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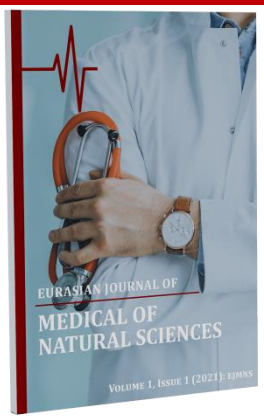

EXPLORING THE FUNCTIONAL MORPHOLOGY OF HUMAN UTERINE TUBES IN THE 21ST CENTURY: UNCOVERING ANATOMICAL INNOVATIONS AND THEIR POTENTIAL CLINICAL USES

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ABSTRACT

Pathologies of the uterine tube (UT) contribute to 25-35% of female factor infertility. Despite being studied centuries ago, these organs have been largely overlooked and neglected, primarily due to the advancements in reproductive medicine. However, challenges persist in achieving optimal fertility outcomes with in vitro fertilization (IVF). A more nuanced understanding of UT morphology and function during normal reproduction can potentially address many obstacles in reproductive medicine.

Throughout the 21st century, numerous insights have emerged, such as the identification of telocytes in the tubal wall responsible for motility and hormone sensory function. The discovery of lymphatic lacunae in the mucosal folds has been instrumental in understanding oocyte capture and tubal fluid recirculation. Additionally, a comprehensive profiling of the immune composition of UT epithelial lining, revealing the presence of regulatory T cells crucial for maternal tolerance towards the semiallogenic embryo, has been achieved. Noteworthy revelations also encompass the sensitivity of UT epithelium to male sex hormones, the recognition of a complex microbiome in the UT, and the identification of UT epithelial cells as the origin of high-grade serous ovarian carcinomas.

Crucially, contemporary morphological directions, including cell culture, tubal organoid development, in silico modeling, tissue engineering, and regenerative medicine, are emerging. These novel insights and approaches hold the potential to enhance clinical practice and contribute to more successful pregnancy outcomes.

Introduction:

Diseases affecting the uterine tube (Fallopian tube or oviduct) contribute significantly to female factor infertility, constituting 25-35% of cases. In a 2018 editorial by Professor Eve C. Feinberg in Fertility and Sterility, the potential replacement of medical therapy for infertility by assisted reproductive techniques was contemplated, raising questions about the relevance of further research into the functional anatomy of uterine tubes [1]. However, the intricate interplay between uterine tube epithelial cells and spermatozoa is well-documented, with positive impacts on sperm functions, selection, and activation (capacitation) [2]. Furthermore, the uterine tube plays a crucial role in creating a specific microenvironment essential for processes such as ovum capture, transport, fertilization, early embryo nutrition, development, and transport towards the uterine cavity. Additionally, the uterine tube amplifies signals from the embryo to the mother [3-5]. Recent discoveries of various functional aspects of uterine tubes contradict assertions about their supposed "needlessness." The 2022 Practice Committee of the Uzbekistan Society for Reproductive Medicine emphasizes reparative tubal surgery options, including a favorable prognosis for surgery addressing distal tubal diseases and recommending tubal cannulation for proximal tubal obstruction in young women with no other significant infertility factor [6].

Historically, anatomists such as Andreas Vesalius in 1543 and notable figures like Gabriel Fallopius, Realdo Colombo, Reinier de Graaf, and Caspar Bartholin in the 15th and 16th centuries provided detailed descriptions of female genital organs. Despite this rich history, the review challenges the perception that nothing new can be discovered in anatomy and aims to present a synthesis of the latest findings on the functional anatomy of uterine tubes, correlating them with previous research results.

