faces many challenges regarding the fertility outcomes of *in vitro* fertilization (IVF). Many obstacles and problems can be resolved by a more detailed understanding of the UT morphology and function during normal reproduction. Over the course of the 21st century, many new insights have been obtained: the presence of a population of telocytes in the tubal wall responsible for normal motility and hormone sensory function, the demonstration of lymphatic lacunae of the mucosal folds necessary for oocyte capture and tubal fluid recirculation, or a thorough profiling of the immune makeup of the UT epithelial lining with the discovery of regulatory T cells presumably important for maternal tolerance towards the semi-allogenic embryo. New discoveries also include the notion that the UT epithelium is male sex hormone-sensitive, and that the UT is not sterile, but harbors a complex microbiome. The UT epithelial cells were also shown to be the cells-of-origin of high-grade serous ovarian carcinomas. Finally, yet importantly, several modern morphological directions have been emerging recently, including cell culture, the development of tubal organoids, *in silico* modelling, tissue engineering and regenerative medicine. All these novel insights and new approaches can contribute to better clinical practice and successful pregnancy outcomes.

Keywords
Uterine tube • Uterine tube functions • Tubal telocytes • Tubal lymphatic lacunae • Tubal immune cell repertoire • High-grade-serous ovarian cancers • Tubal cell cultures and organoids

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Introduction

Uterine tube (Fallopian tube, oviduct) (UT) diseases account for 25-35 % of female factor infertility. Professor Eve C. Feinberg, in her Editorial in the journal *Fertility and Sterility* in 2018, pondered: "Fifty years from now, assisted reproductive techniques may completely replace medical therapy for infertility and obviate the need for functional uterine tubes." [1]. If this were true, further research into the functional anatomy of the UTs would be meaningless. It is well known that the interaction of the UT epithelial cells with the spermatozoa has beneficial effects on sperm functions, selection and activation (capacitation) [2]. Moreover, the UT also provides a particular microenvironment, which is, *in vivo*, crucial for ovum capture and transport and the processes of fertilization, early embryo nutrition, development and transport towards the uterine cavity. The UT also amplifies signals from the embryo to the mother [3-5]. Many functional aspects of the UTs have been discovered only in recent years. Therefore, we consider the statements about their "needlessness"

inappropriate. The 2021 Practice Committee of the American Society for Reproductive Medicine points to options for reparative tubal surgery. According to their expert opinion, surgery for distal tubal diseases (such as hydrosalpinges, fimbrial phimosis or peritubal adhesions) have a good prognosis. Also, tubal cannulation is recommended in the case of proximal tubal obstruction in young women with no other significant infertility factor [6].

In 1543, Andreas Vesalius published the first complex anatomical textbook, "*De Humani Corporis Fabrica*" [7,8]. In the 15th and 16th Centuries, numerous world-famous anatomists described female genital organs in detail, such as Gabriel Fallopius, Realdo Colombo, Reinier de Graaf or Caspar Bartholin [9]. Perhaps this is also why the lay public and experts from various fields of theoretical or clinical medicine think nothing new can be discovered in anatomy, considering the hundreds of years of anatomical study.

The primary purpose of this review is to present a summary of the latest findings on the functional anatomy of the UTs discovered and published during the 21st century and correlate them with our previous research results.

Telocytes – a new cell population inside the tubal wall

In 2005, Popescu *et al.* [10] published their "revolutionary paper" on a new interstitial cell population termed telocytes in the UT wall (first described as interstitial Cajal-like cells). Telocytes have a small cell body, but exquisitely long cytoplasmic projections called telopodes which are difficult to study under the light microscope, because their width is only around 0.2 µm. The most common method of telocyte study is transmission electron microscopy, but immune-histochemistry is also used. Even though there is no specific marker of telocytes, those found in the UT are positive for CD117 (Fig. 1). The cell population of telocytes in the UT wall is organized into different types of sheaths: subepithelial, inner/outer perimuscular, and intramuscular sheaths [11]. According to Cretoiu *et al.* [12], telocytes of the UT express receptors for steroid hormones on their surface. It could provide clues on their sensory function in controlling peristaltic movements of the UT muscle layer – estrogen-mediated acceleration or slowing down under the influence of progesterone. Disrupted distribution and function of telocytes due to various pathological conditions (e.g., acute salpingitis, Chlamydia infection, endometriosis) might be a possible cause of impaired tubal transport function, leading to tubal infertility or ectopic tubal pregnancy [13-16]. Telocytes also have a wide array of other functions, like intercellular signalling between all components of the interstitial compartment, but also with epithelial cells. Hence, there is a high probability that future research will unveil more telocyte functions and their role in other tubal physiological functions and pathologies.