Telocytes – A Novel Cell Population in the Tubal Wall:

In 2005, Popescu et al. [10] published a groundbreaking paper introducing a new interstitial cell population termed telocytes in the uterine tube wall (initially described as interstitial Cajal-like cells). Telocytes possess a small cell body and long cytoplasmic projections called telopodes, challenging study under light microscopy due to their narrow width (approximately 0.2 μm). The primary methods for studying telocytes include transmission electron microscopy and immunohistochemistry, with CD117 being a common marker for those found in the uterine tube (Fig. 1). Telocytes in the uterine tube wall are organized into various types of sheaths, including subepithelial, inner/outer perimuscular, and intramuscular sheaths [11]. According to Cretoiu et al. [12], uterine tube telocytes express receptors for steroid hormones on their surface, suggesting a potential sensory function in regulating peristaltic movements of the uterine tube muscle layer, influenced by estrogen-mediated acceleration or progesterone-induced slowing down. Disruptions in telocyte distribution and function due to various pathological conditions (e.g., acute salpingitis, Chlamydia infection, endometriosis) could potentially impair tubal transport function, leading to tubal infertility or ectopic tubal pregnancy [13-16]. Telocytes also engage in intercellular signaling between components of the interstitial compartment and epithelial cells, hinting at broader roles in tubal physiological functions and pathologies that future research may uncover.

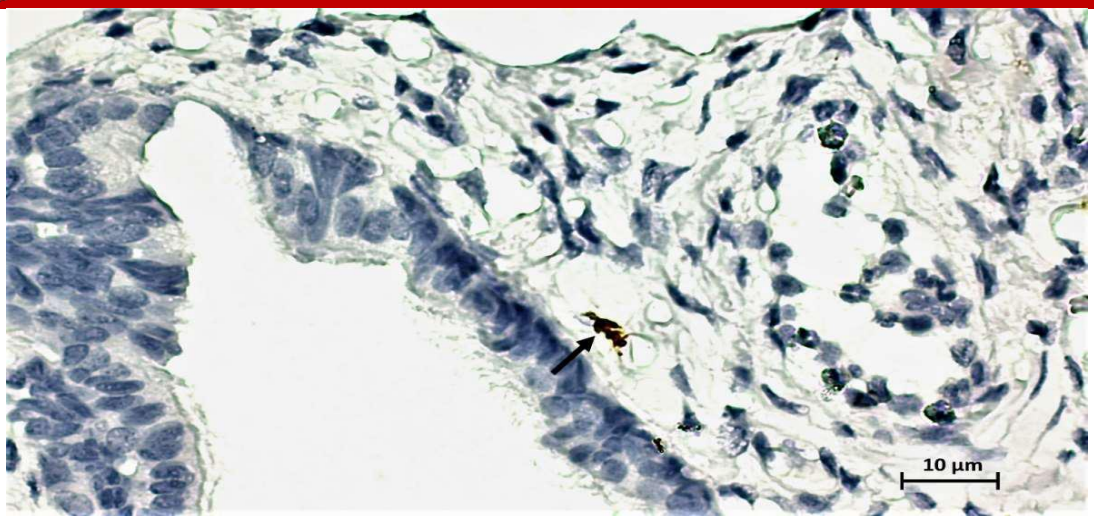

Fig. 1. CD117-positive telocyte-like cell with inconspicuous cell body and emerging projections (telopodes) in the lamina propria of the UT mucosal fold of the ampulla (black arrow).

Central Lymphatic Lacunae within Tubal Mucosal Folds and Fimbriae:

In 1904, Paul Kromer's habilitation thesis marked the initial documentation of expansive spaces within the tubal mucosal folds. Unfortunately, these spaces remained largely overlooked for over a century. Subsequent immunohistochemical investigations unveiled that these wide spaces predominantly occupy the infundibular fimbriae and are particularly abundant in the mucosal folds of the ampulla. Their confirmation of a lymphatic origin through positive markers for lymphatic endothelial cells, such as podoplanin, led to their designation as lymphatic lacunae of tubal mucosal folds and fimbriae (Fig. 2) [17].

These spaces, located in the fimbriae, are believed to play a crucial role in facilitating oocyte retrieval during ovulation. The presence of lymph allows these wide spaces to expand into a tissue resembling erectile tissue, enhancing the ease of capturing the oocyte. Additionally, their secondary function involves regulating the recirculation of tubal fluid [17]. This potential function holds clinical significance, as recent investigations by multiple research teams have shed light on the importance of tubal fluid dynamics in various processes within the uterine tube, particularly before, during, or shortly after fertilization and during the early stages of embryonic development. Tubal fluid dynamics were found to be equally critical alongside its quality and composition [18,19]. Overall, a more comprehensive understanding of these processes has the potential to significantly enhance the success of natural reproduction and refine assisted reproductive techniques.