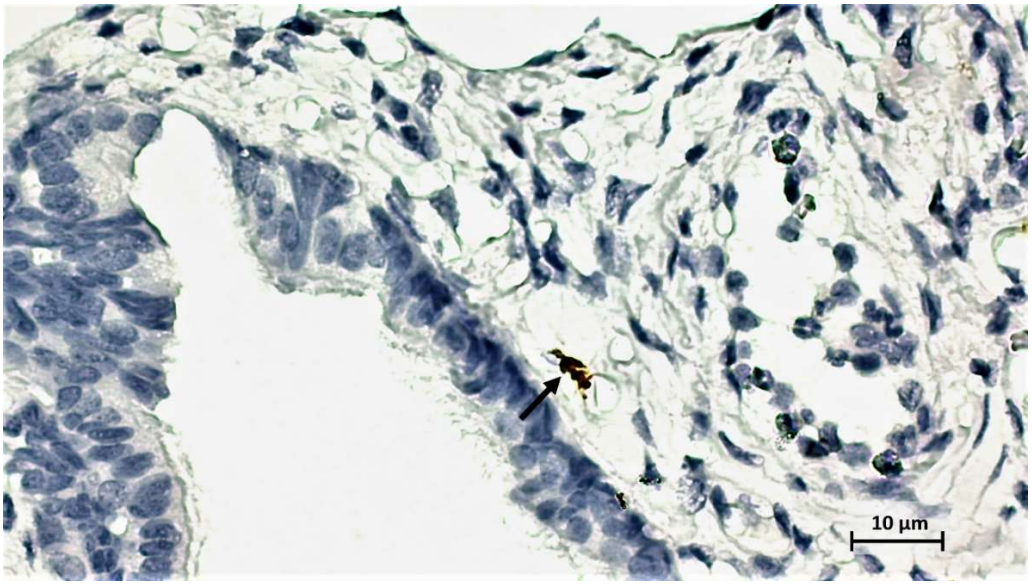

Fig. 1. CD117-positive telocyte-like cell with inconspicuous cell body and emerging projections (telopodes) in the *lamina propria* of the UT mucosal fold of the ampulla (black arrow).

Central lymphatic lacunae of the tubal mucosal folds and fimbriae

In 1904, in the habilitation thesis of Paul Kromer, wide spaces inside the tubal mucosal folds were first described. Unfortunately, these spaces were almost wholly neglected for over 100 years. After immunohistochemical investigation, it was revealed that these wide spaces occupy the infundibular fimbriae and are highly abundant in mucosal folds of the ampulla. Their positivity for markers of lymphatic endothelial cells, e.g. podoplanin, confirmed their lymphatic origin (Fig. 2). They were termed lymphatic lacunae of tubal mucosal folds and fimbriae [17]. The most probable function of these spaces in fimbriae is their role in oocyte pick-up during ovulation. Thanks to the lymph, which can accumulate in these wide spaces, the fimbriae get enlarged into an erectile-like tissue, which makes the oocyte capture easier. The second function is their role in regulating tubal fluid recirculation [17]. This possible function is crucial from the clinical perspective. Only recently, several research teams investigated the importance of tubal fluid dynamics on the various processes occurring in the UT before, at, or shortly after fertilization and during the first days of embryonic development. The tubal fluid dynamics was revealed to be similarly important as its quality and composition [18,19]. All in all, the future elucidation of these processes can significantly improve the success of normal reproduction and refine assisted reproduction techniques. Perhaps, the incomplete knowledge of all the complex processes, including the tubal fluid dynamics, is why the success rate of *in vitro* fertilization (IVF) is far from optimal and can also be the reason for various health complications later in life due to genetic alterations that happen in the earliest stages of embryonic development.

The discovery of tubal immune cell profile

From the point of view of immunology, the UT mucosa is unique – its local populations of immune cells provide surveillance against non-self-pathogens entering the UT from the pelvis or uterine cavity. However, at the same time, these exact immune cells must be "tolerant" towards the non-self-spermatozoa and half non-self (semi-allogeneic) embryo, maintaining an anti-inflammatory environment. Moreover, the UT-sperm interaction further suppresses the innate immune cells and strengthens the anti-inflammatory balance in the UT. Therefore, UT immunity ensures sperm viability before fertilization [20]. The local immune system in the human UT is composed of a mixture of innate and adaptive immune cells. Intraepithelial T lymphocytes represent the dominant lymphoid subset of human tubal epithelium. In the tubal epithelium, the average ratio of CD3+ T lymphocytes to epithelial cells is 1:16. Intraepithelial B lymphocytes are four times less frequent. The average ratio of immune cells to epithelial cells is 1:400 for CD4+ T lymphocytes and 1:15 for CD8+ T lymphocytes, respectively. The UT mucosa also contains macrophages, dendritic cells and a minor population of NK cells and Langerhans cells

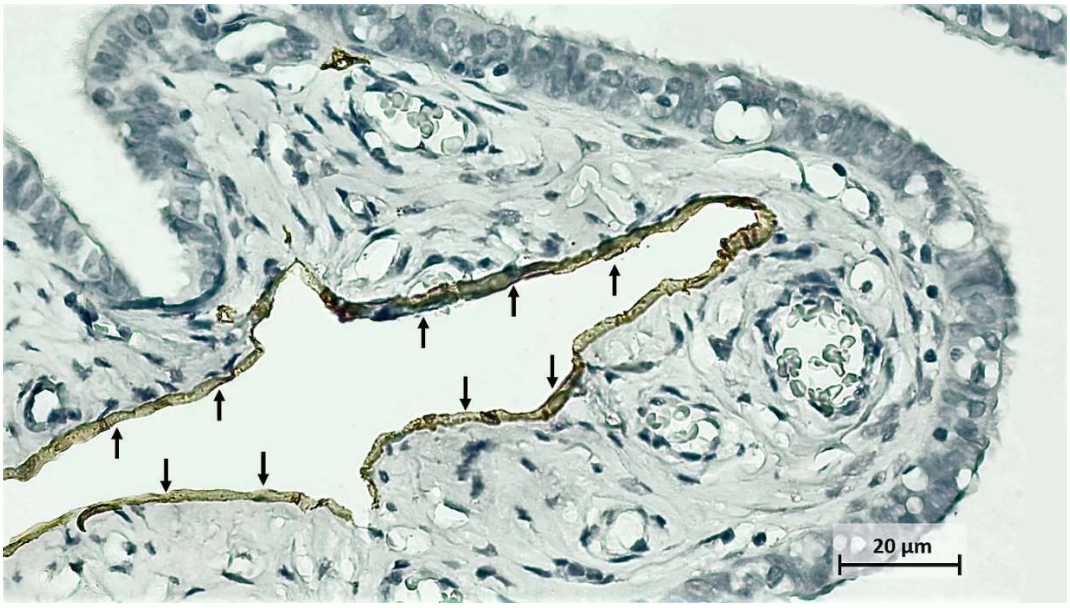

Fig. 2. Podoplanin (clone D2-40) positivity of wide lymphatic lacuna located in the *lamina propria* of the UT mucosal fold of the ampulla (black arrows).

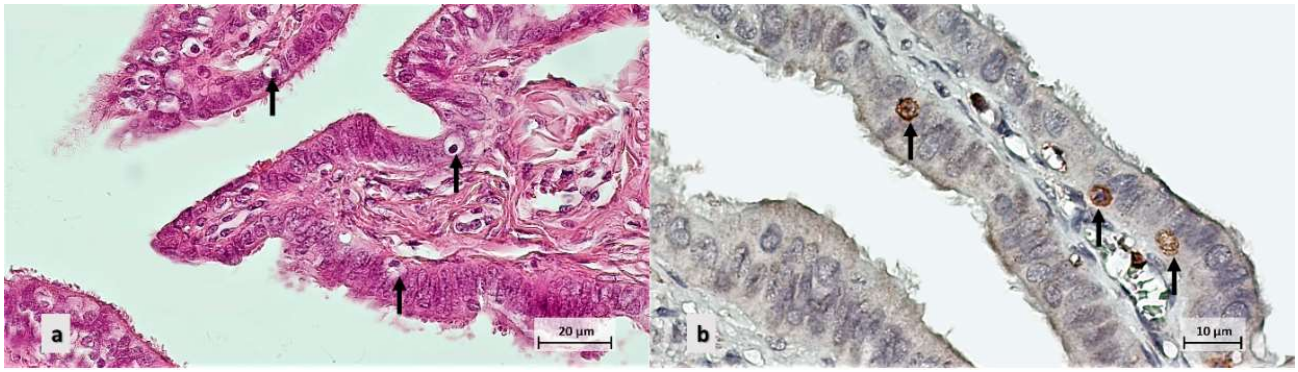

Fig. 3. Hematoxylin and eosin (HE)-stained ampulla of the UT showing the epithelial lining with clearly visible round basal cells with dark hyperchromatic nuclei and cytoplasmic halo (black arrows) (**a**). Immunohistochemical staining with anti-CD45RO confirmed that these "basal cells" are probably T lymphocytes (black arrows) (**b**).