The incomplete comprehension of these intricate processes, including tubal fluid dynamics, may contribute to the suboptimal success rates of in vitro fertilization (IVF) and could potentially lead to health complications later in life due to genetic alterations occurring in the earliest stages of embryonic development.

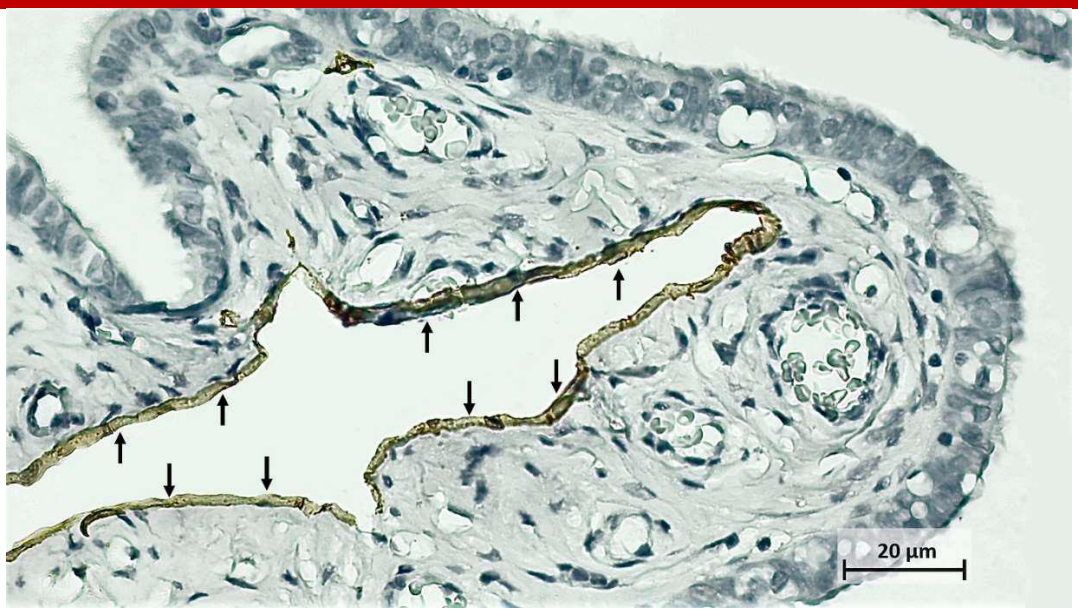

Fig. 2. Podoplanin (clone D2-40) positivity of wide lymphatic lacuna located in the lamina propria of the UT mucosal fold of the ampulla (black arrows).

Discovery of the Immune Cell Profile in the Uterine Tube:

From an immunological perspective, the mucosa of the uterine tube (UT) exhibits uniqueness, as its local immune cell populations serve as vigilant guardians against non-self-pathogens entering the UT from the pelvic or uterine cavity. Simultaneously, these very immune cells must exhibit "tolerance" towards non-self-spermatozoa and partially non-self (semiallogeneic) embryos, maintaining an anti-inflammatory environment. Additionally, the interaction between the UT and sperm further suppresses innate immune cells, reinforcing an anti-inflammatory balance in the UT. Consequently, UT immunity plays a crucial role in ensuring sperm viability before fertilization [20].

The local immune system within the human UT is a combination of innate and adaptive immune cells. In the tubal epithelium, intraepithelial T lymphocytes emerge as the predominant lymphoid subset. The average ratio of CD3+ T lymphocytes to epithelial cells in the tubal epithelium is 1:16, with intraepithelial B lymphocytes being 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. Macrophages, dendritic cells, and a minor population of NK cells and Langerhans cells are also present in the UT mucosa [21,22]. Notably, tubal intraepithelial T lymphocytes were historically described as tubal basal cells in various morphological publications, including official histological nomenclature. A previous immunohistochemical study confirmed their identity as intraepithelial T lymphocytes, likely regulatory T lymphocytes (Tregs), using T lymphocyte-specific antibodies, including anti-CD45RO (Fig. 3) [23].