[21,22]. Surprisingly, for many decades tubal intraepithelial T lymphocytes were described as tubal basal cells in various morphological publications, including official histological nomenclature. We previously conducted an immunohistochemical study which confirmed that these cells are intraepithelial T lymphocytes, most probably regulatory T lymphocytes (Tregs). Their identity was evidenced by applying a palette of T lymphocyte specific antibodies, including anti-CD45RO (Fig. 3) [23].

Interestingly, it seems that the UTs contain a microbiome. The composition and the role of normal vaginal microflora have been long known, but the uterine cavity and the cavity of the UT were considered sterile. Recent research challenged this notion and found that UT contains microflora that can be affected by hormonal levels. The exact roles of these microbes and their influence on reproductive health outcomes are yet to be established [24,25].

Epithelium of the uterine tube is not only female but also male sex hormone-sensitive

It has been known for decades that, similarly to the ovary and uterus, the UTs also undergo hormonally regulated cyclical morphological changes [26]. These changes predominantly affect the epithelial lining, resulting in changes in the epithelial cell height and ciliary beating frequency. For example, epithelial cells are shortest during the menstrual phase, and they subsequently increase in height during the proliferative phase, reaching their maximum height during ovulation. During the period that follows ovulation, secretory cells are the most active, and there is the highest frequency of ciliary beating. In contrast, progesterone causes atrophy, deciliation, apoptosis, and the loss of secretory activity [23,27]. After menopause, there is a significant decrease in the expression of estrogen and progesterone receptors in epithelial cells [28]. However, the effects of excess male sex hormones on tubal morphology and function have been largely unknown. For the first time, Dulohery *et al.* [29] characterized UT alterations caused by long-term exposure to male testosterone levels. After long-term testosterone treatment, the authors found tubal blockage caused by the accumulation of mucus and broken-down epithelial cells in the ampulla (the percentage of ciliated cells in the ampulla was significantly increased) and luminal collapse in the isthmus. Hyperandrogenism in the UT may be linked to the alteration in the secretory composition, tubal transport, and epithelial cell ratio [29]. These results may have a substantial clinical impact because excess testosterone levels affect up to 20 % of the female population worldwide and are a crucial component in the pathogenesis of polycystic ovary syndrome.

Association between tubal epithelium and high-grade serous ovarian cancers

High-grade serous ovarian cancer (HGSOC) is the most common and the deadliest ovarian epithelial cancer. The high lethality, high rate of platinum resistance, and poor survival outcomes are the principal factors for categorizing HGSOC among the most aggressive gynecological cancers. Initially, HGSOC was thought to arise from invaginations of the ovarian surface epithelium that result from normal ovulatory wounds. Trapped ovarian surface epithelium within these so-called cortical inclusion cysts was believed to undergo metaplasia and

accumulate causal mutations. However, clear evidence has recently emerged suggesting that a substantial number of HGSOCs can also originate from the UT epithelium, especially from the epithelium of fimbriae (the finger-like projections located at the ends of the UTs, closest to the ovaries). Serous tubal intra-epithelial carcinomas (STICs), defined as *in situ* neoplasms with increased proliferative capacity, were reported in up to 60 % of sporadic HGSOC cases. Although there are doubts about the origin of HGSOC, there is rising morphologic and molecular evidence that HGSOC actually arise from the UTs *via* its precursor STIC, not from the ovary. These findings may significantly impact current screening modalities, therapeutic interventions, and the discovery of new targetable pathways. In clinical practice, the risk-reducing bilateral salpingo-oophorectomy has been proposed to reduce the subsequent occurrence of serous carcinoma in high-risk patients with BRCA mutations [30-33]. On the other hand, the leading non-genetic causal role in ovarian carcinogenesis is, surprisingly, one physiological cyclical process, the ovulation and ovulation-related inflammation. Follicular fluid exposure to tubal epithelial cells causes up-regulation of inflammatory and DNA repair pathways and induces double-stranded DNA breaks [34].