Remarkably, recent research has challenged the long-standing belief that the UT is sterile, revealing the presence of a microbiome. While the composition and role of normal vaginal microflora have been well-known, the uterine cavity and UT cavity were traditionally considered sterile. The UT's microbiome has been found to be influenced by hormonal levels, and the precise roles of these microbes and their impact on reproductive health outcomes are still under investigation [24,25].

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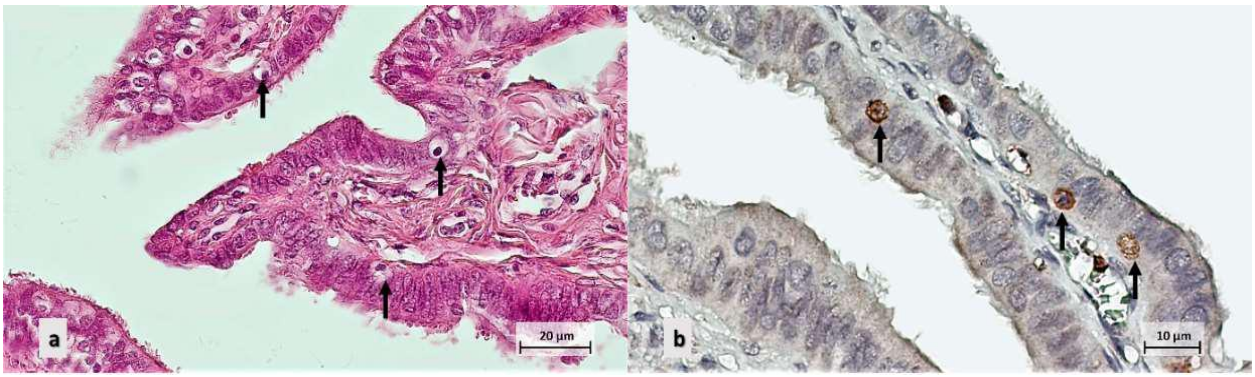

Fig. 3. Hematoxylin and eosin (HE)-stained ampulla of the UT showing the epithelial lining with clearly visible round basal cells with dark hyperchromatic nuclei and cytoplasmic halo (black arrows) (a). Immunohistochemical staining with anti-CD45RO confirmed that these "basal cells" are probably T lymphocytes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

Epithelium of the Uterine Tube Responds to Male Sex Hormones:

For decades, it has been recognized that, akin to the ovary and uterus, the uterine tubes (UTs) undergo cyclic morphological changes regulated by hormones [26]. Primarily affecting the epithelial lining, these changes lead to variations in epithelial cell height and ciliary beating frequency. Notably, during the menstrual phase, epithelial cells are at their shortest, heightening during the proliferative phase and reaching peak height during ovulation. Post-ovulation, secretory cells become most active, displaying the highest ciliary beating frequency. Conversely, progesterone induces atrophy, deciliation, apoptosis, and the loss of secretory activity [23,27]. Following menopause, there is a notable reduction in estrogen and progesterone receptor expression in epithelial cells [28].

However, the impact of elevated male sex hormones on tubal morphology and function has largely remained unknown. Dulohery et al. [29] recently provided groundbreaking insights by characterizing UT alterations resulting from prolonged exposure to male testosterone levels. Long-term testosterone treatment led to tubal blockage due to mucus accumulation and breakdown of epithelial cells in the ampulla, with a significant increase in the percentage of ciliated cells. Additionally, luminal collapse occurred in the isthmus. Hyperandrogenism in the UT appears to be associated with changes in secretory composition, tubal transport, and the ratio of epithelial cells [29]. These findings hold significant clinical relevance, as excess testosterone levels affect approximately 20% of the female population worldwide and play a crucial role in the pathogenesis of polycystic ovary syndrome.