Finally, the American College of Obstetricians and Gynecologists and the American Cancer Society have recommended that surgeons discuss the potential benefits of the prophylactic removal of the UTs for permanent contraception or during surgeries for benign pathologies in every woman at risk for ovarian cancer [35]. Suppose general gynecologists were to consider the removal of the UTs at the time of every hysterectomy and sterilization procedure (the so-called "opportunistic salpingectomy") with the referral of all patients with high grade serous cancers for hereditary cancer counselling and genetic testing. In that case, experts project a potential reduction in the rate of high-grade serous cancers of the ovary/uterine tube/peritoneum by 40 % over the next 20 years [36].

Instead of conclusion - new morphological research directions

From the scientific publications of recent years, it is possible to assume what direction the research in the functional anatomy of the UTs will navigate. The most innovative and scientifically attractive morphological research areas will probably include the following:

In vitro human tubal epithelial cell culture-associated morphological research.

Tubal epithelial cell culture models, both 2D and 3D (spheroids) models are essential tools with a great translational potential for studying epithelial cellular responses to sexually transmitted pathogens, such as *Chlamydia trachomatis* or *Neisseria gonorrhoeae* [37,38] and to spermatozoa (sperm modifies the expression of cytokines, chemokines and growth factors from cultured tubal epithelial cells) [39,40]. Tubal epithelial cells co-culture with ovarian follicles can elucidate questions about cross-talk between the UT and ovum/cumulus oophorus during the reproductive cycle [41]. From the point of view of experimental oncology, *in vitro* tubal epithelial cell cultures are also suitable models for studying differentiation mechanisms, intercellular communication, and transformation to HGSOC [42,43].

Development and characterization of tubal organoids.

Organoids are miniaturized and simplified versions of any human body organ produced *in vitro* in three dimensions that show realistic micro-anatomic features, aiming to decipher human development and diseases. Recently, fetal organoids represent a powerful model to study the underlying basis of human female reproductive tract development, which may help understand Müllerian duct anomalies [44] or the cellular basis for the HGSOC development [45].

In silico modelling in reproductive medicine.

In silico experiments are performed on a computer or via computer simulation and represent one of the cutting-edge research trends, including the study of tubal transport function. A typical example of such trends is the work of Diemer *et al.* [46]. The authors presented a spatio-temporal model of the UT combined with an agent-based description of sperm motion and interaction, offering an alternative for studying sperm migration *in silico*. This model incorporates genital tract geometry and biophysical principles of sperm motion observed *in vitro,* such as positive rheotaxis and thigmotaxis. *In silico* model for sperm migration from the vagina to UTs was successfully tested against *in vivo* data from the scientific literature.

Regenerative medicine approaches and bioengineering trends associated with reproduction.

Current treatment options for tubal infertility/congenital tubal anomalies or acquired defects

are limited and often do not result in tissue function restoration, requiring alternative therapeutic approaches. Nowadays, regenerative medicine combines modern techniques, including stem cells, biomaterial scaffolds, bio-printing, and bio-fabrication of tissues or organoids for treating female reproductive tract-related disorders and dysfunctions in the future. The complexity of the molecular, endocrine and tissue-level interactions regulating female reproduction present challenges for bioengineering approaches to replace female reproductive organs in humans [47,48]. For this reason, tangible success has been achieved only *in vitro* [49] or in animal models [50]. This century's challenge is to transfer the results of laboratory experiments into actual clinical practice.

The impact of tubal environment on early embryonic development.

The UT provides the optimal micro-milieu for early embryonic development. It provides a stable temperature, optimal pH and dynamic fluid secretions to support embryo nutrition, growth and development [51]. With the current development of assisted reproductive techniques (including *in vitro* cultivation of early embryos from the zygote to blastocyst), the physiological function of the UTs in the early development of the embryo is often neglected. It is often forgotten that the UT is the first site of the early embryo–maternal dialogue. Recent scientific results demonstrate that embryo-derived extracellular vesicles may mediate the embryo-maternal dialogue in the UT, potentially carrying signals reflecting embryo quality. So, the UT may sense the quality of the pre-implantation embryos [52,53]. Some recent studies have shown that the UT microenvironment is critical for the development of the embryo and its future health as an adult due to epigenetic programming. Whether circumventions like the UT bypassing during IVF and embryo transfer negatively impact the embryo during this sensitive developmental period requires extensive further research [54].

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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