Association Between Tubal Epithelium and High-Grade Serous Ovarian Cancers:

High-grade serous ovarian cancer (HGSOC) stands as the most prevalent and deadliest form of ovarian epithelial cancer, characterized by its high lethality, platinum resistance, and unfavorable survival outcomes, making it one of the most aggressive gynecological cancers. Originally, it was believed that HGSOC originated from invaginations of the ovarian surface epithelium resulting from normal ovulatory wounds, where trapped ovarian surface epithelium within cortical inclusion cysts underwent metaplasia and accumulated causal mutations. However, recent compelling evidence suggests that a significant proportion of

HGSOCs may also arise from the epithelium of the uterine tube (UT), particularly from the fimbriae's epithelium – the finger-like projections closest to the ovaries. Serous tubal intra-epithelial carcinomas (STICs), characterized by in situ neoplasms with increased proliferative capacity, have been identified in up to 60% of sporadic HGSOC cases. Despite uncertainties about the origin of HGSOC, mounting morphologic and molecular evidence supports the notion that HGSOC may indeed originate from the UTs through its precursor STIC, rather than from the ovary. These revelations hold significant implications for current screening methods, therapeutic approaches, and the identification of new targetable pathways.

In clinical practice, risk-reducing bilateral salpingo-oophorectomy has been proposed to mitigate the subsequent occurrence of serous carcinoma in high-risk patients with BRCA mutations. Surprisingly, beyond genetic factors, a physiological cyclical process—ovulation and ovulation-related inflammation—has emerged as a leading non-genetic contributor to ovarian carcinogenesis. Exposure of tubal epithelial cells to follicular fluid leads to the upregulation of inflammatory and DNA repair pathways, inducing double-stranded DNA breaks.

The Scientific and Practical Center of Obstetrics and Gynecology of Uzbekistan, in collaboration with the Uzbekistan Cancer Society, recommends discussing the potential benefits of prophylactic removal of the UTs for permanent contraception or during surgeries for benign pathologies in every woman at risk for ovarian cancer. Proposals for general gynecologists to consider "opportunistic salpingectomy" at the time of every hysterectomy and sterilization procedure, along with referring patients with high-grade serous cancers for hereditary cancer counseling and genetic testing, could potentially reduce the rate of high-grade serous cancers of the ovary, uterine tube, and peritoneum by 40% over the next 20 years [36]

Instead of a Conclusion - New Directions in Morphological Research:

Recent scientific publications suggest promising directions for future research in the functional anatomy of the uterine tubes (UTs). Innovative and scientifically compelling areas for morphological research may include:

In Vitro Human Tubal Epithelial Cell Culture-Associated Morphological Research:

Utilizing 2D and 3D (spheroids) models of tubal epithelial cell cultures offers translational potential for studying cellular responses to sexually transmitted pathogens and spermatozoa. Coculturing with ovarian follicles allows exploration of cross-talk between the UT and ovum/cumulus oophorus, while in vitro tubal epithelial cell cultures serve as suitable models for studying differentiation mechanisms, intercellular communication, and transformation to high-grade serous ovarian cancer (HGSOC) [37-43].

Development and Characterization of Tubal Organoids:

Fetal organoids provide a powerful model for studying human female reproductive tract development, aiding in understanding Müllerian duct anomalies and the cellular basis for HGSOC development [44,45].

In Silico Modeling in Reproductive Medicine:

In silico experiments, exemplified by spatio-temporal models combined with agent-based descriptions of sperm motion, offer an alternative for studying tubal transport function.

Successful testing against in vivo data from the scientific literature exemplifies the potential of this cutting-edge research trend [46].

Regenerative Medicine Approaches and Bioengineering Trends:

Addressing the limitations of current treatments for tubal infertility, regenerative medicine employs modern techniques like stem cells, biomaterial scaffolds, and bio-printing for developing tissues or organoids. Translating laboratory successes into clinical practice is a crucial challenge for the future [47-50].

The Impact of Tubal Environment on Early Embryonic Development:

Recognizing the UT's role in providing an optimal micro-milieu for early embryonic development is vital. Recent findings suggest that embryo-derived extracellular vesicles may mediate embryo-maternal dialogue in the UT, potentially reflecting embryo quality. The UT's influence on embryo development and future health through epigenetic programming requires further investigation, especially considering circumventions like UT bypassing during in vitro fertilization (IVF) and embryo transfer [51-54].

These emerging research directions hold the potential to deepen our understanding of UT physiology, reproductive disorders, and pave the way for innovative clinical interventions. Continued exploration in these areas promises valuable insights into female reproductive health and may contribute to advancements in reproductive medicine.

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